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Pharmacovigilance Risk Assessment Committee (PRAC) Minutes of the meeting on 28 September – 01 October 2020

Chair: Sabine Straus – Vice-Chair: Martin Huber

Health and safety information

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

Disclaimers

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

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

Note on access to documents

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

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1. Introduction

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

The Chairperson opened the 28 September – 01 October 2020 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 (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.

1.2. Agenda of the meeting on 28 September – 01 October 2020

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

1.3. Minutes of the previous meeting on 31 August – 03 September 2020

The minutes were adopted by written procedure 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 31 August – 03 September 2020 were published on the EMA website on 18 December 2020 ([EMA/PRAC/698632/2020](#)).

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

2.1. Newly triggered procedures

None

2.2. Ongoing procedures

None

2.3. Procedures for finalisation

None

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

3.1. Newly triggered procedures

None

3.2. Ongoing procedures

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 also Annex I 14.1.

4.1.1. Prednisolone (NAP); prednisone (NAP)

Applicant(s): various

PRAC Rapporteur: Anette Kirstine Stark

Scope: Signal of bradycardia

EPITT 19613 – New signal

Lead Member State(s): DK

Background

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

Prednisolone is a corticosteroid, and prednisone is a prodrug for prednisolone. Prednisolone and prednisone are indicated for the treatment of autoimmune diseases, severe allergic reactions and other conditions where anti-inflammatory and immunosuppressive effects are desirable.

During routine signal detection activities, a signal of bradycardia was identified by the EMA, based on 6 cases of prednisolone and 4 cases of prednisone retrieved from EudraVigilance database as well as 2 published cases³. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the available evidence from individual case safety reports and the literature regarding the risk of bradycardia in patients treated with prednisolone and prednisone and agreed that the signal required further investigation. The PRAC agreed to request a cumulative review of cases of bradycardia and sinus bradycardia from the MAHs of originator prednisolone- and prednisone-containing medicinal products.

The PRAC appointed Anette Kirstine Stark as Rapporteur for the signal.

Summary of recommendation(s)

- The MAHs Takeda and Mundipharma for the originator prednisolone- and prednisone-containing medicinal products, respectively, should submit to EMA, within 60 days, a cumulative review of all case reports of bradycardia and sinus bradycardia and related terms, together with a proposal for amending the product information, as appropriate.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.1.2. Remdesivir - VEKLURY (CAP)

Applicant(s): Gilead Sciences Ireland UC

PRAC Rapporteur: Eva Jirsová

Scope: Signal of acute kidney injury

EPITT 19605 – New signal

Lead Member State(s): CZ

Background

Remdesivir is an adenosine nucleotide antiviral prodrug indicated, as Veklury, a centrally authorised product, for the treatment of coronavirus disease 2019 (COVID-19) in adults and adolescents aged 12 years and older with body weight at least 40 kg with pneumonia requiring supplemental oxygen.

During routine signal detection activities, a signal of acute kidney injury was identified by the EMA, based on 157 cases retrieved from EudraVigilance. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

³ Nagakura A, Morikawa Y, Sakakibara H, Miura M. Bradycardia associated with prednisolone in children with severe Kawasaki disease. *J Pediatr.* 2017;185:106-111.e1. <http://doi:10.1016/j.jpeds.2017.02.074>

The PRAC discussed the available evidence from individual case safety reports and the literature regarding the risk of acute kidney injury in patients treated with remdesivir and agreed that the signal required further investigation. Therefore, the PRAC agreed to request a cumulative review of cases of acute kidney injury from the MAH.

Summary of recommendation(s)

- The MAH for Veklury (remdesivir) should submit to EMA, within 60 days, a cumulative review of all case reports of acute kidney injury and related terms from clinical trials, post-marketing, and the literature, together with a proposal for amending the product information and/or the RMP, as appropriate.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.2. New signals detected from other sources

4.2.1. Efavirenz – SUSTIVA (CAP), STOCRIN (CAP); NAP

Applicant(s): Bristol-Myers Squibb Pharma EEIG (Sustiva), Merck Sharp & Dohme B.V. (Stocrin)

PRAC Rapporteur: Ana Sofia Martins

Scope: Signal of microcephaly

EPITT 19595 – New signal

Lead Member State(s): PT

Background

Efavirenz is a non-nucleoside reverse transcriptase inhibitor. Sustiva and Stocrin (efavirenz) are centrally authorised products indicated, in antiviral combination therapy, for the treatment of human immunodeficiency virus-1 (HIV-1) infected adults, adolescents and children, under certain conditions.

The exposure for efavirenz-containing products is estimated to have been more than 1.89 million patient-years worldwide, in the period from first authorisation in 1999 to 2019.

Following the publications by *Williams et al.*⁴ and *Crowell et al.*⁵, a signal of microcephaly was identified by EMA based on two published analyses derived from a prospective cohort study, suggesting an increased risk of microcephaly and neurologic disorders in HIV-exposed but uninfected children exposed in utero exposure to efavirenz. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

Having considered the evidence from the literature the PRAC agreed that the signal required further assessment. The PRAC agreed to request further information from the MAHs, including a cumulative review of cases of microcephaly as well as neurologic and

⁴ Williams PL, Yildirim C, Chadwick EG, et al. Association of maternal antiretroviral use with microcephaly in children who are HIV-exposed but uninfected (SMARTT): a prospective cohort study. *Lancet HIV*. 2020;7(1):e49-e58

⁵ Crowell CS, Williams PL, Yildirim C, et al. Safety of in-utero antiretroviral exposure: neurologic outcomes in children who are HIV-exposed but uninfected. *AIDS*. 2020;34(9):1377-1387

neurodevelopmental disorders following in utero exposure to efavirenz and outside the context of neural tube defects.

Summary of recommendation(s)

- The MAHs for Sustiva and Stocrin (efavirenz) should submit to EMA, within 60 days, a cumulative review of all case reports of microcephaly as well as neurologic and neurodevelopmental disorders following in utero exposure to efavirenz and outside the context of neural tube defects from spontaneous reports, pre-clinical, clinical, registry and the literature. The MAHs should include a proposal to amend the product information and/or the RMP as appropriate.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.3. Signals follow-up and prioritisation

4.3.1. Citalopram (NAP); desvenlafaxine (NAP); escitalopram (NAP); fluoxetine (NAP); fluvoxamine (NAP); milnacipran (NAP); paroxetine (NAP); sertraline (NAP); venlafaxine (NAP); vortioxetine - BRINTELLIX (CAP)

Applicant(s): H. Lundbeck A/S (Brintellix), various

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of post-partum haemorrhage

EPITT 19552 – Follow-up to June 2020

Background

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

The MAHs Eli Lilly, GSK, Lundbeck, Mylan, Pfizer and Pierre Fabre replied to the request for information on the signal of post-partum haemorrhage and the responses were assessed by the Rapporteur.

Discussion

The PRAC assessed the comments from the MAHs for originator medicinal products containing citalopram, desvenlafaxine, escitalopram, fluoxetine, fluvoxamine, milnacipran, paroxetine, sertraline, venlafaxine and vortioxetine on the proposed updates to the product information.

Summary of recommendation(s)

- The MAHs for medicinal products containing citalopram, desvenlafaxine, escitalopram, fluoxetine, fluvoxamine, milnacipran, paroxetine, sertraline, venlafaxine and vortioxetine should submit to the relevant National Competent Authorities (NCAs) of the Member States or to EMA, within 60 days, a variation to amend⁶ the product information.

For the full PRAC recommendation, see [EMA/PRAC/513083/2020](#) published on 26 October 2020 on the EMA website.

⁶ Update of SmPC sections 4.4, 4.6 and 4.8 for medicinal products containing citalopram, desvenlafaxine, escitalopram, fluoxetine, fluvoxamine, milnacipran, paroxetine, sertraline, venlafaxine. Update of SmPC sections 4.4 and 4.6 for Brintellix (vortioxetine). The package leaflets are to be updated accordingly

4.3.2. Pembrolizumab - KEYTRUDA (CAP) - EMEA/H/C/003820/SDA/026

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

PRAC Rapporteur: Menno van der Elst

Scope: Signal of Sjogren's syndrome

EPITT 19564 – Follow-up to May 2020

Background

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

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

Discussion

Having considered the available evidence in EudraVigilance, the literature and the data provided by the MAH, the PRAC agreed that there is sufficient evidence for an association between pembrolizumab and Sjogren's syndrome. The PRAC agreed that the product information for pembrolizumab should be updated accordingly.

Summary of recommendation(s)

- The MAH for Keytruda (pembrolizumab) should submit to EMA, within 60 days, a variation to amend⁷ the product information.

For the full PRAC recommendation, see [EMA/PRAC/513083/2020](#) published on 26 October 2020 on the EMA website.

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. Azathioprine - EMEA/H/C/005055

Scope: Prophylaxis of transplant rejection and treatment of chronic inflammatory bowel disease (IBD) (Crohn's disease or ulcerative colitis), relapsing multiple sclerosis and

⁷ Update of SmPC section 4.8. The package leaflet is to be updated accordingly

generalised myasthenia gravis

5.1.2. 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 COVID-19, eye inflammation and infection

5.1.3. Fedratinib - EMEA/H/C/005026, Orphan

Applicant: Celgene Europe BV

Scope: Treatment of primary myelofibrosis, post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis

5.1.4. Hepatitis b surface antigen - EMEA/H/C/005063

Scope: Prevention of hepatitis B virus infection

5.1.5. Lenalidomide - EMEA/H/C/005348

Scope: Treatment of multiple myeloma

5.1.6. Lenalidomide - EMEA/H/C/005734

Scope: Treatment of multiple myeloma and follicular lymphoma

5.1.7. Lenalidomide - EMEA/H/C/005729

Scope: Treatment of multiple myeloma, myelodysplastic syndromes and follicular lymphoma

5.1.8. Moxetumomab pasudotox - EMEA/H/C/005322, Orphan

Applicant: AstraZeneca AB

Scope: Treatment of relapsed or refractory hairy cell leukaemia (HCL) after receiving at least two prior systemic therapies

5.1.9. Ofatumumab – EMEA/H/C/005410

Scope: Treatment of relapsing forms of multiple sclerosis

5.1.10. Pertuzumab, trastuzumab – EMEA/H/C/005386

Scope: Treatment of early breast cancer, metastatic breast cancer

5.1.11. Potassium - EMEA/H/C/005407, Orphan

Applicant: Advicenne S.A.

Scope: Treatment of distal renal tubular acidosis (dRTA) in patients aged 6 months and older

5.1.12. Remimazolam - EMEA/H/C/005246

Scope: Induction and maintenance of procedural sedation

5.1.13. Risperidone - EMEA/H/C/005406

Scope: Treatment of schizophrenia

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

Scope: Treatment of asthma

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

Scope: Treatment of asthma

5.1.16. Selpercatinib - EMEA/H/C/005375

Scope: Treatment of adults with advanced rearranged during transfection (RET) fusion-positive non-small cell lung cancer (NSCLC) who require systemic therapy; treatment of adults with advanced RET fusion-positive thyroid cancer who require systemic therapy and who have progressed following prior treatment; treatment of adults and adolescents 12 years and older with advanced RET-mutant medullary thyroid cancer (MTC) who require systemic therapy

5.1.17. Setmelanotide - EMEA/H/C/005089, Orphan

Applicant: TMC Pharma (EU) Limited

Scope (accelerated assessment): Treatment of obesity and control of hunger associated with deficiencies in the leptin-melanocortin pathway

5.1.18. Tucatinib - EMEA/H/C/005263

Scope: Treatment of metastatic breast cancer or brain metastases

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

See also Annex I 15.2.

5.2.1. Zoledronic acid - ACLASTA (CAP) - EMEA/H/C/000595/II/0076

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of an updated RMP (version 13.0) in order to bring it in line with revision 2 of GVP module V on 'Risk management systems' including consequential removal/reclassification of a number of important potential risks; to remove the education

material on renal dysfunction and use in patients with severe renal impairment; to remove 'post-dose symptoms' from the list of important identified risks as per the conclusions of LEG 037 adopted in September 2019 and variation II/74/G adopted in March 2020; to update of the targeted questionnaire related to osteonecrosis of the jaw (ONJ) as per the conclusions of LEG 035 adopted in January 2017; to include the completed 5-year registry for study ZOL446H2422 (listed as a category 3 study in the RMP): a non-interventional post-authorisation safety study using health registries to compare safety of Aclasta (zoledronic acid) against oral bisphosphonates and untreated population controls as per the conclusions of variation II/69 adopted in January 2018. The additional risk minimisation measures in Annex II-D on 'Conditions or restrictions with regard to the safe and effective use of the medicinal product' are updated accordingly

Background

Zoledronic acid is a nitrogen-containing bisphosphonate indicated, as Aclasta, for the treatment of osteoporosis in post-menopausal women, in men at increased risk of fracture as well as for the treatment of osteoporosis associated with long-term systemic glucocorticoid therapy, under specific conditions. It is also indicated for the treatment of Paget's disease of the bone in adults.

The PRAC is evaluating a type II variation for Aclasta, a centrally authorised product containing zoledronic acid, to update the RMP including several changes in particular the proposed discontinuation of the education material for prescribers on renal dysfunction and use in patients with severe renal impairment and revision of the patient information pack as additional risk minimisation measures (aRMM). The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this variation.

Summary of advice

- The RMP for Aclasta (zoledronic acid) in the context of the variation procedure under evaluation by the CHMP could be considered acceptable provided that an update to RMP version 13.0 is submitted.
- The PRAC supported the removal of the physician educational material on renal dysfunction and use in patients with severe renal impairment as this risk is well integrated in clinical practice and adequately controlled by routine risk minimisation measures (RMMs) and standard clinical practice guidelines. Regarding the patient information pack, the PRAC supported the removal of the patient educational initiative but considered that the patient reminder card on osteonecrosis of the jaw should be maintained as information is important to patients during the whole year between infusions and can be shared to other healthcare professionals (HCPs) others than prescribers for Aclasta (zoledronic acid). Osteonecrosis outside of jaw should remain an important potential risk in the PSUR safety specifications. Annex II-D should be revised accordingly.

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

See also Annex I 15.3.

5.3.1. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/X/0024/G

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Grouped application consisting of: 1) extension application to introduce a new pharmaceutical form (oral solution, 1 mg/mL); 2) addition of a new indication as treatment of active polyarticular juvenile idiopathic arthritis (pJIA) in patients of 2 years of age and older. The RMP (version 12.1) is updated in accordance. The MAH took the opportunity to align the product information with the latest quality review of documents (QRD) template (version 10.1)

Background

Tofacitinib is a Janus kinase inhibitor indicated, as Xeljanz, for the treatment of adult patients with rheumatoid arthritis, psoriatic arthritis and ulcerative colitis, under specific conditions.

The CHMP is evaluating a grouped application for Xeljanz, a centrally authorised product containing tofacitinib, consisting of an extension application to introduce a new pharmaceutical form and of the addition of a new indication as treatment of active polyarticular juvenile idiopathic arthritis (pJIA) in patients of 2 years of age and older. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this variation.

Summary of advice

- The RMP for Xeljanz (tofacitinib) in the context of the variation procedure under evaluation by the CHMP could be considered acceptable provided that an update to RMP version 12.1 is submitted.
- The MAH should provide the synopsis of the study protocol for the long term safety post marketing observational registry-type study for patient with pJIA, including the study objectives, the primary safety endpoints and how these will be measured. In addition, the MAH is requested to discuss data sources to be used and the feasibility of joining existing disease-registries. In terms of additional risk minimisation measures (aRMM), the MAH should provide a discussion whether the current aRMM needs to be updated or tailored to be applicable for the pJIA indication. In case of a new registry study, information about new registry should also be included in the key elements for healthcare professionals (HCP) material. Finally, the MAH is requested to discuss the need for further RMM (routine or additional RMM) to address the use of vaccines that are part of national immunisation schemes for paediatric population that may include live/attenuated vaccines.

5.3.2. 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

Background

Ustekinumab is an immunoglobulin G (IgG1κ) monoclonal antibody indicated, as Stelara, for the treatment of adult patients with Crohn's disease, ulcerative colitis (UC), psoriatic arthritis and plaque psoriasis, under specific conditions. It is also indicated for the treatment of paediatric plaque psoriasis in children and adolescent patients from the age of 6 years and older, under specific conditions.

The CHMP is evaluating grouped type II variations for Stelara, a centrally authorised product containing ustekinumab, consisting of an update of the product information to reflect the results of five year data (week 272) from study 3003 (listed as a category 3 study in the RMP) evaluating the safety and efficacy of ustekinumab maintenance therapy in adult patients with moderately to severely active Crohn's disease and two year data (week 96) from study 3001 (listed as a category 3 study in the RMP) evaluating the safety and efficacy of ustekinumab induction and maintenance therapy in subjects with moderately to severely active UC. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this variation.

Summary of advice

- The RMP for Stelara (ustekinumab) in the context of the variation procedure under evaluation by the CHMP could be considered acceptable provided that an update to RMP version 18.1 is submitted.
- While it is acknowledged that the analysis of major adverse cardiovascular events (MACE) in Crohn's and UC has limitations, given the findings to date of the Psoriasis Longitudinal Assessment and Registry (PSOLAR)⁸ study, the MAH should explore the possibility of evaluating the association with MACE in the planned PASS⁹ using SWIBREG¹⁰ and the planned PASS¹¹ using SNDS¹². In addition, the MAH should explore the possibility of evaluating all-cause mortality in both PASS studies as it is considered that this could contextualise the data on MACE. Finally, the MAH should provide a cumulative review on listeria meningitis in the next PSUR¹³.

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.

⁸ A multicentre, open registry of patients with plaque psoriasis who are candidates for systemic therapy including biologics

⁹ An observational PASS to describe the safety of ustekinumab and other ulcerative colitis treatments in a cohort of patients with ulcerative colitis using SWIBREG

¹⁰ Swedish Inflammatory Bowel Disease Register

¹¹ An observational PASS to describe the safety of ustekinumab and other ulcerative colitis treatments in a cohort of patients with ulcerative colitis using SNDS

¹² Système National des Données de Santé

¹³ Data lock point (DLP): 31/12/2020

6.1.1. Bosutinib - BOSULIF (CAP) - PSUSA/00010073/202003

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Bosutinib is a protein kinase inhibitor indicated, as Bosulif, for the treatment of adult patients with Philadelphia chromosome-positive chronic myelogenous leukaemia (Ph+ CML), under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Bosulif, a centrally authorised medicine containing bosutinib 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 Bosulif (bosutinib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include photosensitivity reaction as an undesirable effect with a frequency 'common' and as a warning on the risk of photosensitivity. Therefore, the current terms of the marketing authorisation(s) should be varied¹⁴.
- In the next PSUR, the MAH should provide a cumulative review of cases of thyroid dysfunction with a causality assessment and a discussion on the plausible mechanism(s).

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. Brentuximab vedotin - ADCETRIS (CAP) - PSUSA/00010039/202002

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

Background

Brentuximab vedotin is an antibody-drug conjugate indicated, as Adcetris, for the treatment of adult patients with CD¹⁵30+ Hodgkin lymphoma (HL), for the treatment of adult patients with systemic anaplastic large cell lymphoma (sALCL) as well as for the treatment of adult patients with CD30+ cutaneous T-cell lymphoma (CTCL) under certain conditions.

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

¹⁴ 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

¹⁵ Cluster of differentiation

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance Adcetris (brentuximab vedotin) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include infusion site extravasation 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 provide a detailed cumulative review of cases of demyelinating polyneuropathies and provide a discussion on the article by *Fargeot et al.* (2020)¹⁷ and provide a discussion on a plausible mechanism with a proposal for updating the product information and risk minimisation measures, as appropriate. The MAH should also provide a cumulative review of cases of ear disorders. Finally, the MAH should provide a cumulative review of cases of infusion site pain and revise the terms related to infusion site extravasation 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.

6.1.3. Burosumab - CRYSVITA (CAP) - PSUSA/00010669/202002

Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

Background

Burosumab is a recombinant human monoclonal antibody indicated, as Crysvida, for the treatment of X-linked hypophosphataemia with radiographic evidence of bone disease in children 1 year of age and older and adolescents with growing skeletons.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Crysvida, a centrally authorised medicine containing burosumab 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 Crysvida (burosumab) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAH should provide a detailed cumulative review of cases of medication errors with focus when the use of burosumab is contraindicated. The MAH should also monitor cases of ectopic mineralisation.

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 Fargeot et al. Brentuximab vedotin treatment associated with acute and chronic inflammatory demyelinating polyradiculoneuropathies. *J Neurol Neurosurg & Psychiatry*. 2020;91:786-788

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. Esketamine¹⁸ - SPRAVATO (CAP) - PSUSA/00010825/202003

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

Background

Esketamine is an antagonist of the N-methyl-D-aspartate (NMDA) receptor indicated, as Spravato, in combination with a selective serotonin reuptake inhibitor (SSRI) or a serotonin-norepinephrine reuptake inhibitor (SNRI), for the treatment of adults with treatment-resistant major depressive disorder, who have not responded to at least two different treatments with antidepressants.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Spravato, a centrally authorised medicine containing esketamine 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 Spravato (esketamine) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.

Additionally, having taken into account the new features of the medicinal product, notably the route of administration in a new therapeutic area for esketamine and the need for additional risk minimisation measures, the PRAC recommended that Spravato (esketamine) should be maintained on the additional monitoring list under the optional scope.

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. Fingolimod - GILENYA (CAP) - PSUSA/00001393/202002

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

Background

Fingolimod is a sphingosine 1-phosphate receptor modulator indicated, as Gilenya, for the treatment of highly active relapsing remitting multiple sclerosis, as single disease modifying therapy (DMT), under certain conditions.

¹⁸ Centrally authorised product(s) only

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Gilenya (fingolimod) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the existing warning on liver function to liver injury to include details on reported cases of acute liver failure and signs of liver injury. Acute hepatic failure should be also added as an undesirable effect with a frequency 'not known'. In addition, the existing warning on herpes viral infection should be amended to reflect that serious, life-threatening, and sometimes fatal cases of encephalitis, meningitis and meningoencephalitis caused by herpes simplex and varicella zoster have been reported and to give advice on discontinuation of the treatment with Gilenya (fingolimod). Therefore, the current terms of the marketing authorisation(s) should be varied¹⁹.
- The PRAC agreed on the content of a direct healthcare professional communication ([DHPC](#)) along with a communication plan for its distribution.
- In the next PSUR, the MAH should provide updated cumulative reviews of cases of congenital malformations and of cases of neurodevelopmental disorders in children exposed in utero to fingolimod during the first trimester. The MAH should also monitor the use and type of contraceptive methods used, investigate the reasons for pregnancy in case of hormonal contraceptive use and analyse the potential interaction of the medicinal product with these contraceptives, and provide a detailed discussion on the use of contraceptive data before and after application of the contraindication measures. The MAH should also closely monitor the paediatric population and provide a cumulative review of cases of hearing loss, providing a possible causality mechanism. Furthermore, the MAH should provide detailed reviews of cases of hepatitis E, convulsion and cryptococcal meningitis (CM). Finally, the MAH should provide reviews of cases of progressive multifocal leukoencephalopathy (PML), liver injury and severe drug-induced liver injury (DILI).

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

6.1.6. Fremanezumab - AJOVY (CAP) - PSUSA/00010758/202003

Applicant: Teva GmbH

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

Background

¹⁹ 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

Fremanezumab is a humanised immunoglobulin G2 (IgG2Δa/kappa) monoclonal antibody indicated, as Ajovy, for the prophylaxis of migraine in adults who have at least 4 migraine days per month.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Ajovy, a centrally authorised medicine containing fremanezumab 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 Ajovy (fremanezumab) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAH should provide a cumulative review of serious cases of constipation with a proposal for updating the product information, as appropriate. The MAH should also add Stevens-Johnson syndrome (SJS) to the PSUR list of safety concern as an important potential risk.

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. Oritavancin - ORBACTIV (CAP) - PSUSA/00010368/202003

Applicant: Menarini International Operations Luxembourg S.A.

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

Background

Oritavancin is a semisynthetic glycopeptide antibiotic indicated, as Orbactiv, for the treatment of acute bacterial skin and skin structure infections (ABSSSI) in adults.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Orbactiv (oritavancin) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the existing warning on infusion related reactions and to add dyspnoea, chest pain and pyrexia as undesirable effects with a frequency 'uncommon' and tremor, abdominal pain, hypoxia, chest discomfort, chills, back pain and neck pain with a frequency 'rare'. In addition, a warning on infusion related reactions should be added. Therefore, the current terms of the marketing authorisation(s) should be varied²⁰.

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 frequency of PSUR submission should be revised from 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.

6.1.8. Ruxolitinib - JAKAVI (CAP) - PSUSA/00010015/202002

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

Background

Ruxolitinib is a selective inhibitor of the Janus associated kinases indicated, as Jakavi, for the treatment of disease-related splenomegaly or symptoms in adult patients with chronic idiopathic myelofibrosis, under certain conditions. It is also indicated for the treatment of adult patients with polycythaemia vera, under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Jakavi, a centrally authorised medicine containing ruxolitinib 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 Jakavi (ruxolitinib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include hepatitis B virus (HBV) reactivation and pancytopenia as undesirable effects with a frequency 'not known' and 'common' respectively. In addition, the existing warning on HBV should be amended. Therefore, the current terms of the marketing authorisation(s) should be varied²¹.
- In the next PSUR, the MAH should provide a cumulative review of cases of tendon disorders with a proposal for updating the product information, as appropriate. The MAH should also provide cumulative reviews of cases of Kaposi's sarcoma and human herpesvirus 8 (HHV-8) reactivation.

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.

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

6.2.1. Imiquimod - ALDARA (CAP), ZYCLARA (CAP); NAP - PSUSA/00001729/202001

Applicants: Meda AB (Aldara, Zyclara), various

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

Background

Imiquimod is an immune response modifier indicated for the topical treatment, in adults, of external genital and perianal warts (condylomata acuminata), small superficial basal cell carcinomas (sBCCs) and clinically typical, nonhyperkeratotic, nonhypertrophic actinic keratoses (AKs), under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Aldara and Zyclara, centrally authorised medicines containing imiquimod, and nationally authorised medicines containing imiquimod 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 imiquimod-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the package leaflet should be updated to reflect the risk of exacerbation of autoimmune disorders. Therefore, the current terms of the marketing authorisations should be varied²².
- In the next PSUR, the MAHs should monitor cases of white blood cell and platelet disorders, depression, pemphigus and pemphigoid, autoimmune conditions worsening including multiple sclerosis, multiple sclerosis relapse as well as cases of amyotrophic lateral sclerosis.

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. Clobetasol (NAP) - PSUSA/00000799/202002

Applicant(s): various

PRAC Lead: Laurence de Fays

Scope: Evaluation of a PSUSA procedure

Background

²² Update of the package leaflet. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

Clobetasol is a topical corticosteroid indicated for the treatment of inflammatory and pruritic manifestations of steroid-responsive dermatoses that are resistant to less potent corticosteroids.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing clobetasol 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 clobetasol-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning on osteonecrosis, serious infections and systemic immunosuppression following long-term use of clobetasol beyond the recommended doses as well as a warning highlighting the recommended usage of clobetasol. Therefore, the current terms of the marketing authorisation(s) should be varied²³.
- In the next PSUR, the MAHs should provide a detailed review of cases of misuse of clobetasol for a prolonged duration to further characterise the extent and impact of this risk. In addition, the important potential risk of 'misuse for prolonged duration' should be reclassified as an important identified risk in PSURs. The MAHs should also provide a detailed discussion on off-label use and distinguish the use of clobetasol for non-medical purposes especially for cosmetic uses.

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

6.3.2. Etoposide (NAP) - PSUSA/00001333/202002

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Etoposide is a topoisomerase inhibitor indicated for the treatment of neoplastic diseases, under certain conditions.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing etoposide 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 etoposide-containing medicinal product(s) in the approved indication(s) remains unchanged.

²³ Update of SmPC sections 4.2 and 4.4. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAHs should provide a cumulative review of cases of progressive multifocal leukoencephalopathy (PML) and other opportunistic infections with a proposal for updating the product information, as appropriate. The MAHs should also closely monitor specific risks associated with use in the paediatric population, including harmful influence of excipients and the occurrence of renal failure associated with oral formulations. In addition, the MAHs should provide a separate discussion on thromboembolic events for authorised and off-label use.

The PRAC discussed the recent update of the product information of product(s) containing etoposide phosphate, which is the prodrug of etoposide, reflecting a warning on acute renal failure in high dose administration of etoposide phosphate and total body irradiation when used for haematopoietic stem cell transplantation. The PRAC agreed that MAHs of etoposide-containing products should assess the need to update their product information accordingly. Further consideration should be given at the level of CMDh.

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

6.3.3. Hydroxyethyl starch (HES) (NAP) - PSUSA/00001694/202003

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Hydroxyethyl starch (HES) is a synthetic colloid indicated for intravenous use for infusion for the treatment of hypovolemia due to acute blood loss when crystalloids alone are not considered sufficient.

In the context of the ongoing assessment of the submitted PSUR(s), the PRAC discussed the assessment report, the need to request additional data as well as further expert advice.

Summary of conclusions

- The PRAC agreed on a request for supplementary information (RSI) to the MAHs.
- The PRAC agreed on the need to convene an ad-hoc expert group meeting on 11 November 2020. The PRAC adopted a list of questions (LoQ).
- The PRAC adopted a LoQ to the authors *Futier et al.* of the FLASH study²⁴.
- The PRAC recommendation is due at the December 2020²⁵ PRAC meeting.

²⁴ Fluid loading in abdominal surgery: saline versus hydroxyethyl starch: a double-blinded multicentre prospective randomised trial

²⁵ Scheduled on 23-26 November 2020

6.3.4. Ibuprofen (NAP); ibuprofen lysine²⁶ (NAP); ibuprofen, caffeine (NAP) - PSUSA/00010649/202002

Applicant(s): various

PRAC Lead: John Joseph Borg

Scope: Evaluation of a PSUSA procedure

Background

Ibuprofen and ibuprofen lysine²⁷ are non-steroidal anti-inflammatory drugs (NSAID) indicated for the symptomatic relief of headache, toothache, sore throat, period pain, muscular and joint pain, back pain and minor arthritis pain. It is also indicated for the symptomatic relief of pain and fever in common cold or influenza. Ibuprofen is also formulated in combination with caffeine, a mild stimulant methylxanthine, used as an analgesic adjuvant.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of ibuprofen-, ibuprofen lysine- and ibuprofen/caffeine-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include photosensitivity reactions 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 MAHs should provide a cumulative review of cases of eosinophilic pneumonia 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.

6.3.5. Levosalbutamol²⁹ (NAP), salbutamol (NAP) - PSUSA/00010330/202001

Applicant(s): various

PRAC Lead: Melinda Palfi

Scope: Evaluation of a PSUSA procedure

Background

Salbutamol is a sympathomimetic indicated in acting bronchodilation in reversible airways obstruction due to asthma, chronic bronchitis and emphysema. It is also indicated for the

²⁶ All indication(s) except for ductus arteriosus

²⁷ All indication(s) except ductus arteriosus

²⁸ 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

²⁹No medicinal product with a valid marketing authorisation containing levosalbutamol in the European Economic Area (EEA) at the time of this assessment procedure

treatment of status asthmaticus and to arrest uncomplicated labour between 22 and 37 weeks of gestation in patients with no medical or obstetric contraindication to tocolytic therapy under certain conditions.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing salbutamol 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 salbutamol-containing medicinal product(s) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAHs should provide a cumulative review of cases of dental caries, gingivitis or other related health problems of the oral cavity and provide a discussion on the possible mechanisms to clarify the role of the active substance or salbutamol inhaled formulations with a proposal for updating the product information, as appropriate. The MAHs should also provide cumulative reviews of cases of psychiatric symptoms in the adult and paediatric populations, also assessing the influence of the route of administration, dosage form and dose together 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.

6.3.6. Lisdexamfetamine (NAP) - PSUSA/00010289/202002

Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Background

Lisdexamfetamine is an amphetamine indicated for the treatment of attention deficit/hyperactivity disorder (ADHD) in children aged 6 years and over when response to previous methylphenidate treatment is considered clinically inadequate, under certain conditions.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of lisdexamfetamine-containing medicinal product(s) in the approved indication(s) remains unchanged.

- Nevertheless, the product information should be updated to include syncope as an undesirable effect with a frequency 'uncommon'. Therefore, the current terms of the marketing authorisation(s) should be varied³⁰.
- In the next PSUR, the MAH should provide a cumulative review of cases of suicidality. The MAH should also provide a detailed characterisation of cases of pregnancy and lactation.

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.

6.3.7. Mequitazine (NAP) - PSUSA/00001986/202001

Applicant(s): various

PRAC Lead: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

Background

Mequitazine is a histamine H1-receptor antagonist indicated for the symptomatic treatment of seasonal and perennial allergic rhinitis, urticaria and conjunctivitis.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing mequitazine 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 mequitazine-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include tremor as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied³¹.
- In the next PSUR, the MAH should provide a cumulative review of cases of drug reaction with eosinophilia and systemic symptoms (DRESS) or other severe cutaneous adverse reactions (SCARs). The MAH should also provide a detailed analysis of the effectiveness of the risk minimisation measure implemented to prevent accidental exposure and monitor the evolution of the number of cases of contraindicated use in children below 2 years old with a proposal for additional risk minimisation measures, as appropriate. In addition, the MAH should monitor cases of withdrawal syndrome.

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.

³⁰ 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

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

6.3.8. Mesalazine (NAP) - PSUSA/00001990/202002

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Mesalazine is an anti-inflammatory drug indicated for the treatment of inflammatory bowel disease (IBD), including Crohn's disease and ulcerative colitis, and in chronic non-classifiable inflammatory bowel disease.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing mesalazine 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 mesalazine-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) as a warning and as undesirable effects with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied³².
- In the next PSUR, the MAHs should provide a cumulative review of cases of drug reaction with eosinophilia and systemic symptoms (DRESS) with a proposal for updating the product information, as appropriate. The MAHs should provide a discussion on foetal effects during maternal treatment based on the article by *Ek et al.*³³ and propose additional risk minimisation measures, as appropriate. The MAHs should also provide a detailed discussion on the inclusion of nephrogenic diabetes insipidus in the product information. Finally, the MAHs should provide a review of cases of pneumonia.

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

6.3.9. Phenobarbital (NAP) - PSUSA/00002370/202001

Applicant(s): various

PRAC Lead: Maia Uusküla

Scope: Evaluation of a PSUSA procedure

Background

³² Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

³³ Ek S and Rosenberg S. Mesalazine as a cause of fetal anemia and hydrops fetalis - A case report. *Medicine (Baltimore)*. 2017; 96(50): e9277

Phenobarbital is a barbiturate indicated for the treatment of epilepsy, prophylaxis of convulsions and for the short-term treatment of insomnia. The solution for injection formulation is also indicated as a co-adjuvant in anaesthesia.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing phenobarbital 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 phenobarbital-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning on hyperammonaemia in patients treated concomitantly with valproate and phenobarbital. Therefore, the current terms of the marketing authorisation(s) should be varied³⁴.

The PRAC considered that the MAHs should review and analyse cases of congenital malformations following in utero exposure to phenobarbital and of cases of neurodevelopmental disorders in children exposed in utero to phenobarbital with an assessment on the dose-effect relationship and an analysis of monotherapy in sub-groups and provide a discussion of the plausible biologic mechanism with a proposal for updating the product information, as appropriate. In addition, the PRAC considered that MAHs should provide a detailed discussion on the use of phenobarbital during pregnancy and whether advice on contraception for women of child-bearing potential should be added considering the risk of teratogenicity and the potential for failure of therapeutic effect of oral hormonal contraceptives due to enzyme induction, as appropriate. The MAHs should also consider the need to include in the product information the importance of specialist medical advice, the need to regularly review antiepileptic treatment especially when a woman is planning to become pregnant, and a warning that in pregnant women being treated for epilepsy, sudden discontinuation of antiepileptic drug (AED) therapy should be avoided with a proposal for additional risk minimisation measures, as appropriate. Further consideration should be given at the level of CMDh.

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

6.3.10. Potassium para-aminobenzoate (NAP) - PSUSA/00010130/202002

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Potassium para-aminobenzoate is an antifibrotic agent indicated for the treatment of induratio penis plastica (IPP) or Peyronie's disease and for the treatment of scleroderma.

³⁴ Update of SmPC section 4.5. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing potassium para-aminobenzoate 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 potassium para-aminobenzoate-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include warnings on severe cutaneous adverse reactions (SCARs) and on hypersensitivity reactions. In addition, drug reaction with eosinophilia and systemic symptoms (DRESS) and hypersensitivity reactions including immunoallergic hepatitis should be added as undesirable effects with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied³⁵.
- In the next PSUR, the MAH should monitor cases of photosensitivity.

The PRAC considered that the MAH(s) should be requested to provide a cumulative review of cases of liver disorders, together with a complete causality assessment with a proposal for updating the product information, as appropriate. Further consideration should be given at the level of CMDh.

The PRAC also considered that the MAH(s) should discuss the information on serum potassium level measurement for patients at risk for developing hyperkalaemia, with a proposal for updating the product information, as appropriate. Further consideration should be given at the level of CMDh.

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

6.3.11. Saccharomyces boulardii (NAP) - PSUSA/00009284/202002

Applicant(s): various

PRAC Lead: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

Background

Saccharomyces boulardii is a non-pathogenic live yeast indicated for the prevention and treatment of diarrhoea of different aetiologies, in complement to rehydration and dietetic measures.

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

Summary of recommendation(s) and conclusions

³⁵ 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

- Based on the review of the data on safety and efficacy, the benefit-risk balance of saccharomyces boulardii-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include sepsis in critically ill or immunocompromised patients as an undesirable effect with a frequency 'not known' and to add a cross-reference on the warning on sepsis. Therefore, the current terms of the marketing authorisation(s) should be varied³⁶.
- In the next PSUR, the MAH should provide a cumulative review of cases of Stevens–Johnson syndrome (SJS) including an evaluation on the history of skin reactions, concomitantly administered medicinal products, severity of reaction, presence of HLA³⁷-alleles and outcomes of de-challenge/re-challenge.

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.

6.3.12. Vancomycin (NAP) - PSUSA/00003097/202001

Applicant(s): various

PRAC Lead: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

Background

Vancomycin is a glycopeptide antibiotic indicated for the treatment of serious infections caused by certain bacteria in patients of all ages. It is also indicated to prevent bacterial endocarditis in patients undergoing surgery and to treat infections in patients undergoing peritoneal dialysis. It is also indicated for the treatment of *Clostridium difficile* infections (CDI).

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing vancomycin 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 vancomycin-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include toxic epidermal necrolysis (TEN) as an undesirable effect with a frequency 'very rare' and to remove the undesirable effect Lyell's syndrome. In addition, a warning on severe bullous reactions should be removed and warnings should be added on severe cutaneous adverse reactions (SCARs), on haemorrhagic occlusive retinal vasculitis (HORV) following intracameral or intravitreal administration and on increased risk of acute kidney injury with concomitant piperacillin/tazobactam treatment and their interaction with

³⁶ Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

³⁷ Human leukocyte antigen

vancomycin. Therefore, the current terms of the marketing authorisation(s) should be varied³⁸.

- In the next PSUR, the MAHs for parenteral formulations should provide a cumulative review of cases of haemolytic anaemia 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. Submission of PSURs for medicinal products referred to in Articles 10(1), 10a, 14, 16a of Directive 2001/83/EC as amended is not required any longer. The EURD list should be updated accordingly.

6.3.13. Verapamil (NAP) - PSUSA/00003105/202001

Applicant(s): various

PRAC Lead: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

Background

Verapamil is a selective calcium channel blocker indicated for the treatment of hypertension and coronary artery disease including various types of angina pectoris, post-myocardial infarction angina in patients without heart failure if beta-blockers are not indicated, disturbance of cardiac rhythm in paroxysmal supraventricular tachycardia, atrial fibrillation and atrial flutter with rapid atrioventricular conduction. The intravenous formulation is also indicated for the treatment of supraventricular tachyarrhythmias.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing verapamil 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 verapamil-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include the drug-drug interaction between verapamil and metformin that may reduce the efficacy of metformin. In addition, acute respiratory distress syndrome should be added as a clinical manifestation of overdose. Therefore, the current terms of the marketing authorisation(s) should be varied³⁹.
- In the next PSUR, the MAHs should closely monitor cases of accidental and intentional overdose/suicide and cases of off-label use of verapamil in cluster headache.

³⁸ Update of SmPC sections 4.4, 4.5 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

³⁹ Update of SmPC sections 4.5 and 4.9. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

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

6.4. Follow-up to PSUR/PSUSA procedures

See Annex I 16.4.

6.5. Variation procedure(s) resulting from PSUSA evaluation

6.5.1. Naltrexone hydrochloride, bupropion hydrochloride - MYSIMBA (CAP) - EMEA/H/C/003687/II/0044/G

Applicant: Orexigen Therapeutics Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: Grouped variations consisting of: 1) update of section 4.5 of the SmPC to add a warning concerning the interaction between naltrexone/bupropion and digoxin as requested in the conclusions of the latest periodic safety update report single assessment (PSUSA) procedure (PSUSA/00010366/201909) adopted in April 2020. The package leaflet is updated accordingly; 2) update of section 4.8 of the SmPC to include drug-induced lupus erythematosus with naltrexone/bupropion and its individual substances. The package leaflet is updated accordingly

Background

Naltrexone is a mu-opioid antagonist and bupropion an inhibitor of neuronal dopamine and norepinephrine reuptake. In combination, naltrexone/bupropion is indicated, as Mysimba, as an adjunct to a reduced-calorie diet and increased physical activity, for the management of weight in adult patients (≥ 18 years) with an initial body mass index (BMI) of ≥ 30 kg/m² (obese), or ≥ 27 kg/m² to < 30 kg/m² (overweight) in the presence of one or more weight-related co-morbidities.

Following the evaluation of the most recently submitted PSUR(s) for the above mentioned medicine(s), the PRAC requested the MAH to submit a variation to EMA to update the product information in line with the conclusions of the periodic safety update report single assessment (PSUSA) regarding the interaction with digoxin and to include drug-induced lupus erythematosus as an undesirable effect. For further background, see [PRAC minutes April 2020](#). The type II variation was assessed by the PRAC Rapporteur.

The PRAC is responsible for adopting an outcome based on the assessment report from the PRAC Rapporteur, to be further considered at the level of the CHMP, responsible for adopting an opinion on this variation.

Summary of recommendation(s)

- Based on the review of the submitted data and the Rapporteur's assessment, the PRAC agreed with the update of the product information⁴⁰ to include a warning concerning the interaction between naltrexone/bupropion and digoxin that may decrease plasma digoxin levels. In addition, the PRAC agreed with the addition of drug-induced lupus

⁴⁰ Update of SmPC sections 4.5 and 4.8. The package leaflet is updated accordingly

erythematosus with naltrexone/bupropion and its individual substances as an undesirable effect with a frequency 'not known'.

Based on the available evidence, the PRAC considered that the MAH(s) of bupropion-containing products should be requested to review the causal association between bupropion and the occurrence of cutaneous lupus erythematosus as well as aggravation of systemic lupus erythematosus considering and update their product information accordingly. Further consideration should be given at the level of CMDh.

6.5.2. Pirfenidone - ESBRIET (CAP) - EMEA/H/C/002154/II/0066/G, Orphan

Applicant: Roche Registration GmbH

PRAC Rapporteur: Rhea Fitzgerald

Scope: Grouped variations consisting of: 1) update of sections 4.4 and 4.8 of the SmPC in order to amend an existing warning on drug-induced liver injury (DILI) as requested in the conclusions of LEG 015 concluded in February 2020, assessing a review of cases of serious hepatic reactions and cases of hyponatremia and adequacy of the risk minimisation measures (RMM) of the product information requested in the conclusions of periodic safety update single assessment (PSUSA) procedure (PSUSA/00002435/201902) adopted in September 2019. The package leaflet and the RMP (version 10.0) are updated accordingly. In addition, the MAH took the opportunity to amend the package leaflet to reflect 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' as well as minor changes; 2) update of sections 4.4 and 4.8 of the SmPC in order to add a warning on hyponatraemia and to add hyponatraemia to the list undesirable effects as requested in the conclusions of LEG 015 assessing a review of cases of hyponatremia requested in the conclusions of PSUSA procedure (PSUSA/00002435/201902)

Background

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

Following the evaluation of the most recently submitted PSUR(s) for the above mentioned medicine(s), the PRAC requested the MAH to submit a variation to EMA to update the product information to amend an existing warning on drug-induced liver injury (DILI) in line with the conclusions of the periodic safety update report single assessment (PSUSA). For further background, see [PRAC minutes September 2019](#) and [PRAC minutes February 2020](#). The type II variation was assessed by the PRAC Rapporteur.

The PRAC is responsible for adopting an outcome based on the assessment report from the PRAC Rapporteur, to be further considered at the level of the CHMP, responsible for adopting an opinion on this variation.

Summary of recommendation(s)

- Based on the review of the submitted data and the Rapporteur's assessment, the PRAC agreed with the update of the product information⁴¹ to amend the existing warning on drug-induced liver injury (DILI), as well as to include hyponatraemia as a warning and as an undesirable effect with a frequency 'uncommon'. The PRAC also agreed with the

⁴¹ Update of SmPC sections 4.4 and 4.8 and of Annex II-D. The package leaflet is updated accordingly

updated RMP including the introduction of a targeted DILI questionnaire and an update of the healthcare professional (HCP) safety checklist as an additional risk minimisation measure to prompt the evaluation of patient with symptoms/signs of liver injury.

- The PRAC agreed on the content of a direct healthcare professional communication ([DHPC](#)) on new recommendations to prevent DILI along with a communication plan for its distribution.

6.6. Expedited summary safety reviews⁴²

See Annex I 16.6.

7. Post-authorisation safety studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)⁴³

See also Annex I 17.1.

7.1.1. Alemtuzumab – LEMTRADA (CAP) - EMEA/H/C/PSP/S/0087

Applicant: Sanofi Belgium

PRAC Rapporteur: Anette Kirstine Stark

Scope: Protocol for a non-interventional PASS to investigate the risk of mortality in patients prescribed Lemtrada (alemtuzumab) relative to comparable patients using other disease modifying therapies: a cohort study

Background

Alemtuzumab is a selective immunosuppressant indicated, as Lemtrada, a centrally authorised product, as a single disease modifying therapy (DMT) in adults with highly active relapsing remitting multiple sclerosis (RRMS) for patients with highly active disease despite a full and adequate course of treatment with at least one DMT or patients with rapidly evolving severe relapsing remitting multiple sclerosis defined by 2 or more disabling relapses in one year, and with 1 or more gadolinium enhancing lesions on brain magnetic resonance imaging (MRI) or a significant increase in T2 lesion load as compared to a previous recent MRI.

Further to the evaluation of the referral procedure under Article 20 of Regulation (EC) No 726/2004 ([EMEA/H/A-20/1483](#)) in 2019, a non-interventional PASS was imposed to the MAH to investigate the risk of mortality in patients prescribed Lemtrada (alemtuzumab) relative to comparable patients using other disease modifying therapies. In order to fulfil the obligation to conduct a PASS ([Annex II-D](#)) imposed in accordance with Article 107n(3) of Directive 2001/83/EC, the MAH Sanofi Belgium submitted to EMA on 07 July 2020 a protocol for the PASS for review by the PRAC.

Endorsement/Refusal of the protocol

- Having considered protocol version 1.0 in accordance with Article 107n of Directive 2001/83/EC, the PRAC objected to the draft protocol, as the Committee considered that

⁴² Requirement to the compassionate use opinion to submit expedited summary safety reports for review accompanied by a summary of remdesivir distribution, in addition to the 6-monthly or annual PSURs falling within the pandemic period

⁴³ In accordance with Article 107n of Directive 2001/83/EC

that the proposed design of the study does not fulfil the study objectives at this stage. In particular, the MAH should revise the feasibility analysis, and analyse data already available for the period 2013-2020.

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

7.1.2. Alemtuzumab – LEMTRADA (CAP) - EMEA/H/C/PSP/S/0088

Applicant: Sanofi Belgium

PRAC Rapporteur: Anette Kirstine Stark

Scope: Protocol for a non-interventional PASS to investigate drug utilisation and safety monitoring patterns for Lemtrada (alemtuzumab)

Background

Alemtuzumab is a selective immunosuppressant indicated, as Lemtrada a centrally authorised product, as a single disease modifying therapy (DMT) in adults with highly active relapsing remitting multiple sclerosis (RRMS) for patients with highly active disease despite a full and adequate course of treatment with at least one DMT or patients with rapidly evolving severe relapsing remitting multiple sclerosis defined by 2 or more disabling relapses in one year, and with 1 or more gadolinium enhancing lesions on brain magnetic resonance imaging (MRI) or a significant increase in T2 lesion load as compared to a previous recent MRI.

Further to the evaluation of the referral procedure under Article 20 of Regulation (EC) No 726/2004 ([EMEA/H/A-20/1483](#)) in 2019, a drug utilisation study (DUS) was imposed to the MAH to assess compliance with the revised therapeutic indication and contraindications and effectiveness of measures to minimise the risk of cardiovascular and cerebrovascular adverse events in close temporal association with Lemtrada (alemtuzumab) infusion and immune-mediated adverse reactions. In order to fulfil the obligation to conduct a PASS ([Annex II-D](#)) imposed in accordance with Article 107n(3) of Directive 2001/83/EC, the MAH Sanofi Belgium submitted to EMA protocol for a PASS entitled: a non-interventional PASS to investigate drug utilisation and safety monitoring patterns for Lemtrada (alemtuzumab) for review by the PRAC.

Endorsement/Refusal of the protocol

- Having considered protocol version 1.0 in accordance with Article 107n of Directive 2001/83/EC, the PRAC objected to the draft protocol, as the Committee considered that that the proposed design of the study does not fulfil the study objectives at this stage. In particular, the MAH should provide a revised data analysis, monitoring plan and feasibility analysis, especially on proxy definitions for indication(s) and contraindication(s) and monitoring issues.
- The MAH should submit a revised PASS protocol within 60 days to the EMA. A 60 day-assessment timetable will be followed.

7.2. Protocols of PASS non-imposed in the marketing authorisation(s)⁴⁴

See also Annex I 17.2.

7.2.1. Alemtuzumab - LEMTRADA (CAP) - EMEA/H/C/003718/MEA 006.3

Applicant: Sanofi Belgium

PRAC Rapporteur: Anette Kirstine Stark

Scope: MAH's request to discontinue pregnancy registry study OBS13436: an international Lemtrada pregnancy exposure cohort in multiple sclerosis [final clinical study report (CSR) initially expected in December 2021]

Background

Alemtuzumab is a selective immunosuppressant indicated, as Lemtrada a centrally authorised product, as a single disease modifying therapy (DMT) in adults with highly active relapsing remitting multiple sclerosis (RRMS) for patients with highly active disease despite a full and adequate course of treatment with at least one DMT or patients with rapidly evolving severe relapsing remitting multiple sclerosis defined by 2 or more disabling relapses in one year, and with 1 or more gadolinium enhancing lesions on brain magnetic resonance imaging (MRI) or a significant increase in T2 lesion load as compared to a previous recent MRI.

As part of the RMP for Lemtrada (alemtuzumab), the MAH was requested to conduct a pregnancy registry study. The MAH submitted a proposal for terminating the study which was assessed by the Rapporteur. The PRAC was requested to provide advice to CHMP on the proposal submitted by the MAH.

Summary of advice

- Based on the review of the available data and the assessment from the Rapporteur, the PRAC did not agree with the proposal from the MAH to discontinue the pregnancy registry study as further details are required before final conclusions on the role of alemtuzumab in congenital malformations can be drawn. The MAH should present further safety evaluation of pregnancy outcomes in the next PSUR.

7.3. Results of PASS imposed in the marketing authorisation(s)⁴⁵

7.3.1. Iron^{46 47} (NAP) - EMEA/H/N/PSR/J/0026

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

PRAC Rapporteur: Tiphaine Vaillant

Scope: MAH's response to PSR/J/0026 [results for a joint study on intravenous iron: evaluation of the risk of severe hypersensitivity reactions, as imposed in the conclusions of the referral under Article 31 of Directive 2001/83/EC (EMEA/H/A-31/1322) for intravenous

⁴⁴ 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

⁴⁵ In accordance with Article 107p-q of Directive 2001/83/EC

⁴⁶ Intravenous (IV)

⁴⁷ Iron(III)-hydroxide dextran complex, iron sucrose complex/iron(III)-hydroxide sucrose complex, ferric carboxymaltose complex, iron(III) isomaltoside complex, sodium ferric gluconate complex

(IV) iron-containing medicines in 2013]] as per the request for supplementary information (RSI) adopted in July 2020

Background

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

In line with the conclusions reached in 2013 of the referral procedure under Article 31 of Directive 2001/83/EC ([EMEA/H/A-31/1322](#)) conducted by the PRAC for IV iron-containing medicines, MAHs were required as a condition to the marketing authorisations ([Annex IV](#)) to conduct a PASS to assess the risk of anaphylactic or severe immediate hypersensitivity reactions. For further information see [PRAC minutes February 2013](#), [PRAC minutes March 2017](#) and [PRAC minutes October 2019](#)⁴⁸.

The MAH (on behalf of the consortium) submitted a final study report for assessment by the Rapporteur. The PRAC discussed the final study results in addition to the MAH's responses to the request for supplementary information (RSI). For further information, see [PRAC minutes July 2020](#).

Summary of recommendation(s) and conclusions

- Based on the review of the final report of the non-interventional PASS entitled 'intravenous iron post-authorisation safety study (PASS): evaluation of the risk of severe hypersensitivity reactions', the MAH's responses to the RSI and the assessment from the Rapporteur, the PRAC considered that a further request for supplementary information (RSI) was necessary before a recommendation could be made on the benefit-risk balance of IV iron-containing medicines concerned by the PASS final report. The MAH should further elucidate the possibility to obtain interpretable results to the objectives that justified the set-up of this study. In particular, the use of other European databases and/or registries should be considered as well as the set-up of a new study.
- The MAH should submit responses to the request for supplementary information within 60 days to EMA. A 60 day-assessment timetable will be followed.

7.3.2. Teicoplanin (NAP) - EMEA/H/N/PSR/S/0025

Applicant(s): Sanofi (Targocid)

PRAC Rapporteur: Martin Huber

Scope: MAH's response to PSR/S/0025 [results for a PASS study: a prospective, observational cohort, evaluating the incidence of nephrotoxicity and other adverse events of interest in patients treated with the higher recommended teicoplanin loading dose (12mg/kg twice a day), and comparison with external historical comparator data] as per the request for supplementary information (RSI) adopted in May 2020

Background

Teicoplanin is a glycopeptide antibiotic used for parenteral treatment of infections under certain conditions. Following the conclusion of a referral procedure under Article 30 of

⁴⁸ Held 30 September–03 October 2019

Directive 2001/83/EC ([EMEA/H/A-30/1301](#)) in 2013, a PASS was included as an obligation to the marketing authorisation ([Annex IV](#)) in order to evaluate the safety of Targocid (teicoplanin) in adults with Gram-positive infections who are exposed to the higher loading dose of 12mg/kg twice a day (24 mg/kg/day). In June 2015, the PRAC adopted a protocol for a prospective, observational cohort, evaluating the incidence of nephrotoxicity and other adverse events of interest in patients treated with the higher recommended teicoplanin loading dose (12mg/kg twice a day), and comparison with external historical comparator data. For further background, see [PRAC minutes April 2014](#), [PRAC minutes September 2014](#), [PRAC minutes June 2015](#) and [PRAC minutes May 2018](#).

The final study report version 1 dated 20 January 2020 was submitted to EMA by the MAH Sanofi on 2 March 2020 including an addendum report version 1 dated 09 June 2020 for a prospective, observational cohort, evaluating the incidence of nephrotoxicity and other adverse events of interest in patients treated with the higher recommended teicoplanin loading dose (12 mg/kg twice a day), and comparison with external historical comparator data). The PRAC discussed the final study results together with the MAH's responses to the request for supplementary information (RSI). For further background, see [PRAC minutes May 2020](#).

Summary of recommendation(s) and conclusions

- Based on the review of the final report version 1 of the non-interventional PASS, its addendum version 1, the MAH's responses to the RSI and the assessment from the Rapporteur, the PRAC agreed that changes to the product information and the conditions of the marketing authorisation(s) are warranted. Nevertheless, the PRAC considered that a further request for supplementary information (RSI) was necessary before a recommendation could be drawn on the benefit-risk balance of medicinal product(s) containing teicoplanin concerned by the PASS final report.
- The MAH should submit responses to the request for supplementary information within 30 days to EMA. A 30 day-assessment timetable will be followed.

7.4. Results of PASS non-imposed in the marketing authorisation(s)⁴⁹

See Annex I 17.4.

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

See Annex I 17.5.

7.6. Others

See also Annex I 17.6.

7.6.1. Canagliflozin - INVOKANA (CAP) - EMEA/H/C/002649/MEA 009.2

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Martin Huber

⁴⁹ 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

Scope: Third feasibility assessment for a drug utilisation study (DUS) to evaluate the drug utilisation patterns of canagliflozin-containing medicines including off-label usage in type 1 diabetes mellitus (T1DM) and the risk of diabetic ketoacidosis (DKA) using EU databases on market uptake and exposure within the European Union

Background

Canagliflozin is a sodium-glucose co-transporter-2 (SGLT2) inhibitor indicated as Inkovana for the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise, as monotherapy when metformin is considered inappropriate due to intolerance or contraindications, or in addition to other medicinal products for the treatment of diabetes.

Further to the evaluation of the referral procedure under Article 20 of Regulation (EC) No 726/2004 ([EMA/H/A-20/1419](#)) in 2016, a drug utilisation study (DUS) was requested to be conducted as a category 3 study in the RMP from a European setting in order to evaluate drug utilisation pattern of canagliflozin including off-label usage for type 1 diabetes mellitus (T1DM). For further background, see [PRAC minutes February 2016](#), [PRAC minutes December 2016](#)⁵⁰ and [PRAC minutes September 2018](#). The MAH Janssen-Cilag International NV submitted to EMA on 29 June 2020 a third feasibility assessment dated 22 June 2020 for a drug utilisation study for assessment by the Rapporteur.

Summary of advice

- Based on the review of the third feasibility assessment for a DUS and the assessment from the Rapporteur, the PRAC agreed that this post-authorisation measure cannot be considered fulfilled in light of the potential higher off-label use in T1DM than expected, that the diabetic ketoacidosis (DKA) risk in type 2 diabetes mellitus (T2DM) is not comparable to T1DM patients, and in light of the uncertainties that remain regarding the prescribing behaviour over time following the approval of other SGLT inhibitors in the T1DM indication. In addition, the PRAC concluded that future feasibility assessments for a DUS are no longer needed. The PRAC supported that a time trend analysis should be carried out to evaluate drug utilisation patterns of canagliflozin over time as part of a PASS.
- The MAH should submit to EMA, within 180 days, a full PASS protocol to evaluate drug utilisation patterns of canagliflozin in T1DM over time using appropriate healthcare databases.

7.6.2. Canagliflozin, metformin - VOKANAMET (CAP) - EMA/H/C/002656/MEA 008.2

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Menno van der Elst

Scope: Third feasibility assessment for a drug utilisation study (DUS) to evaluate the drug utilisation patterns of canagliflozin-containing medicines including off-label usage in type 1 diabetes mellitus (T1DM) and the risk of diabetic ketoacidosis (DKA) using EU databases on market uptake and exposure within the European Union

Background

⁵⁰ Held 28 November–01 December 2016

Canagliflozin is a sodium-glucose co-transporter-2 (SGLT2) inhibitor and metformin a biguanide. In combination, canagliflozin/metformin is indicated, as Vokanamet, in adults with type 2 diabetes mellitus as an adjunct to diet and exercise: in patients insufficiently controlled on their maximally tolerated doses of metformin alone in combination with other medicinal products for the treatment of diabetes, in patients insufficiently controlled with metformin and these medicinal products as well as in patients already being treated with the combination of canagliflozin and metformin as separate tablets.

Further to the evaluation of the referral procedure under Article 20 of Regulation (EC) No 726/2004 ([EMA/H/A-20/1419](#)) in 2016, a drug utilisation study (DUS) was requested to be conducted as a category 3 study in the RMP from a European setting in order to evaluate drug utilisation pattern of canagliflozin including off-label usage for type 1 diabetes mellitus (T1DM). For further background, see [PRAC minutes February 2016](#), [PRAC minutes December 2016](#)⁵¹ and [PRAC minutes September 2018](#). The MAH Janssen-Cilag International NV submitted to EMA on 29 June 2020 a third feasibility assessment dated 22 June 2020 for a drug utilisation study for assessment by the Rapporteur.

- The MAH should submit to EMA, within 180 days, a full PASS protocol to evaluate drug utilisation patterns of canagliflozin in T1DM over time using appropriate healthcare databases.

7.7. New Scientific Advice

None

7.8. Ongoing Scientific Advice

None

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

None

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.

⁵¹ Held 28 November–01 December 201

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

10.1.1. Andexanet alfa – ONDEXXYA (CAP) – EMEA/H/C/004108/II/0011

Applicant: Portola Netherlands B.V.

PRAC Rapporteur: Menno van der Elst; PRAC Co-Rapporteur: Brigitte Keller-Stanislawsk

Scope: PRAC consultation on an update of sections 4.4 and 4.5 of the SmPC in order to add a new warning on use of heparin after administration of andexanet based on spontaneous reports, medical literature reports, clinical trials and in vitro data. The package leaflet is updated accordingly. The MAH took the opportunity to introduce some additional editorial changes throughout the product information

Background

Andexanet alfa is a recombinant form of human factor Xa (FXa) protein indicated, as Ondexxya, for adult patients treated with a direct FXa inhibitor (apixaban or rivaroxaban) when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding.

A type II variation proposing to update the product information of Ondexxya (andexanet alfa) to add a new warning on use of heparin after administration of andexanet is under evaluation at the CHMP. The PRAC was requested to provide advice on this variation.

Summary of advice

- Based on the review of the available data and the assessment, the PRAC reviewed and agreed on the content of a direct healthcare professional communication ([DHPC](#)) in order to avoid use of andexanet prior to heparinisation, along with a communication plan for its distribution.

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Martin Huber

Scope: PRAC consultation on an update of sections 4.4 and 4.8 of the SmPC to reflect progressive multifocal leukoencephalopathy (PML) in the setting of mild lymphopenia based on data submitted in the ongoing PSUSA/00010143/201903 due for recommendation at the November 2019 PRAC meeting. The package leaflet is updated accordingly. Additionally, the Product Information has been updated in line with the quality review of documents (QRD) template (version 10.1)

Background

Dimethyl fumarate is an antineoplastic and immunomodulator agent indicated, as Tecfidera, for the treatment of adult patients with relapsing remitting multiple sclerosis (RRMS).

A type II variation proposing to update the product information of Tecfidera (dimethyl fumarate) on the risk of progressive multifocal leukoencephalopathy (PML) is under evaluation at the CHMP. The PRAC was requested to provide advice on this variation and more specifically on the proposed DHPC and communication plan. For further background, see [PRAC minutes September 2019](#), [PRAC minutes November 2019](#)⁵² and [PRAC minutes May 2020](#).

Summary of advice

- Based on the review of the available data and the assessment, the PRAC reviewed and agreed on the content of a direct healthcare professional communication ([DHPC](#)) in order to update recommendations in the light of cases of progressive multifocal leukoencephalopathy (PML) in the setting of mild lymphopenia, along with a communication plan for its distribution.
- The PRAC also advised to inform relevant patient organisations on the distribution of the DHPC once available on the EMA website. This was proposed to be done on a national level at the discretion of the National Competent Authorities (NCAs) of the Member States.

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.

⁵² Held 28-31 October 2019

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

11.1. Safety related variations of the marketing authorisation

11.1.1. Gadobenic acid (NAP), gadoteridol (NAP) - DK/H/xxxx/96, DK/H/xxxx/118

Applicant(s): Bracco (Multihance (gadobenic acid), Prohance (gadoteridol))

PRAC Lead: Anette Kirstine Stark

Scope: PRAC consultation on national worksharing variations to update the RMPs to include study to evaluate the effect of gadolinium containing agents (GdCAs) exposure during pregnancy and pregnancy outcomes, as required in the conclusions of the referral procedure under Article 31 of Directive 2001/83/EC on gadolinium containing agents (GdCAs) concluded in 2017 (EMEA/H/A-31/1437)

Background

Gadolinium containing medicinal products are used as a paramagnetic contrast agent in diagnostic magnetic resonance imaging (MRI). Prohance is a nationally approved medicinal product containing gadoteridol, a macrocyclic agent used for central nervous system (CNS) and whole-body scans including head, neck, liver, breast, musculoskeletal system and soft tissue. Multihance is a nationally approved medicinal product containing gadobenic acid, an intravenous linear agent used for liver scans.

Further to the evaluation of a referral procedure under Article 31 of Directive 2001/83/EC of gadolinium contrast agents (GdCAs) ([EMEA/H/A-31/1437](#)) in 2017, restrictions and suspensions for some intravenous linear agents were recommended in order to prevent any risks that could potentially be associated with gadolinium brain deposition. For further background, see [PRAC minutes March 2016](#), [PRAC minutes June 2016](#), [PRAC minutes July 2016](#), [PRAC minutes October 2016](#)⁵³, [PRAC minutes December 2016](#)⁵⁴, [PRAC minutes March 2017](#), [PRAC minutes April 2017](#), [PRAC minutes May 2017](#), [PRAC minutes June 2017](#) and [PRAC minutes July 2017](#).

In the context of the evaluation of worksharing variation procedures for Prohance (gadoteridol) and Multihance (gadobenic acid) to update their RMP in order to replace the requested observational study on pregnancy and on pregnancy outcomes following exposure to gadobenic acid and gadoteridol with two non-clinical studies in mice, Denmark requested PRAC advice on its assessments.

Summary of advice

- Based on the review of the available information and assessments, the PRAC advised that the two studies in mice cannot replace an observational study of women exposed to gadobenic acid and gadoteridol during pregnancy. Due to the low number of available subjects, the PRAC also considered that it is unlikely that the observational study in humans could deliver meaningful results, namely to adequately evaluate the effect of GdCA exposure during pregnancy and on pregnancy outcomes in an acceptable timeframe. In order to gain further insight in the extent of exposure of gadobenic acid

⁵³ Held 26-29 September 2016

⁵⁴ Held 28 November–01 December 2016

and gadoteridol during pregnancy and on pregnancy outcomes, the PRAC advised to include in the relevant RMP specific adverse reaction follow-up questionnaires as routine pharmacovigilance activities.

- Finally, the PRAC considered that the same approach applies to the other authorised GDCAs (except intra-articular formulations).

11.2. Other requests

None

12. Organisational, regulatory and methodological matters

12.1. Mandate and organisation of the PRAC

12.1.1. PRAC meeting dates 2022-2024

The EMA Secretariat presented to PRAC the meeting dates for the period of 2022-2024 for publication following CHMP adoption. The PRAC endorsed the document.

12.1.2. PRAC working group - Best practice guide on using PRAC plenary time efficiently and effectively – update on the implementation of quantitative goals –Q3 2020

In line with the adopted PRAC best practice guidance (BPG) on Committee efficiency (see [PRAC minutes May 2016](#) and [PRAC minutes June 2018](#)) and the adopted implementation plan for the BPG including goals to measure compliance with the recommendations (see [PRAC minutes June 2016](#) and [PRAC minutes June 2018](#)), the EMA secretariat informed the PRAC about the quantitative measures collected for the Q2 2020 of PRAC meetings. For previous update, see [PRAC minutes July 2020](#).

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. In addition, the EMA Secretariat provided the PRAC with an update on COVID-19-observational research initiatives. Finally, the EMA Secretariat presented to PRAC the proposed EMA's vaccine outreach strategy in order for EMA to more proactively monitor

public concerns on vaccines, understand knowledge gaps and reach out to the public and communicate on vaccine science. It also has as an objective to support ongoing work of EU countries, the European Commission (EC) and other EU bodies and adopt a longer-term approach within the EU network in order to fulfil the priorities on vaccines that EMA has reflected in the [Regulatory Science Strategy to 2025](#). PRAC members were invited to provide written comments by 30 November 2020.

12.4.2. PRAC strategic review and learning meeting (SRLM) under the German presidency of the European Union (EU) Council - Langen, Germany, 22 October 2020 – Agenda (virtual meeting)

PRAC lead: Brigitte Keller-Stanislawski, Martin Huber

The PRAC was presented with a draft agenda for the 'PRAC strategic review and learning meeting (SRLM)', to be held jointly remotely with the Paediatric Committee (PDCO) and the Committee on Advanced Therapy (CAT) on 22 October 2020 under the German presidency of the Council of the European Union (EU).

12.5. Cooperation with International Regulators

None

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

None

12.7. PRAC work plan

None

12.8. Planning and reporting

12.8.1. Marketing authorisation applications (MAA) forecast for 2020 – planning update dated Q3 2020

The EMA Secretariat presented to PRAC for information a quarterly updated report on marketing authorisation applications planned for submission (the business 'pipeline').

12.8.2. PRAC workload statistics – Q3 2020

The EMA secretariat informed the PRAC of the quarterly and cumulative figures to estimate the evolution of the workload of the PRAC for Q3 2020, by reflecting on the number of procedures and agenda items covered at each PRAC plenary meeting. For previous update, see [PRAC minutes July 2020](#).

12.9. Pharmacovigilance audits and inspections

12.9.1. Pharmacovigilance systems and their quality systems

None

12.9.2. Pharmacovigilance inspections

None

12.9.3. Pharmacovigilance audits

None

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

12.10.1. Periodic safety update reports

None

12.10.2. Granularity and Periodicity Advisory Group (GPAG)

PRAC lead: Menno van der Elst, Maia Uusküla

None

12.10.3. PSURs repository

None

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

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

Post-meeting note: following the PRAC meeting of October 2020, the updated EURD list was adopted by the CHMP and CMDh at their October 2020 meetings and published on the EMA website on 21/10/2020, see:

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

12.11. Signal management

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

PRAC lead: Menno van der Elst

None

12.12. Adverse drug reactions reporting and additional monitoring

12.12.1. Management and reporting of adverse reactions to medicinal products

None

12.12.2. Additional monitoring

None

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

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

Post-meeting note: The updated additional monitoring list was published on the EMA website on 28/10/2020, see: [Home>Human Regulatory>Post-authorisation>Pharmacovigilance>Medicines under additional monitoring>List of medicines under additional monitoring](#)

12.13. EudraVigilance database

12.13.1. Activities related to the confirmation of full functionality

None

12.14. Risk management plans and effectiveness of risk minimisations

12.14.1. Risk management systems

None

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

None

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

PRAC lead: Sabine Straus

As a follow-up to the July 2020 discussion (for background, see [PRAC minutes July 2020](#)) and in line with the [PRAC work plan 2020](#), the EMA Secretariat presented to PRAC the updated proposal for draft revision 3 of GVP module XVI on 'Risk minimisation measures: selection of tools and effectiveness indicators' and its new draft Addendum II on methods for effectiveness evaluation. The PRAC endorsed them for a 2-weeks consultation at CHMP, CAT, PDCO, CMDh and the Pharmacovigilance Inspectors Working Group (PhVIWG) and noted the planned schedule for finalisation after EMA review and PRAC adoption before initiating the public consultation. With regard to the comment that risk minimisation measures (RMM) should be decided upon and designed based on evidence and user-testing and that more guidance in this respect should be added, the PRAC agreed to take this

forward within the PRAC Impact Engagement Workstream and consider guidance in the future based on PRAC pilots in 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

12.18. Risk communication and transparency

12.18.1. Public participation in pharmacovigilance

None

12.18.2. Safety communication

None

12.18.3. PRAC meeting highlights – COVID-19 related procedures

The EMA Secretariat presented to PRAC a proposal to expand the current format of the PRAC meeting highlights to include information on coronavirus (COVID-19)-related procedures discussed at the PRAC as part of a phased approach. The PRAC agreed with the proposal.

12.19. Continuous pharmacovigilance

12.19.1. Incident management

None

12.20. Others

12.20.1. Article 58⁵⁵ (EU-M4all) and centralised procedures - parallel application submissions

The EMA Secretariat presented to PRAC on the initiative, in cooperation with the World Health Organization (WHO), to run a parallel assessment for a scientific opinion intended exclusively for markets outside of the European Union (EU) under Article 58 (so called EU-M4all) and marketing authorisation(s) for initial marketing authorisation application(s) on high priority medicines for human use, including vaccines. Further details on the procedural aspects were shared with the Committee. PRAC members were requested to provide written comments on the proposed assessment report template by 19 October 2020.

12.20.2. Collection of data on adverse events related to medicinal products through registries – survey results

PRAC Lead: Sabine Straus, Martin Huber, Menno van der Elst, Ulla Wändel Liminga

The EMA Secretariat presented to PRAC the results of the survey on the collection of data on adverse events related to medicinal products through registries. In April 2020, the EMA launched a survey that run until August 2020 to gather information on the current practices and capability of registries registered in the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) resources database to collect, manage and share data on adverse events related to medicines. The results of the survey showed that the majority of responding registries collects data related to adverse events, although approaches and detail of information collected varied.

Post-meeting note: On 19 October 2020, the survey results were presented at the EMA workshop on the draft guideline on registry-based studies ([EMA/428155/2020](https://www.ema.europa.eu/en/press-room/2020/10/15/2020-10-15-01)).

13. Any other business

None

14. Annex I – Signals assessment and prioritisation⁵⁶

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 timetables⁵⁷.

⁵⁵ 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)

⁵⁶ 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

⁵⁷ Either MA(s)'s submission within 60 days followed by a 60 day-timetable assessment or MAH's submission cumulative review within an ongoing or upcoming PSUR/PSUSA procedure (if the DLP is within 90 days), and no disagreement has been raised before the meeting

14.1.1. Isatuximab – SARCLISA (CAP)

Applicant(s): Sanofi-aventis groupe

PRAC Rapporteur: Eva Segovia

Scope: Signal of anaphylactic reaction

EPITT 19598 – New signal

Lead Member State(s): ES

14.2. New signals detected from other sources

None

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. Abiraterone acetate - EMEA/H/C/005408

Scope: Treatment of metastatic prostate cancer

15.1.2. Bevacizumab - EMEA/H/C/005286

Scope: Treatment of metastatic carcinoma of the colon or rectum, metastatic breast cancer and recurrence of platinum-sensitive epithelial ovarian, fallopian tube or primary peritoneal cancer; first-line treatment of patients with unresectable advanced, metastatic or recurrent non-small cell lung cancer; first line treatment of patients with advanced and/or metastatic renal cell cancer

15.1.3. Bevacizumab - EMEA/H/C/005556

Scope: Treatment of metastatic carcinoma of the colon or rectum, metastatic breast cancer and recurrence of platinum-sensitive epithelial ovarian, fallopian tube or primary peritoneal cancer; first-line treatment of patients with unresectable advanced, metastatic or recurrent non-small cell lung cancer; first line treatment of patients with advanced and/or metastatic renal cell cancer

15.1.4. Fostemsavir - EMEA/H/C/005011

Scope: Treatment in combination with other antiretrovirals of adults with multidrug resistant human immunodeficiency virus-1 (HIV-1) infection for whom it is otherwise not possible to construct a suppressive anti-viral regimen due to resistance, intolerance or safety considerations

15.1.5. [Insulin aspart - EMEA/H/C/004965](#)

Scope: Treatment of diabetes mellitus

15.1.6. [Ioflupane \(¹²³I\) - EMEA/H/C/005135](#)

Scope: Detection of loss of functional dopaminergic neuron terminals in the striatum

15.1.7. [Sunitinib - EMEA/H/C/005419](#)

Scope: Treatment of gastrointestinal stromal tumour (GIST) and metastatic renal cell carcinoma (MRCC) and pancreatic neuroendocrine tumours (pNET)

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. [Aprepitant - EMEND \(CAP\) - EMEA/H/C/000527/II/0063](#)

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Annika Folin

Scope: Submission of an updated RMP (version 5.1) in order to remove all safety concerns and information related to both 40 mg and 165 mg capsules strengths and the postoperative nausea and vomiting indication (PONV), as well as to update data in the post-authorisation exposure and epidemiology section following the removal of the two capsule strengths (40 mg and 165 mg) and the removal of the PONV indication as approved in variation IB/0062/G finalised at CHMP in June 2020

15.2.2. [Dapagliflozin - EDISTRIDE \(CAP\) - EMEA/H/C/004161/WS1844/0039; FORXIGA \(CAP\) - EMEA/H/C/002322/WS1844/0057](#)

Applicant: AstraZeneca AB

PRAC Rapporteur: Annika Folin

Scope: Re-categorisation of study D169C00011: a retrospective cohort study on the risk of diabetic ketoacidosis (DKA) to determine the effectiveness of additional risk minimisation measures (aRMMs) in place for DKA by assessing the impact of the risk minimisation measures (RMMs) on the risk of DKA in type 1 diabetes mellitus (T1DM) patients who are treated with dapagliflozin in Europe, from a category 1 to a category 3 study in the RMP (version 20). Annex II-D on 'Conditions or restrictions with regard to the safe and effective use of the medicinal product' is updated accordingly

15.2.3. [Filgrastim - RATIOGRASTIM \(CAP\) - EMEA/H/C/000825/II/0069](#)

Applicant: Ratiopharm GmbH

PRAC Rapporteur: Kirsti Villikka

Scope: Submission of an updated RMP (version 10.0) in order to remove the additional pharmacovigilance activity on `cooperation with the Severe Chronic Neutropenia International Registry (SCNIR) and analysis of corresponding Ratiograstim/Tevagrastim (filgrastim)-SCNIR data

15.2.4. Filgrastim - TEVAGRASTIM (CAP) - EMEA/H/C/000827/II/0077

Applicant: Teva GmbH

PRAC Rapporteur: Kirsti Villikka

Scope: Submission of an updated RMP (version 10.0) in order to remove the additional pharmacovigilance activity on `cooperation with the Severe Chronic Neutropenia International Registry (SCNIR) and analysis of corresponding Ratiograstim/Tevagrastim (filgrastim)-SCNIR data

15.2.5. Fosaprepitant - IVEMEND (CAP) - EMEA/H/C/000743/II/0043

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Annika Folin

Scope: Submission of an updated RMP (version 5.1) to remove all safety concerns and to update data in the post-authorisation exposure and epidemiology sections

15.2.6. Ibrutinib - IMBRUVICA (CAP) - EMEA/H/C/003791/II/0061, Orphan

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Submission of an updated RMP (version 16.2) in order to introduce changes to safety concerns following the conclusions of renewal procedure R/049 finalised in April 2019. The MAH took the opportunity to include additional changes related to two post-authorisation measures, namely the postponement of the completion date of study PCI-32765MCL3002 (listed as a category 3 study in the RMP): a randomized, double-blind, placebo-controlled phase 3 study of the Bruton's tyrosine kinase (BTK) inhibitor, PCI-32765 (ibrutinib), in combination with bendamustine and rituximab (BR) in subjects with newly diagnosed mantle cell lymphoma and the removal of study 54179060CLL1017 on drug-drug interaction (DDI) in line with the conclusions of variation II/058 finalised in April 2020

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. Pregabalin - LYRICA (CAP) - EMEA/H/C/000546/WS1919/0109; PREGABALIN PFIZER (CAP) - EMEA/H/C/003880/WS1919/0038

Applicant: Upjohn EESV

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Submission of an updated RMP (version 13.0) to include results from recently completed PASS studies, namely: 1) study A0081359: a population-based cohort study of pregabalin to characterize pregnancy outcomes; 2) study A0081106: a 12-month open-label study to evaluate the safety and tolerability of pregabalin as adjunctive therapy in paediatric subjects 1 month to 16 years of age with partial onset seizures and paediatric and adult subjects 5 to 65 years of age with primary generalized tonic-clonic seizures; 3) study A0081042: a double-blind, placebo-controlled, parallel-group, multicentre study of the efficacy and safety of pregabalin as adjunctive therapy in children 1 month through <4 years of age with partial onset seizures; 4) study A0081105: a randomized, double-blind, placebo-controlled, parallel group, multicentre trial of pregabalin as adjunctive therapy in paediatric and adult subjects with primary generalized tonic-clonic seizures. In addition, information on study A0081096: a prospective randomized 12-week controlled study of visual field change in subjects with partial seizures receiving pregabalin or placebo has been updated as well as study A0081365: a phase 4, randomised, double-blind, double-dummy, placebo- and active-controlled, single-dose, six-way crossover study to evaluate the potential for abuse with pregabalin (added as a new FDA⁵⁸-imposed PASS). The clinical study report (CSR) for study A0081359 is included in the submission

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

As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of the updated versions of the RMP for the below mentioned medicine(s).

15.3.1. Adalimumab - HULIO (CAP) - EMEA/H/C/004429/X/0016

Applicant: Mylan S.A.S

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension application to add a new strength of 20 mg solution for injection. The RMP (version 3.1) is updated in accordance

15.3.2. Adalimumab - HUMIRA (CAP) - EMEA/H/C/000481/II/0198

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension of indication to include treatment of moderately to severely active ulcerative colitis in paediatric patients. As a consequence, sections 4.1, 4.2, 5.1 and 5.2 of the SmPC for the 40mg/0.8mL, 40mg/0.4mL and 80mg/0.8mL presentations are updated. Furthermore, sections 5.1 and 5.2 of the SmPC for the 20mg/0.2mL presentation are updated. The package leaflet and the RMP (version 15.0) are updated in accordance

⁵⁸ United States Food and Drug Administration

15.3.3. Afamelanotide - SCENESSE (CAP) - EMEA/H/C/002548/II/0033, Orphan

Applicant: Clinuvel Europe Limited

PRAC Rapporteur: Martin Huber

Scope: Update of section 4.8 of the SmPC to revise the frequencies of adverse drug reactions (ADRs) based on safety reports and to add new ADRs based on post-marketing spontaneous reports as requested in the conclusions of the renewal procedure (R/0026) finalised in September 2019. The package leaflet and the RMP (version 9.0) are updated accordingly. The RMP is also brought 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 introduce minor editorial changes in section 2 of the SmPC and Annex III-A on labelling

15.3.4. Apalutamide - ERLEADA (CAP) - EMEA/H/C/004452/II/0008

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Tiphaine Vaillant

Scope: 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 ARN-509-003 (SPARTAN) (listed as a post-authorisation efficacy study (PAES)) in Annex II): a multicentre, randomised, double-blind, placebo-controlled, phase 3 study of apalutamide (ARN-509) in men with non-metastatic (M0) castration-resistant prostate cancer. The package leaflet, Annex II and the RMP (version 3.1) are updated accordingly. The MAH took also the opportunity to update the list of local representatives in the package leaflet

15.3.5. Axicabtagene ciloleucel - YESCARTA (CAP) - EMEA/H/C/004480/II/0028, Orphan

Applicant: Kite Pharma EU B.V., ATMP⁵⁹

PRAC Rapporteur: Anette Kirstine Stark

Scope: Update of sections 4.4, 4.8 and 5.1 of the SmPC to update the safety information based on updates from study KTE-C19-101: a phase 1/2 multicentre study evaluating the safety and efficacy of Yescarta (axicabtagene ciloleucel (KTE-C19)) in subjects with refractory aggressive non-Hodgkin lymphoma (ZUMA-1). The updates include data from: 1) phase 2 safety management ZUMA-1 cohort 4 intended to assess the impact of earlier interventions on the rate and severity of cytokine release syndrome (CRS) and neurologic events; 2) a 36-month analysis from ZUMA-1 cohorts 1 and 2. The RMP (version 3.1) is updated accordingly

15.3.6. 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

⁵⁹ Advanced therapy medicinal product

15.3.7. Blinatumomab - BLINCYTO (CAP) - EMEA/H/C/003731/II/0030, Orphan

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Eva Jirsová

Scope: Extension of indication to include the treatment of Philadelphia chromosome positive CD19⁶⁰ positive B-cell precursor acute lymphoblastic leukaemia (ALL) in adult and paediatric patients with relapsed or refractory ALL and adult patients in first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1%. 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 10.0) are updated accordingly

15.3.8. Botulinum toxin type A - NUCEIVA (CAP) - EMEA/H/C/004587/X/0005

Applicant: Evolus Pharma Limited

PRAC Rapporteur: Adam Przybylkowski

Scope: Extension application to add a new strength of 50 U for botulinum toxin type A for powder for solution for injection in vial (glass) for intramuscular administration. The RMP (version 3.0) is updated accordingly

15.3.9. Budesonide, formoterol - BIRESP SPIROMAX (CAP) - EMEA/H/C/003890/II/0033/G

Applicant: Teva Pharma B.V.

PRAC Rapporteur: Hans Christian Siersted

Scope: Grouped variation consisting of: 1) extension of indication to include adolescents of 12 years and older for the regular treatment of asthma, where the use in combination of an inhaled corticosteroid and long-acting β_2 adrenoceptor agonist is appropriate, either in patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short-acting β_2 adrenoceptor agonists, or in patients already adequately controlled on both inhaled corticosteroids and long-acting β_2 adrenoceptor agonists. The extension to the indication is based upon data from the literature. As a consequence, sections 4.1, 4.2, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 3.0) are updated accordingly. In addition, the MAH took the opportunity to make an administrative update to the Greek, Islandic, Irish and Maltese local representatives. Furthermore, the product information is brought in line with the latest quality review of documents (QRD) template (version 10.1); 2) update of sections 4.2, 5.1 and 5.2 of the SmPC to update the information on paediatric data and section 4.4 of the SmPC to remove the warning regarding the risk of growth retardation in children and the guidance on how to address this risk as agreed during the assessment of the initial application for Budesonide/Formoterol Teva Pharma B.V finalised in January 2020

15.3.10. Budesonide, formoterol - DUORESP SPIROMAX (CAP) - EMEA/H/C/002348/II/0033/G

Applicant: Teva Pharma B.V.

⁶⁰ Cluster of differentiation 19

PRAC Rapporteur: Hans Christian Siersted

Scope: Grouped variation consisting of: 1) extension of indication to include adolescents of 12 years and older for the regular treatment of asthma, where the use in combination of an inhaled corticosteroid and long-acting β 2 adrenoceptor agonist is appropriate, either in patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short-acting β 2 adrenoceptor agonists, or in patients already adequately controlled on both inhaled corticosteroids and long-acting β 2 adrenoceptor agonists. The extension to the indication is based upon data from the literature. As a consequence, sections 4.1, 4.2, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 3.0) are updated accordingly. In addition, the MAH took the opportunity to make an administrative update to the Greek, Islandic, Irish and Maltese local representatives. Furthermore, the product information is brought in line with the latest quality review of documents (QRD) template (version 10.1); 2) update of sections 4.2, 5.1 and 5.2 of the SmPC to update the information on paediatric data and section 4.4 of the SmPC to remove the warning regarding the risk of growth retardation in children and the guidance on how to address this risk as agreed during the assessment of the initial application for Budesonide/Formoterol Teva Pharma B.V finalised in January 2020

15.3.11. Buprenorphine - BUVIDAL (CAP) - EMEA/H/C/004651/X/0008/G

Applicant: Camurus AB

PRAC Rapporteur: Tiphaine Vaillant

Scope: Grouped applications consisting of: 1) line extension to add a new strength of 160 mg for prolonged-release solution for injection pharmaceutical form. The MAH took the opportunity to align the product information with the latest quality review of documents (QRD) template (version 10.1) and to implement new text regarding the content of ethanol in accordance with the EMA document on 'information for the package leaflet regarding ethanol used as an excipient in medicinal products for human use' in the package leaflet; 2) quality/manufacturing aspect related variation

15.3.12. 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'

15.3.13. Clopidogrel - ISCOVER (CAP) - EMEA/H/C/000175/WS1820/0142; PLAVIX (CAP) - EMEA/H/C/000174/WS1820/0140

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Update of section 4.2 of the SmPC in order to add 600 mg as an alternative loading dose to the existing 300 mg to be used at initiation of treatment in the indication of secondary prevention of atherothrombotic events in adult patients suffering from acute coronary syndrome. This update is based on a bibliographic review of published studies. The package leaflet and the RMP (version 2.0) are updated accordingly

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

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Anette Kirstine Stark

Scope: Grouped applications consisting of: 1) extension application to add two new pharmaceutical forms coated granules (20 mg, 30 mg, 40 mg, 50 mg, 110 mg, 150 mg) and powder and solvent for oral solution (6.25 mg/mL); 2) extension of indication to include treatment of venous thromboembolic events (VTE) and prevention of recurrent VTE in paediatric patients from birth to less than 18 years of age for Pradaxa (dabigatran etexilate) 75 mg, 110 mg, 150 mg capsules based on paediatric trials, namely study 1160.106: an open-label, randomized, parallel-group, active-controlled, multi-centre non-inferiority study of dabigatran etexilate versus standard of care for venous thromboembolism treatment in children from birth to less than 18 years of age, and study 1160.108: an open label, single arm safety prospective cohort study of dabigatran etexilate for secondary prevention of venous thromboembolism in children from 0 to less than 18 years. As a consequence, sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.7, 4.8, 4.9, 5.1, 5.2 and 5.3 of the SmPC are updated. The package leaflet and labelling are updated in accordance. The RMP (version 37.0) is updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet

15.3.15. Dacomitinib - VIZIMPRO (CAP) - EMEA/H/C/004779/II/0003/G

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Menno van der Elst

Scope: Grouped variations to update sections 4.2 and 5.2 of the SmPC in order to revise the dosing recommendation for patients with hepatic impairment and to include relevant pharmacokinetics data based on results of study A7471058: a phase 1, open-label, single-dose, parallel-group study to evaluate the plasma pharmacokinetics and safety of dacomitinib in participants with severely impaired hepatic function relative to participants with normal hepatic function. As a consequence, the MAH proposed to remove 'safety in patient with severe hepatic impairment' as missing information from the list of safety concerns in the RMP. In addition, the MAH took the opportunity to bring the product information in line with the latest quality review of documents (QRD) template (version 10.1). The MAH took also the opportunity to update the RMP to include study A7471064: a single arm study to evaluate the safety of dacomitinib for the first-line treatment of participants in India with metastatic non-small-cell lung carcinoma (NSCLC) with epidermal growth factor receptor (EGFR)-activating mutations as a category 3 study. The RMP (version 1.1) is updated accordingly

15.3.16. Dolutegravir - TIVICAY (CAP) - EMEA/H/C/002753/X/0058/G

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Martin Huber

Scope: Grouped application consisting of: 1) extension application to add a new pharmaceutical form associated with a new strength (5 mg dispersible tablet). The new presentation is indicated for the treatment of human immunodeficiency virus (HIV) infected children from 4 weeks of life and weighing at least 3 kg; 2) update of the currently approved SmPC, labelling and package leaflet for the existing film-coated tablets (10 mg, 25 mg and 50 mg) for children of 6 years and older and weighing at least 15 kg, based on pharmacokinetic (PK), safety, and efficacy data from study P1093: a phase 1/2, multicentre, open-label pharmacokinetic, safety, tolerability and antiviral activity of dolutegravir, a novel integrase inhibitor, in combination regimens in HIV-1 infected infants, children and adolescents and PK and safety data from relevant sub-studies nested within study ODYSSEY (PENTA 20): a phase 2/3 randomised trial of dolutegravir (DTG)-based antiretroviral therapy vs. standard of care (SOC) in children with HIV infection starting first-line or switching to second-line antiretroviral therapy (ART). In addition, the MAH took the opportunity to amend section 4.1 of SmPC to clarify that children should be 'aged at least 6 years' as the current approved indication is inclusive of those aged 6 years. The RMP (version 16) is updated in accordance

15.3.17. Durvalumab - IMFINZI (CAP) - EMEA/H/C/004771/II/0023

Applicant: AstraZeneca AB

PRAC Rapporteur: David Olsen

Scope: Update of sections 4.2 and 5.1 of the SmPC in order to introduce a new posology regimen of 1,500 mg every 4 weeks (Q4W) for the approved indication of the treatment of patients with locally advanced, unresectable non-small cell lung cancer (NSCLC) whose tumours express programmed death-ligand 1 (PD-L1) on $\geq 1\%$ of tumour cells and whose disease has not progressed following platinum based chemoradiation therapy. The RMP (version 4.1) is updated accordingly

15.3.18. Esketamine - SPRAVATO (CAP) - EMEA/H/C/004535/II/0001/G

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Kirsti Villikka

Scope: Grouped variations consisting of: 1) extension of indication to include a new indication for the rapid reduction of depressive symptoms in adult patients with a moderate to severe depressive episode of major depressive disorder (MMD) who have current suicidal ideation with intent. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 the SmPC are updated. The package leaflet and the RMP (version 2.1) are updated accordingly; 2) addition of a new pack size (multipack) of 24 nasal spray devices (multipack of 8 packs of 3 nasal spray devices) corresponding to 4 weeks of treatment in the new indication. The package leaflet and labelling are updated in accordance. In addition, the MAH took the opportunity to clarify the wording in Annex II-D on 'Conditions or restrictions with regard to the safe and effective use of the medicinal product'

15.3.19. Human normal immunoglobulin - PRIVIGEN (CAP) - EMEA/H/C/000831/II/0161/G

Applicant: CSL Behring GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Grouped variations consisting of: 1) update of sections 4.4, 4.8 and 5.1 of the SmPC in order to amend an existing warning on haemolytic anaemia and to update safety information based on final results from study IgPro10_5003 (listed as a category 3 study in the RMP): an observational hospital-based cohort study in the US to evaluate Privigen (human normal immunoglobulin) use and haemolytic anaemia in adults and children and the Privigen (human normal immunoglobulin) safety profile in children with chronic inflammatory demyelinating polyneuropathy (CIDP). The package leaflet is updated accordingly; 2) update of sections 4.8 and 5.1 of the SmPC in order to update the list of adverse drug reactions based on final results from study IgPro10_3004: a prospective open-label single-arm study of the pharmacokinetics and safety of intravenous Privigen (human normal immunoglobulin) (IgPro10) in Japanese subjects with primary immunodeficiency. The RMP (version 8.0) is updated accordingly. In addition, the MAH took the opportunity to align the SmPC with the EU core SmPC for human normal immunoglobulin for intravenous administration (IVIg) (EMA/CHMP/BPWP/94038/2007 Rev. 5), to update the local representative for Bulgaria in the package leaflet and to bring the product information in line with the latest quality review of documents (QRD) template (version 10.1)

15.3.20. Imipenem, cilastatin, relebactam - RECARBRIO (CAP) - EMEA/H/C/004808/II/0001

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Extension of indication to include treatment of hospital-acquired pneumonia (HAP) including ventilator-associated pneumonia (VAP), with or without concurrent bacteraemia in adults. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated. The package leaflet and the RMP (version 1.1) are updated in accordance. Furthermore, the MAH introduced editorial corrections in the product information and brought it in line with the latest quality review of documents (QRD) template (version 10.1)

15.3.21. Lacosamide - LACOSAMIDE UCB (CAP) - EMEA/H/C/005243/WS1782/0006; VIMPAT (CAP) - EMEA/H/C/000863/WS1782/0088

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension of indication to include the treatment as adjunctive therapy of primary generalised tonic-clonic seizures in adults, adolescents and children from 4 years of age with idiopathic generalised epilepsy. 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 15.1) are updated in accordance. Furthermore, the MAH took the opportunity to bring the product information in line with the latest quality review of documents (QRD) template (version 10.1), to align the product information of Lacosamide UCB (lacosamide) with the product information of Vimpat (lacosamide) and to implement some minor corrections in the Bulgarian, Czech, Danish, French, German, Hungarian, Polish and Spanish versions of the product information

15.3.22. [Liraglutide - SAXENDA \(CAP\) - EMEA/H/C/003780/II/0026](#)

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to include treatment as an adjunct to a healthy nutrition and physical activity counselling for weight management in adolescent patients from the age of 12 years and above with body weight above 60 kg and obesity (body mass index (BMI) corresponding to ≥ 30 kg/m² for adults) based on study NN8022-4180: effect of liraglutide for weight management in pubertal adolescent subjects with obesity, 56-week, double-blind, randomised, parallel-group, placebo-controlled multi-national trial followed by a 26-week period off study-drug. 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 32.0) are updated in accordance. The application relates to paediatric studies submitted according to Article 46 of the paediatric regulation

15.3.23. [Metreleptin - MYALEPTA \(CAP\) - EMEA/H/C/004218/II/0012, Orphan](#)

Applicant: Amryt Pharmaceuticals DAC

PRAC Rapporteur: Adam Przybylkowski

Scope: Update of section 4.4 of the SmPC in order to add a new warning on the risk of autoimmune disease following exposure to metreleptin. The package leaflet and the key elements to be included in the guide/training material for healthcare professionals are updated accordingly. The RMP (version 2.0) is also updated in accordance

15.3.24. [Nintedanib - OFEV \(CAP\) - EMEA/H/C/003821/II/0038](#)

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Update of sections 4.5, 4.6 and 5.2 of the SmPC in order to add drug-drug interaction information with ethinylestradiol/levonorgestrel as a combined oral contraceptive based on final results from clinical study 1199-0340: a phase 1, open-label, 2-period cross-over, fixed-sequence design trial investigating the effect of multiple oral doses of nintedanib on the single dose kinetics of a combination of ethinylestradiol/levonorgestrel in female patients with systemic sclerosis associated interstitial lung disease (SSc-ILD). The package leaflet and the RMP (version 10) are updated accordingly

15.3.25. [Nivolumab - OPDIVO \(CAP\) - EMEA/H/C/003985/II/0080](#)

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include treatment of adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma (OSCC) after prior fluoropyrimidine- and platinum-based chemotherapy. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 16.0) are updated in accordance

15.3.26. Ocrelizumab - OCREVUS (CAP) - EMEA/H/C/004043/II/0020

Applicant: Roche Registration GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Submission of the final report for study 17-1133 (listed as a category 3 study in the RMP): a study assessing the effects of ocrelizumab on embryo-foetal and pre- and postnatal development when administered once weekly for up to 23-weeks intravenously to pregnant cynomolgus monkeys (in fulfilment of MEA 006). The RMP (version 5.0) is updated accordingly

15.3.27. Pegaspargase - ONCASPAR (CAP) - EMEA/H/C/003789/II/0036/G

Applicant: Les Laboratoires Servier

PRAC Rapporteur: Annika Folin

Scope: Grouped variations consisting of: 1) submission of the results for study 12-266 A(12): an open label single arm phase 2 trial evaluating the efficacy and toxicity of treatment regimens including Oncaspar (pegaspargase) in adults aged 18-60 with newly diagnosed Philadelphia chromosome-negative acute lymphoblastic leukaemia ; 2) submission of the results for study CAALL-F01: a prospective multicentre cohort study evaluating Oncaspar (pegaspargase) used in the first-line treatment of children and adolescents with acute lymphoblastic leukaemia (ALL) along with multi-agent chemotherapy. As a consequence, Annex II is updated to remove both studies (i.e. post-authorisation safety studies (PAES)). Additionally, the product information is updated to remove the need for additional monitoring and to implement editorial changes. The RMP (version 4.1) is updated accordingly

15.3.28. Pembrolizumab - KEYTRUDA (CAP) - EMEA/H/C/003820/II/0091

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to include first-line treatment of unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer in adults based on the results from study KEYNOTE-177: an international, randomised, open-label phase 3 trial of pembrolizumab versus chemotherapy in MSI-H or dMMR stage IV colorectal carcinoma. As a consequence, sections 4.1, 4.2 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 29.1) are updated in accordance. The MAH took the opportunity to introduce minor correction in section 4.4 of the SmPC on immune related endocrinopathies

15.3.29. 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. Belimumab - BENLYSTA (CAP) - PSUSA/00009075/202003

Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.2. Betaine anhydrous⁶¹ - CYSTADANE (CAP) - PSUSA/00000390/202002

Applicant: Recordati Rare Diseases

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.3. Bevacizumab - AVASTIN (CAP); MVASI (CAP); ZIRABEV (CAP) - PSUSA/00000403/202002

Applicant(s): Amgen Technology (Ireland) Unlimited Company (Mvasi), Pfizer Europe MA EEIG (Zirabev), Roche Registration GmbH (Avastin)

PRAC Rapporteur: Hans Christian Siersted

Scope: Evaluation of a PSUSA procedure

16.1.4. Brimonidine⁶² - MIRVASO (CAP) - PSUSA/00010093/202002

Applicant: Galderma International

PRAC Rapporteur: Rhea Fitzgerald

⁶¹ Centrally authorised product(s) only

⁶² Centrally authorised product(s) only

Scope: Evaluation of a PSUSA procedure

16.1.5. Caplacizumab - CABLIVI (CAP) - PSUSA/00010713/202002

Applicant: Ablynx NV

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.1.6. Carglumic acid - CARBAGLU (CAP) - PSUSA/00000564/202001

Applicant: Recordati Rare Diseases

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.1.7. Ceftazidime, avibactam - ZAVICEFTA (CAP) - PSUSA/00010513/202002

Applicant: Pfizer Ireland Pharmaceuticals

PRAC Rapporteur: Rugile Pilviniene

Scope: Evaluation of a PSUSA procedure

16.1.8. Ceftolozane, tazobactam - ZERBAXA (CAP) - PSUSA/00010411/202003

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.9. Chlormethine - LEDAGA (CAP) - PSUSA/00010587/202002

Applicant: Helsinn Birex Pharmaceuticals Limited

PRAC Rapporteur: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

16.1.10. Cholic acid⁶³ - KOLBAM⁶⁴ - PSUSA/00010182/202003

Applicant: Retrophin Europe Ltd

PRAC Rapporteur: Agni Kapou

Scope: Evaluation of a PSUSA procedure

⁶³ Indicated in the treatment of inborn errors in primary bile acid synthesis due to sterol 27-hydroxylase (presenting as cerebrotendinous xanthomatosis, CTX) deficiency, 2- (or α -) methylacyl-CoA racemase (AMACR) deficiency or cholesterol 7 α -hydroxylase (CYP7A1) deficiency

⁶⁴ Commission decision on the withdrawal of the marketing authorisation(s) for Kolbam (cholic acid) dated 13 July 2020

16.1.11. Ciclosporin⁶⁵ - IKERVIS (CAP); VERKAZIA (CAP) - PSUSA/00010362/202003

Applicant(s): Santen Oy

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.1.12. Dabigatran - PRADAXA (CAP) - PSUSA/00000918/202003

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

16.1.13. Damoctocog alfa pegol - JIVI (CAP) - PSUSA/00010732/202002

Applicant: Bayer AG

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.14. Diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA), poliomyelitis (inactivated), haemophilus type b conjugate vaccine (adsorbed) - VAXELIS (CAP) - PSUSA/00010469/202002

Applicant: MCM Vaccine B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.15. Doravirine - PIFELTRO (CAP) - PSUSA/00010729/202002

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.1.16. Doravirine, lamivudine, tenofovir disoproxil - DELSTRIGO (CAP) - PSUSA/00010731/202002

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.1.17. Eftrenonacog alfa - ALPROLIX (CAP) - PSUSA/00010499/202003

Applicant: Swedish Orphan Biovitrum AB (publ)

⁶⁵ Topical use only

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.18. Eluxadoline - TRUBERZI (CAP) - PSUSA/00010528/202003

Applicant: Allergan Pharmaceuticals International Limited

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.19. Emtricitabine, rilpivirine, tenofovir alafenamide - ODEFSEY (CAP) - PSUSA/00010514/202002

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.1.20. Epoetin beta - NEORECORMON (CAP) - PSUSA/00001239/202002

Applicant: Roche Registration GmbH

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.21. Eravacycline - XERAVA (CAP) - PSUSA/00010718/202002

Applicant: Tetrphase Pharmaceuticals Ireland Limited

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.22. Ex vivo expanded autologous human corneal epithelial cells containing stem cells - HOLOCLAR (CAP) - PSUSA/00010352/202002

Applicant: Holostem Terapie Avanzate s.r.l., ATMP⁶⁶

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

16.1.23. Ferric maltol - FERACCRU (CAP) - PSUSA/00010476/202002

Applicant: Norgine B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

⁶⁶ Advanced therapy medicinal product

16.1.24. Florbetaben (¹⁸F) - NEURACEQ (CAP) - PSUSA/00010094/202002

Applicant: Life Radiopharma Berlin GmbH

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.25. Fluticasone furoate, umeclidinium, vilanterol - ELEBRATO ELLIPTA (CAP); TEMYBRIC ELLIPTA (CAP); TRELEGY ELLIPTA (CAP) - PSUSA/00010653/202003

Applicant(s): GlaxoSmithKline Trading Services Limited

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

16.1.26. Guanfacine - INTUNIV (CAP) - PSUSA/00010413/202003

Applicant: Shire Pharmaceuticals Ireland Limited

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

16.1.27. Hepatitis B (rDNA⁶⁷) vaccine (adjuvanted, adsorbed) - FENDRIX (CAP) - PSUSA/00001598/202002

Applicant: GlaxoSmithKline Biologicals

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

16.1.28. Human coagulation factor X - COAGADEX (CAP) - PSUSA/00010481/202003

Applicant: BPL Bioproducts Laboratory GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.29. Ibalizumab - TROGARZO (CAP) - PSUSA/00010797/202003

Applicant: Theratechnologies Europe Limited

PRAC Rapporteur: David Olsen

Scope: Evaluation of a PSUSA procedure

16.1.30. Ibritumomab tiuxetan - ZEVALIN (CAP) - PSUSA/00001704/202002

Applicant: Ceft Biopharma s.r.o.

PRAC Rapporteur: Anette Kirstine Stark

⁶⁷ Recombinant deoxyribonucleic acid

Scope: Evaluation of a PSUSA procedure

16.1.31. Influenza vaccine (surface antigen, inactivated, prepared in cell cultures) - FLUCELVAX TETRA (CAP) - PSUSA/00010737/202003

Applicant: Seqirus Netherlands B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.32. Lanadelumab - TAKHZYRO (CAP) - PSUSA/00010743/202002

Applicant: Shire Pharmaceuticals Ireland Limited

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

16.1.33. Meropenem, vaborbactam - VABOREM (CAP) - PSUSA/00010727/202002

Applicant: Menarini International Operations Luxembourg S.A.

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

16.1.34. Nitisinone - ORFADIN (CAP) - PSUSA/00002169/202002

Applicant: Swedish Orphan Biovitrum International AB

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.1.35. Ospemifene - SENSHIO (CAP) - PSUSA/00010340/202002

Applicant: Shionogi B.V.

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

16.1.36. Pirfenidone - ESBRIET (CAP) - PSUSA/00002435/202002

Applicant: Roche Registration GmbH

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

16.1.37. Plasmodium falciparum and hepatitis B vaccine (recombinant, adjuvanted) - MOSQUIRIX (Art 58⁶⁸) - EMEA/H/W/002300/PSUV/0045

Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUR procedure

16.1.38. Rasburicase - FASTURTEC (CAP) - PSUSA/00002613/202002

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.39. Reslizumab - CINQAERO (CAP) - PSUSA/00010523/202002

Applicant: Teva B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.40. Ribociclib - KISQALI (CAP) - PSUSA/00010633/202003

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Hans Christian Siersted

Scope: Evaluation of a PSUSA procedure

16.1.41. Ropeginterferon alfa-2b - BESREMI (CAP) - PSUSA/00010756/202002

Applicant: AOP Orphan Pharmaceuticals AG

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Evaluation of a PSUSA procedure

16.1.42. Rotigotine - LEGANTO (CAP); NEUPRO (CAP) - PSUSA/00002667/202002

Applicant(s): UCB Pharma S.A.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.1.43. Safinamide - XADAGO (CAP) - PSUSA/00010356/202002

Applicant: Zambon S.p.A.

PRAC Rapporteur: Rhea Fitzgerald

⁶⁸ Article 58 of Regulation (EC) No 726/2004 allows the Committee for Medicinal Products for Human Use (CHMP) to give opinions, in co-operation with the World Health Organisation (WHO) on medicinal products for human use that are intended exclusively for markets outside of the European Union (EU)

Scope: Evaluation of a PSUSA procedure

16.1.44. Solriamfetol - SUNOSI (CAP) - PSUSA/00010831/202003

Applicant: Jazz Pharmaceuticals Ireland Limited

PRAC Rapporteur: Julia Pallos

Scope: Evaluation of a PSUSA procedure

16.1.45. Telotristat - XERMELO (CAP) - PSUSA/00010639/202002

Applicant: Ipsen Pharma

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.46. Tildrakizumab - ILUMETRI (CAP) - PSUSA/00010720/202003

Applicant: Almirall S.A

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.47. Tivozanib - FOTIVDA (CAP) - PSUSA/00010636/202002

Applicant: EUSA Pharma (Netherlands) B.V.

PRAC Rapporteur: Rugile Pilviniene

Scope: Evaluation of a PSUSA procedure

16.1.48. Trastuzumab emtansine - KADCYLA (CAP) - PSUSA/00010136/202002

Applicant: Roche Registration GmbH

PRAC Rapporteur: Hans Christian Siersted

Scope: Evaluation of a PSUSA procedure

16.1.49. Ulipristal acetate⁶⁹ - ESMYA (CAP); ULIPRISTAL ACETATE GEDEON RICHTER (CAP) - PSUSA/00009325/202002

Applicant(s): Gedeon Richter Plc.

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

16.1.50. Upadacitinib - RINVOQ (CAP) - PSUSA/00010823/202002

Applicant: AbbVie Deutschland GmbH & Co. KG

⁶⁹ Indicated for the treatment of moderate to severe symptoms of uterine fibroids only

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

16.1.51. Velaglucerase alpha - VPRIV (CAP) - PSUSA/00003103/202002

Applicant: Shire Pharmaceuticals Ireland Limited

PRAC Rapporteur: Martin Huber

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. Dexmedetomidine - DEXDOR (CAP); NAP - PSUSA/00000998/202003

Applicants: Orion Corporation (Dexdor), various

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.2.2. Dexrazoxane - SAVENE (CAP); NAP - PSUSA/00001001/202002

Applicants: Clinigen Healthcare B.V. (Savene), various

PRAC Rapporteur: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

16.2.3. Glycopyrronium ⁷⁰ - SIALANAR (CAP); NAP - PSUSA/00010529/202003

Applicants: Proveca Pharma Limited (Sialanar), various

PRAC Rapporteur: Zane Neikena

Scope: Evaluation of a PSUSA procedure

16.2.4. Hepatitis B vaccine (rDNA⁷¹) - HBVAXPRO (CAP); NAP - PSUSA/00001597/202002

Applicants: MSD Vaccins (HBVaxPro), various

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.2.5. Timolol, travoprost - DUOTRAV (CAP); NAP - PSUSA/00002962/202002

Applicants: Novartis Europharm Limited (DuoTrav), various

PRAC Rapporteur: Eva Segovia

⁷⁰ Indicated for the treatment of severe sialorrhea (chronic pathological drooling)

⁷¹ Recombinant deoxyribonucleic acid

Scope: Evaluation of a PSUSA procedure

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

16.3.1. Acetylsalicylic acid, atorvastatin, ramipril (NAP) - PSUSA/00010280/202002

Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.3.2. Amitriptyline hydrochloride, chlordiazepoxide (NAP) - PSUSA/00000171/202002

Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.3.3. Aprotinin (NAP) - PSUSA/00000230/202002

Applicant(s): various

PRAC Lead: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

16.3.4. Bicalutamide (NAP) - PSUSA/00000407/202002

Applicant(s): various

PRAC Lead: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

16.3.5. Cilostazol (NAP) - PSUSA/00010209/202002

Applicant(s): various

PRAC Lead: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.3.6. Clobazam (NAP) - PSUSA/00000798/202002

Applicant(s): various

PRAC Lead: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

16.3.7. Gaxilose (NAP) - PSUSA/00010283/202001

Applicant(s): various

PRAC Lead: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

16.3.8. Haemophilus type b and meningococcal group C conjugate vaccine (NAP) - PSUSA/00001583/202002

Applicant(s): various

PRAC Lead: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

16.3.9. Haemophilus type b conjugate vaccine (NAP) - PSUSA/00001584/202002

Applicant(s): various

PRAC Lead: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

16.3.10. Human coagulation factor VIII inhibitor bypassing fraction (NAP) - PSUSA/00009174/202002

Applicant(s): various

PRAC Lead: Sonja Hrabcik

Scope: Evaluation of a PSUSA procedure

16.3.11. Human plasma⁷² (NAP) - PSUSA/00001635/202002

Applicant(s): various

PRAC Lead: Brigitte Keller-Stanislowski

Scope: Evaluation of a PSUSA procedure

16.3.12. Influenza vaccine (split virion, inactivated)⁷³ (NAP) - PSUSA/00010298/202003

Applicant(s): various

PRAC Lead: Brigitte Keller-Stanislowski

Scope: Evaluation of a PSUSA procedure

16.3.13. Influenza vaccine (split virion, inactivated, prepared in cell cultures) (NAP) - PSUSA/00010299/202003

Applicant(s): various

PRAC Lead: Brigitte Keller-Stanislowski

Scope: Evaluation of a PSUSA procedure

⁷² Pooled and treated for virus inactivation only

⁷³ All except centrally authorised product(s)

16.3.14. Influenza vaccine (surface antigen, inactivated) (NAP) - PSUSA/00001744/202003

Applicant(s): various

PRAC Lead: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.3.15. Influenza vaccine (surface antigen, inactivated, adjuvanted) (NAP) - PSUSA/00010300/202003

Applicant(s): various

PRAC Lead: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.3.16. Ipratropium (NAP) - PSUSA/00001780/202001

Applicant(s): various

PRAC Lead: Melinda Palfi

Scope: Evaluation of a PSUSA procedure

16.3.17. Ipratropium, salbutamol (NAP) - PSUSA/00001781/202001

Applicant(s): various

PRAC Lead: Melinda Palfi

Scope: Evaluation of a PSUSA procedure

16.3.18. Labetalol (NAP) - PSUSA/00001814/202002

Applicant(s): various

PRAC Lead: Karen Pernille Harg

Scope: Evaluation of a PSUSA procedure

16.3.19. Lorazepam (NAP) - PSUSA/00001909/202001

Applicant(s): various

PRAC Lead: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

16.3.20. Mannitol⁷⁴ (NAP) - PSUSA/00010005/202002

Applicant(s): various

PRAC Lead: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

⁷⁴ All indication(s) except for cystic fibrosis

16.3.21. Mefloquine (NAP) - PSUSA/00001955/202002

Applicant(s): various

PRAC Lead: Karen Pernille Harg

Scope: Evaluation of a PSUSA procedure

16.3.22. Sevoflurane (NAP) - PSUSA/00002698/202001

Applicant(s): various

PRAC Lead: Ronan Grimes

Scope: Evaluation of a PSUSA procedure

16.3.23. Tick-borne encephalitis vaccine (inactivated) (NAP) - PSUSA/00002951/202001

Applicant(s): various

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.4. Follow-up to PSUR/PSUSA procedures

16.4.1. Dexmedetomidine - DEXDOR (CAP) - EMEA/H/C/002268/LEG 016.1

Applicant: Orion Corporation

PRAC Rapporteur: Ulla Wändel Liminga

Scope: MAH's response to LEG 016 [analysis of available mortality data from controlled clinical trials in the dexmedetomidine development programme as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00000998/201903) adopted in November 2019] as per the request for supplementary information (RSI) adopted in May 2020

16.4.2. Emicizumab - HEMLIBRA (CAP) - EMEA/H/C/004406/REC 004.1

Applicant: Roche Registration GmbH

PRAC Rapporteur: Amelia Cupelli

Scope: MAH's response to REC 004 [detailed review of type and frequencies of occurrence of injection site reactions in post-marketing settings as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00010668/201905) adopted in December 2019] as per the request for supplementary information (RSI) adopted at CHMP in April 2020

16.5. Variation procedure(s) resulting from PSUSA evaluation

None

16.6. Expedited summary safety reviews⁷⁵

16.6.1. Remdesivir - VEKLURY (CAP) - EMEA/H/C/005622/MEA 017.2

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Eva Jirsová

Scope: Fourth expedited monthly summary safety report for remdesivir for September 2020 including spontaneously reported data and data from compassionate use and expanded access programmes for the duration of the coronavirus disease (COVID-19) pandemic

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)⁷⁶

17.1.1. Asfotase alfa– STRENSIQ (CAP) - EMEA/H/C/PSA/S/0050.1

Applicant: Alexion Europe SAS

PRAC Rapporteur: Rhea Fitzgerald

Scope: MAH's response to PSA/S/0050 [substantial amendment to a protocol previously agreed in May 2016 (PSP/0032.1) for study ALX-HPP-501: an observational, longitudinal, prospective, long-term registry of patients with hypophosphatasia to collect information on the epidemiology of the disease, including clinical outcomes and quality of life, and to evaluate safety and effectiveness data in patients treated with Strensiq (asfotase alfa)] as per the request for supplementary information (RSI) adopted in April 2020

17.1.2. Buprenorphine – SIXMO (CAP) - EMEA/H/C/PSP/S/0086.2

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

PRAC Rapporteur: Adam Przybylkowski

Scope: MAH's response to PSP/S/0086.1 [protocol for study MOLTeNI-2019-01: a prospective, observational (non-interventional), post-authorisation safety cohort study to evaluate the incidence of breakages and insertion/removal complications of buprenorphine implants (Sixmo) in routine clinical care] as per the request for supplementary information (RSI) adopted in June 2020

17.1.3. Cidofovir (NAP) - EMEA/H/N/PSA/S/0058

Applicant: Tillomed Laboratories Ltd. (Cidofovir Emcure Pharma)

⁷⁵ Requirement to the compassionate use opinion to submit expedited summary safety reports for review accompanied by a summary of remdesivir distribution, in addition to the 6-monthly or annual PSURs falling within the pandemic period

⁷⁶ In accordance with Article 107n of Directive 2001/83/EC

PRAC Rapporteur: Rugile Pilviniene

Scope: Substantial amendment to a protocol previously agreed in November 2018 (PSP/S/0052.3) for cidofovir exposure registry study: a non-interventional, prospective, exposure (safety outcome) registry study of cidofovir to further elucidate the characteristics of the different patient populations for cidofovir use, to evaluate patterns and compare rates of adverse events occurring in the on-label group with events occurring in the off-label group; and to assess patient outcome following treatment in specified indication

17.2. Protocols of PASS non-imposed in the marketing authorisation(s)⁷⁷

17.2.1. Dimethyl fumarate - TECFIDERA (CAP) - EMEA/H/C/002601/MEA 007.1

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Martin Huber

Scope: Amendment to a protocol previously agreed in November 2017 for study 109MS401 (ESTEEM): a multicentre, global, observational study to collect information on safety and to document the drug utilisation of Tecfidera (dimethyl fumarate) when used in routine medical practice in the treatment of relapsing multiple sclerosis [final clinical study report (CSR) expected due date: Q4/2024] together with the fifth annual progress report of the study

17.2.2. Esketamine - SPRAVATO (CAP) - EMEA/H/C/004535/MEA 002

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Kirsti Villikka

Scope: Protocol for a pregnancy registry study (listed as a category 3 study in the RMP) using the National Pregnancy Registry for Psychiatric Medications (NPRPM) in order to further characterise the impact of the missing information of use during pregnancy on the safety profile of esketamine nasal spray and obtain information on the frequency of major malformations (from initial opinion/marketing authorisation) [final report expected in 4Q 2024]

17.2.3. Esketamine - SPRAVATO (CAP) - EMEA/H/C/004535/MEA 003

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Kirsti Villikka

Scope: Protocol for a survey to assess the effectiveness of Spravato (esketamine) educational materials (i.e. healthcare professional (HCP) guide, patient guide, checklist) for additional risk minimisation measures in the European Union related to understanding and management of the important identified risks with esketamine treatment (from initial opinion/marketing authorisation) [final clinical study report (CSR) expected in 4Q/2022]

⁷⁷ In accordance with Article 107m of Directive 2001/83/EC, supervised by PRAC in accordance with Article 61a (6) of Regulation (EC) No 726/2004

17.2.4. Flutemetamol (¹⁸F) - VIZAMYL (CAP) - EMEA/H/C/002557/MEA 002.4

Applicant: GE Healthcare AS

PRAC Rapporteur: Martin Huber

Scope: MAH's response to MEA 002.3 [amendment to a previously agreed protocol in December 2015 for study GE067-027 CPR in order to evaluate the effectiveness of Vizamyl (flutemetamol (¹⁸F)) educational training programme/reader training in Europe and to assess the frequency of image classification errors in clinical practice [final study report expected in Q1 2021]] as per the request for supplementary information (RSI) adopted in April 2020, together with the first recruitment report

17.2.5. Gilteritinib - XOSPATA (CAP) - EMEA/H/C/004752/MEA 004

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Martin Huber

Scope: Protocol for study 2215-PV-0001: a cross-sectional survey study among healthcare professionals (HCPs) to assess awareness and knowledge, an evaluation of the effectiveness of a Xospata (gilteritinib) routine risk minimisation measures (RMM) and an additional risk minimisation measure (aRMM)

17.2.6. Infliximab - REMSIMA (CAP) - EMEA/H/C/002576/MEA 021

Applicant: Celltrion Healthcare Hungary Kft.

PRAC Rapporteur: Kimmo Jaakkola

Scope: Protocol for study CT-P13 4.9: an observational, prospective cohort study to evaluate safety of Remsima (infliximab) subcutaneous in patients with ankylosing spondylitis, psoriatic arthritis, and psoriasis

17.2.7. Inotersen - TEGSEDI (CAP) - EMEA/H/C/004782/MEA 007

Applicant: Akcea Therapeutics Ireland Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Protocol for study TEG4005: a pregnancy surveillance programme of infants and women exposed to Tegsedi (inotersen) during pregnancy

17.2.8. Micafungin - MYCAMINE (CAP) - EMEA/H/C/000734/MEA 015.12

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Martin Huber

Scope: MAH's response to MEA 015.11 [protocol for study 9463-PV-0002 (listed as a category 3 study in the RMP): a non-interventional PASS/survey on the effectiveness of the updated prescriber checklist for Mycamine (micafungin)] as per the request for supplementary information (RSI) adopted in May 2020

17.2.9. Patisiran - ONPATTRO (CAP) - EMEA/H/C/004699/MEA 002.5

Applicant: Alnylam Netherlands B.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: MAH's response to MEA 002.4 [protocol for study ALN-TTR02-0009: a prospective observational study on the safety of Onpattro (patisiran) in a real-world cohort of hereditary transthyretin amyloidosis (hATTR) patients] as per the request for supplementary information (RSI) adopted in July 2020

17.2.10. Sotagliflozin - ZYNQUISTA (CAP) - EMEA/H/C/004889/MEA 004.2

Applicant: Navigant Germany GmbH

PRAC Rapporteur: Martin Huber

Scope: MAH's response to MEA 004.1 [protocol for a nested, case-control study to evaluate the risk of malignancies (bladder, renal, breast, Leydig cell, pancreatic, thyroid and prostate cancers) in adult patients with type 1 diabetes mellitus (T1DM) using sotagliflozin in existing healthcare databases in Europe and in the United States [final clinical study report (CSR) expected in April 2030]] as per the request for supplementary information (RSI) adopted in April 2020

17.2.11. Tafamidis - VYNDAQEL (CAP) - EMEA/H/C/002294/MEA 016.1

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Tiphaine Vaillant

Scope: MAH's response to MEA 016 [amendment to a protocol previously agreed by CHMP for study B3461001: a sub-analysis of 'transthyretin amyloidosis outcomes survey (THAOS)': a global, multicentre, longitudinal, observational survey of patients with documented transthyretin (TTR) gene mutations or wild-type ATTR amyloidosis, in order to evaluate the effects of tafamidis in non-V30M patients] as per the request for supplementary information (RSI) adopted in June 2020

17.2.12. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/MEA 013.1

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: MAH's response to MEA 013 [protocol for study A3921344 (listed as a category 3 study in the RMP): an active surveillance, post-authorisation study to characterise the safety of tofacitinib in patients with moderately to severely active ulcerative colitis (UC) in the real-world setting using data from the Swedish Quality Register for Inflammatory Bowel Disease (SWIBREG) registry as requested in the conclusions of procedure X/0005/G finalised in May 2018 and in the conclusions of the referral procedure under Article 20 of Regulation (EC) No 726/2004 (EMEA/H/A-20/1485) finalised in November 2019] as per the request for supplementary information (RSI) adopted in May 2020

17.3. Results of PASS imposed in the marketing authorisation(s)⁷⁸

None

17.4. Results of PASS non-imposed in the marketing authorisation(s)⁷⁹

17.4.1. 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'. 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 IMvigora210 is introduced

17.4.2. Levetiracetam - KEPPRA (CAP) - EMEA/H/C/000277/II/0189

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Laurence de Fays

Scope: Submission of the final clinical study report (CSR) for PASS EUPAS26595: a retrospective cohort study comparing the incidence of acute renal failure in patients with epilepsy exposed to levetiracetam versus other antiepileptic drugs using real world data from a claim database in the US

17.4.3. Rivaroxaban - XARELTO (CAP) - EMEA/H/C/000944/II/0080

Applicant: Bayer AG

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of the final report from a survey on physicians' awareness and understanding of the educational materials on the prescriber guide (listed as a category 3 study in the RMP)

17.4.4. Safinamide - XADAGO (CAP) - EMEA/H/C/002396/II/0035

Applicant: Zambon S.p.A.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Submission of the final clinical study report (CSR) for study Z7219N02 (listed as a category 3 study in the RMP): a European multicentre retrospective-prospective cohort study to observe safinamide safety profile and pattern of use in clinical practice during the first post-commercialisation phase (SYNAPSES). The RMP (version 6.2) is updated

⁷⁸ In accordance with Article 107p-q of Directive 2001/83/EC

⁷⁹ 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

accordingly

17.4.5. Turoctocog alfa - NOVOEIGHT (CAP) - EMEA/H/C/002719/II/0035

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of section 5.1 of the SmPC to include the results of completed study NN7008-3553 (GUARDIAN 5) (listed as a category 3 study in the RMP): a multi-centre non-interventional study of safety and efficacy of turoctocog alfa (recombinant factor VIII (rFVIII)) during long-term treatment of severe and moderately severe haemophilia A (FVIII = <2%). The RMP (version 7) 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. Alglucosidase alfa - MYOZYME (CAP) - EMEA/H/C/000636/MEA 024.13

Applicant: Genzyme Europe BV

PRAC Rapporteur: Adrien Inoubli

Scope: MAH's response to MEA 024.12 [annual report 2019 on adverse events and/or lack of efficacy, immunological data, follow-up growth disturbances in children and data on urinary hexose tetrasaccharide (Hex4) from the Pompe registry: a global, multicentre, observational and voluntary programme designed to collect uniform and meaningful clinical data related to the onset, progression, and treated course of patients with Pompe disease irrespective of treatment status. The registry aims at detecting adverse events and/or lack of efficacy in patients, and at collecting immunological data, and follow-up growth disturbances in children] as per the request for supplementary information (RSI) adopted in March 2020

17.5.2. Alglucosidase alfa - MYOZYME (CAP) - EMEA/H/C/000636/MEA 025.13

Applicant: Genzyme Europe BV

PRAC Rapporteur: Adrien Inoubli

Scope: MAH's response to MEA 025.12 [annual report 2019 on data on patients with renal or hepatic insufficiency from the Pompe registry: a global, multicentre, observational and voluntary programme designed to collect uniform and meaningful clinical data related to the onset, progression, and treated course of patients with Pompe disease irrespective of treatment status. The registry aims at detecting adverse events and/or lack of efficacy in patients, and at collecting immunological data, and follow-up growth disturbances in children] as per the request for supplementary information (RSI) adopted in March 2020

17.5.3. Fingolimod - GILENYA (CAP) - EMEA/H/C/002202/MEA 012.9

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Tiphaine Vaillant

Scope: Ninth annual interim report for study D2404: a multinational pregnancy exposure

registry in patients with multiple sclerosis (MS) taking Gilenya (fingolimod) from the pregnancy intensive monitoring programme (PRIM)

17.5.4. Guanfacine - INTUNIV (CAP) - EMEA/H/C/003759/MEA 005.4

Applicant: Shire Pharmaceuticals Ireland Limited

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Second annual progress report for a drug utilisation study (DUS) of Intuniv (guanfacine extended release) in European countries: a non-imposed, non-interventional, multi-country DUS using retrospective database analysis (DUS-database: EUPAS18735) and a prescriber survey (DUS-survey: EUPAS18739) [final report expected in June 2022]

17.5.5. Sapropterin - KUVAN (CAP) - EMEA/H/C/000943/MEA 003.10

Applicant: BioMarin International Limited

PRAC Rapporteur: Rhea Fitzgerald

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

17.5.6. Ulipristal acetate - ESMYA (CAP) - EMEA/H/C/002041/MEA 026.2

Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Annika Folin

Scope: Annual update for an observational study using EU registries with biomarker data, as requested in the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 completed in May 2018 (EMA/H/A-20/1460)] as per the request for supplementary information (RSI) adopted in January 2019

17.5.7. Ulipristal acetate - ESMYA (CAP) - EMEA/H/C/002041/MEA 027.2

Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Annika Folin

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

17.6. Others

17.6.1. Insulin lispro - HUMALOG (CAP) - EMEA/H/C/000088/LEG 034

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Annika Folin

Scope: First report of the batch-specific adverse drug event review and analysis as requested in the conclusions of procedure X/0169 finalised in November 2019

17.6.2. Insulin lispro - LIPROLOG (CAP) - EMEA/H/C/000393/LEG 027

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Annika Folin

Scope: First report of the batch-specific adverse drug event review and analysis as requested in the conclusions of procedure X/0130 finalised in November 2019

17.6.3. Naltrexone hydrochloride, bupropion hydrochloride - MYSIMBA (CAP) - EMEA/H/C/003687/MEA 003.8

Applicant: Orexigen Therapeutics Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: Second feasibility assessment report for study NB-451: an observational retrospective study based on secondary data analysis using existing databases, in order to evaluate the potential population of patients or prescriptions in each database and confirm the ability to use each database for the drug utilisation study (DUS) of Mysimba (naltrexone hydrochloride/bupropion hydrochloride) in selected European countries to describe the demographic and baseline characteristics of users of Mysimba (naltrexone hydrochloride/bupropion hydrochloride)

17.6.4. Ulipristal acetate - ESMYA (CAP) - EMEA/H/C/002041/MEA 024.2

Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Annika Folin

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

17.7. New Scientific Advice

None

17.8. Ongoing Scientific Advice

None

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

None

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. Dinutuximab beta - QARZIBA (CAP) - EMEA/H/C/003918/S/0022 (without RMP)

Applicant: EUSA Pharma (Netherlands) B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Annual reassessment of the marketing authorisation

18.2. Conditional renewals of the marketing authorisation

18.2.1. Burosumab - CRYSVITA (CAP) - EMEA/H/C/004275/R/0019 (without RMP)

Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Conditional renewal of the marketing authorisation

18.2.2. Ex vivo expanded autologous human corneal epithelial cells containing stem cells - HOLOCLAR (CAP) - EMEA/H/C/002450/R/0032 (with RMP)

Applicant: Holostem Therapie Avanzate s.r.l., ATMP⁸⁰

PRAC Rapporteur: Rhea Fitzgerald

Scope: Conditional renewal of the marketing authorisation

18.2.3. Polatuzumab vedotin - POLIVY (CAP) - EMEA/H/C/004870/R/0003 (with RMP)

Applicant: Roche Registration GmbH

PRAC Rapporteur: Annika Folin

Scope: Conditional renewal of the marketing authorisation

18.2.4. Vandetanib - CAPRELSA (CAP) - EMEA/H/C/002315/R/0046 (without RMP)

Applicant: Genzyme Europe BV

⁸⁰ Advanced therapy medicinal product

PRAC Rapporteur: Tiphaine Vaillant

Scope: Conditional renewal of the marketing authorisation

18.3. Renewals of the marketing authorisation

18.3.1. Cabazitaxel - JEVTANA (CAP) - EMEA/H/C/002018/R/0042 (with RMP)

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Tiphaine Vaillant

Scope: 5-year renewal of the marketing authorisation

18.3.2. Dexamethasone - NEOFORDEX (CAP) - EMEA/H/C/004071/R/0016 (without RMP)

Applicant: Laboratoires CTRS

PRAC Rapporteur: Tiphaine Vaillant

Scope: 5-year renewal of the marketing authorisation

18.3.3. Eftrenonacog alfa - ALPROLIX (CAP) - EMEA/H/C/004142/R/0032 (without RMP)

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: 5-year renewal of the marketing authorisation

18.3.4. Elotuzumab - EMPLICITI (CAP) - EMEA/H/C/003967/R/0024 (without RMP)

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: 5-year renewal of the marketing authorisation

18.3.5. Emtricitabine, tenofovir alafenamide - DESCOVY (CAP) - EMEA/H/C/004094/R/0051 (without RMP)

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: 5-year renewal of the marketing authorisation

18.3.6. Human coagulation factor X - COAGADDEX (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

18.3.7. Ixekizumab - TALTZ (CAP) - EMEA/H/C/003943/R/0039 (with RMP)

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: 5-year renewal of the marketing authorisation

18.3.8. Pitolisant - WAKIX (CAP) - EMEA/H/C/002616/R/0024 (without RMP)

Applicant: Bioprojet Pharma

PRAC Rapporteur: Kirsti Villikka

Scope: 5-year renewal of the marketing authorisation

18.3.9. Selexipag - UPTRAVI (CAP) - EMEA/H/C/003774/R/0030 (with RMP)

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Adrien Inoubli

Scope: 5-year renewal of the marketing authorisation

18.3.10. Trifluridine, tipiracil - LONSURF (CAP) - EMEA/H/C/003897/R/0020 (without RMP)

Applicant: Les Laboratoires Servier

PRAC Rapporteur: Annika Folin

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 28 September – 01 October 2020 meeting.

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Sabine Straus	Chair	Netherlands	No interests declared	Full involvement
Jan Neuhauser	Member	Austria	No interests declared	Full involvement
Sonja Hrabcik	Alternate	Austria	No interests declared	Full involvement
Jean-Michel Dogné	Member	Belgium	No interests declared	Full involvement
Laurence de Fays	Alternate	Belgium	No restrictions applicable to this meeting	Full involvement
Maria Popova-Kiradjieva	Member	Bulgaria	No interests declared	Full involvement
Nikica Mirošević	Member	Croatia	No interests	Full

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Skvrce			declared	involvement
Željana Margan Koletić	Alternate	Croatia	No interests declared	Full involvement
Helena Panayiotopoulou	Member	Cyprus	No interests declared	Full involvement
Panagiotis Psaras	Alternate	Cyprus	No interests declared	Full involvement
Eva Jirsová	Member	Czech Republic	No interests declared	Full involvement
Jana Lukacisinova	Alternate	Czech Republic	No interests declared	Full involvement
Anette Kirstine Stark	Member	Denmark	No interests declared	Full involvement
Hans Christian Siersted	Alternate	Denmark	No restrictions applicable to this meeting	Full involvement
Maia Uusküla	Member	Estonia	No interests declared	Full involvement
Kirsti Villikka	Member	Finland	No interests declared	Full involvement
Kimmo Jaakkola	Alternate	Finland	No interests declared	Full involvement
Adrien Inoubli	Member	France	No interests declared	Full involvement
Tiphaine Vaillant	Alternate	France	No interests declared	Full involvement
Martin Huber	Member (Vice-Chair)	Germany	No interests declared	Full involvement
Brigitte Keller-Stanislawski	Alternate	Germany	No interests declared	Full involvement
Agni Kapou	Member	Greece	No interests declared	Full involvement
Sophia Trantza	Alternate	Greece	No interests declared	Full involvement
Julia Pallos	Member	Hungary	No participation in final deliberations and voting on:	4.2.1. Efavirenz – SUSTIVA (CAP), STOCRIN (CAP); NAP 5.1.6. Fedratinib – (CAP MAA) 6.3.4. Ibuprofen (NAP); ibuprofen lysine (NAP); ibuprofen, caffeine (NAP) 15.3.25. Nivolumab – OPDIVO

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				(CAP) 18.3.4. Elotuzumab - EMPLICITI (CAP)
Melinda Palfi	Alternate	Hungary	No interests declared	Full involvement
Guðrún Stefánsdóttir	Member	Iceland	No participation in discussion, final deliberations and voting on:	15.3.7. Blinatumomab - BLINCYTO (CAP) 16.1.3. Bevacizumab - AVASTIN (CAP); MVASI (CAP); ZIRABEV (CAP) 17.2.5. Gilteritinib - XOSPATA (CAP) 17.2.8. Mycastatin - MYCAMINE (CAP)
Rhea Fitzgerald	Member	Ireland	No restrictions applicable to this meeting	Full involvement
Ronan Grimes	Alternate	Ireland	No interests declared	Full involvement
Amelia Cupelli	Member	Italy	No interests declared	Full involvement
Ilaria Baldelli	Alternate	Italy	No interests declared	Full involvement
Zane Neikena	Member	Latvia	No interests declared	Full involvement
Zane Stade	Alternate	Latvia	No interests declared	Full involvement
Rugile Pilviniene	Member	Lithuania	No interests declared	Full involvement
John Joseph Borg	Member	Malta	No interests declared	Full involvement
Benjamin Micallef	Alternate	Malta	No interests declared	Full involvement
Menno van der Elst	Member	Netherlands	No interests declared	Full involvement
Liana Gross-Martirosyan	Alternate	Netherlands	No interests declared	Full involvement
David Olsen	Member	Norway	No participation in final deliberations and voting on:	6.3.45. Ibuprofen (NAP); ibuprofen lysine (NAP);

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				ibuprofen, caffeine (NAP) 7.3.1. Iron (NAP) 16.1.13. Damoctocog alfa pegol - JIVI (CAP) 17.4.3. Rivaroxaban - XARELTO (CAP)
Karen Pernille Harg	Alternate	Norway	No interests declared	Full involvement
Adam Przybylkowski	Member	Poland	No interests declared	Full involvement
Katarzyna Ziolkowska	Alternate	Poland	No interests declared	Full involvement
Ana Diniz Martins	Member	Portugal	No interests declared	Full involvement
Marcia Silva	Alternate	Portugal	No interests declared	Full involvement
Roxana Stefania Stroe	Member	Romania	No interests declared	Full involvement
Alexandra-Maria Spurni	Alternate	Romania	No interests declared	Full involvement
Michal Radik	Member	Slovakia	No interests declared	Full involvement
Marek Juracka	Alternate	Slovakia	No interests declared	Full involvement
Gabriela Jazbec	Member	Slovenia	No interests declared	Full involvement
Eva Segovia	Member	Spain	No interests declared	Full involvement
Maria del Pilar Rayon	Alternate	Spain	No interests declared	Full involvement
Ulla Wändel Liminga	Member	Sweden	No interests declared	Full involvement
Annika Folin	Alternate	Sweden	No interests declared	Full involvement
Milou Daniel Drici	Member	Independent scientific expert	No restrictions applicable to this meeting	Full involvement
Birgitta Grundmark	Member	Independent scientific expert	No interests declared	Full involvement
Daniel Morales	Member	Independent scientific expert	No interests declared	Full involvement
Hedvig Nordeng	Member	Independent scientific expert	No interests declared	Full involvement
Antoine Pariente	Member	Independent scientific expert	No restrictions applicable to this meeting	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Stefan Weiler	Member	Independent scientific expert	No participation in discussion, final deliberations and voting on:	16.1.49. Ulipristal acetate - ESMYA (CAP); ULIPRISTAL ACETATE GEDEON RICHTER (CAP) 17.5.6. Ulipristal acetate - ESMYA (CAP) 17.5.7. Ulipristal acetate - ESMYA (CAP) 17.6.4. Ulipristal acetate - ESMYA (CAP)
Raymond Anderson	Member	Healthcare Professionals' Representative	No interests declared	Full involvement
Roberto Frontini	Alternate	Healthcare Professionals' Representative	No restrictions applicable to this meeting	Full involvement
Cathalijne van Doorne	Member	Patients' Organisation Representative	No interests declared	Full involvement
Virginie Hivert	Alternate	Patients' Organisation Representative	No restrictions applicable to this meeting	Full involvement
Fabrice Moore	Expert - via telephone*	Belgium	No interests declared	Full involvement
Flora Musuamba Tshinai	Expert - via telephone*	Belgium	No interests declared	Full involvement
Françoise Wuillaume	Expert - via telephone*	Belgium	No interests declared	Full involvement
Annette Cleveland Nielsen	Expert - via telephone*	Denmark	No restrictions applicable to this meeting	Full involvement
Helle Esbjørn Kristensen	Expert - via telephone*	Denmark	No interests declared	Full involvement
Pernille Gammelgaard	Expert - via telephone*	Denmark	No interests declared	Full involvement
Helle Gerda Olsen	Expert - via telephone*	Denmark	No interests declared	Full involvement
Aynur Sert	Expert - via telephone*	Denmark	No interests declared	Full involvement
Emma Stadsbjerg	Expert - via telephone*	Denmark	No interests declared	Full involvement
Anita Vibsig Neutzsky-Wulff	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
Mette Juul Wikkelsø	Expert - via telephone*	Denmark	No interests declared	Full involvement
Päivi Susanna Worsøe	Expert - via telephone*	Denmark	No restrictions applicable to this meeting	Full involvement
Martin Zahle Larsen	Expert - via telephone*	Denmark	No interests declared	Full involvement
Krõõt Aab	Expert - via telephone*	Estonia	No interests declared	Full involvement
Jeremie Botton	Expert - via telephone*	France	No interests declared	Full involvement
Mariem Loukil	Expert - via telephone*	France	No interests declared	Full involvement
Thomas Grüger	Expert - via telephone*	Germany	No interests declared	Full involvement
Dennis Lex	Expert - via telephone*	Germany	No participation in discussion, final deliberations and voting on:	7.2.2. Dimethyl fumarate - TECFIDERA (CAP) 10.1.3. Dimethyl fumarate - TECFIDERA (CAP)
Vivien Molitor	Expert - via telephone*	Germany	No interests declared	Full involvement
Wiebke Seemann	Expert - via telephone*	Germany	No interests declared	Full involvement
Eleanor Carey	Expert - via telephone*	Ireland	No restrictions applicable to this meeting	Full involvement
Grainne Kirwan	Expert - via telephone*	Ireland	No interests declared	Full involvement
Charlotte Backman	Expert - via telephone*	Sweden	No interests declared	Full involvement
Filip Josephson	Expert - via telephone*	Sweden	No interests declared	Full involvement
A representative from the European Commission attended the meeting				
Meeting run with support from relevant EMA staff				

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

20. Annex III - List of acronyms and abbreviations

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

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

21. Explanatory notes

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

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

(Items 2 and 3 of the PRAC minutes)

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

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

Signals assessment and prioritisation

(Item 4 of the PRAC minutes)

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

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

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

Risk Management Plans (RMPs)

(Item 5 of the PRAC minutes)

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

Assessment of Periodic Safety Update Reports (PSURs)

(Item 6 of the PRAC minutes)

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

Post-authorisation Safety Studies (PASS)

(Item 7 of the PRAC minutes)

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

Product related pharmacovigilance inspections

(Item 9 of the PRAC minutes)

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

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

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