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Human Medicines Division

Pharmacovigilance Risk Assessment Committee (PRAC) Minutes of meeting on 30 August – 02 September 2021

Chair: Sabine Straus – Vice-Chair: Martin Huber

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

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1. Introduction

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

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

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

Discussions, deliberations and voting took place in full respect of the restricted involvement of Committee members and experts in line with the relevant provisions of revision 3 of the Rules of Procedure ([EMA/PRAC/567515/2012 Rev.3](#)). 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 remotely). All decisions, recommendations and advice were agreed unanimously, unless otherwise specified.

The PRAC Chair welcomed Tiphaine Vaillant, as the new member for France, leaving the position of alternate vacant until further notice.

1.2. Agenda of the meeting on 30 August - 02 September 2021

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

1.3. Minutes of the previous meetings on 05-08 July 2021 and 05 August 2021

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

Post-meeting note: the PRAC minutes of the meeting held on 05-08 July 2021 and 05 August 2021 were published on the EMA website respectively on 10 May 2022 ([EMA/PRAC/171547/2022](#)) and on 12 May 2022 ([EMA/PRAC/178649/2022](#)).

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

2.1. Newly triggered procedures

None

2.2. Ongoing procedures

None

2.3. Procedures for finalisation

None

2.4. Planned public hearings

None

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

3.1. Newly triggered procedures

None

3.2. Ongoing procedures

None

3.3. Procedures for finalisation

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 16.4.

4.1.1. Coronavirus (COVID-19) mRNA³ vaccine (nucleoside-modified) - COMIRNATY (CAP)

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

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

³ Messenger ribonucleic acid

Scope: Signal of multisystem inflammatory syndrome in children

EPITT 19732 – New signal

Lead Member State(s): NL

Background

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

Denmark issued a rapid alert informing the EU Member States of a case of multisystem inflammatory syndrome in children (MIS-C) in a child with a temporal relationship to vaccination. A signal of MIS-C was identified based on seven cases retrieved from EudraVigilance, with one case from the literature. A cumulative review was also provided by the MAH in the framework of the eighth monthly summary safety review (MSSR). See 6.6.1.

The Rapporteur confirmed that the signal needed initial analysis and prioritisation by PRAC.

Discussion

Having considered the available evidence from one well-described case in a child who experienced MIS-C after vaccination with Comirnaty (COVID-19 mRNA vaccine (nucleoside-modified)), the EudraVigilance and literature review together with the Rapporteur's assessment, PRAC agreed that further evaluation on the signal of MIS-C is warranted. PRAC also agreed to widen the scope to both MIS-C and multisystem inflammatory syndrome in adults (MIS-A) in view of a case reported in an adult and further review the evidence for all authorised COVID-19 vaccines.

Summary of recommendation(s)

- The MAHs for Comirnaty (COVID-19 mRNA vaccine (nucleoside-modified)), Spikevax (COVID-19 mRNA vaccine (nucleoside-modified)), COVID-19 vaccine Janssen (COVID-19 vaccine (Ad26.COVS-S [recombinant])) and Vaxzevria (COVID-19 vaccine (ChAdOx1-S [recombinant])) should submit to EMA, within 21 days, a cumulative review of multisystem inflammatory syndrome (MIS). The MAHs should discuss the need for an update of the product information and/or RMP as warranted.
- A 30-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. Ibrutinib – IMBRUVICA (CAP)

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Signal of sudden death/cardiac death with ibrutinib and concomitant angiotensin-converting enzyme (ACE) inhibitors⁴ from a clinical trial⁵

⁴ Benazepril, captopril, cilazapril, enalapril, enalaprilat, fosinopril, imidapril, lisinopril, perindopril, quinapril, ramipril, trandolapril, zofenopril and combinations

⁵ Study 2013-001944-76 (FLAIR): a phase 3 study evaluating first-line treatment with ibrutinib+rituximab versus fludarabine, cyclophosphamide and rituximab in patients with chronic lymphocytic leukaemia who are up to 75 years of age

EPITT 19726 – New signal

Lead Member State(s): HR

Background

Ibrutinib is a Bruton's tyrosine kinase (BTK) inhibitor indicated, as Imbruvica, a centrally authorised medicine, as a single agent for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL), as a single agent or in combination with rituximab or obinutuzumab for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL), as a single agent or in combination with bendamustine and rituximab (BR) for the treatment of adult patients with CLL who have received at least one prior therapy as well as a single agent for the treatment of adult patients with Waldenström's macroglobulinaemia (WM) who have received at least one prior therapy, or in first line treatment for patients unsuitable for chemo-immunotherapy. It is also indicated in combination with rituximab for the treatment of adult patients with WM.

Following the notification by the MAH of Imbruvica (ibrutinib) of an emerging safety issue (ESI) identified during an interim analysis of the FLAIR study, a signal of sudden death/cardiac death with ibrutinib and concomitant angiotensin-converting enzyme (ACE) inhibitors was validated. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by PRAC.

Discussion

Having considered the findings from the FLAIR study submitted by the MAH as an ESI and the available evidence from the last PSUR, PRAC agreed that further evaluation on the signal of sudden death/cardiac death with ibrutinib and concomitant ACE inhibitors is warranted. PRAC considered initially on the distribution of a direct healthcare professional communication (DHPC) along with a communication plan. At the organisational, regulatory and methodological matters (ORGAM)⁶ meeting on 16 September 2021, PRAC adopted a refined recommendation and agreed eventually that a DHPC should not be distributed at this stage.

Summary of recommendation(s)

- The MAH should submit to EMA, within 30 days, a review of relative rates of sudden death or cardiac death in patients treated with ACE-inhibitors that have been randomised to ibrutinib-containing regimens or regimens without ibrutinib in randomised clinical studies. The MAH should also report on potassium values for patients receiving ACE inhibitors in the study and provide a review of underlying risk factors together with a discussion on potential mechanism for possible interaction between ibrutinib and ACE inhibitors. The MAH should also include a cumulative analysis of cases from all available sources reporting sudden cardiac death, sudden death, cardiac death and fatal cases from cardiac disorders with the use of ibrutinib with special interest in cases of concomitant ACE inhibitors. Finally, the MAH should provide a discussion on the need for risk minimisation measures, including a proposal to update the product information as warranted.
- A 30-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

⁶ Extended to specific COVID-19-related procedure(s) during EMA business continuity plan (BCP)

4.3. Signals follow-up and prioritisation

4.3.1. Coronavirus (COVID-19) mRNA⁷ vaccine (nucleoside-modified) - COMIRNATY (CAP) – EMEA/H/C/005735/SDA/032.1

Applicant(s): BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Signal of myocarditis and pericarditis

EPITT 19712 – Follow-up to July 2021

Background

For background information, see [PRAC minutes July 2021](#).

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

Discussion

Based on the responses from the MAH and the Rapporteur's assessment, and taking into account the update of the product information dated July 2021 to reflect myocarditis and pericarditis as well as the ongoing procedure to include myocarditis and pericarditis as an important identified risk in the RMP, PRAC agreed that at this stage, no further change to the previous PRAC recommendation is warranted.

Summary of recommendation(s)

- In the next monthly summary safety report(s) (MSSR), the MAH for Comirnaty (COVID-19 mRNA vaccine (nucleoside-modified)) should continuously monitor cases of myocarditis and pericarditis. As soon as new relevant information becomes available, the MAH should further characterise this risk and propose to update the product information as applicable.

4.3.2. Coronavirus (COVID-19) mRNA⁸ vaccine (nucleoside-modified) - SPIKEVAX (CAP) – EMEA/H/C/005791/SDA/033.1

Applicant(s): Moderna Biotech Spain, S.L.

PRAC Rapporteur: Hans Christian Siersted

Scope: Signal of myocarditis and pericarditis

EPITT 19713 – Follow-up to July 2021

Background

For background information, see [PRAC minutes July 2021](#).

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

Discussion

⁷ Messenger ribonucleic acid

⁸ Messenger ribonucleic acid

Based on the responses from the MAH and the Rapporteur's assessment, and taking into account the update of the product information dated July 2021 to reflect myocarditis and pericarditis as well as the ongoing procedure to include myocarditis and pericarditis as an important identified risk in the RMP, PRAC agreed that at this stage, no further change to the previous PRAC recommendation is warranted.

Summary of recommendation(s)

- In the next monthly summary safety report(s) (MSSR), the MAH for Spikevax (COVID-19 mRNA vaccine (nucleoside-modified)) should continuously monitor cases of myocarditis and pericarditis. As soon as new relevant information becomes available, the MAH should further characterise this risk and propose to update the product information as applicable.

4.3.3. Coronavirus (COVID-19) vaccine (ChAdOx1-S [recombinant]) - VAXZEVRIA (CAP) - EMEA/H/C/005675/SDA/047.1

Applicant(s): AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: Signal of capillary leak syndrome

EPITT 19672 – Follow-up to June 2021

Background

For background information, see [PRAC minutes June 2021](#).

The MAH replied to the further request for information on the signal of capillary leak syndrome (CLS) and the responses were assessed by the Rapporteur.

Discussion

Based on the available evidence from the literature, the responses from the MAH together with the Rapporteur's assessment, PRAC agreed that at present no definitive mechanism could be identified to explain the episodes of CLS observed following vaccination with Vaxzevria (COVID-19 vaccine (ChAdOx1-S [recombinant])).

Summary of recommendation(s)

- In the next monthly summary safety report(s) (MSSR) and PSUR, the MAH should monitor and discuss any new relevant information that could explain the potential triggering role of Vaxzevria (COVID-19 vaccine (ChAdOx1-S [recombinant])) or other vaccines in CLS episodes and other potential post-vaccination inflammatory disorders, including any new data on cytokine levels after vaccination.

4.3.4. Fluoroquinolones: ciprofloxacin (NAP); delafloxacin - QUOFENIX (CAP); levofloxacin – QUINSAIR (CAP), NAP; lomefloxacin (NAP); moxifloxacin (NAP); norfloxacin (NAP); ofloxacin (NAP); pefloxacin (NAP); prulifloxacin (NAP); rufloxacin (NAP)

Applicant(s): A. Menarini Industrie Farmaceutiche Riunite s.r.l. (Quofenix), Chiesi Farmaceutici S.p.A. (Quinsair), various

PRAC Rapporteur: Karen Pernille Harg

Scope: Signal of acquired thrombotic thrombocytopenia purpura

EPITT 19669 – Follow-up to April 2021

Background

For background information, see [PRAC minutes April 2021](#).

EMA performed a cumulative review of relevant cases in EudraVigilance of acquired thrombotic thrombocytopenia purpura associated with systemic fluoroquinolones, together with a literature review. The Rapporteur prepared a further assessment of the available data.

Discussion

PRAC considered the available evidence from case reports in EudraVigilance, including an analysis of EudraVigilance data, a review of the literature and the results of a descriptive comparative cohort analysis together with the Rapporteur's assessment. PRAC agreed that there is insufficient evidence at present to confirm a causal association between systemic fluoroquinolones and thrombotic thrombocytopenia purpura. Therefore, PRAC concluded that routine pharmacovigilance should be applied.

Summary of recommendation(s)

- The MAHs for fluoroquinolones, namely ciprofloxacin-, delafloxacin-, levofloxacin-, lomefloxacin-, moxifloxacin-, norfloxacin-, ofloxacin-, pefloxacin-, prulifloxacin- and rufloxacin-containing products for systemic use should monitor cases of acquired thrombotic thrombocytopenia purpura as part of routine safety surveillance.

4.3.5. [Methotrexate - JYLAMVO \(CAP\) - EMEA/H/C/003756/SDA/003, NORDIMET \(CAP\) - EMEA/H/C/003983/SDA/004.1; NAP](#)

Applicant(s): Nordic Group B.V. (Nordimet), Therakind (Europe) Limited (Jylamvo); various

PRAC Rapporteur: Martin Huber

Scope: Signal of progressive multifocal leukoencephalopathy (PML)

EPITT 18473 – Follow-up to May 2021

Background

For background information, see [PRAC minutes May 2021](#).

The MAHs replied to the further request for information on the signal of progressive multifocal leukoencephalopathy (PML) and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence from case reports in EudraVigilance, the literature, responses from the MAHs together with the Rapporteur's assessment, PRAC agreed that a definite causality between methotrexate and PML cannot be established at present, however, a contributory role of methotrexate in the development of PML cannot be excluded either. In order to raise awareness amongst healthcare professionals (HCPs) and to advise patients appropriately, PRAC agreed that an update of the product information is warranted to add PML as a warning.

Summary of recommendation(s)

- The MAHs for methotrexate-containing products should submit to EMA or to the relevant National Competent Authorities (NCAs) of the Member States as applicable, within 60 days, a variation to amend⁹ the product information.

For the full PRAC recommendation, see [EMA/PRAC/468914/2021](#) published on 27 September 2021 on the EMA website.

4.3.6. Ponatinib – ICLUSIG (CAP) - EMEA/H/C/002695/SDA/018

Applicant(s): Incyte Biosciences Distribution B.V.

PRAC Rapporteur: Annika Folin

Scope: Signal of panniculitis

EPITT 19681 – Follow-up to May 2021

Background

For background information, see [PRAC minutes May 2021](#).

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

Discussion

Having considered the available evidence from case reports in EudraVigilance, the responses from the MAH together with the Rapporteur's assessment, PRAC agreed that there is at least a reasonable possibility for a causal association between ponatinib and panniculitis. Therefore, PRAC agreed that an update of the product information is warranted to add panniculitis as an undesirable effect with a frequency rare.

Summary of recommendation(s)

- The MAH for Iclusig (ponatinib) should submit to EMA, within 60 days, a variation to amend¹⁰ the product information.

For the full PRAC recommendation, see [EMA/PRAC/468914/2021](#) published on 27 September 2021 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

PRAC provided advice to CHMP 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.

⁹ Update of SmPC section 4.4. The package leaflet is to be updated accordingly

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

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. Amivantamab - EMEA/H/C/005454

Scope: Treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating epidermal growth factor receptor (EGFR) exon 20 insertion mutations, after failure of platinum-based chemotherapy

5.1.2. Arimoclomol - EMEA/H/C/005203, Orphan

Applicant: Orphazyme A/S

Scope: Treatment of Niemann-Pick disease type C (NPC)

5.1.3. Budesonide, micronised - EMEA/H/C/005653, Orphan

Applicant: Calliditas Therapeutics AB

Scope (accelerated assessment): Treatment of primary immunoglobulin A (IgA) nephropathy

5.1.4. Casirivimab, imdevimab – MEA/H/C/005814

Scope: treatment of confirmed coronavirus disease 2019 (COVID-19) in patients aged 12 years and older and weighing at least 40 kg that do not require supplemental oxygen for COVID-19 and who are at high risk of progressing to severe COVID-19 as well as for the prevention of COVID-19 in individuals aged 12 years and older and weighing at least 40 kg under certain conditions

5.1.5. Ciltacabtagene autoleucel - EMEA/H/C/005095, Orphan

Applicant: Janssen-Cilag International NV, ATMP¹¹

Scope (accelerated assessment): Treatment of multiple myeloma

5.1.6. Eptinezumab - EMEA/H/C/005287

Scope: Prophylaxis of migraine in adults

5.1.7. Finerenone - EMEA/H/C/005200

Scope: Treatment to delay progression of kidney disease and to reduce the risk of cardiovascular mortality and morbidity in adults with chronic kidney disease (stage 3 and 4 with albuminuria) and type 2 diabetes (T2DM)

5.1.8. Hepatitis B surface antigen – EMEA/H/C/005466

Scope: Prevention of infection caused by all known subtypes of the hepatitis B virus in

¹¹ Advanced therapy medicinal product

adults

5.1.9. Inebilizumab - EMEA/H/C/005818, Orphan

Applicant: Viela Bio

Scope: Treatment of adults with neuromyelitis optica spectrum disorders

5.1.10. Linzagolix choline - EMEA/H/C/005442

Scope: Management of heavy menstrual bleeding (HMB) associated with uterine fibroids

5.1.11. Pneumococcal polysaccharide conjugate vaccine (adsorbed) - EMEA/H/C/005477

Scope: Immunisation for the prevention of invasive disease and pneumonia caused by *Streptococcus pneumoniae*

5.1.12. Regdanvimab - EMEA/H/C/005854

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

5.1.13. Sotorasib - EMEA/H/C/005522

Scope: Treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC)

5.1.14. Sotrovimab - EMEA/H/C/005676

Scope: Treatment of coronavirus disease 2019 (COVID-19)

5.1.15. Tepotinib - EMEA/H/C/005524

Scope: Treatment of adult patients with advanced non-small cell lung cancer (NSCLC)

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

See Annex I 15.2.

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

See also Annex I 15.3.

5.3.1. Dapagliflozin - FORXIGA (CAP) - EMEA/H/C/002322/II/0071

Applicant: AstraZeneca AB

PRAC Rapporteur: Annika Folin

Scope: Removal of the indication for 'the treatment of patients with type 1 diabetes mellitus (T1DM) as an adjunct to insulin in patients with body mass index (BMI) ≥ 27 kg/m² when insulin alone does not provide adequate glycaemic control despite optimal insulin therapy' and related additional risk minimisation measures from Annex II for Forxiga (dapagliflozin)

5 mg film-coated tablets. As a consequence, affected sections of the SmPC of the 5 mg tablets are updated. The package leaflet is updated in accordance. A combined SmPC/package leaflet with the 10 mg tablets has been submitted. The RMP (version 26.s1) is updated accordingly

Background

Dapagliflozin is a sodium-glucose co-transporter-2 (SGLT2) inhibitor indicated, as Forxiga, for the treatment of type 2 diabetes mellitus (T2DM), type 1 diabetes mellitus (T1DM), heart failure and chronic kidney disease under certain conditions.

CHMP is evaluating a type II variation for Forxiga, a centrally authorised product containing dapagliflozin, to remove the indication for the treatment of patients with type 1 diabetes mellitus (T1DM) and related additional risk minimisation measures from Annex II for the 5 mg film-coated tablets. PRAC is responsible for providing advice to CHMP on the necessary updates to the RMP to support this type II variation.

Summary of advice

- The RMP for Forxiga (dapagliflozin) in the context of the variation procedure under evaluation by PRAC and CHMP could be considered acceptable provided that an update to RMP version 26.1 and satisfactory responses to the request for supplementary information (RSI) are submitted.
- PRAC considered that the important identified risk of 'diabetes ketoacidosis including events with atypical presentation' should remain unchanged in the RMP. In addition, all measures related to the T1DM indication, including specific additional risk minimisation measures (aRMM) to mitigate the risk of risk of diabetic ketoacidosis (DKA) and imposed PASS D1695C00011¹², should be removed.
- PRAC agreed on the content of a direct healthcare professional communication ([DHPC](#)) along with a communication plan for its distribution.

6. Periodic safety update reports (PSURs)

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

See also Annex I 16.1.

6.1.1. Brivaracetam - BRIVIACT (CAP) - PSUSA/00010447/202101

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

Background

Brivaracetam displays a high and selective affinity for synaptic vesicle protein 2A (SV2A). It is indicated, as Briviact, as adjunctive therapy in the treatment of partial onset seizures with

¹² A retrospective cohort study on the risk of DKA

or without secondary generalisation in adults, adolescents and children from 4 years of age with epilepsy.

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Briviact, a centrally authorised medicine containing brivaracetam 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 Briviact (brivaracetam) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to reflect that in the context of brivaracetam overdose, adverse drug reactions such as nausea, vertigo, balance disorder, anxiety, fatigue, irritability, aggression, insomnia, depression and suicidal ideation have been reported. Therefore, the current terms of the marketing authorisation(s) should be varied¹³.

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.

6.1.2. Budesonide¹⁴ - JORVEZA (CAP) - PSUSA/00010664/202101

Applicant: Dr. Falk Pharma GmbH

PRAC Rapporteur: Zane Neikena

Scope: Evaluation of a PSUSA procedure

Background

Budesonide is a non-halogenated glucocorticosteroid indicated, as Jorveza, for the treatment of eosinophilic esophagitis (EoE) in adults older than 18 years of age.

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Jorveza, a centrally authorised medicine containing budesonide 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 Jorveza (budesonide) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include angioedema as an undesirable effect with a frequency 'uncommon'. Therefore, the current terms of the marketing authorisation(s) should be varied¹⁵.

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

¹³ Update of SmPC section 4.9. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion

¹⁴ Centrally authorised product(s) only

¹⁵ Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion

6-monthly to yearly and the list of Union reference dates (EURD list) will be updated accordingly.

6.1.3. Dolutegravir - TIVICAY (CAP); dolutegravir, abacavir, lamivudine - TRIUMEQ (CAP); dolutegravir, lamivudine - DOVATO (CAP) - PSUSA/00010075/202101

Applicant(s): ViiV Healthcare B.V.

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Dolutegravir is a human immunodeficiency virus (HIV) integrase inhibitor. Abacavir and lamivudine are potent selective inhibitors of HIV-1 and HIV-2. Dolutegravir is indicated in combination with other anti-retroviral medicinal products for the treatment of HIV infected adults, adolescents and children under certain conditions. Dolutegravir/lamivudine or dolutegravir/abacavir/lamivudine in combination are indicated for the treatment of HIV infected adults and adolescents under certain conditions.

Based on the assessment of the PSURs, PRAC reviewed the benefit-risk balance of Tivicay, Triumeq and Dovato, centrally authorised medicines containing dolutegravir, dolutegravir/abacavir/lamivudine and dolutegravir/lamivudine respectively and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Tivicay (dolutegravir), Triumeq (dolutegravir/abacavir/lamivudine) and Dovato (dolutegravir/lamivudine) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add panic attack as an undesirable effect with a frequency 'uncommon'. Therefore, the current terms of the marketing authorisation(s) should be varied¹⁶.
- The MAH should submit to EMA, within 60 days, a cumulative review of cases of suicide/self-injury and propose to update the product information as warranted.
- The MAH should submit to EMA, within 60 days, all available data from study 207709 (RESPOND study)¹⁷ and propose to update the product information as warranted.
- In the next PSUR, the MAH should closely monitor cases of severe cutaneous adverse reactions (SCARs), thrombocytopenia, myocarditis, holoprosencephaly or midline defects and hyperglycaemia and diabetes mellitus.

The frequency of PSUR submission should be revised from 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.

¹⁶ Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion

¹⁷ International cohort consortium of infectious disease: a prospective, multi-cohort collaboration study including data from 17 cohorts and over 29,000 people living with HIV across Europe and Australia

6.1.4. Inotersen - TEGSEDI (CAP) - PSUSA/00010697/202101

Applicant: Akcea Therapeutics Ireland Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

Background

Inotersen is a 2'-O-2-methoxyethyl (2-MOE) phosphorothioate antisense oligonucleotide (ASO) inhibitor of human transthyretin (TTR) production. It is indicated for the treatment of stage 1 or stage 2 polyneuropathy in adult patients with hereditary transthyretin amyloidosis (hATTR).

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Tegsedi, a centrally authorised medicine containing inotersen 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 Tegsedi (inotersen) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend an existing warning for patients undergoing liver transplantation in order to perform monthly liver function tests in patients with a prior liver transplant. Therefore, the current terms of the marketing authorisation(s) should be varied¹⁸.
- In the next PSUR, the MAH should provide cumulative reviews of lymphocyte count decreased, white blood cell count decreased, neutrophil count decreased, pancytopenia, nephrotic syndrome, myocarditis and angioedema. For relevant reviews, the MAH should propose to update the product information as warranted.

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC. The frequency of submission of the subsequent PSURs should be changed from 6-monthly to yearly and the list of Union reference dates (EURD list) will be updated accordingly.

6.1.5. Liraglutide - SAXENDA (CAP); VICTOZA (CAP) - PSUSA/00001892/202012

Applicant(s): Novo Nordisk A/S

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

Background

Liraglutide is a glucagon-like peptide-1 (GLP-1) analogue indicated as an adjunct to a reduced-calorie diet and increased physical activity for weight management in adult patients and as an adjunct to a healthy nutrition and increased physical activity for weight management in adolescent patients under certain conditions. It is also indicated for the treatment of adults, adolescents and children aged 10 years and above with insufficiently

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

controlled type 2 diabetes mellitus (T2DM) as an adjunct to diet and exercise under certain conditions.

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Saxenda and Victoza, centrally authorised medicines containing liraglutide 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 Saxenda and Victoza (liraglutide) in the approved indication(s) remains unchanged.
- Nevertheless, the product information for Saxenda (liraglutide) should be updated to add headache as an undesirable effect with a frequency 'very common'. Therefore, the current terms of the marketing authorisation(s) should be varied¹⁹.
- The current terms of the marketing authorisation(s) for Victoza (liraglutide) should be maintained.
- In the next PSUR, the MAH should provide an overview of cases of medication errors, together with a discussion on patterns for medication errors.

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.

6.1.6. Sarilumab - KEVZARA (CAP) - PSUSA/00010609/202101

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

Background

Sarilumab is a human monoclonal antibody as an immunoglobulin (Ig)G1 indicated in combination with methotrexate (MTX) for the treatment of moderately to severely active rheumatoid arthritis (RA) in adult patients who have responded inadequately to, or who are intolerant to one or more disease modifying anti rheumatic drugs (DMARDs). Sarilumab can be given in monotherapy in case of intolerance to MTX or when treatment with MTX is inappropriate.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Kevzara (sarilumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the existing warning on gastrointestinal perforation to add diverticulitis. Diverticulitis and leukopenia should

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

be also added as undesirable effects with a frequency 'uncommon' and 'common' respectively. Therefore, the current terms of the marketing authorisation(s) should be varied²⁰.

The frequency of PSUR submission should be revised from 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.

6.1.7. Ticagrelor - BRILIQUE (CAP) - PSUSA/00002948/202012

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

Background

Ticagrelor is a cyclopentyltriazolopyrimidine (CPTP) indicated in combination with acetylsalicylic acid (ASA) for the prevention of atherothrombotic events in adult patients with acute coronary syndromes (ACS) or a history of myocardial infarction (MI) and a high risk of developing an atherothrombotic event.

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Brilique, a centrally authorised medicine containing ticagrelor, 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 Brilique (ticagrelor) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add an interaction between ticagrelor and rosuvastatin, leading to an increased risk for rosuvastatin accumulation and in some cases, to possible renal function decrease, increased creatine phosphokinase (CPK) level and rhabdomyolysis. Therefore, the current terms of the marketing authorisation(s) should be varied²¹.
- In the next PSUR, the MAH should provide an overview of cases of medication errors, together with a discussion on patterns for medication errors. In addition, the MAH should include a cumulative review on drug-drug interaction between ticagrelor and atorvastatin. Finally, the MAH should monitor the off-label use in sickle cell disease in children.

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.

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 CHMP for adoption of an opinion

²¹ Update of SmPC section 4.5. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

Background

Ustekinumab is a fully human immunoglobulin (Ig)G1κ monoclonal antibody indicated for the treatment of Crohn's disease, ulcerative colitis, plaque psoriasis, paediatric plaque psoriasis and psoriatic arthritis (PsA) under certain conditions.

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Stelara, a centrally authorised medicine containing ustekinumab 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 Stelara (ustekinumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add a warning on opportunistic infections and to amend the existing warning on lactation. In addition, bullous pemphigoid should be added as an undesirable effect with a frequency 'very rare'. Furthermore, for the concentrate for solution for infusion formulation, serious infusion related reactions should be added as a warning and the section on undesirable effect should be refined. Therefore, the current terms of the marketing authorisation(s) should be varied²².
- In the next PSUR, the MAH should provide cumulative reviews of cases of pemphigus, lymphoma, lupus erythematosus including systemic and cutaneous forms and lupus-like syndrome, vitiligo, immunoglobulin (Ig)A nephropathy, fixed drug eruption and opportunistic infections. The MAH should also discuss any new cases of Ewing's sarcoma and of reversible cerebral vasoconstriction syndrome. In addition, the MAH should discuss the article by *Svedborn et al.*²³ and comment whether any update to the product information is warranted. Moreover, the MAH should provide a cumulative review on breastfeeding including any new information regarding ustekinumab excretion into breastmilk.
- Taking into account additional data submitted by the MAH in the PSUR, further analyses to support the need for an update of the product information with a warning on cardiovascular events²⁴ are warranted. The MAH should submit to EMA an updated RMP to include the proposed additional analyses of cardiovascular events in patients with psoriasis and psoriatic arthritis in Sweden and Denmark as an additional pharmacovigilance activity (listed as category 3) within the next regulatory opportunity or within six months at the latest.

²² Update of SmPC sections 4.4, 4.6 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion

²³ Svedborn A, Nikamo P, Stahle M, 2020, Interaction between Smoking and HLA-C*06:02 on the response to ustekinumab in psoriasis, *Journal of Investigative Dermatology*, vol. 140, no. 8, pp. 1653-1656

²⁴ As previously advised following procedure LEG 049.1 finalised in June 2021

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

6.1.9. Voretigene neparvovec - LUXTURNA (CAP) - PSUSA/00010742/202101

Applicant: Novartis Europharm Limited, ATMP²⁵

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

Background

Voretigene neparvovec is a recombinant adeno-associated viral (AAV) vector serotype 2 capsid containing human retinal pigment epithelium-specific 65 kilodalton protein (RPE65) complementary deoxyribonucleic acid (cDNA). It is indicated for the treatment of adult and paediatric patients with vision loss due to inherited retinal dystrophy caused by confirmed biallelic RPE65 mutations and who have sufficient viable retinal cells.

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Luxturna, a centrally authorised medicine containing voretigene neparvovec 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 Luxturna (voretigene neparvovec) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include (chorio)retinal atrophy as a warning and as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied²⁶.

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC. The frequency of submission of the subsequent PSURs should be changed from 6-monthly to yearly and the list of Union reference dates (EURD list) will be updated accordingly.

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

See also Annex I 16.2.

6.2.1. Pregabalin - LYRICA (CAP); PREGABALIN PFIZER (CAP); NAP - PSUSA/00002511/202101

Applicants: Upjohn EESV (Lyrica, Pregabalin Pfizer), various

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

²⁵ Advanced therapy medicinal product

²⁶ Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion

Background

Pregabalin is a gamma-aminobutyric acid analogue [(S)-3-(aminomethyl)-5-methylhexanoic acid] indicated for the treatment of peripheral and central neuropathic pain in adults, for the treatment of generalised anxiety disorder (GAD) in adults and as an adjunctive therapy in adults with partial seizures with or without secondary generalisation.

Based on the assessment of the PSURs, PRAC reviewed the benefit-risk balance of Lyrica and Pregabalin Pfizer, centrally authorised medicines containing pregabalin, and nationally authorised medicine(s) containing pregabalin 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 pregabalin-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add Parkinsonism as an undesirable effect with a frequency 'rare'. Therefore, the current terms of the marketing authorisations should be varied²⁷.
- The MAH for Lyrica and Pregabalin Pfizer (pregabalin) should submit to EMA, within 90 days, an updated review of cases of abuse and dependence in patients without a history of substance disorder. The MAH should propose to update the product information as warranted.
- The MAH for Lyrica and Pregabalin Pfizer (pregabalin) should submit to EMA, within 30 days, comments on the letter sent to prescribers from Northern Ireland (NI) Health and Social Care Board regarding the removal of pregabalin from NI formulary for neuropathic pain.
- In the next PSUR, the MAH(s) should provide cumulative reviews of cases of priapism and of paralysis. In addition, the MAH(s) should review new cases related to pregnancy outcomes and congenital malformations.

The frequency of PSUR submission should be revised from 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. 17.3. PSUR single assessment (PSUSA) procedures including nationally authorised products (NAPs) only

See also Annex I 16.3.

6.3.1. 5-fluorouracil²⁸ (NAP) - PSUSA/00000007/202012

Applicant(s): various

PRAC Lead: Martin Huber

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

²⁸ Intravenous (IV) use only

Scope: Evaluation of a PSUSA procedure

Background

5-fluorouracil is a pyrimidine analogue acting as an antimetabolite to uracil. It is indicated intravenously for the treatment of gastrointestinal neoplasm malignant, head and neck cancer, epidermoid carcinoma, breast carcinoma/adenocarcinoma, malignant respiratory tract neoplasm, liver tumour, cervix carcinoma, bladder carcinoma, ovarian carcinoma/adenocarcinoma, prostatic carcinoma and uterine carcinoma under certain conditions.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing 5-fluorouracil for intravenous (IV) use 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 5-fluorouracil-containing medicinal product(s) for IV use in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to revise the existing warning on cardiotoxicity and to add stress cardiomyopathy (Takotsubo syndrome) as an undesirable effect with a frequency 'not known'. The existing warning on encephalopathies should be also revised and posterior reversible encephalopathy syndrome (PRES) and lactic acidosis added as undesirable effects with a frequency 'not known'. In addition, the product information should be updated to add tumour lysis syndrome (TLS) as a warning and as an undesirable effect with a frequency 'not known'. Finally, cutaneous lupus erythematosus and pneumatosis intestinalis should be added as undesirable effects with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied²⁹.
- In the next PSUR, the MAH(s) should further monitor literature concerning screening methods for dihydropyrimidine dehydrogenase (DPD) deficiency and treatment of DPD deficient patients. In addition, the MAH(s) should include cumulative reviews of 5-fluorouracil, vitamin B1 deficiency and Wernicke's encephalopathy, of cholangitis, of cardiac tamponade and pericardial effusion and of colitis, including neutropenic colitis. The MAH(s) should propose to update the product information as warranted.

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

6.3.2. Allopurinol (NAP) - PSUSA/00000095/202012

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

²⁹ Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position

Allopurinol is a xanthine-oxidase inhibitor indicated for the treatment of gout, primary and secondary hyperuricemia and resulting diseases, for reducing urate/uric acid formation in conditions where urate/uric acid deposition has already occurred or is a predictable clinical risk.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing allopurinol 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 allopurinol-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add information on introduction of allopurinol at low dosage to reduce the risk of adverse drug reactions. In addition, diarrhoea and aseptic meningitis should be added as undesirable effects with a frequency 'uncommon' and 'not known' respectively. Therefore, the current terms of the marketing authorisation(s) should be varied³⁰.
- In the next PSUR, the MAH(s) should include cumulative reviews of cases of lichenoid reactions and lichen planus, of precancerous skin lesions, of drug-drug interactions with azathioprine and related severe adverse drug reactions as well as of ichthyosis. The MAH Aspen should add cumulative reviews of cases of glomerulonephritis and of suspected overdose. The MAH Ace should provide a cumulative review of cases of diarrhoea associated with parenteral formulations.

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. Amiodarone (NAP) - PSUSA/00000166/202012

Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

Background

Amiodarone is an antiarrhythmic agent indicated orally for the prevention of recurrence of life-threatening ventricular tachycardia or ventricular fibrillation, symptomatic and disabling documented ventricular tachycardia and for documented supraventricular tachycardia, when the necessity of a treatment is established and in case of resistance or contraindication to other therapeutics. It is also indicated orally for the treatment of documented supraventricular tachycardia to slow down or reduce atrial fibrillation or atrial flutter and for the prevention of arrhythmic death in patients at high risk because of either symptomatic congestive heart failure or recent myocardial infarction, associated with a low ejection fraction or asymptomatic premature ventricular contractions. Intravenously, amiodarone is indicated when a rapid therapeutic response is required or when oral administration is not possible for the treatment of severe heart rhythm disorders, especially supraventricular

³⁰ Update of SmPC sections 4.2 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position

rhythm disorders with fast ventricular rate, tachycardia associated with Wolff-Parkinson-White syndrome and documented symptomatic and disabling ventricular rhythm disorders.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing amiodarone 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 amiodarone-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add the interaction between amiodarone and sirolimus. Hallucination, neutropenia and agranulocytosis should be also added as undesirable effects with a frequency 'not known' and libido decreased with a frequency 'common'. Therefore, the current terms of the marketing authorisation(s) should be varied³¹.

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

6.3.4. Amitriptyline (NAP); amitriptyline, amitriptylinoxide (NAP); amitriptylinoxide (NAP) - PSUSA/00010374/202101

Applicant(s): various

PRAC Lead: Agni Kapou

Scope: Evaluation of a PSUSA procedure

Background

Amitriptyline and amitriptylinoxide are tricyclic antidepressants. Alone or in combination, amitriptyline and amitriptyline/amitriptylinoxide are indicated for the treatment of major depressive disorder in adults, treatment of neuropathic pain in adults, prophylactic treatment of chronic tension type headache (CTTH) in adults, prophylactic treatment of migraine in adults and for the treatment of nocturnal enuresis in children aged 6 years and above. Amitriptylinoxide alone is indicated for the treatment of depressive illnesses under certain conditions.

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

³¹ Update of SmPC sections 4.5 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position

- Nevertheless, the product information should be updated to include interaction between amitriptyline, amitriptylinoxide and duloxetine and to update the existing warnings on overdose in children and on Brugada syndrome. Therefore, the current terms of the marketing authorisation(s) should be varied³².
- In the next PSUR, the MAH(s) should provide detailed reviews of cases of serotonin syndrome, dementia, autism spectrum disorder and attention deficit hyperactivity disorder, type 2 diabetes dysregulation and new onset diabetes, pregnancy, lactation and congenital malformations, drug reaction with eosinophilia and systemic symptoms (DRESS), rhabdomyolysis, kidney injury/renal failure, purpura, porphyri, encephalopathy, interaction with warfarin as well as interaction between anticholinergic drugs (amitriptyline) and acetylcholinesterase inhibitors (AChEI).

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.

PRAC considered that the additional signs and symptoms of paediatric intoxication, interaction with duloxetine and Brugada syndrome are also relevant for medicinal product(s) containing amitriptyline/perphenazine and other fixed dose combination(s) containing amitriptyline. Further consideration is to be given at CMDh.

6.3.5. Amitriptyline, perphenazine (NAP) - PSUSA/00000170/202101

Applicant(s): various

PRAC Lead: Agni Kapou

Scope: Evaluation of a PSUSA procedure

Background

Amitriptyline is a tricyclic antidepressant and perphenazine a piperazine derivative of phenothiazide. In combination, amitriptyline/perphenazine is indicated for the treatment of moderate to severe anxiety and/or agitation and depressed mood, in patients with depression in whom anxiety and/or agitation are moderate or severe, in patients with anxiety and depression associated with chronic physical disease, in patients in whom depression and anxiety cannot be clearly differentiated, neurotic conditions accompanying by mental or neurological diseases, depressive conditions in alcoholism or drug addiction as well as for the treatment of atypical depressive conditions in schizophrenic patients.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing amitriptyline/perphenazine 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 amitriptyline/perphenazine-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include interaction between amitriptyline/perphenazine and duloxetine and to update the existing warnings on

³² Update of SmPC sections 4.5 and 4.9. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position

overdose in children and on Brugada syndrome. Therefore, the current terms of the marketing authorisation(s) should be varied³³.

- In the next PSUR, the MAH(s) should provide detailed reviews of cases of serotonin syndrome, dementia, type 2 diabetes dysregulation and new onset diabetes, pregnancy, lactation and congenital malformations, autonomic dysreflexia, drug reaction with eosinophilia and systemic symptoms (DRESS) and hypersensitivity, drug-induced liver injury (DILI), insomnia, somnolence, tardive dyskinesia, overdose, use in paediatrics and adolescents/children intoxication, respiratory arrest with amitriptyline overdose, use in patients with pheochromocytoma and movement disorders.

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.

PRAC considered that the additional signs and symptoms of paediatric intoxication, interaction with duloxetine and Brugada syndrome are also relevant for medicinal product(s) containing amitriptyline in other fixed dose combination(s). Further consideration is to be given at CMDh.

6.3.6. Betamethasone (NAP) - PSUSA/00000391/202101

Applicant(s): various

PRAC Lead: Ronan Grimes

Scope: Evaluation of a PSUSA procedure

Background

Betamethasone is a corticosteroid indicated as an adjunct to conventional therapy in the management of various musculoskeletal/rheumatic, collagen, dermatologic disorders and allergic and hypersensitivity reactions known to be responsive to corticosteroid therapy.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing betamethasone 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 betamethasone-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add a warning on pheochromocytoma crisis for betamethasone for systemic use. In addition, a warning on neonatal hypoglycaemia should be added to the product information for betamethasone for parenteral use. Therefore, the current terms of the marketing authorisation(s) should be varied³⁴.

³³ Update of SmPC sections 4.5 and 4.9. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position

³⁴ Update of SmPC sections 4.4 and 4.6. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to 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.

6.3.7. Carbamazepine (NAP) - PSUSA/00000539/202012

Applicant(s): various

PRAC Lead: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

Background

Carbamazepine is an antiepileptic, neurotropic and psychotropic agent. It is indicated for the treatment of epilepsy, alcohol withdrawal syndrome, idiopathic trigeminal neuralgia and trigeminal neuralgia due to multiple sclerosis and idiopathic glossopharyngeal neuralgia. It is also indicated for the treatment of painful diabetic neuropathy, diabetes insipidus centralis, polyuria and polydipsia of neurohormonal origin.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing carbamazepine 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 carbamazepine-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to reflect the interaction between carbamazepine and brivaracetam and to include warnings and recommendations on use during pregnancy and in women of childbearing potential. In addition, hyperammonaemia should be added as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied³⁵.
- In the next PSUR, the MAH for the originator carbamazepine-containing product(s) should include a review on the risk of transient splenic lesions after withdrawal of carbamazepine.

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

6.3.8. Cefoperazone (NAP) - PSUSA/00000597/202101

Applicant(s): various

PRAC Lead: Rugilė Pilvinienė

Scope: Evaluation of a PSUSA procedure

Background

³⁵ Update of SmPC sections 4.4, 4.5, 4.6 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position

Cefoperazone is a semisynthetic third-generation cephalosporin antibiotic indicated for the treatment of respiratory tract infections, urinary tract infections, peritonitis, cholecystitis, cholangitis and other intra-abdominal infections, septicaemia, meningitis, skin and soft tissue infections, infections of bones and joints, pelvic inflammatory disease, endometritis, gonorrhoea and other infections of the genital tract, caused by susceptible organisms. Cefoperazone sodium is also indicated in the prophylaxis of post-operative infection in patients undergoing abdominal and gynaecological surgery, cardiovascular and orthopaedic surgery under certain conditions.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing cefoperazone 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 cefoperazone-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add haematuria as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied³⁶.
- In the next PSUR, the MAH should further monitor any new information relating to antimicrobial resistance.

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.

6.3.9. Hydrochlorothiazide, spironolactone (NAP) - PSUSA/00001662/202101

Applicant(s): various

PRAC Lead: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

Background

Hydrochlorothiazide is a diuretic and spironolactone an anti-mineralo-corticoid. In combination, hydrochlorothiazide/spironolactone is indicated for the treatment of oedema in patients with congestive heart failure, hepatic cirrhosis with oedema and/or ascites and nephrotic syndrome.

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

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

- Nevertheless, the product information should be updated to add a warning on acute respiratory toxicity. In addition, acute respiratory distress syndrome (ARDS) should be added as an undesirable effect with a frequency 'very rare'. Therefore, the current terms of the marketing authorisation(s) should be varied³⁷.
- In the next PSUR, the MAH(s) should monitor cases of loss of libido, vestibulodynia and dyspareunia associated with spironolactone use in female patients.

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

PRAC considered that the risk of ARDS is also relevant for medicinal product(s) containing hydrochlorothiazide as a single agent and in fixed dose combination(s) other than hydrochlorothiazide/spironolactone. Further consideration is to be given at CMDh.

6.4. Follow-up to PSUR/PSUSA procedures

See Annex I 16.4.

6.5. Variation procedure(s) resulting from PSUSA evaluation

See also Annex I 16.5.

6.5.1. Coronavirus (COVID-19) vaccine (Ad26.COV2-S, recombinant) - COVID-19 VACCINE JANSSEN (CAP) - EMEA/H/C/005737/II/0014

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of section 4.8 of the SmPC to include lymphadenopathy, paraesthesia, hypoesthesia, diarrhea, vomiting and tinnitus as adverse drug reactions (ADRs) as per the conclusions of post-authorisation measure MEA 014.2 (monthly summary safety report (MSSR)) finalised in July 2021. In addition, the MAH took the opportunity to add editorial changes in sections 6.4 and 6.6 of the SmPC in line with the WHO³⁸ recommendation. Finally, Annex III-A on Labelling is updated to increase readability

Background

COVID-19 vaccine (Ad26.COV2-S [recombinant]) is a monovalent vaccine composed of a recombinant, replication-incompetent human adenovirus type 26 vector that encodes a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) full-length spike (S) glycoprotein indicated as COVID-19 vaccine Janssen, a centrally authorised vaccine for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older.

Following the evaluation of a recently submitted monthly summary safety report (MSSR) finalised in July 2021 for the above-mentioned medicine(s), PRAC requested the MAH to submit variations to update the product information in line with the conclusions of previous MSSR procedures. For background information, see [PRAC minutes July 2021](#). PRAC is responsible for adopting an outcome based on the assessment report from the PRAC

³⁷ Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position

³⁸ World Health Organization

Rapporteur, to be further considered at the level of CHMP, responsible for adopting an opinion on this variation.

Summary of advice/conclusion(s)

- Based on the available data and the Rapporteur's assessment, PRAC agreed to amend³⁹ the product information to add diarrhoea and paraesthesia as undesirable effects with a frequency 'uncommon' as well as lymphadenopathy, vomiting, hypoesthesia and tinnitus with a frequency 'rare'.

6.6. Expedited summary safety reviews⁴⁰

6.6.1. Coronavirus (COVID-19) mRNA⁴¹ vaccine (nucleoside-modified) - COMIRNATY (CAP) - EMEA/H/C/005735/MEA 002.7

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

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

Background

Nucleoside-modified messenger ribonucleic acid (mRNA) vaccine is indicated, as Comirnaty, for active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in people aged 12 years and older.

PRAC assessed the eighth monthly summary safety report (MSSR) for Comirnaty (COVID-19 mRNA vaccine (nucleoside-modified)) as part of the safety monitoring of the vaccine. At the plenary meeting, PRAC adopted its conclusions.

Summary of advice/conclusion(s)

- In the next MSSR⁴², the MAH should provide cumulative reviews and data. The MAH should provide cumulative reviews of cases of paraesthesia and hypoaesthesia, rhabdomyolysis and rheumatoid arthritis as well as a refined observed/expected (O/E) analysis of cases of thromboembolic events. Moreover, the MAH should include cumulative reviews of cases of myasthenia gravis, Guillain-Barré syndrome (GBS), acute disseminated encephalomyelitis (ADEM), haemorrhagic and ischaemic stroke, capillary leak syndrome, herpes zoster and appendicitis. The MAH should investigate the potential mechanism for each topic and propose to update the product information and/or RMP as warranted. Regarding menstrual disorders or post-menopausal haemorrhages, the MAH should provide an updated analysis. Finally, the MAH should discuss the publication by *Koh et al.*⁴³ on neuralgic amyotrophy.

³⁹ Update of SmPC section 4.8. The package leaflet is updated accordingly

⁴⁰ Submission of expedited summary safety reports for review in addition to the requirements for submission of PSUR(s) falling within the pandemic period and requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC

⁴¹ Messenger ribonucleic acid

⁴² Submission date on 15 September 2021

⁴³ Koh et al., Neuralgic amyotrophy following COVID-19 mRNA vaccination, doi: 10.1093/qjmed/hcab216

6.6.2. Coronavirus (COVID-19) mRNA⁴⁴ vaccine (nucleoside-modified) - SPIKEVAX (CAP) - EMEA/H/C/005791/MEA 011.6

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Hans Christian Siersted

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

Background

COVID-19 nucleoside-modified messenger ribonucleic acid (mRNA) vaccine is indicated, as Spikevax, for active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 12 years of age and older.

PRAC assessed the seventh monthly summary safety report (MSSR) for Spikevax (COVID-19 mRNA vaccine (nucleoside-modified)) as part of the safety monitoring of the vaccine. At the plenary meeting, PRAC adopted its conclusions.

Summary of advice/conclusion(s)

- In the next MSSR⁴⁵, the MAH should provide cumulative reviews and data. The MAH should include a cumulative review of cases of acute disseminated encephalomyelitis (ADEM), including a review of cases of encephalitis as well as a detailed review of cases of Guillain-Barré syndrome (GBS). The MAH should also provide cumulative reviews of cases of thrombosis with thrombocytopenia syndrome (TTS), transverse myelitis. In addition, an overview of fatal cases with/without vaccine failure should be included. Furthermore, the MAH should include reviews of cases of neuralgic amyotrophy and rheumatoid arthritis flare up as well as a review of any new cases on capillary leak syndrome (CLS) including cases of capillary permeability increased. Finally, the MAH should include cumulative reviews of rhabdomyolysis, menstrual disorder or post-menopausal haemorrhage and herpes zoster.

6.6.3. Coronavirus (COVID-19) vaccine (Ad26.COVID-19-S, recombinant) - COVID-19 VACCINE JANSSEN (CAP) - EMEA/H/C/005737/MEA 014.4

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Fifth expedited monthly summary safety report (MSSR) for COVID-19 Vaccine Janssen (COVID-19 vaccine (Ad26.COVID-19-S, recombinant)) during the coronavirus disease (COVID-19) pandemic

Background

COVID-19 vaccine (Ad26.COVID-19-S [recombinant]) is a monovalent vaccine composed of a recombinant, replication-incompetent human adenovirus type 26 vector that encodes a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) full-length spike (S) glycoprotein indicated as COVID-19 vaccine Janssen, a centrally authorised vaccine for active

⁴⁴ Messenger ribonucleic acid

⁴⁵ Submission date on 15 September 2021

immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older.

PRAC assessed the fifth monthly summary safety report (MSSR) for COVID-19 vaccine Janssen (COVID-19 vaccine (Ad26.COVID-19-S, recombinant)) as part of the safety monitoring of the vaccine. At the plenary meeting, PRAC adopted its conclusions.

Summary of advice/conclusion(s)

- The MAH should submit to EMA, within 7 days, further data from ongoing clinical trials, namely study COV3009⁴⁶ and study COV3001⁴⁷, with respect to venous thromboembolism (VTE). The MAH should also provide an in-depth discussion on the overall potential for a causal relationship between the vaccine and VTE and propose to update the product information and/or the RMP as warranted.
- In the next MSSR⁴⁸, the MAH should provide cumulative reviews and data. The MAH should include cumulative reviews of tinnitus, inflammatory cardiac conditions including myocarditis and pericarditis, transverse myelitis, menstrual disorder or post-menopausal haemorrhage and acute kidney injury. The MAH should also provide observed/expected (O/E) analysis for cases of blindness. Regarding hepatic disorders, the MAH should include a causality assessment together with a proposal to update the product information and/or RMP as warranted.
- In the following MSSR⁴⁹, the MAH should provide a cumulative review of cases of encephalitis including acute disseminated encephalomyelitis (ADEM) together with a proposal to update the product information and/or RMP as warranted.
- In the next PSUR, the MAH should provide a detailed review of cases of blindness, the outcome of the pregnancies in women that have been exposed to the vaccine during pregnancy. In addition, the MAH should include a review of cases reporting vaccination failure together with information on variants of SARS-CoV-2 where relevant.

6.6.4. Coronavirus (COVID-19) vaccine (ChAdOx1-S [recombinant]) - VAXZEVRIA (CAP) - EMEA/H/C/005675/MEA 027.5

Applicant: AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: Sixth expedited monthly summary safety report (MSSR) for Vaxzevria (COVID-19 vaccine (ChAdOx1-S [recombinant])) during the coronavirus disease (COVID-19) pandemic

Background

Coronavirus (COVID-19) vaccine (ChAdOx1-S [recombinant]) is a monovalent vaccine composed of a single recombinant, replication-deficient chimpanzee adenovirus (ChAdOx1) vector encoding the S glycoprotein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) indicated, as Vaxzevria, a centrally authorised vaccine, for active

⁴⁶ Study COV3009: a randomized, double-blind, placebo-controlled phase 3 study to assess the efficacy and safety of Ad26.COVID-19-S (COVID-19 Vaccine Janssen) for the prevention of SARS-CoV-2-mediated COVID-19 in adults aged 18 years and older

⁴⁷ Study COV3001: a randomized, double-blind, placebo-controlled phase 3 study to assess the efficacy and safety of Ad26.COVID-19-S for the prevention of SARS-CoV-2-mediated COVID-19 in adults aged 18 years and older

⁴⁸ Submission date on 15 September 2021

⁴⁹ Submission date on 15 October 2021

immunisation to prevent COVID-19 caused by SARS-CoV-2, in individuals 18 years of age and older.

PRAC assessed the sixth monthly summary safety report (MSSR) for Vaxzevria (COVID-19 vaccine (ChAdOx1-S [recombinant])) as part of the safety monitoring of the vaccine. At the plenary meeting, PRAC adopted its conclusions.

Summary of advice/conclusion(s)

- The MAH should submit to EMA, within 7 days, a variation⁵⁰ to refine the warning relating to thrombosis with thrombocytopenia (TTS).
- The MAH should submit to EMA, within 7 days, a variation⁵¹ to add Guillain-Barré syndrome (GBS) to the product information as an undesirable effect with a frequency 'very rare'. The RMP should be updated to include GBS as an important identified risk.
- In the next MSSR⁵², the MAH should provide cumulative reviews and data. The MAH should provide a detailed review of cases of disseminated intravascular coagulation (DIC). The MAH should also include reviews of cases of thrombosis including cerebral venous sinus thrombosis (CVST) without thrombocytopenia. In addition, the MAH should provide an updated review of cases of myocarditis and pericarditis, a detailed review of cases of acute macular outer retinopathy (AMOR) as well as an updated review relating to menstrual disorders.
- In the next PSUR, the MAH should discuss hypotheses for a mechanism leading to GBS following vaccination, including a synergistic or triggering role of vaccination in patients with comorbidities.

7. Post-authorisation safety studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)⁵³

See also Annex I 17.1.

7.1.1. Cidofovir (NAP) - EMEA/H/N/PSA/S/0058.2

Applicant: Tillomed Laboratories Ltd. (Cidofovir Emcure Pharma)

PRAC Rapporteur: Rugile Pilviniene

Scope: MAH's response to PSA/S/0058.1 [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] as per the request for supplementary information (RSI) adopted in May 2021

Background

⁵⁰ SmPC section 4.4. The package leaflet is to be updated accordingly

⁵¹ SmPC section 4.8. The package leaflet is to be updated accordingly

⁵² Submission date on 15 September 2021

⁵³ In accordance with Article 107n of Directive 2001/83/EC

Cidofovir is an antiviral for systemic use indicated for the treatment of cytomegalovirus (CMV) retinitis in adults with acquired immunodeficiency syndrome (AIDS) and without renal dysfunction.

The MAH for Cidofovir Emcure Pharma (cidofovir) submitted to EMA a substantial amendment to a protocol previously agreed in November 2018 for an exposure registry study to further elucidate the characteristics of the different patient populations for cidofovir use and gather details of adverse events and patient outcome following treatment in a specified indication. The study was imposed to the MAH to address the identified important potential risk of off-label use including intraocular administration. For further background, see [PRAC minutes November 2018](#)⁵⁴, [PRAC minutes October 2020](#) and [PRAC minutes May 2021](#). PRAC is responsible for evaluating the substantial amendment to the PASS protocol together with the MAH's response to a second request for supplementary for information (RSI).

Endorsement/Refusal of the protocol

- Having considered protocol version 2.0 in accordance with Article 107o of Directive 2001/83/EC, PRAC confirmed that the study is non-interventional and the substantial amendments to the PASS protocol are endorsed.

7.1.2. Levonorgestrel (NAP) - EMEA/H/N/PSA/S/0073

Applicant: Bayer Pharma AG (Jaydess, Luadei)

PRAC Rapporteur: Annika Folin

Scope: Substantial amendment to a protocol previously agreed in November 2019 (PSA/S/0044) for study EURAS-LCS12: a European active surveillance study of LCS-12 (levonorgestrel intrauterine contraceptive system releasing 12 µg levonorgestrel/24h in vitro), an intra-uterine device (IUD) for Jaydess and Luadei (levonorgestrel) to investigate whether LCS-12 is associated with an increased risk of unintended pregnancy compared to Mirena (levonorgestrel-releasing intrauterine system) and to copper IUDs

Background

Levonorgestrel is a progestogen indicated as an intrauterine delivery system for contraception for a period up to three years.

Study EURAS-LCS12 was imposed as part of the conditions to the marketing authorisation(s) for Jaydess/Luadei (levonorgestrel) in order to further investigate whether there are differences in unintended pregnancy rates with levonorgestrel intrauterine contraceptive system (LCS12) compared to copper intra-uterine device (IUD) and other levonorgestrel-containing IUD.

The MAH for Jaydess/Luadei (levonorgestrel) submitted to EMA a substantial amendment to a protocol previously agreed in November 2019 for study EURAS-LCS12. PRAC is responsible for evaluating the substantial amendment to the PASS protocol. For further background, see [PRAC minutes November 2019](#)⁵⁵.

Endorsement/Refusal of the protocol

⁵⁴ Held 29-31 October 2018

⁵⁵ Held 28-31 October 2019

- Having considered protocol version 4.0 in accordance with Article 107o of Directive 2001/83/EC, PRAC objected to the draft protocol for the above-listed medicinal product(s). PRAC agreed that the PASS is non-interventional, but the study design does not fulfil the study objectives at this stage.
- PRAC considered that the MAH should discuss the possibility to limit recruitment into the copper IUDs cohort. In the context of the new proposed analysis method, the MAH should also provide further justifications relating to well-established risk factors.
- The MAH should submit a revised PASS protocol within 60 days to EMA. A 60 day-assessment timetable will be followed.

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

See Annex I 17.2.

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

See also Annex I 17.3.

7.3.1. Aprotinin (NAP) - EMEA/H/N/PSR/S/0030

Applicant: Nordic Group BV (Trasylol)

PRAC Rapporteur: Laurence de Fays

Scope: MAH's response to PSR/S/0030 [results for a Nordic aprotinin patient registry to record utilisation information on patients at cardiac surgery centres] as per the request for supplementary information (RSI) adopted in April 2021

Background

Aprotinin is an antifibrinolytic indicated for the prevention of excessive blood loss under certain conditions.

Further to the conclusions dated 2013 of the referral procedure under Article 31 of Directive 2001/83/EC (EMEA/H/A-1267) for antifibrinolytics containing aprotinin, aminocaproic acid and tranexamic acid, the MAH for Trasylol (aprotinin) was required to conduct a registry, in order to monitor the pattern of use of aprotinin.

In line with the conclusions reached in 2013 of the referral procedure under Article 31 of Directive 2001/83/EC (EMEA/H/A-1267) conducted by CHMP for antifibrinolytics containing aprotinin, aminocaproic acid and tranexamic acid, the MAH for Trasylol (aprotinin) was required to conduct a registry in order to monitor the pattern of use of aprotinin.

The MAH for Trasylol (aprotinin) submitted to EMA the final results of the study entitled: 'Nordic Aprotinin Patient Registry (NAPaR): a multicentre, non-interventional PASS with active surveillance via patient exposure registry' enrolling patients undergoing cardiac surgery on cardiopulmonary bypass and exposed to aprotinin at all centres in EU. PRAC is responsible for issuing a recommendation on the final study results including the assessment

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

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

of the MAH's response to a request for supplementary information (RSI) adopted in April 2021. For background, see [PRAC minutes April 2021](#).

Summary of recommendation(s) and conclusions

- Based on the review of the final report of the registry study, the MAH's response to the RSI and the assessment from the Rapporteur, PRAC considered that a further RSI was necessary before a final recommendation could be issued.
- The MAH should further discuss the need of risk minimisation measures and/or pharmacovigilance activities to limit off-label use of aprotinin in patients in whom a positive benefit-risk balance of aprotinin has not been established. In addition, the MAH should propose to update the product information as warranted.
- The MAH should submit responses to the RSI within 60 days to EMA. A 60 day-assessment timetable will be followed.

7.3.2. Iron^{58 59} (NAP) - EMEA/H/N/PSR/J/0026

Applicant(s): Mesama Consulting (on behalf of a consortium) (CosmoFer, Diafer, Fer Arrow Ferinject, FerMed, Fer Mylan, Fer Panpharma, Ferracin, Ferrisat, Ferrlecit, Fer Sandoz, IJzerhydroxide saccharose complex Teva, Järnsackaros Rechon, Monofer, Venofer)

PRAC Rapporteur: Tiphaine Vaillant

Scope: MAH's response to PSR/J/0026 [results of 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 (IV) iron-containing medicines in 2013] as per the request for supplementary information (RSI) adopted in March 2021

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 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.

The MAH (on behalf of a consortium) submitted to EMA the final study report for assessment by the Rapporteur. PRAC is responsible for issuing a recommendation on the final study results including the assessment of the MAH's response to the third request for supplementary information (RSI) adopted in March 2021. For background, see [PRAC minutes July 2020](#), [PRAC minutes October 2020](#)⁶⁰ and [PRAC minutes March 2021](#).

Summary of recommendation(s) and conclusions

⁵⁸ Intravenous (IV)

⁵⁹ Iron (III)-hydroxide dextran complex, iron sucrose complex/iron(III)-hydroxide sucrose complex, ferric carboxymaltose complex, iron(III) isomaltoside complex, sodium ferric gluconate complex

⁶⁰ Held 28 September – 01 October 2020

- Based on the review of the final report of the PASS version 1.1, the MAH's responses to the RSI and the assessment from the Rapporteur, PRAC agreed that further investigation on anaphylaxis is not feasible in the framework of the PASS procedure at this stage. The obligation to perform the PASS is considered fulfilled. PRAC concluded that routine pharmacovigilance is appropriate to monitor the risk of hypersensitivity and closely monitored in future PSURs.
- PRAC recommended to vary the terms of the marketing authorisation(s) by removing the study from the conditions with regard to the safe and effective use of the medicinal product to be implemented by the Member States. PRAC concluded that there is no need to change the risk minimisation measures in place in light of the current evidence.

7.3.3. Lisdexamfetamine dimesylate (NAP) - EMEA/H/N/PSR/S/0033

Applicant(s): Shire Pharmaceuticals Ireland Limited (Elvanse Adult)

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Results of study SPD489-825 to evaluate the long-term cardiovascular safety of lisdexamfetamine (LDX) in adults in order to estimate in real-world settings the incidence rate and the adjusted incidence rate ratios of the composite major adverse cardiovascular events (MACE) endpoint in a cohort of adult patients who are current new users of LDX (LDX cohort) as compared with a cohort of remote users of other attention-deficit hyperactivity disorder (ADHD) treatments

Background

Lisdexamfetamine dimesylate is a therapeutically inactive amphetamine prodrug indicated for the treatment of attention-deficit/hyperactivity disorder (ADHD) in adult patients.

At the time of the initial marketing authorisation(s) of Elvanse Adult (lisdexamfetamine dimesylate), a cohort study of incidence of major adverse cardiovascular events (MACE) in new adult users of lisdexamfetamine and remote adult users of other ADHD treatments was imposed to the MAH.

The MAH for of Elvanse Adult (lisdexamfetamine dimesylate) submitted to EMA the final report for study SPD489-825: a long-term study using Danish and Swedish national registers to evaluate cardiovascular safety of lisdexamfetamine in adults in order to estimate in real-world settings the incidence rate and the adjusted incidence rate ratios of the composite MACE endpoint in a cohort of adult patients who are current new users of lisdexamfetamine as compared with a cohort of remote users of other ADHD treatments for assessment by the Rapporteur. PRAC is responsible for issuing a recommendation on the final study results.

Summary of recommendation(s) and conclusions

- Based on the review of the final report of the PASS version 1.0 and the assessment from the Rapporteur, PRAC agreed that the risk-benefit balance of medicinal product(s) containing lisdexamfetamine dimesylate concerned by the PASS final report remains unchanged. The contraindications and warnings currently in place concerning the cardiovascular risk remain relevant. The obligation to perform the PASS is considered fulfilled.
- The MAH should update the RMP accordingly at the next regulatory opportunity. Long-term safety relating to cardiovascular and cerebrovascular effects in adults should be retained as missing information in the RMP summary of safety concerns.

7.4. Results of PASS non-imposed in the marketing authorisation(s)⁶¹

See Annex I 17.4.

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

See Annex I 17.5.

7.6. Others

See Annex I 17.6.

7.7. New Scientific Advice

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

7.8. Ongoing Scientific Advice

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

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

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

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

8.1. Annual reassessments of the marketing authorisation

See Annex I 18.1.

8.2. Conditional renewals of the marketing authorisation

See Annex I 18.2.

8.3. Renewals of the marketing authorisation

See Annex I 18.3.

9. Product related pharmacovigilance inspections

9.1. List of planned pharmacovigilance inspections

None

⁶¹ In accordance with Article 61a (6) of Regulation (EC) No 726/2004, in line with the revised variations regulation for any submission as of 04 August 2013

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 CHMP or EMA

10.1. Safety related variations of the marketing authorisation

None

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

None

10.3. Other requests

10.3.1. Coronavirus (COVID-19) vaccine (ChAdOx1-S [recombinant]) - VAXZEVRIA (CAP) - EMEA/H/A-5(3)/1507

Applicant: AstraZeneca AB

PRAC Lead: Jean-Michel Dogné, Brigitte Keller-Stanislawski

Scope: PRAC consultation on possible further characterisation of the risk of thrombosis with thrombocytopenia syndrome (TTS) considering the results of the study 'natural history of coagulopathy and use of anti-thrombotic agents in patients and persons vaccinated against SARS-COV-2' (EUPAS40414) in the context of the ongoing procedure under Article 5(3) of Regulation (EC) No 726/2004, on request of CHMP

Background

Coronavirus (COVID-19) vaccine (ChAdOx1-S [recombinant]) is a monovalent vaccine composed of a single recombinant, replication-deficient chimpanzee adenovirus (ChAdOx1) vector encoding the S glycoprotein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) indicated, as Vaxzevria, a centrally authorised vaccine, for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in individuals 18 years of age and older.

Following the conclusion of a possible link between Vaxzevria (COVID-19 vaccine (ChAdOx1-S [recombinant])) and thrombosis in combination with thrombocytopenia (TTS) (for background, see [PRAC minutes April 2021](#)), the European Commission (EC) triggered a procedure under Article 5(3) of Regulation (EC) No 726/2004, and requested EMA to perform a further analysis and stratification of data to better characterise the benefit-risk of Vaxzevria (COVID-19 vaccine (ChAdOx1-S [recombinant])) in different age groups and/or sex as well as possible other risk factors that could be identified.

In the context of this procedure, CHMP requested PRAC to provide advice.

Summary of advice

- Having considered the progress report of study on 'natural history of coagulopathy and use of anti-thrombotic agents in patients and persons vaccinated against SARS-COV-2', PRAC considered that the data do not provide any new information at this stage to further characterise the risk of TTS following administration of Vaxzevria (COVID-19 vaccine (ChAdOx1-S [recombinant])) according to age groups or gender, or to identify risk factors. The MAH should conduct further characterisation of the risk of TTS as part of routine pharmacovigilance activities and in PASS as described in the RMP.

10.4. Scientific Advice

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

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

11.1. Safety related variations of the marketing authorisation

11.1.1. Azathioprine (NAP) - DK/H/0843/001/II/021, DK/H/0843/001/II/023

Applicant: Ebewe Pharma Ges.m.b.H (Azathioprin Ebewe 50 mg film-coated tablets)

PRAC Lead: Hans Christian Siersted

Scope: PRAC consultation on national variations proposing to update the product information on concomitant use of intrauterine devices (IUDs) and azathioprine therapy, on request of Denmark

Background

Azathioprine is an immunosuppressive agent indicated alone or in combination with other immunosuppressive agents for prophylaxis of organ transplant rejection, severe active rheumatoid arthritis, severe or moderately severe inflammatory intestinal disease (Crohn's disease or ulcerative colitis), systemic lupus erythematosus, dermatomyositis and polymyositis, auto-immune chronic active hepatitis, polyarteritis nodosa, auto-immune haemolytic anaemia and chronic refractory idiopathic thrombocytopenic purpura.

In the context of ongoing type II variation procedures evaluating proposals to update the product information on concomitant use of intrauterine devices (IUDs) and azathioprine therapy, Denmark as reference Member State (RMS) for the medicinal product, requested PRAC advice on its assessment.

Summary of advice

- Based on the review of the available information and evidence, PRAC agreed that data is scarce, and literature findings and clinical practice guidelines are conflicting. PRAC supported the RMS that the proposed wording is not suitable for inclusion in the product

information. PRAC advised to explore this concomitant use of IUDs and azathioprine therapy in the next PSUR⁶².

11.2. Other requests

None

12. Organisational, regulatory and methodological matters

12.1. Mandate and organisation of PRAC

12.1.1. Mandate of PRAC Vice-Chairperson - prolongation

In line with Article 3⁶³ of the Rules of Procedure of PRAC ([EMA/PRAC/567515/2012 Rev.3](#)), and following confirmation of the current vice-Chair's interest in prolonging his mandate, PRAC voted to prolong, for a further three years, the mandate of Martin Huber as a vice-Chair. 29 members voted in favour of the prolongation out of 31 cast votes. His mandate will start as of September 2021.

12.1.2. PRAC Rules of Procedure - revision

The EMA Secretariat presented to PRAC a revision of the PRAC rules of procedure (RoP) in order to reflect the proposal to relaunch face-to-face (F2F) committee meetings as part of a pilot as well as the possibility to hold Committee meetings in hybrid setting in emergency situations. PRAC adopted the revised RoP. See also 12.1.3.

Post-meeting note: PRAC RoP revision 3 were published on the EMA website on 15 October 2021 ([EMA/PRAC/567515/2012 Rev.3](#)).

12.1.3. Relaunch of face-to-face scientific Committee meetings - pilot

The EMA Secretariat presented to PRAC a pilot to relaunch face-to-face scientific Committee meetings from the end of October 2021 alternating on-site meetings with remote meetings. The current plan is to hold the November 2021⁶⁴ PRAC meeting as a face-to-face meeting. The pilot will be dependent on the current coronavirus (COVID-19) situation. Further updates and instructions will be given in due course.

12.2. Coordination with EMA Scientific Committees or CMDh-v

12.2.1. Advanced therapy medicinal products (ATMP) - Evaluation and grading of neurotoxicities for chimeric antigen receptor-T (CAR-T) cells ATMPs - proposal

The EMA Secretariat presented to PRAC a draft document entitled 'EMA recommendation on the evaluation and grading of neurotoxicity for chimeric antigen receptor-T (CAR-T) cells advanced therapy medicinal products (ATMP)'. This was preliminary discussed on immune effector-associated neurotoxicity syndromes (ICANS) at CAT in July 2021 showing interest

⁶² Data lock point (DLP): December 2024

⁶³ The Chair and Vice-Chair of PRAC shall be elected by and from amongst its members for a term of three years, which may be prolonged once

⁶⁴ Held 25-28 October 2021

of using this grading system for regulatory purpose. PRAC was invited to provide written comments by 08 September 2021.

Post-meeting note: the EMA recommendation on the evaluation and grading of neurotoxicity for CAR-T cells ATMPs was adopted by PRAC by written adopted on 08 September 2021. Further discussion will be held at CAT.

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 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.

12.4.2. PRAC strategic review and learning meeting (SRLM) under the Slovenian presidency of the European Union (EU) Council – Remote meeting, 22 September 2021 - agenda

PRAC lead: Polona Golmajer

At the organisational, regulatory and methodological matters (ORGAM) meeting on 16 September 2021, PRAC was presented with an agenda for the 'PRAC strategic review and learning meeting (SRLM)' under the Slovenian presidency of the Council of the European Union (EU). The meeting will be a joint one with CMDh and will be held remotely on 22 September 2021.

12.5. Cooperation with International Regulators

12.5.1. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) - Pharmacoepidemiology discussion group (PEpiDG) - new guideline on 'general principles on planning and designing pharmaco-epidemiological studies that utilise real-world data (RWD) for safety assessment of a medicine – call for nomination of PRAC expert

The EMA Secretariat presented to PRAC a call for PRAC expression of interest to contribute to the development of a new International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline entitled 'general principles on planning and designing pharmaco-epidemiological studies that utilise real-world data for safety assessment of a medicine'. PRAC was also presented the current status that include the establishment of a formal expert working group. The work will start as of September 2021 for a duration of three years.

Post-meeting note: Annalisa Capuano was nominated as PRAC representative.

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

12.6.1. Coronavirus (COVID-19)-medicines monitoring – COVID-19 infection and medicines in pregnancy – update

PRAC lead: Sabine Straus, Ulla Wändel Liminga

The EMA Secretariat updated PRAC on the current knowledge on the impact of coronavirus (COVID-19) in pregnancy including treatments used, treatment and vaccine safety and ongoing studies. This included a status update on the CONSIGN⁶⁵ consortium project. PRAC noted the update.

12.7. PRAC work plan

12.7.1. PRAC work plan 2021 - update

PRAC lead: Sabine Straus, Martin Huber

At the organisational, regulatory and methodological matters (ORGAM) meeting on 16 September 2021, the EMA Secretariat presented to PRAC a mid-year status update on the activities described in the PRAC work plan 2021. PRAC will initiate its work plan for 2022 taking into account the activities completed, progress made, priorities identified at the level of the Committee, EMA, Heads of Medicines Agencies (HMA) and EU network as well as the EMA business continuity plan (BCP).

12.8. Planning and reporting

12.8.1. EU Pharmacovigilance system - quarterly workload measures and performance indicators – Q2 2021 and predictions

The EMA Secretariat presented to PRAC an overview of the quarterly figures on the EMA pharmacovigilance system-related workload and performance indicators. For previous update, see [PRAC minutes May 2021](#).

12.9. Pharmacovigilance audits and inspections

12.9.1. Pharmacovigilance systems and their quality systems

None

12.9.2. Pharmacovigilance inspections

None

12.9.3. Pharmacovigilance audits

None

⁶⁵ Covid-19 infectiON and medicineS In pregnancy

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)

None

12.10.3. PSURs repository

None

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

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

Post-meeting note: following the PRAC meeting of September 2021, the updated EURD list was adopted by CHMP and CMDh at their September 2021 meetings and published on the EMA website on 22 September 2021, see:

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

12.11. Signal management

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

PRAC lead: Menno van der Elst

PRAC was updated on the progress from the signal management review technical (SMART) working group meeting on methods held on 13 July 2021. The presentation focussed on an update on ongoing activities, including observed to expected (O/E) analyses, heterologous vaccination and EudraVigilance data analysis system (EVDAS) dashboards made available to the network to support transparency and communication. Further update will be planned in due course.

12.12. Adverse drug reactions reporting and additional reporting

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

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 29 September 2021, see: [Home>Human Regulatory>Post-authorisation>Pharmacovigilance>Medicines under additional monitoring>List of medicines under additional monitoring](#)

12.13. EudraVigilance database

12.13.1. Activities related to the confirmation of full functionality

None

12.14. 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' – Addendum III on 'Pregnancy prevention programme and other pregnancy-specific risk minimisation measures'

PRAC lead: Sabine Straus

The EMA Secretariat presented to PRAC, on behalf of the drafting group, the draft addendum III on 'Pregnancy prevention programme (PPP) and other pregnancy-specific risk minimisation measures' of GVP module XVI on 'Risk minimisation measures: selection of tools and effectiveness indicators' before initiating a public consultation. PRAC endorsed the addendum III guidance. As part of the next steps, the guidance will be presented to other committees including CHMP, undergo EMA/European Commission (EC) legal checks, and published for public consultation.

Post-meeting note: Module XVI Addendum III – Pregnancy prevention programme and other 5 pregnancy-specific risk minimisation measures ([EMA/608947/2021](#)) was published on 14 March 2022 for public consultation until 31 May 2022.

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

12.15.3. Registry-based studies –guideline - update

PRAC lead: Sabine Straus, Ulla Wändel Liminga, Patricia McGettigan

At the organisational, regulatory and methodological matters (ORGAM) meeting on 16 September 2021, the EMA Secretariat presented to PRAC (for background, see [PRAC minutes June 2020](#)) the draft final guideline on registry-based studies following the public consultation and endorsement by the EMA cross-committee task force on registries and CHMP. PRAC supported the guidance document.

Post-meeting note: the final 'guideline on registry-based studies' ([EMA/426390/2021](#)) was published on 26 October 2021 on the EMA website.

12.15.4. Coronavirus (COVID-19) pandemic - observational COVID-19 vaccine safety studies – progress overview

At the organisational, regulatory and methodological matters (ORGAM) meeting on 16 September 2021, the EMA Secretariat provided PRAC with an outline and a progress update of EMA-funded studies on the safety monitoring of coronavirus (COVID-19) vaccines. Further updates will be provided in due course.

12.16. Community procedures

12.16.1. Referral procedures for safety reasons

None

12.17. Renewals, conditional renewals, annual reassessments

None

12.18. Risk communication and transparency

12.18.1. Public participation in pharmacovigilance

None

12.18.2. Safety communication

None

12.19. Continuous pharmacovigilance

12.19.1. Incident management

None

12.20. Impact of pharmacovigilance activities

None

12.21. Others

12.21.1. Lifecycle regulatory submissions raw data project (LRSR) - presentation

At the organisational, regulatory and methodological matters (ORGAM) meeting on 16 September 2021, the EMA Secretariat presented to PRAC the lifecycle regulatory submissions raw data project (LRSR). The purpose of the LRSR is to determine the regulatory benefit of access to raw data by building capacity and capability to receive, store, manage and analyse raw data. The project is part of the data analytics programme and aims at building EU network capability to analyse big data submissions. The project will put in place procedures and safeguards to process raw data, including clinical and non-clinical data, in accordance with data protection legislation. PRAC was presented the work done so far and the next steps. Updates will be scheduled in due course.

13. Any other business

None

14. Annex I – Signals assessment and prioritisation⁶⁶

14.1. New signals detected from EU spontaneous reporting systems

As per agreed criteria for new signal(s), PRAC adopted without further plenary discussion the recommendation of the Rapporteur to request MAH(s) to submit a cumulative review following standard timetables⁶⁷.

14.1.1. Alemtuzumab – LEMTRADA (CAP)

Applicant: Sanofi Belgium

PRAC Rapporteur: Anette Kirstine Stark

Scope: Signal of autoimmune encephalitis

EPITT 19710 – New signal

⁶⁶ 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

⁶⁷ Submission of cumulative review(s) within 60 days followed by a 60-day-timetable assessment or within an ongoing or upcoming PSUR/PSUSA procedure (if the data lock point (DLP) is within 90 days), and no disagreement was raised before the meeting

Lead Member State(s): DK

14.1.2. Durvalumab – IMFINZI (CAP)

Applicant: AstraZeneca AB

PRAC Rapporteur: David Olsen

Scope: Signal of arthralgia

EPITT 19709 – New signal

Lead Member State(s): NO

14.1.3. Obinutuzumab – GAZYVARO (CAP)

Applicant: Roche Registration GmbH

PRAC Rapporteur: Annika Folin

Scope: Signal of non-overt disseminated intravascular coagulation (DIC)

EPITT 19711 – New signal

Lead Member State(s): SE

14.1.4. Pregabalin – LYRICA (CAP); NAP

Applicant(s): Upjohn EESV, various

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Signal of toxic epidermal necrolysis

EPITT 19723 – New signal

Lead Member State(s): NL

14.1.5. Tocilizumab – ROACTEMRA (CAP)

Applicant: Roche Registration GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Signal of sarcoidosis

EPITT 18860 – New signal

Lead Member State(s): DE

14.2. New signals detected from other sources

15. Annex I – Risk management plans

15.1. Medicines in the pre-authorisation phase

As per agreed criteria, 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. Vildagliptin, metformin hydrochloride - EMEA/H/C/005738

Scope: Treatment of type 2 diabetes mellitus (T2DM)

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

As per agreed criteria, 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. Aflibercept - EYLEA (CAP) - EMEA/H/C/002392/II/0075

Applicant: Bayer AG

PRAC Rapporteur: Tiphaine Vaillant

Scope: Submission of an updated RMP (version 30.1) to include a follow-up questionnaire on intraocular pressure (IOP) increase and timing of IOP increase report submission. In addition, the MAH proposed to simplify the educational material consisting of a prescriber guide and injection video based on collected data and following consultation with a panel of ophthalmologists, as per the conclusions of variation II/0068 concluded in March 2021

15.2.2. Alectinib - ALECENSA (CAP) - EMEA/H/C/004164/II/0033

Applicant: Roche Registration GmbH

PRAC Rapporteur: Jana Lukacisinova

Scope: Submission of an updated RMP (version 3.1) in order to remove the safety concern of 'long term safety' as missing information based on a report of cumulative safety data from pivotal study BO28984 (ALEX): a randomized, multicentre, phase 3, open-label study of alectinib versus crizotinib in treatment-naive anaplastic lymphoma kinase-positive advanced non-small cell lung cancer (NSCLC). In addition, the MAH took the opportunity to update the RMP to remove from the pharmacovigilance plan study BO40643: a survey measuring the effectiveness of the risk minimisation activities to prescribers: correct implementation of Alecensa (alectinib) label guidance by prescribers of the following important identified risks: interstitial lung disease (ILD)/pneumonitis, hepatotoxicity, photosensitivity, bradycardia, severe myalgia and creatine phosphokinase (CPK) elevations, following the conclusions of variation II/0030 concluded in February 2021

15.2.3. Bazedoxifene - CONBRIZA (CAP) - EMEA/H/C/000913/II/0054

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Martin Huber

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

15.2.4. [Coronavirus \(COVID-19\) mRNA⁶⁸ vaccine \(nucleoside-modified\) - SPIKEVAX \(CAP\) - EMEA/H/C/005791/II/0022](#)

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Hans Christian Siersted

Scope: Submission of an updated RMP (version 2.0) to include clinical safety data from study mRNA-1273 P203 (NCT04649151): a phase 2/3, randomised, observer-blind, placebo-controlled study evaluating the safety, reactogenicity and effectiveness of the mRNA-1273 vaccine in healthy adolescents aged ≥ 12 to < 18 years

15.2.5. [Emtricitabine, tenofovir disoproxil - TRUVADA \(CAP\) - EMEA/H/C/000594/II/0169](#)

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Submission of an updated RMP (version 16.1) to remove completed study GS-EU-276-4487 (as a category 3 study in the RMP): a prospective, longitudinal, observational registry of emtricitabine/tenofovir disoproxil fumarate for human immunodeficiency virus 1 (HIV-1) pre-exposure prophylaxis (PrEP) in the European Union

15.2.6. [Insulin lispro - HUMALOG \(CAP\) - EMEA/H/C/000088/WS2115/0191; LIPROLOG \(CAP\) - EMEA/H/C/000393/WS2115/0151](#)

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Annika Folin

Scope: Submission of an updated RMP (version 11.1) to reflect the completion of a routine pharmacovigilance activity: a post-approval safety surveillance for monthly lot-specific adverse event review and analysis monitoring events on hypersensitivity, local injection site reactions, immunogenicity, lack of drug effect and increased drug effects and hypoglycaemia comparing events from the new manufacturing process with events reported using drug substance from both the historic and concurrent process. In addition, the MAH took this opportunity to modify milestones for a post-approval safety surveillance programme for severe hypoglycaemia following the use of a new presentation (Tempo pen)

15.2.7. [Ritonavir - NORVIR \(CAP\) - EMEA/H/C/000127/II/0161](#)

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Submission of an updated RMP (version 7.1) in order to bring it in line with revision 2.0.1 of the guidance on the format of RMP in the EU (template). In addition, the MAH reviewed the information contained in the RMP and removed the important identified risk of toxicity of Norvir (ritonavir) oral solution in preterm neonates, removed missing information regarding use of ritonavir in elderly patients. Finally, the MAH proposed to provide an analysis of the antiretroviral pregnancy registry (APR) data with PSUR submission(s)

⁶⁸ Messenger ribonucleic acid

15.2.8. [Simoctocog alfa - NUWIQ \(CAP\) - EMEA/H/C/002813/WS2064/0043; VIHUMA \(CAP\) - EMEA/H/C/004459/WS2064/0024](#)

Applicant: Octapharma AB

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of an updated RMP (version 11) to remove the following completed studies: 1) study GENA-05: immunogenicity, efficacy and safety of treatment with simoctocog alfa in previously untreated patients with severe haemophilia A; 2) study GENA-15: extension study for patients who completed GENA-05 (NuProtect)- to investigate immunogenicity, efficacy and safety of treatment with simoctocog alfa. As a consequence, 'safety in previously untreated patients', 'children < 2 years' and 'immune tolerance induction' are removed as missing information in the list of safety concerns. Finally, the RMP is brought in line with revision 2 of GVP module V on 'Risk management systems'

15.2.9. [Sitagliptin - JANUVIA \(CAP\) - EMEA/H/C/000722/WS2082/0075; RISTABEN \(CAP\) - EMEA/H/C/001234/WS2082/0068; TESAVEL \(CAP\) - EMEA/H/C/000910/WS2082/0075; XELEVIA \(CAP\) - EMEA/H/C/000762/WS2082/0080 sitagliptin, metformin hydrochloride - EFFICIB \(CAP\) - EMEA/H/C/000896/WS2082/0101; JANUMET \(CAP\) - EMEA/H/C/000861/WS2082/0101; RISTFOR \(CAP\) - EMEA/H/C/001235/WS2082/0089; VELMETIA \(CAP\) - EMEA/H/C/000862/WS2082/0104](#)

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Submission of an updated RMP (version 10.1) to reflect clinical trial exposure to sitagliptin in patients of 10-17 years of age in the safety specifications and implement the already assessed clinical data from procedure WS1727 finalised in January 2020 for Januvia, Ristaben, Tesavel, Xelevia (sitagliptin) and from procedure WS1898 finalised in September 2020 for Efficib, Janumet, Ristfor, Velmetia (sitagliptin/metformin)

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

As per agreed criteria, 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 - YUFLYMA \(CAP\) - EMEA/H/C/005188/X/0005](#)

Applicant: Celltrion Healthcare Hungary Kft.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension application to introduce a new strength of 80 mg solution for injection. The RMP (version 1.1) is updated accordingly

15.3.2. [Alirocumab - PRALUENT \(CAP\) - EMEA/H/C/003882/II/0065](#)

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of section 5.1 of the SmPC in order to include information on the effect of alirocumab on the neurocognitive function based on final results from study R727-CL-1532 (listed as a category 3 study in the RMP): an interventional study to evaluate the neurocognitive function during the treatment, as well as the effect of the medicinal product in comparison with placebo on lipoproteins and to assess the safety and tolerability. The RMP (version 6.0) is updated accordingly

15.3.3. Andexanet alfa - ONDEXXYA (CAP) - EMEA/H/C/004108/II/0022/G

Applicant: Alexion Europe SAS

PRAC Rapporteur: Menno van der Elst

Scope: Grouped variations consisting of: 1) update of sections 4.4, 4.8 and 5.1 of the SmPC based the final study report from study 14-505 (ANNEXA-4): a prospective, open-label study of andexanet alfa in patients receiving a factor Xa inhibitor who have acute major bleeding to confirm safety and efficacy in patients with acute major bleeds. The provision of this study report fulfils specific obligation 001. As a consequence, it is deleted from Annex II-E on 'Specific obligations to complete post-authorisation measures for the conditional marketing authorisation'. The package leaflet is updated accordingly. The MAH took the opportunity to implement editorial changes in the Annexes. The RMP (version 2.4) is updated accordingly; 2) change to the summary of pharmacovigilance system due to a change of qualified person responsible for pharmacovigilance (QPPV)

15.3.4. Autologous peripheral blood T cells CD⁶⁹4 and CD8 selected and CD3 and CD28 activated transduced with retroviral vector expressing anti-CD19 CD28/CD3-zeta chimeric antigen receptor and cultured - TECARTUS (CAP) - EMEA/H/C/005102/II/0008/G, Orphan

Applicant: Kite Pharma EU B.V., ATMP⁷⁰

PRAC Rapporteur: Menno van der Elst

Scope: Grouped variations consisting of: 1) extension of indication to include treatment of adult patients with relapsed or refractory (r/r) B-cell acute lymphoblastic leukaemia (B-ALL); 2) change the drug product dose specification for the new indication. As a consequence, sections 2.2, 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The package leaflet, labelling and the RMP (version 1.1) are updated in accordance. Furthermore, the product information is brought in line with the latest quality review of documents (QRD) template (version 10.2)

15.3.5. Baloxavir marboxil - XOFLUZA (CAP) - EMEA/H/C/004974/X/0003/G

Applicant: Roche Registration GmbH

PRAC Rapporteur: Sonja Hrabcik

Scope: Grouped applications consisting of: 1) extension application to add a new strength of 80 mg; 2) addition of a new pack size of 1 tablet for 40 mg strength. The RMP (version 1.2) is updated in accordance. Furthermore, the product information is brought in line with

⁶⁹ Cluster of differentiation

⁷⁰ Advanced therapy medicinal product

the latest quality review of documents (QRD) template (version 10.2) to update the local representatives with the United Kingdom (Northern Ireland)

15.3.6. [Bosutinib - BOSULIF \(CAP\) - EMEA/H/C/002373/II/0050/G](#)

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Martin Huber

Scope: Grouped variations consisting of an update of sections 4.2, 4.4, 4.8 and 5.1 of the SmPC in order to reflect results from: 1) study B1871039 (listed as a specific obligation (SOB) in Annex II) : a phase 4 safety and efficacy study of bosutinib in patients with Philadelphia chromosome positive chronic myeloid leukaemia (CML) previously treated with one or more tyrosine kinase inhibitors. As a consequence, the study is removed from Annex II-E on 'Specific obligations to complete post-authorisation measures for the conditional marketing authorisation' of the product information and the MAH requested a switch from the conditional marketing authorisation to a full marketing authorisation; 2) study B1871040 (listed a category 3 study in the RMP): an open-label bosutinib treatment extension study for subjects with CML who have previously participated in bosutinib studies B1871006 or B1871008. The package leaflet is updated accordingly. The RMP (version 6.0) is updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives for Belgium, Luxemburg, Germany and Northern Ireland in the package leaflet. The MAH also requested the deletion of the medicinal product from the additional monitoring list

15.3.7. [Brivaracetam - BRIVIACT \(CAP\) - EMEA/H/C/003898/II/0032/G](#)

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Adam Przybylkowski

Scope: Grouped variations consisting of: 1) extension of indication to include patients from 1 month to 4 years of age for treatment with Briviact (brivaracetam). As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The RMP (version 8.0) is updated accordingly. Furthermore, the product information is brought in line with the latest quality review of documents (QRD) template (version 10.2). The MAH took the opportunity to implement minor editorial updates; 2) extension of the shelf life after the first opening of Briviact (brivaracetam) oral solution (supported by real time data); 3) addition of a 1 mL oral syringe and its adaptor for the paediatric population. The package leaflet and labelling are updated in accordance

15.3.8. [Cabotegravir - VOCABRIA \(CAP\) - EMEA/H/C/004976/II/0004](#)

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Martin Huber

Scope: Update of sections 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC based on week 124 results from the FLAIR study: a phase 3, randomized, open-label study to evaluate the efficacy, safety and tolerability of the combined treatment cabotegravir and rilpivirine. The package leaflet and the RMP (version 2.0) are updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet, to introduce editorial changes and corrections throughout the product information and to bring

the product information in line with the latest quality review of documents (QRD) template (version 10.2)

15.3.9. Cladribine - MAVENCLAD (CAP) - EMEA/H/C/004230/II/0020

Applicant: Merck Europe B.V.

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Update of sections 4.2 and 4.4 of the SmPC in order to change posology recommendations by adding an advice on preventive measures to avoid liver injury and to add a new warning on liver function and liver injury based on a review of post-approval data in the MAH's safety database, non-clinical, clinical trial data and scientific literature. The package leaflet and the RMP (version 1.6) are updated accordingly

15.3.10. Crizotinib - XALKORI (CAP) - EMEA/H/C/002489/II/0072

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Tiphaine Vaillant

Scope: Extension of indication to include treatment of paediatric patients aged ≥ 6 to < 18 years with relapsed or refractory systemic anaplastic lymphoma kinase (ALK)-positive anaplastic large cell lymphoma (ALCL) and with unresectable, recurrent, or refractory ALK-positive inflammatory myofibroblastic tumour (IMT) based on the results from: 1) study ADVL0912: a phase 1/2 study of crizotinib, an oral small molecule inhibitor of ALK and C-Met, in children with relapsed/refractory solid tumours and anaplastic large cell lymphoma; 2) study A8081013: a phase 1b open-label study of the safety and clinical activity of crizotinib in tumours with genetic events involving the ALK gene locus. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 8.0) are updated in accordance. In addition, the MAH took the opportunity to update the anatomical therapeutic chemical (ATC) code for crizotinib. Moreover, the MAH took the opportunity to implement a minor change in the list of local representatives in the package leaflet

15.3.11. Darunavir, cobicistat, emtricitabine, tenofovir alafenamide - SYMTUZA (CAP) - EMEA/H/C/004391/II/0037

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Submission of the final report from final clinical study GS-US-292-0109 (listed as a category 3 study in the RMP): a phase 3, open-label study to evaluate switching from a tenofovir disoproxil fumarate (TDF)-containing combination regimen to a tenofovir alafenamide (TAF)-containing combination single tablet regimen (STR) in virologically-suppressed human immunodeficiency virus 1 (HIV-1) positive subjects final safety and efficacy. The RMP (version 7.1) is updated accordingly

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

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Martin Huber

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

15.3.13. Dimethyl fumarate - TECFIDERA (CAP) - EMEA/H/C/002601/II/0073

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Martin Huber

Scope: Extension of indication to include treatment of relapsing remitting multiple sclerosis (RRMS) in paediatrics patients from 10 years of age and over based on results from study 109MS306: an open-Label, randomized, multicentre, multiple-dose, active-controlled, parallel-group, efficacy and safety study of dimethyl fumarate in children from 10 to less than 18 years of age with RRMS with optional open-label extension. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.3 of the SmPC are updated. The package leaflet and the RMP (version 11.4) is updated in accordance. The MAH requested an extension of the market protection of one additional year in line with the guidance on elements required to support the significant clinical benefit in comparison with existing therapies of a new therapeutic indication in accordance with Article 14(11) of Regulation (EC) 726/2004

15.3.14. Dinutuximab beta - QARZIBA (CAP) - EMEA/H/C/003918/II/0027/G, Orphan

Applicant: EUSA Pharma (Netherlands) B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Grouped variations consisting of: 1) anatomical therapeutic chemical (ATC) code change to L01XC16 according to the World Health Organization (WHO); 2) update of section 4.8 of the SmPC in order to amend the overall incidence of reported adverse reactions based on post marketing data. In addition, minor changes are introduced in the SmPC, package leaflet and labelling in order to harmonise the product information with other regulatory regions; 3) submission of an updated RMP (version 10.00) in order to include an alignment to post marketing data (PSUR#6) and to introduce updates on the important identified risks and important potential risks. In addition, the MAH took the opportunity to introduce some linguistic corrections on Swedish, Finnish, Italian, Spanish, and Portuguese EMA annexes

15.3.15. Elbasvir, grazoprevir - ZEPATIER (CAP) - EMEA/H/C/004126/II/0029

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Extension of indication to include treatment of chronic hepatitis C (CHC) in paediatric patients 12 years of age and older who weigh at least 30 kg. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and

the RMP (version 4.1) are updated in accordance. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet

15.3.16. Febuxostat - ADENURIC (CAP) - EMEA/H/C/000777/II/0062

Applicant: Menarini International Operations Luxembourg S.A.

PRAC Rapporteur: Jan Neuhauser

Scope: Update of sections 4.4 and 4.5 of the SmPC in order to amend an existing warning on the drug-drug interaction information with mercaptopurine/azathioprine based on final results from study FAI-01 (listed as a category 3 study in the RMP): a phase 1, drug-drug interaction study investigating the pharmacokinetic (PK) profile of 6-mercaptopurine following coadministration of two doses febuxostat and azathioprine in healthy subjects. The RMP (version 9.0) is updated accordingly

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

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Nikica Mirošević Skvrce

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

15.3.18. Filgotinib - JYSELECA (CAP) - EMEA/H/C/005113/II/0006

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Update of sections 4.5 and 5.2 of the SmPC in order to update pharmacokinetic information on the effect of filgotinib on organic anion transporting polypeptide (OATP)/ cytochrome P450 3A4 (CYP3A), OATP/ breast cancer resistance protein (BCRP), and OATP substrates based on final results from study GS-US-417-5937: a phase 1, randomised, two-way crossover, open-label, single and multiple dose, single centre study to evaluate the effect of filgotinib on a mixed OATP/CYP3A, OATP/BCRP and OATP substrates using phenotypic probes. The package leaflet and the RMP (version 2.1) are updated accordingly

15.3.19. Galsulfase - NAGLAZYME (CAP) - EMEA/H/C/000640/II/0086

Applicant: BioMarin International Limited

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Submission of the final report from the mucopolysaccharidosis (MPS VI clinical surveillance programme (CSP) (listed as a specific obligation (SOB002) in Annex II): an observational CSP to characterise the natural progression of MPS VI; to evaluate the long-term safety and efficacy data from Naglazyme (galsulfase) treatment; to collect information on the effect of Naglazyme (galsulfase) treatment on lactation, growth and development of infants of Naglazyme (galsulfase) treated mothers and to evaluate the effects of Naglazyme

(galsulfase) treatment on children under 5 years of age. The RMP (version 6.4) is updated accordingly to remove gastrointestinal haemorrhage, hepatic impairment and thrombocytopenia from the list of important potential risks

15.3.20. Givosiran - GIVLAARI (CAP) - EMEA/H/C/004775/II/0006, Orphan

Applicant: Alnylam Netherlands B.V.

PRAC Rapporteur: Martin Huber

Scope: Update of section 4.8 of the SmPC to add 'blood homocysteine increase' as a new adverse drug reaction (ADR) and update of section 4.4 of the SmPC to add a related warning. The package leaflet and the RMP (version 1.1) are updated accordingly. In addition, the MAH took the opportunity to make editorial changes to the product information and to update the local representative details for Malta and Cyprus

15.3.21. Guselkumab - TREMFYA (CAP) - EMEA/H/C/004271/II/0028

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of sections 4.8 and 5.1 of the SmPC to reflect 5 years data from the final study reports of pivotal psoriasis studies (listed as category 3 studies in the RMP), namely: 1) study PSO3001: a phase 3, multicentre, randomized, double-blind, placebo and active comparator-controlled study evaluating the efficacy and safety of guselkumab in the treatment of subjects with moderate to severe plaque-type psoriasis; 2) study PSO3002: a phase 3, multicentre, randomized, double-blind, placebo and active comparator-controlled study evaluating the efficacy and safety of guselkumab for the treatment of subjects with moderate to severe plaque-type psoriasis with randomized withdrawal and retreatment. In the long-term extension part of these studies subjects received open-label guselkumab every 8 weeks (q8w) starting at week 52 in PSO3001 and at week 76 in PSO3002, with the last dose at week 252 and the last safety follow-up visit at week 264. The RMP (version 8.1) is updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet

15.3.22. Ixazomib - NINLARO (CAP) - EMEA/H/C/003844/II/0033, Orphan

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Annika Folin

Scope: Submission of the final report for the final analysis of overall survival (OS) for study C16010 (listed as an obligation in Annex II): a phase 3, randomised, double-blind multicentre study comparing ixazomib in combination with lenalidomide and dexamethasone (LenDex) versus placebo plus LenDex in adult patients with relapsed and/or refractory multiple myeloma. Annex II-D on 'Conditions or restrictions with regard to the safe and effective use of the medicinal product' and the RMP (version 7.0) are updated accordingly

15.3.23. Lacosamide - LACOSAMIDE ACCORD (CAP) - EMEA/H/C/004443/X/0007

Applicant: Accord Healthcare S.L.U.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension application to introduce a new pharmaceutical form (solution for infusion), a new strength and a new route of administration (intravenous use). The RMP (version 1.0) is updated accordingly

15.3.24. Lacosamide - LACOSAMIDE UCB (CAP) - EMEA/H/C/005243/WS2049/0009/G; VIMPAT (CAP) - EMEA/H/C/000863/WS2049/0091/G

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Grouped applications consisting of: 1) extension of indication to include patients from 1 month to 4 years of age for treatment of partial-onset seizures with or without secondary generalisation as monotherapy and adjunctive therapy. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The RMP (version 16.0) is updated accordingly; 2) change of a measuring or administration device; 3) extension of the shelf-life of the finished product. The package leaflet and labelling are updated in accordance

15.3.25. Lanadelumab - TAKHZYRO (CAP) - EMEA/H/C/004806/II/0022, Orphan

Applicant: Shire Pharmaceuticals Ireland Limited

PRAC Rapporteur: Kirsti Villikka

Scope: Update of sections 4.8 and 5.1 of the SmPC to reflect the result of study DX-2930-04 (HELP study extension): an open-label study to evaluate the long-term safety and efficacy of lanadelumab (DX-2930) for prevention against acute attacks of hereditary angioedema (HAE). The RMP (version 2.0) is updated accordingly and in line with revision 2.0.1 of the guidance on the format of RMP in the EU (template). In addition, the MAH took the opportunity to include a refrigeration statement for the multi-pack pre-filled syringe in the product information

15.3.26. Lorlatinib - LORVIQUA (CAP) - EMEA/H/C/004646/II/0015

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Extension of indication to include the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) previously not treated with an ALK inhibitor based on results from study 1006 (CROWN) (listed as a specific obligation (SOB) in Annex II): a phase 3 randomised open-label study of lorlatinib monotherapy versus crizotinib monotherapy in the first-line treatment of patients with advanced ALK-positive NSCLC. As a consequence, sections 4.1, 4.2 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 3.0) are updated accordingly. In addition, the applicant proposed to downgrade the SOB to conduct a single arm study in patients who progressed after alectinib or ceritinib to a recommendation and convert the conditional marketing authorisation to a full marketing authorisation (MA)

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

Applicant: GlaxoSmithKline Trading Services Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Grouped variations consisting of: 1) extension of indication to include treatment of eosinophilic granulomatosis with polyangiitis (EGPA). As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 7.0) are updated in accordance. In addition, the MAH took the opportunity to update the local representative for Italy in the package leaflet; 2) addition of a new pack size of 9x100mg/mL multipack for pre-filled pens 100 mg/mL solution for injection and another pack size of 9x100mg/mL multipack for pre-filled syringes 100 mg/mL solution for injection. As a consequence, sections 6.5 and 8 of the SmPC and the package leaflet are updated accordingly. Annex III-A on 'labelling' is also updated to include information relating to the new pack sizes

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

Applicant: GlaxoSmithKline Trading Services Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include treatment of hypereosinophilic syndrome (HES). As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. In addition, section 6.6 of the SmPC for the powder for solution for injection presentations is updated. The package leaflet and the RMP (version 7.0) are updated in accordance. The MAH took the opportunity to update the local representative for Italy in the package leaflet

15.3.29. Mepolizumab - NUCALA (CAP) - EMEA/H/C/003860/X/0042

Applicant: GlaxoSmithKline Trading Services Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension application to introduce a new strength of 40 mg for Nucala (mepolizumab) solution for injection in a pre-filled syringe for subcutaneous use to be used in children aged 6 to 11 years. The RMP (version 8.0) is updated accordingly

15.3.30. Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/II/0105

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of sections 4.4, 4.8 and 5.1 of the SmPC based on final results from study CA209205 (listed as a post-authorisation efficacy study (PAES) in Annex II): a phase 2, open-label, multi-cohort, single-arm study of nivolumab in patients with classical Hodgkin's lymphoma. The RMP (version 20.3) is updated accordingly

15.3.31. Olaparib - LYNPARZA (CAP) - EMEA/H/C/003726/II/0048

Applicant: AstraZeneca AB

PRAC Rapporteur: Ilaria Baldelli

Scope: Update of section 5.1 of the SmPC of olaparib tablet based on results from study D0816C00020 (OPINION) (listed as a post-authorisation efficacy study (PAES) in Annex II): a phase 3b single arm, multicentre study, investigating olaparib as a maintenance treatment in patients with platinum-sensitive relapsed ovarian, fallopian tube or primary peritoneal cancer following 2 or more lines of platinum based chemotherapy and who did not have a known deleterious or suspected deleterious germline breast cancer susceptibility gene (gBRCA) mutation. Annex II-D on 'Conditions or restrictions with regard to the safe and effective use of the medicinal product' is updated accordingly. The RMP (version 22.1) is updated accordingly

15.3.32. Ozanimod - ZEPOSIA (CAP) - EMEA/H/C/004835/II/0005

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Update of sections 4.4 and 4.8 of the SmPC in order to amend an existing warning on progressive multifocal leukoencephalopathy (PML) and to add PML to the list of adverse drug reactions (ADRs) with a frequency 'rare' based on a PML case observed in study RPC01-3001 open-label extension (OLE): a phase 3, multicentre, randomized, double-blind, double-dummy, active controlled, parallel group study to evaluate the efficacy and safety of ozanimod (RPC1063) administered orally to relapsing multiple sclerosis patients. The package leaflet and the RMP (version 1.3) are updated accordingly

15.3.33. Padeliporfin - TOOKAD (CAP) - EMEA/H/C/004182/II/0013

Applicant: STEBA Biotech S.A

PRAC Rapporteur: Maia Uusküla

Scope: Extension of indication to modify the wording of the existing indication to treatment of adult patients with previously untreated, unilateral, low-risk, adenocarcinoma of the prostate with a life expectancy ≥ 10 years and clinical stage T1c or T2a, International Society of Urological Pathology (ISUP) grade group ≤ 2 , based on high-resolution biopsy strategies, prostate-specific antigen (PSA) ≤ 10 ng/mL, low core positivity. As a consequence, section 4.1 of the SmPC is updated. The RMP (version 6.0) is updated accordingly

15.3.34. Paliperidone - PALIPERIDONE JANSSEN-CILAG INTERNATIONAL (CAP) - EMEA/H/C/005486/X/0002/G

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Grouped applications consisting of: 1) extension application to introduce two new strengths of 700 mg and 1000 mg prolonged-release suspension for injection. The RMP (version 10.1) is updated accordingly; 2) change of the (invented) name of the medicinal product from Paliperidone Janssen-Cilag International to Byannli; 3) deletion of the 25 mg, 50 mg, 75 mg, 100 mg and 150 mg/100 mg strengths from the Paliperidone Janssen-Cilag marketing authorisation (EU/1/20/1453/001-006)

15.3.35. Pertuzumab - PERJETA (CAP) - EMEA/H/C/002547/II/0059

Applicant: Roche Registration GmbH

PRAC Rapporteur: Anette Kirstine Stark

Scope: Submission of the final clinical study report for study WO29217 (BERENICE): a multicentre, multinational, phase 2 study to evaluate Perjeta (pertuzumab) in combination with trastuzumab and standard neoadjuvant anthracycline-based chemotherapy in patients with epidermal growth factor receptor 2 (HER2)-positive, locally advanced, inflammatory, or early-stage breast cancer. The RMP (version 14.0) is updated accordingly

15.3.36. Pyronaridine, artesunate - PYRAMAX (Art 58⁷¹) - EMEA/H/W/002319/II/0023/G

Applicant: Shin Poong Pharmaceutical Co., Ltd.

PRAC Rapporteur: Tiphaine Vaillant

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

15.3.37. Remdesivir - VEKLURY (CAP) - EMEA/H/C/005622/II/0016

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Eva Jirsová

Scope: Extension of indication to include treatment of adults with pneumonia not requiring supplemental oxygen (moderate COVID-19) based on: 1) part A of study GS-US-540-5774: a phase 3, randomized, open-label, multicentre study comparing 2 remdesivir (RDV) regimens (5 days and 10 days) versus standard of care in 584 participants with moderate COVID 19; 2) study CO-US-540-5776 (adaptive COVID-19 treatment trial (ACTT)): a National Institute of Allergy and Infectious Diseases (NIAID)-sponsored phase 3, multicentre, adaptive, randomized, double blind, placebo controlled trial on the safety and efficacy study of investigational therapeutics for the treatment of COVID-19. As a consequence, sections 4.1 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 1.2) are updated in accordance

⁷¹ 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)

15.3.38. Rilpivirine - REKAMBYS (CAP) - EMEA/H/C/005060/II/0004

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Update of sections 4.2, 4.8, 5.1 and 5.2 of the SmPC to update safety and efficacy information based on week 124 results from the FLAIR study: a phase 3, randomised, open-label study to evaluate the efficacy, safety and tolerability of the combined treatment cabotegravir and rilpivirine. The package leaflet and the RMP (version 3.1) are updated accordingly. The MAH took the opportunity to introduce editorial changes and corrections throughout the product information

15.3.39. Saxagliptin - ONGLYZA (CAP) - EMEA/H/C/001039/WS2098/0053; saxagliptin, metformin hydrochloride - KOMBOGLYZE (CAP) - EMEA/H/C/002059/WS2098/0051

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Submission of the final report from study D1680C00016 (MEASURE HF) (listed as a category 3 study in the RMP): a 24-week, multicentre, randomised, double-blind, parallel group, placebo-controlled study to investigate the effects of saxagliptin and sitagliptin on cardiac dimensions and function in patients with type 2 diabetes mellitus (T2DM) and heart failure. The RMP (version 16) is updated accordingly

15.3.40. Secukinumab - COSENTYX (CAP) - EMEA/H/C/003729/II/0076

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Eva Segovia

Scope: Update of sections 4.2 and 5.1 of the SmPC in order to introduce a new posology regimen for adult plaque psoriasis patients and psoriatic arthritis patients with concomitant moderate to severe plaque psoriasis based on the final results of study CAIN457A2324 (and exposure-response modelling): a randomised, double-blind, multicentre study assessing short (16 weeks) and long-term efficacy (up to 1 year), safety, and tolerability of sub-cutaneous secukinumab in subjects of body weight 90 kg or higher with moderate to severe chronic plaque-type psoriasis. The package leaflet and the RMP (version 9.0) are updated accordingly

15.3.41. Siponimod - MAYZENT (CAP) - EMEA/H/C/004712/X/0007

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Extension application to add a new strength of 1 mg film-coated tablet. The RMP (version 3.0) is updated in accordance

15.3.42. Sugammadex - BRIDION (CAP) - EMEA/H/C/000885/II/0042

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Kirsti Villikka

Scope: Update of sections 4.2, 4.8, 5.1 and 5.2 of the SmPC in order to change posology recommendations and update safety, efficacy and pharmacokinetic information in children and adolescents (2-17 years) following P46/025 and based on final results from study P089MK8616: a phase 4 double-blind, randomised, active comparator-controlled clinical trial to study the efficacy, safety and pharmacokinetics of sugammadex (MK-8616) for reversal of neuromuscular blockade in paediatric participants. In addition, the MAH took the opportunity to implement some minor editorial changes throughout the product information. The package leaflet is updated in accordance and the MAH took the opportunity to update the list of local representatives. The RMP (version 7.2) is also updated accordingly and in line with revision 2.0.1 of the guidance on the format of RMP in the EU (template)

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

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

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

15.3.44. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/X/0030/G

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Grouped application consisting of: 1) extension application to add a new strength (22 mg prolonged-release tablet); 2) update of sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC of Xeljanz (tofacitinib) 11 mg prolonged-release tablets in order to include the treatment of adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic agent, as an alternative to the immediate release film-coated tablets. Section 4.2 of the SmPC of Xeljanz (tofacitinib) film-coated tablets is also updated to include switching with the prolonged-release tablet in the treatment of UC. The package leaflet and the RMP (version 15.1) are updated accordingly

15.3.45. Upadacitinib - RINVOQ (CAP) - EMEA/H/C/004760/II/0009

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Update of sections 4.4 and 5.1 of the SmPC in order to amend the existing warning on vaccination based on the final results from vaccination sub-study within study M13-538 (listed as a category 3 study in the RMP): an open-label extension to assess the impact of upadacitinib treatment with a stable background of methotrexate on immunological responses following administration of a pneumococcal vaccine in rheumatoid arthritis patients. The RMP (version 5.0) is updated accordingly

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

Based on the assessment of the following PSURs, 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 listed-below procedures 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. Albutrepenonacog alfa - IDELVION (CAP) - PSUSA/00010497/202101

Applicant: CSL Behring GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.2. Asparaginase⁷² - SPECTRILA (CAP) - PSUSA/00010445/202101

Applicant: medac Gesellschaft für klinische Spezialpräparate mbH

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.1.3. Atazanavir, cobicistat - EVOTAZ (CAP) - PSUSA/00010404/202101

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

16.1.4. Autologous peripheral blood T cells CD⁷³4 and CD8 selected and CD3 and CD28 activated transduced with retroviral vector expressing anti-CD19 CD28/CD3-zeta chimeric antigen receptor and cultured - TECARTUS (CAP) - PSUSA/00010903/202101

Applicant: Kite Pharma EU B.V., ATMP⁷⁴

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

⁷² Centrally authorised product(s) only

⁷³ Cluster of differentiation

⁷⁴ Advanced therapy medicinal product

16.1.5. Avapritinib - AYVAKYT (CAP) - PSUSA/00010878/202101

Applicant: Blueprint Medicines (Netherlands) B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.6. Beclometasone, formoterol, glycopyrronium bromide - RIARIFY (CAP); TRIMBOW (CAP); TRYDONIS (CAP) - PSUSA/00010617/202101

Applicant(s): Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.1.7. Belantamab mafodotin - BLENREP (CAP) - PSUSA/00010869/202102

Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

16.1.8. Bictegravir, emtricitabine, tenofovir alafenamide - BIKTARVY (CAP) - PSUSA/00010695/202102

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.9. Birch bark extract⁷⁵ - EPISALVAN (CAP) - PSUSA/00010446/202101

Applicant: Amryt GmbH

PRAC Rapporteur: Zane Neikena

Scope: Evaluation of a PSUSA procedure

16.1.10. Botulinum toxin type A - NUCEIVA (CAP) - PSUSA/00010796/202101

Applicant: Evolus Pharma Limited

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.11. Brexpiprazole - RXULTI (CAP) - PSUSA/00010698/202101

Applicant: Otsuka Pharmaceutical Netherlands B.V.

PRAC Rapporteur: Michal Radik

⁷⁵ Centrally authorised product(s) only

Scope: Evaluation of a PSUSA procedure

16.1.12. [Bulevirtide - HEPCLUDEX \(CAP\) - PSUSA/00010873/202101](#)

Applicant: MYR GmbH

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.13. [Ceftolozane, tazobactam - ZERBAXA \(CAP\) - PSUSA/00010411/202012](#)

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.14. [Cenegermin - OXERVATE \(CAP\) - PSUSA/00010624/202101](#)

Applicant: Dompe farmaceutici S.p.A.

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.1.15. [Concentrate of proteolytic enzymes enriched in bromelain - NEXOBRID \(CAP\) - PSUSA/00010028/202012](#)

Applicant: MediWound Germany GmbH

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.16. [Dapagliflozin, metformin - EBYMECT \(CAP\); XIGDUO \(CAP\) - PSUSA/00010294/202101](#)

Applicant(s): AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.17. [Dapivirine - DAPIVIRINE VAGINAL RING 25 MG \(Art 58⁷⁶\) - EMEA/H/W/002168/PSUV/0008](#)

Applicant: International Partnership for Microbicides Belgium AISBL

PRAC Rapporteur: Jan Neuhauser; PRAC Co-rapporteur: Not applicable

Scope: Evaluation of a PSUR procedure

⁷⁶ Article 58 of Regulation (EC) No 726/2004 allows the Committee for Medicinal Products for Human Use (CHMP) to give opinions, in co-operation with the World Health Organisation (WHO) on medicinal products for human use that are intended exclusively for markets outside of the European Union (EU)

16.1.18. Darolutamide - NUBEQA (CAP) - PSUSA/00010843/202101

Applicant: Bayer AG

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.1.19. Defatted powder of Arachis hypogaea L., semen (peanuts) - PALFORZIA (CAP) - PSUSA/00010902/202101

Applicant: Aimmune Therapeutics Ireland Limited

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

16.1.20. Elbasvir, grazoprevir - ZEPATIER (CAP) - PSUSA/00010519/202101

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.1.21. Epoetin zeta - RETACRIT (CAP), SILAPO (CAP) - PSUSA/00001241/202012

Applicant(s): Pfizer Europe MA EEIG (Retacrit), Stada AG (Silapo)

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.22. Eptacog alfa - NOVOSEVEN (CAP) - PSUSA/00001245/202012

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.23. Glucagon⁷⁷ - BAQSIMI (CAP) - PSUSA/00010826/202101

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

16.1.24. Glycerol phenylbutyrate - RAVICTI (CAP) - PSUSA/00010454/202101

Applicant: Immedica Pharma AB

PRAC Rapporteur: Ilaria Baldelli

Scope: Evaluation of a PSUSA procedure

⁷⁷ Centrally authorised product(s) only

16.1.25. Guselkumab - TREMFYA (CAP) - PSUSA/00010652/202101

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.26. Imipenem, cilastatin, relebactam - RECARBRIO (CAP) - PSUSA/00010830/202101

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.27. Indacaterol, glycopyrronium, mometasone - ENERZAIR BREEZHALER (CAP); ZIMBUS BREEZHALER (CAP) - PSUSA/00010861/202101

Applicant(s): Novartis Europharm Limited

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.1.28. L-lysine hydrochloride, L-arginine hydrochloride - LYSAKARE (CAP) - PSUSA/00010786/202101

Applicant: Advanced Accelerator Applications

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.29. Lonococog alfa - AFSTYLA (CAP) - PSUSA/00010559/202101

Applicant: CSL Behring GmbH

PRAC Rapporteur: Sonja Hrabcik

Scope: Evaluation of a PSUSA procedure

16.1.30. Macimorelin - MACIMORELIN CONSILIENT HEALTH (CAP) - PSUSA/00010746/202101

Applicant: Consilient Health Limited

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.31. Meningococcal group-B vaccine (rDNA⁷⁸, component, adsorbed) - BEXSERO (CAP) - PSUSA/00010043/202101

Applicant: GSK Vaccines S.r.l

⁷⁸ Recombinant deoxyribonucleic acid

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.32. Mercaptamine⁷⁹ - CYSTADROPS (CAP) - PSUSA/00010574/202101

Applicant: Recordati Rare Diseases

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

16.1.33. Metreleptin - MYALEPTA (CAP) - PSUSA/00010700/202101

Applicant: Amryt Pharmaceuticals DAC

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.34. Neratinib - NERLYNX (CAP) - PSUSA/00010712/202101

Applicant: Pierre Fabre Medicament

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.35. Nilotinib - TASIGNA (CAP) - PSUSA/00002162/202101

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

16.1.36. Osilodrostat - ISTURISA (CAP) - PSUSA/00010820/202101

Applicant: Recordati Rare Diseases

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

16.1.37. Patisiran - ONPATTRO (CAP) - PSUSA/00010715/202102

Applicant: Alnylam Netherlands B.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

16.1.38. Phenylephrine, ketorolac - OMIDRIA (CAP) - PSUSA/00010419/202101

Applicant: Omeros Ireland Limited

⁷⁹ Indicated for the treatment of corneal cystine crystal deposit only

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.1.39. Quadrivalent influenza vaccine (recombinant, prepared in cell culture) - SUPEMTEK (CAP) - PSUSA/00010886/202101

Applicant: Sanofi Pasteur

PRAC Rapporteur: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

16.1.40. Roflumilast - DAXAS (CAP) - PSUSA/00002658/202101

Applicant: AstraZeneca AB

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

16.1.41. Romosozumab - EVENITY (CAP) - PSUSA/00010824/202101

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

16.1.42. Simoctocog alfa - NUWIQ (CAP); VIHUMA (CAP) - PSUSA/00010276/202101

Applicant(s): Octapharma AB

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.43. Smallpox vaccine (live, modified vaccinia virus Ankara) - IMVANEX (CAP) - PSUSA/00010119/202101(with RMP)

Applicant: Bavarian Nordic A/S

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.44. Tasimelteon - HETLIOZ (CAP) - PSUSA/00010394/202101

Applicant: Vanda Pharmaceuticals Netherlands B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.45. Tezacaftor, ivacaftor - SYMKEVI (CAP) - PSUSA/00010730/202102

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Rhea Fitzgerald
Scope: Evaluation of a PSUSA procedure

16.1.46. Vismodegib - ERIVEDGE (CAP) - PSUSA/00010140/202101

Applicant: Roche Registration GmbH
PRAC Rapporteur: Annika Folin
Scope: Evaluation of a PSUSA procedure

16.1.47. Vonicog alfa - VEYVONDI (CAP) - PSUSA/00010714/202012

Applicant: Baxalta Innovations GmbH
PRAC Rapporteur: Ulla Wändel Liminga
Scope: Evaluation of a PSUSA procedure

16.1.48. Zanamivir⁸⁰ - DECTOVA (CAP) - PSUSA/00010763/202101

Applicant: GlaxoSmithKline Trading Services Limited
PRAC Rapporteur: Ulla Wändel Liminga
Scope: Evaluation of a PSUSA procedure

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

16.2.1. Alendronic acid, colecalciferol - ADROVANCE (CAP), FOSAVANCE (CAP), VANTAVO (CAP), NAP; alendronic acid, calcium, colecalciferol - NAP - PSUSA/00000079/202101

Applicants: Organon N.V. (Adrovanche, Fosavance, Vantavo), various
PRAC Rapporteur: Jan Neuhauser
Scope: Evaluation of a PSUSA procedure

16.2.2. Repaglinide - NOVONORM (CAP); PRANDIN (CAP); NAP - PSUSA/00002618/202012

Applicants: Novo Nordisk A/S (NovoNorm, Prandin), various
PRAC Rapporteur: Menno van der Elst
Scope: Evaluation of a PSUSA procedure

⁸⁰ Centrally authorised product(s) only

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

16.3.1. Alendronate (NAP) - PSUSA/00000078/202101

Applicant(s): various

PRAC Lead: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

16.3.2. Alitretinoin⁸¹ (NAP) - PSUSA/00010710/202101

Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.3.3. Alizapride (NAP) - PSUSA/00000091/202101

Applicant(s): various

PRAC Lead: Laurence de Fays

Scope: Evaluation of a PSUSA procedure

16.3.4. Altizide, spironolactone (NAP) - PSUSA/00002781/202101

Applicant(s): various

PRAC Lead: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

16.3.5. Anthrax vaccine (NAP) - PSUSA/00010771/202012

Applicant(s): various

PRAC Lead: Brigitte Keller-Stanislowski

Scope: Evaluation of a PSUSA procedure

16.3.6. Antithrombin III (NAP) - PSUSA/00003159/202012

Applicant(s): various

PRAC Lead: Ilaria Baldelli

Scope: Evaluation of a PSUSA procedure

16.3.7. Azelastine (NAP) - PSUSA/00000277/202012

Applicant(s): various

PRAC Lead: Jan Neuhauser

⁸¹ Oral use only

Scope: Evaluation of a PSUSA procedure

16.3.8. Betahistine (NAP) - PSUSA/00000389/202012

Applicant(s): various

PRAC Lead: Zane Neikena

Scope: Evaluation of a PSUSA procedure

16.3.9. Betamethasone dipropionate, calcipotriol (NAP) - PSUSA/00000393/202101

Applicant(s): various

PRAC Lead: Ronan Grimes

Scope: Evaluation of a PSUSA procedure

16.3.10. Betamethasone dipropionate, clotrimazole (NAP) - PSUSA/00000394/202101

Applicant(s): various

PRAC Lead: Ronan Grimes

Scope: Evaluation of a PSUSA procedure

16.3.11. Betamethasone dipropionate, salicylic acid (NAP) - PSUSA/00000395/202101

Applicant(s): various

PRAC Lead: Ronan Grimes

Scope: Evaluation of a PSUSA procedure

16.3.12. Betamethasone sodium phosphate, neomycin sulfate (NAP) - PSUSA/00000397/202101

Applicant(s): various

PRAC Lead: Ronan Grimes

Scope: Evaluation of a PSUSA procedure

16.3.13. Betamethasone valerate, clioquinol (NAP) - PSUSA/00000398/202101

Applicant(s): various

PRAC Lead: Ronan Grimes

Scope: Evaluation of a PSUSA procedure

16.3.14. Betamethasone valerate, fusidic acid (NAP) - PSUSA/00000399/202101

Applicant(s): various

PRAC Lead: Ronan Grimes

Scope: Evaluation of a PSUSA procedure

16.3.15. Betula verrucosa^{82 83 84} (NAP) - PSUSA/00010815/202101

Applicant(s): various

PRAC Lead: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

16.3.16. Caffeine, drotaverine hydrochloride, metamizole sodium (NAP) - PSUSA/00001996/202101

Applicant(s): various

PRAC Lead: Marek Juracka

Scope: Evaluation of a PSUSA procedure

16.3.17. Calcitriol (NAP) - PSUSA/00000495/202101

Applicant(s): various

PRAC Lead: Ilaria Baldelli

Scope: Evaluation of a PSUSA procedure

16.3.18. Carboprost (NAP) - PSUSA/00000560/202101

Applicant(s): various

PRAC Lead: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

16.3.19. Cefoperazone, sulbactam (NAP) - PSUSA/00000598/202101

Applicant(s): various

PRAC Lead: Rugilė Pilvinienė

Scope: Evaluation of a PSUSA procedure

16.3.20. Celecoxib (NAP) - PSUSA/00000616/202012

Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.3.21. Cyproheptadine (NAP) - PSUSA/00000902/202012

Applicant(s): various

PRAC Lead: Melinda Palfi

⁸² Allergen for therapy

⁸³ De-centrally authorised product(s) only

⁸⁴ Sublingual tablet(s) only

Scope: Evaluation of a PSUSA procedure

16.3.22. Dapoxetine (NAP) - PSUSA/00000928/202012

Applicant(s): various

PRAC Lead: Annika Folin

Scope: Evaluation of a PSUSA procedure

16.3.23. Desmopressin (NAP) - PSUSA/00000964/202012

Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.3.24. Diacerein (NAP) - PSUSA/00001026/202012

Applicant(s): various

PRAC Lead: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

16.3.25. Doxazosin (NAP) - PSUSA/00001169/202012

Applicant(s): various

PRAC Lead: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

16.3.26. Exemestane (NAP) - PSUSA/00001345/202012

Applicant(s): various

PRAC Lead: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

16.3.27. Famciclovir (NAP) - PSUSA/00001349/202012

Applicant(s): various

PRAC Lead: Jana Lukacisinova

Scope: Evaluation of a PSUSA procedure

16.3.28. Ferric carboxymaltose⁸⁵ (NAP) - PSUSA/00010865/202101

Applicant(s): various

PRAC Lead: Zane Neikena

⁸⁵ Parenteral preparation(s) only

Scope: Evaluation of a PSUSA procedure

16.3.29. Iron dextran (NAP) - PSUSA/00010696/202101

Applicant(s): various

PRAC Lead: Zane Neikena

Scope: Evaluation of a PSUSA procedure

16.3.30. Iron isomaltoside⁸⁶ (NAP) - PSUSA/00010866/202101

Applicant(s): various

PRAC Lead: Zane Neikena

Scope: Evaluation of a PSUSA procedure

16.3.31. Iron sucrose⁸⁷ (NAP) - PSUSA/00010864/202101

Applicant(s): various

PRAC Lead: Zane Neikena

Scope: Evaluation of a PSUSA procedure

16.3.32. Levonorgestrel, ethinylestradiol; ethinylestradiol⁸⁸ (NAP) - PSUSA/00010442/202101

Applicant(s): various

PRAC Lead: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

16.3.33. Lormetazepam (NAP) - PSUSA/00001910/202012

Applicant(s): various

PRAC Lead: Sonja Hrabcik

Scope: Evaluation of a PSUSA procedure

16.3.34. Pseudoephedrine, triprolidine (NAP) - PSUSA/00003047/202012

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.3.35. Rupatadine (NAP) - PSUSA/00002673/202012

Applicant(s): various

⁸⁶ Parenteral preparation(s) only

⁸⁷ Parenteral preparation(s) only

⁸⁸ Combination pack only

PRAC Lead: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

16.3.36. Sodium iron gluconate⁸⁹ (NAP) - PSUSA/00010867/202101

Applicant(s): various

PRAC Lead: Zane Neikena

Scope: Evaluation of a PSUSA procedure

16.3.37. Tobramycin^{90 91} (NAP) - PSUSA/00009316/202012

Applicant(s): various

PRAC Lead: Ilaria Baldelli

Scope: Evaluation of a PSUSA procedure

16.4. Follow-up to PSUR/PSUSA procedures

16.4.1. Docetaxel - TAXOTERE (CAP) - EMEA/H/C/000073/LEG 039.1

Applicant: Sanofi Mature IP

PRAC Rapporteur: Tiphaine Vaillant

Scope: MAH's response to LEG 039 [detailed review on the potential risk for decreased efficacy of docetaxel when used along with any selective cyclooxygenase-2 (Cox-2) inhibitors as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00001152/201911) adopted in July 2020] as per the request for supplementary information (RSI) adopted in April 2021

16.4.2. Etanercept - ENBREL (CAP) - EMEA/H/C/000262/LEG 174

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Eva Segovia

Scope: Cumulative review of cases of dyslipidaemia including clinical trial data, published medical literature, and post-marketing events reported in the MAH's global safety database, in line with the conclusions of the PSUR single assessment (PSUSA) procedure for infliximab (PSUSA/00010759/201908) adopted in April 2020 and as requested following the conclusions of LEG 0161 for infliximab dated December 2020

16.4.3. Sitagliptin - JANUVIA (CAP) - EMEA/H/C/000722/LEG 041

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Cumulative review and analysis on the risk of malignancies/neoplasms particularly

⁸⁹ Parenteral preparation(s) only

⁹⁰ Nebuliser solution only

⁹¹ Non-centrally authorised product(s) only

pancreatic carcinoma from clinical trials, literature and post-marketing data as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00010673/202008) adopted in March 2021

16.4.4. Sitagliptin - RISTABEN (CAP) - EMEA/H/C/001234/LEG 019

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Cumulative review and analysis on the risk of malignancies/neoplasms particularly pancreatic carcinoma from clinical trials, literature and post-marketing data as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00010673/202008) adopted in March 2021

16.4.5. Sitagliptin - TESAVEL (CAP) - EMEA/H/C/000910/LEG 035

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Cumulative review and analysis on the risk of malignancies/neoplasms particularly pancreatic carcinoma from clinical trials, literature and post-marketing data as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00010673/202008) adopted in March 2021

16.4.6. Sitagliptin - XELEVIA (CAP) - EMEA/H/C/000762/LEG 040

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Cumulative review and analysis on the risk of malignancies/neoplasms particularly pancreatic carcinoma from clinical trials, literature and post-marketing data as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00010673/202008) adopted in March 2021

16.4.7. Sitagliptin, metformin hydrochloride - EFFICIB (CAP) - EMEA/H/C/000896/LEG 020

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Cumulative review and analysis on the risk of malignancies/neoplasms particularly pancreatic carcinoma from clinical trials, literature and post-marketing data as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00010673/202008) adopted in March 2021

16.4.8. Sitagliptin, metformin hydrochloride - JANUMET (CAP) - EMEA/H/C/000861/LEG 020

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Cumulative review and analysis on the risk of malignancies/neoplasms particularly

pancreatic carcinoma from clinical trials, literature and post-marketing data as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00010673/202008) adopted in March 2021

16.4.9. Sitagliptin, metformin hydrochloride - RISTFOR (CAP) - EMEA/H/C/001235/LEG 016

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Cumulative review and analysis on the risk of malignancies/neoplasms particularly pancreatic carcinoma from clinical trials, literature and post-marketing data as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00010673/202008) adopted in March 2021

16.4.10. Sitagliptin, metformin hydrochloride - VELMETIA (CAP) - EMEA/H/C/000862/LEG 020

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Cumulative review and analysis on the risk of malignancies/neoplasms particularly pancreatic carcinoma from clinical trials, literature and post-marketing data as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00010673/202008) adopted in March 2021

16.5. Variation procedure(s) resulting from PSUSA evaluation

16.5.1. Coronavirus (COVID-19) mRNA⁹² vaccine (nucleoside-modified) - SPIKEVAX (CAP) - EMEA/H/C/005791/II/0015/G

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Hans Christian Siersted

Scope: Grouped variations to address PRAC requests raised as per the conclusions of the second and third monthly safety summary report (MSSR) procedures (MEA 011.1 and MEA 011.2) respectively: 1) update of sections 4.4 of the SmPC to provide additional safety information regarding hypersensitivity and anaphylaxis, as requested by PRAC in the second MSSR. The package leaflet is updated accordingly; 2) update of section 4.8 of the SmPC to include 'delayed injection site reaction' as an adverse reaction with a frequency 'common', as requested by PRAC in the third MSSR. The package leaflet is updated accordingly. In addition, the MAH submitted a justification for not adding diarrhoea to the product information as an adverse reaction as requested by PRAC in the third MSSR and took the opportunity to introduce minor editorial changes in the product information

16.5.2. Emicizumab - HEMLIBRA (CAP) - EMEA/H/C/004406/II/0025

Applicant: Roche Registration GmbH

PRAC Rapporteur: Ilaria Baldelli

⁹² Messenger ribonucleic acid

Scope: Update of sections 4.4, 4.8 and 5.1 of the SmPC concerning immunogenicity and loss of efficacy due to anti-emicizumab antibodies as requested in the conclusions of the latest periodic safety update report single assessment (PSUSA) procedure (PSUSA/00010668/202011) adopted in June 2021, together with a review of haemorrhagic cases as requested in the conclusions of the PSUSA procedure (PSUSA/00010668/202005) finalised in January 2021. The RMP (version 3.0) is updated accordingly

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, PRAC adopted the conclusion of the Rapporteurs on their assessment for the below-listed medicines without further plenary discussion.

17.1. Protocols of PASS imposed in the marketing authorisation(s)⁹³

17.1.1. Lenalidomide – REVLIMID (CAP) - EMEA/H/C/PSA/S/0075

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Tiphaine Vaillant

Scope: Substantial amendment to a protocol previously agreed in December 2017 (PSA/S/0016.2) for study CC-5013-MDS-012: a post-authorisation, non-interventional, retrospective, drug-utilisation study (DUS) to describe the pattern of use of lenalidomide in patients with myelodysplastic syndromes (MDS)

17.1.2. Methylphenidate hydrochloride (NAP) - EMEA/H/N/PSA/S/0074

Applicant: Medice Arzneimittel Pütter GmbH & Co. KG (Medikinet)

PRAC Rapporteur: Martin Huber

Scope: Substantial amendment to a protocol previously agreed in November 2020 (PSP/S/0064.5): a multicentre, observational, prospective PASS to evaluate the safety concerns of long-term cardiovascular and psychiatric risks within the adult attention deficit/hyperactivity disorder (ADHD) population taking Medikinet Retard (methylphenidate hydrochloride) according to normal standard clinical practice

17.1.3. Parathyroid hormone – NATPAR (CAP) - EMEA/H/C/PSA/S/0053.3

Applicant: Shire Pharmaceuticals Ireland Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: MAH's response to PSA/S/0053.2 [substantial amendment to a protocol previously agreed in March 2018 (PSA/S/0026) for study PARADIGHM (physicians advancing disease knowledge in hypoparathyroidism): a registry for subjects with chronic hypoparathyroidism to explore physicians advancing disease knowledge in hypoparathyroidism] as per the request for supplementary information (RSI) adopted in November 2020

⁹³ In accordance with Article 107n of Directive 2001/83/EC

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

17.2.1. Alpelisib - PIQRAY (CAP) - EMEA/H/C/004804/MEA 003

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Menno van der Elst

Scope: Protocol for study CBYL719C2005: a survey among healthcare professionals treating patients with metastatic breast cancer in selected European countries to evaluate their knowledge on management of hyperglycemia when using Piqray (alpelisib) as included in the educational material

17.2.2. Cabotegravir - VOCABRIA (CAP) - EMEA/H/C/004976/MEA 004.1

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Martin Huber

Scope: MAH's response to MEA 004 [protocol for study 215162 (listed as a category 3 study in the RMP): a prospective observational cohort study to monitor for hepatotoxicity and regimen discontinuation due to liver related adverse events among patients initiating cabotegravir-containing antiretroviral regimen [final clinical study report (CSR): expected in March 2027] as per the request for supplementary information (RSI) adopted in April 2021

17.2.3. Cabotegravir - VOCABRIA (CAP) - EMEA/H/C/004976/MEA 005.1

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Martin Huber

Scope: MAH's response to MEA 005 [protocol for study 215163: a study on pregnancy and neonatal outcomes following prenatal exposure to cabotegravir long acting (CAB LA) – data from the European Pregnancy and Paediatric human immunodeficiency virus (HIV) Cohort Collaboration (EPPICC)] as per the request for supplementary information (RSI) adopted in April 2021

17.2.4. Cabotegravir - VOCABRIA (CAP) - EMEA/H/C/004976/MEA 006.1

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Martin Huber

Scope: MAH's response to MEA 006 [protocol for study 215325: a study on pregnancy and neonatal outcomes following prenatal exposure to cabotegravir – data from the Antiretroviral Pregnancy Registry (APR)] as per the request for supplementary information (RSI) adopted in April 2021

⁹⁴ In accordance with Article 107m of Directive 2001/83/EC, supervised by PRAC in accordance with Article 61a (6) of Regulation (EC) No 726/2004

17.2.5. [Coronavirus \(COVID-19\) mRNA⁹⁵ vaccine \(nucleoside-modified\) - SPIKEVAX \(CAP\) - EMEA/H/C/005791/MEA 004.3](#)

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Hans Christian Siersted

Scope: MAH's response to MEA 004.2 [protocol for a study (listed as a category 3 study in the RMP): a post-authorisation active surveillance safety study using secondary data to monitor real-world safety of the COVID-19 mRNA-1273 vaccine in Europe [final clinical study report (CSR) expected in December 2023]] as per the request for supplementary information (RSI) adopted in July 2021

17.2.6. [Coronavirus \(COVID-19\) mRNA⁹⁶ vaccine \(nucleoside-modified\) - SPIKEVAX \(CAP\) - EMEA/H/C/005791/MEA 034.1](#)

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Hans Christian Siersted

Scope: MAH's response to MEA 034 [protocol for a study monitoring the safety of Spikevax (COVID-19 vaccine) in pregnancy: an observational study using routinely collected health data in five European countries] as per the request for supplementary information (RSI) adopted in July 2021

17.2.7. [Fenofibrate, pravastatin sodium - PRAVAFENIX \(CAP\) - EMEA/H/C/001243/MEA 007.8](#)

Applicant: Laboratoires SMB s.a.

PRAC Rapporteur: Tiphaine Vaillant

Scope: MAH's response to MEA 007.6 [amendment to a protocol previously agreed in 2014 for study POSE (Pravafenix Observational Study in Europe) (EUPAS13661): a European, observational, three-year cohort comparative study on the safety of the fixed dose combination pravastatin 40 mg/fenofibrate 160 mg (Pravafenix) versus statin alone in real clinical practice] as per the request for supplementary information (RSI) adopted in April 2021

17.2.8. [Filgotinib - JYSELECA \(CAP\) - EMEA/H/C/005113/MEA 011](#)

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Protocol for study GS-EU-417-9050: a non-interventional post-authorisation cross-sectional safety study evaluating the effectiveness of the additional risk minimisation measures for filgotinib use in patients with rheumatoid arthritis within the German registry Rheumatoide Arthritis: Beobachtung der Biologika-Therapie (RABBIT)

⁹⁵ Messenger ribonucleic acid

⁹⁶ Messenger ribonucleic acid

17.2.9. Filgotinib - JYSELECA (CAP) - EMEA/H/C/005113/MEA 012

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Protocol for study GS-EU-417-5885: a non-interventional post-authorisation cross-sectional safety study evaluating the effectiveness of the additional risk minimisation measures for filgotinib use in patients with rheumatoid arthritis within the Anti-Rheumatic Treatment in Denmark (DANBIO) register

17.2.10. Filgotinib - JYSELECA (CAP) - EMEA/H/C/005113/MEA 013

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Protocol for study GS-EU-417-5884: a non-interventional post-authorisation cross-sectional safety study evaluating the effectiveness of the additional risk minimisation measures for filgotinib use in patients within the Spanish Register of Adverse Events of Biological Therapies in Rheumatoid Diseases (BIOBADASER)]

17.2.11. Filgotinib - JYSELECA (CAP) - EMEA/H/C/005113/MEA 014

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Protocol for study GS-EU-417-9052: a non-interventional post-authorisation cross-sectional safety study evaluating the effectiveness of the additional risk minimisation measures for filgotinib use in patients with rheumatoid arthritis within British Society for Rheumatology Biologics Register Rheumatoid Arthritis (BSRBR-RA)

17.2.12. Filgotinib - JYSELECA (CAP) - EMEA/H/C/005113/MEA 015

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Protocol for study GS-EU-417-9051: a non-interventional post-authorisation cross-sectional safety study evaluating the effectiveness of the additional risk minimisation measures for filgotinib use in patients with rheumatoid arthritis within the Anti-Rheumatic Treatment in Sweden (ARTIS) register

17.2.13. Inotersen - TEGSEDI (CAP) - EMEA/H/C/004782/MEA 001.6

Applicant: Akcea Therapeutics Ireland Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: MAH's response to MEA 001.5 [amendment to a protocol previously agreed in September 2020 for study TEG4001: a prospective, non-interventional, long-term, multinational cohort safety study of patients with hereditary transthyretin amyloidosis with polyneuropathy (hATTR-PN)] as per the request for supplementary information (RSI) adopted in April 2021

17.2.14. Isatuximab - SARCLISA (CAP) - EMEA/H/C/004977/MEA 002.1

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Eva Segovia

Scope: MAH's response to MEA 002 [protocol for study SARSAC09715: a non-interventional PASS survey to evaluate the effectiveness of isatuximab educational materials to minimise the risk of interference for blood typing (minor antigen) (positive indirect Coombs' test)] as per the request for supplementary information (RSI) adopted in March 2021

17.2.15. Naltrexone hydrochloride, bupropion hydrochloride - MYSIMBA (CAP) - EMEA/H/C/003687/MEA 003.10

Applicant: Orexigen Therapeutics Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: Third feasibility assessment report and protocol for study NB-451: an observational retrospective drug utilisation study (DUS) of Mysimba (naltrexone hydrochloride/bupropion hydrochloride) in Europe and the United States to describe the demographic and baseline characteristics of users of Mysimba (naltrexone hydrochloride/bupropion hydrochloride), evaluate patterns of Mysimba (naltrexone hydrochloride/bupropion hydrochloride) initiation and use

17.2.16. Netarsudil - RHOKIINSA (CAP) - EMEA/H/C/004583/MEA 001.2

Applicant: Aerie Pharmaceuticals Ireland Limited

PRAC Rapporteur: Eva Segovia

Scope: MAH's response to MEA 001.1 [protocol for study AR-13324-OBS02: a non-interventional, observational cohort study of 2-year of treatment with Rhokiinsa (netarsudil) compared with non-Rhokiinsa (netarsudil) ocular hypotensive therapy in patients with elevated intraocular pressure due to primary open angle glaucoma or ocular hypertension [final clinical study report (CSR) expected in June 2026]] as per the request for supplementary information (RSI) adopted in March 2021

17.2.17. Ozanimod - ZEPOSIA (CAP) - EMEA/H/C/004835/MEA 001.1

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Maria del Pilar Rayon

Scope: MAH's response to MEA 001 [protocol for study RPC-1063-MS-004 (listed as a category 3 study in the RMP): a post authorisation multinational long-term non-interventional study (ORION) study on ozanimod real world safety [final clinical study report (CSR) expected in December 2031] as per the request for supplementary information (RSI) adopted in March 2021

17.2.18. Somapacitan - SOGROYA (CAP) - EMEA/H/C/005030/MEA 002

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Martin Huber

Scope: Protocol for study NN8640-4515: a multinational, multicentre, prospective, open label, single-arm, observational, non-interventional PASS to investigate long-term safety of somapacitan in adults with growth hormone deficiency (AGHD) under normal clinical practice conditions (from initial marketing authorisation/opinion)

17.2.19. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/MEA 017

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Protocol for study A3921352: an active surveillance, post-authorisation study to characterise the safety of tofacitinib in patients with moderately to severely active ulcerative colitis in the real-world setting using data from the united registries for clinical assessment and research (UR-CARE) in the European Union (EU)

17.2.20. Trastuzumab deruxtecan - ENHERTU (CAP) - EMEA/H/C/005124/MEA 003

Applicant: Daiichi Sankyo Europe GmbH

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Protocol for an EU survey of relevant healthcare professionals on the understanding of key risk minimisation measures pertaining to interstitial lung disease (ILD)/pneumonitis with trastuzumab deruxtecan treatment (from initial marketing authorisation/opinion)

17.2.21. Venetoclax - VENCLYXTO (CAP) - EMEA/H/C/004106/MEA 002.8

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Eva Jirsová

Scope: Amendment to a protocol previously agreed in September 2019 for study P16-562 (listed as a category 3 study in the RMP): a prospective observational study to assess the long-term safety profile of venetoclax in a Swedish cohort of chronic lymphocytic leukaemia (CLL) patients

17.2.22. Zanamivir - DECTOVA (CAP) - EMEA/H/C/004102/MEA 003

Applicant: GlaxoSmithKline Trading Services Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Protocol for study 208140: an intravenous (IV) zanamivir pregnancy registry to evaluate pregnancy outcomes among women exposed to IV zanamivir at any time during pregnancy (from initial marketing authorisation/opinion)

17.3. Results of PASS imposed in the marketing authorisation(s)⁹⁷

17.3.1. Dexamfetamine (NAP) - EMEA/H/N/PSR/S/0028

Applicant: Medice Arzneimittel Pütter GmbH & Co. KG

⁹⁷ In accordance with Article 107p-q of Directive 2001/83/EC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: MAH's response to PSR/S/0028 [results of a PASS to evaluate the long-term safety of dexamfetamine to assess the incidence proportion and incidence rate for cardiovascular, psychiatric, growth and sexual maturity related adverse events in children with a diagnosis of attention deficit hyperactivity disorder (ADHD) who have been treated with dexamfetamine, methylphenidate or lisdexamfetamine as recorded in healthcare databases of three countries. The study also compares the risk of long-term cardiovascular, psychiatric, growth and sexual maturity-related adverse events of dexamfetamine versus methylphenidate or lisdexamfetamine in each database] as per the request for supplementary information (RSI) adopted in April 2021

17.3.2. Dexamfetamine (NAP) - EMEA/H/N/PSR/S/0029

Applicant: Medice Arzneimittel Pütter GmbH & Co. KG

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: MAH's response to PSR/S/0029 [Results of a drug utilisation study (DUS) to collect data on abuse, misuse, overdose, diversion and dependence related to dexamfetamine in five European countries] as per the request for supplementary information (RSI) adopted in April 2021

17.4. Results of PASS non-imposed in the marketing authorisation(s)⁹⁸

17.4.1. Axicabtagene ciloleucel - YESCARTA (CAP) - EMEA/H/C/004480/II/0040, Orphan

Applicant: Kite Pharma EU B.V., ATMP⁹⁹

PRAC Rapporteur: Anette Kirstine Stark

Scope: Submission of the final study report for non-interventional study KT-EU-471-0116 (listed as category 3 study in the RMP): a quantitative testing of healthcare provider knowledge about Yescarta (axicabtagene ciloleucel) risk minimisation measures

17.4.2. Dapivirine - DAPIVIRINE VAGINAL RING 25 MG (Art 58¹⁰⁰) - EMEA/H/W/002168/II/0011

Applicant: International Partnership for Microbicides Belgium AISBL

PRAC Rapporteur: Jan Neuhauser

Scope: Submission of the final report from study MTN-16 (EMBRACE) (listed as a category 3 study in the RMP): an observational cohort study in women with exposure to active and non-active investigational product who became pregnant in phase 3 trial MTN-020 (ASPIRE) and open-label extension study MTN-025 (HOPE) and who subsequently enrolled in study MTN-016. This study assessed pregnancy and delivery outcomes in these women and infant follow up for the first year of life. The RMP (version 0.8) is updated accordingly

⁹⁸ 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

⁹⁹ Advanced therapy medicinal product

¹⁰⁰ 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)

17.4.3. [Dibotermin alfa - INDUCTOS \(CAP\) - EMEA/H/C/000408/II/0100](#)

Applicant: Medtronic BioPharma B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Submission of the final study report from study EUPAS32916 (listed as a category 3 study in the RMP): an observational study to evaluate the effectiveness of additional risk minimisation measures for InductOs (dibotermin alfa). The product information and the RMP (version 2.1) are updated accordingly. In addition, the MAH took the opportunity to submit study protocol for study EUPAS32916 as suggested by PRAC

17.4.4. [Etanercept - ENBREL \(CAP\) - EMEA/H/C/000262/II/0244](#)

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Eva Segovia

Scope: Submission of the final report from study B1801310 (BIKER) (listed as a category 3 study in the RMP): an observational PASS of etanercept and methotrexate in the treatment of juvenile idiopathic arthritis (JIA) using data obtained from participants in the German Biologics JIA registry (BIKER) to monitor long-term safety and effectiveness of etanercept in the treatment of JIA in regular clinical practice

17.4.5. [Herpes zoster vaccine \(recombinant, adjuvanted\) - SHINGRIX \(CAP\) - EMEA/H/C/004336/II/0045](#)

Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Sonja Hrabcik

Scope: Update of section 4.4 of the SmPC in order to add a new warning on an increased risk of Guillain-Barré syndrome (GBS) after vaccination with Shingrix (herpes zoster vaccine) observed in a post-marketing observational study in individuals aged 65 years or older. The package leaflet and the RMP (version 5.1) are updated accordingly. In addition, the MAH took the opportunity to make some editorial changes to the SmPC and to update the list of local representatives in the package leaflet

17.4.6. [Human normal immunoglobulin - HYQVIA \(CAP\) - EMEA/H/C/002491/II/0070/G](#)

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Grouped variations consisting of: 1) update of section 4.6 of the SmPC in order to update information on pregnancy and breast-feeding based on the final results from study 161301 (listed as a category 3 study in the RMP): an observational pregnancy registry study to collect long-term safety data from women treated with HyQvia (human normal immunoglobulin). The package leaflet and the RMP (version 12.0) are updated accordingly. In addition, the MAH took the opportunity to implement minor corrections and editorial changes to the SmPC; 2) submission of an updated RMP (version 12.0) to update the educational material (additional risk minimisation measures) as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00001633/202005) finalised in January 2021

17.4.7. [Insulin glargine, lixisenatide - SULIQUA \(CAP\) - EMEA/H/C/004243/II/0023](#)

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Menno van der Elst

Scope: Submission of the final study report from study EUPAS 19769 (listed as a category 3 study in the RMP): a registry to monitor the occurrence of events of interest including acute pancreatitis, pancreatic cancer and thyroid cancer, especially medullary carcinoma of the thyroid (MCT), among adult type 2 diabetes patients treated with lixisenatide using data from national registers and databases in Italy and Belgium (in fulfilment of post-authorisation measure (PAM) MEA 005.3)

17.4.8. [Lixisenatide - LYXUMIA \(CAP\) - EMEA/H/C/002445/II/0033](#)

Applicant: sanofi-aventis groupe

PRAC Rapporteur: Annika Folin

Scope: Submission of the final report of study EUPAS 19769 (listed as a category 3 study in the RMP): a registry to monitor the occurrence of events of interest including acute pancreatitis, pancreatic cancer and thyroid cancer, especially medullary carcinoma of the thyroid, among adult type 2 diabetes patients treated with lixisenatide using data from national registers and databases in Italy and Belgium. The RMP (version 7.0) is updated accordingly (in fulfilment of post-authorisation measure (PAM) MEA 008.5)

17.4.9. [Pegfilgrastim - NEULASTA \(CAP\) - EMEA/H/C/000420/II/0116](#)

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Submission of the final report from study 20170701 (listed as a category 3 study in the RMP): an observational study to assess the effectiveness of the Neulasta (pegfilgrastim) patient alert card and to measure medication errors related to the use of the on-body injector. The RMP (version 8.0) is updated accordingly

17.4.10. [Talimogene laherparepvec - IMLYGIC \(CAP\) - EMEA/H/C/002771/II/0044](#)

Applicant: Amgen Europe B.V., ATMP¹⁰¹

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Submission of the final report from study 20180099 (listed as a category 3 study in the RMP): a cross-sectional survey to evaluate physician knowledge of safety messages included in the physician education booklet (PEB) for Imlygic (talimogene laherparepvec)

17.4.11. [Trastuzumab - ONTRUZANT \(CAP\) - EMEA/H/C/004323/II/0036](#)

Applicant: Samsung Bioepis NL B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Submission of the final report from clinical study SB3-G31-BC-E (listed as a

¹⁰¹ Advanced therapy medicinal product

category 3 study in the RMP): an observational cohort study assessing the long-term cardiac safety (for cardiac safety and survival cohort) and survival (survival only cohort and cardiac safety and survival cohort) in patients who received treatment with trastuzumab. The RMP (version 5.0) is updated accordingly

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

17.5.1. Acridinium - BRETARIS GENUAIR (CAP) - EMEA/H/C/002706/ANX 001.9

Applicant: AstraZeneca AB

PRAC Rapporteur: Adam Przybylkowski

Scope: Third interim report for study D6560R00004, formerly M/34273/44, (listed as a category 1 in Annex II and the RMP): an observational study evaluating the risk of cardiovascular endpoints of acridinium bromide-containing products versus other chronic obstructive pulmonary disease (COPD) medications in COPD patients - sub-study report addressing the acute myocardial infarction (AMI) report and stroke components of the PASS programme

17.5.2. Acridinium - EKLIRA GENUAIR (CAP) - EMEA/H/C/002211/ANX 001.9

Applicant: AstraZeneca AB

PRAC Rapporteur: Adam Przybylkowski

Scope: Third interim report for study D6560R00004, formerly M/34273/44, (listed as a category 1 in Annex II and the RMP): an observational study evaluating the risk of cardiovascular endpoints of acridinium bromide-containing products versus other chronic obstructive pulmonary disease (COPD) medications in COPD patients - sub-study report addressing the acute myocardial infarction (AMI) report and stroke components of the PASS programme

17.5.3. Acridinium, formoterol fumarate dihydrate - BRIMICA GENUAIR (CAP) - EMEA/H/C/003969/ANX 003.6

Applicant: AstraZeneca AB

PRAC Rapporteur: Adam Przybylkowski

Scope: Third interim report for study D6560R00004, formerly M/34273/44, (listed as a category 1 in Annex II and the RMP): an observational study evaluating the risk of cardiovascular endpoints of acridinium bromide-containing products versus other chronic obstructive pulmonary disease (COPD) medications in COPD patients - sub-study report addressing the acute myocardial infarction (AMI) report and stroke components of the PASS programme

17.5.4. Acridinium, formoterol fumarate dihydrate - DUAKLIR GENUAIR (CAP) - EMEA/H/C/003745/ANX 003.6

Applicant: AstraZeneca AB

PRAC Rapporteur: Adam Przybylkowski

Scope: Third interim report for study D6560R00004, formerly M/34273/44, (listed as a category 1 in Annex II and the RMP): an observational study evaluating the risk of cardiovascular endpoints of acridinium bromide-containing products versus other chronic obstructive pulmonary disease (COPD) medications in COPD patients - sub-study report addressing the acute myocardial infarction (AMI) report and stroke components of the PASS programme

17.5.5. Apremilast - OTEZLA (CAP) - EMEA/H/C/003746/MEA 008.1

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Eva Segovia

Scope: Second yearly report for study CC 10004 PSA-012: evaluation of the long-term safety and safety outcomes for psoriatic arthritis patients treated with Otezla (apremilast) in the British Society for Rheumatology Psoriatic Arthritis Register (BSRBR-PsA) [final clinical study report (CSR) expected in Q2 2026]

17.5.6. Brodalumab - KYNTHEUM (CAP) - EMEA/H/C/003959/MEA 002.5

Applicant: LEO Pharma A/S

PRAC Rapporteur: Eva Segovia

Scope: Second study progress report for study NIS-KYNTHEUM-1345: an observational PASS investigating the risk of suicidal behaviour, serious infections, major adverse cardiovascular events (MACE) and malignancy in psoriasis patients treated with brodalumab. The brodalumab assessment of hazards: a multinational safety (BRAHMS) study in electronic healthcare databases [final report expected in Q3 2030]

17.5.7. Coronavirus (COVID-19) mRNA¹⁰² vaccine (nucleoside-modified) - COMIRNATY (CAP) - EMEA/H/C/005735/MEA 010

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Interim report for study C4591012: a post-emergency use authorisation active safety surveillance study among individuals in the veteran's affairs health system receiving Comirnaty (COVID-19 mRNA vaccine) in real-world use [final clinical study report (CSR) expected in December 2023]

17.5.8. Delamanid - DELTYBA (CAP) - EMEA/H/C/002552/MEA 002.4

Applicant: Otsuka Novel Products GmbH

PRAC Rapporteur: Laurence de Fays

Scope: MAH's response to MEA 002.3 [fourth annual progress report for study 242-12-402 (listed as a category 3 study in the RMP): a multicentre EU-wide observational non-interventional post-authorisation study to assess the safety and drug usage of delamanid (OPC-67683) in routine medical practice in multidrug-resistant tuberculosis patients (Delamanid registry)] as per the request for supplementary information (RSI) adopted in

¹⁰² Messenger ribonucleic acid

February 2021

17.5.9. Dimethyl fumarate - SKILARENCE (CAP) - EMEA/H/C/002157/MEA 001.5

Applicant: Almirall S.A

PRAC Rapporteur: Annika Folin

Scope: Third annual interim results for study M-41008-40 (listed as a category 3 study in the RMP): an observational PASS in European psoriasis registers to evaluate the long-term safety of Skilarence (dimethyl fumarate) used for the treatment of patients with moderate to severe psoriasis [future due date(s): end of data collection: Q1 2027; final study report expected within a year of availability of the final data set]

17.5.10. Dimethyl fumarate - TECFIDERA (CAP) - EMEA/H/C/002601/MEA 007.3

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Martin Huber

Scope: MAH's response to MEA 007.2 [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] as per the request for supplementary information (RSI) adopted in April 2021, together with the sixth annual progress report for the study

17.5.11. Dimethyl fumarate - TECFIDERA (CAP) - EMEA/H/C/002601/MEA 008.7

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Martin Huber

Scope: Fifth annual progress report for study 109MS402 (listed as a category 3 study in the RMP): Biogen multiple sclerosis (MS) pregnancy exposure registry to prospectively evaluate pregnancy outcomes in women with MS who were exposed to a registry-specified Biogen MS product during the eligibility window for that product

17.5.12. Fenofibrate, pravastatin sodium - PRAVAFENIX (CAP) - EMEA/H/C/001243/MEA 007.9

Applicant: Laboratoires SMB s.a.

PRAC Rapporteur: Tiphaine Vaillant

Scope: MAH's response to MEA 007.7 [interim results for study POSE (Pravafenix Observational Study in Europe) (EUPAS13661): a European, observational, three-year cohort comparative study on the safety of the fixed dose combination pravastatin 40 mg/ fenofibrate 160 mg (Pravafenix) versus statin alone in real clinical practice] as per the request for supplementary information (RSI) adopted in April 2021

17.5.13. Filgrastim - FILGRASTIM HEXAL (CAP) - EMEA/H/C/000918/MEA 007.11

Applicant: Hexal AG

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to MEA 007.11 [tenth annual report for study EP06-501 (SMART): a non-interventional, prospective, long-term safety data collection of Zarzio/Filgrastim Hexal (filgrastim) in healthy unrelated stem cell donors undergoing peripheral blood progenitor cell (PBPC) mobilisation [final clinical study report (CSR) expected in December 2024]] as per the request for supplementary information (RSI) adopted in June 2021

17.5.14. Filgrastim - ZARZIO (CAP) - EMEA/H/C/000917/MEA 007.11

Applicant: Sandoz GmbH

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to MEA 007.11 [tenth annual report for study EP06-501 (SMART): a non-interventional, prospective, long-term safety data collection of Zarzio/Filgrastim Hexal (filgrastim) in healthy unrelated stem cell donors undergoing peripheral blood progenitor cell (PBPC) mobilisation [final clinical study report (CSR) expected in December 2024]] as per the request for supplementary information (RSI) adopted in June 2021

17.5.15. Fingolimod - GILENYA (CAP) - EMEA/H/C/002202/MEA 012.10

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Tiphaine Vaillant

Scope: Tenth 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)

17.5.16. Flutemetamol (¹⁸F) - VIZAMYL (CAP) - EMEA/H/C/002557/MEA 003.3

Applicant: GE Healthcare AS

PRAC Rapporteur: Martin Huber

Scope: First study progress report for study GE-067-028: a post-authorisation survey of nuclear medicine physicians and radiologists in Europe to evaluate trends and patterns in Vizamyl (flutemetamol (¹⁸F)) use in everyday clinical practice in the EU

17.5.17. Guanfacine - INTUNIV (CAP) - EMEA/H/C/003759/MEA 005.5

Applicant: Shire Pharmaceuticals Ireland Limited

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Third 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] together with MAH's response to MEA 005.4 as adopted in October 2020

17.5.18. Influenza vaccine (live attenuated, nasal) - FLUENZ TETRA (CAP) - EMEA/H/C/002617/MEA 004.12

Applicant: AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: Annual report for the passive enhanced safety surveillance (ESS) D2560C00008: a post-marketing non-interventional cohort study of the safety of live attenuated influenza vaccine (LAIV) in subjects 2 through 17 years of age for the 2020-2021 influenza season

17.5.19. Insulin lispro - HUMALOG (CAP) - EMEA/H/C/000088/MEA 028.8

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Annika Folin

Scope: Eighth interim report (batches released to the market between 01 April 2020 to 31 March 2021 [period 2]): a post-approval safety surveillance for monthly lot-specific adverse event review and analysis to evaluate any potential change in the frequency of hypersensitivity, local site injection reactions, immunogenicity, hypoglycaemia and lack of drug effect events comparing events from the new manufacturing process with events reported using drug substance from both the historic and concurrent process

17.5.20. Insulin lispro - LIPROLOG (CAP) - EMEA/H/C/000393/MEA 021.8

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Annika Folin

Scope: Eighth interim report (batches released to the market between 01 April 2020 to 31 March 2021 [period 2]): a post-approval safety surveillance for monthly lot-specific adverse event review and analysis to evaluate any potential change in the frequency of hypersensitivity, local site injection reactions, immunogenicity, hypoglycaemia and lack of drug effect events comparing events from the new manufacturing process with events reported using drug substance from both the historic and concurrent process

17.5.21. Luspatercept - REBLOZYL (CAP) - EMEA/H/C/004444/MEA 002

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Laurence de Fays

Scope: First annual report for study ACE-536-LTFU-001: a study to evaluate the long-term safety, including thromboembolic events (TEEs) and progression to acute myeloid leukaemia (AML) and/or other malignancies/pre malignancies of luspatercept in patients who have participated in company-sponsored luspatercept clinical trials [final clinical study report (CSR) expected in Q2 2029]

17.5.22. Lutetium (¹⁷⁷Lu) oxodotreotide - LUTATHERA (CAP) - EMEA/H/C/004123/MEA 001.7

Applicant: Advanced Accelerator Applications

PRAC Rapporteur: Adam Przybylkowski

Scope: Second quarterly progress report for study A-LUT-T-E02-402 (SALUS study) (listed

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

17.5.23. Octocog alfa - KOVALTRY (CAP) - EMEA/H/C/003825/MEA 005.3

Applicant: Bayer AG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Annual interim report 2020 for epidemiological study 15689: an evaluation of adverse events of special interest (AESI) in the European PEDIatric NETwork (PedNet) for haemophilia management registry

17.5.24. Ravulizumab - ULTOMIRIS (CAP) - EMEA/H/C/004954/MEA 008

Applicant: Alexion Europe SAS

PRAC Rapporteur: Kimmo Jaakkola

Scope: First interim analysis safety report (biennial interim report) for study M07-001 (listed as a category 3 study in the RMP): a prospective registry for an observational, multicentre, multinational study of patients with paroxysmal nocturnal haemoglobinuria (PNH)

17.5.25. Ulipristal acetate - ESMYA (CAP) - EMEA/H/C/002041/MEA 026.3

Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Annika Folin

Scope: Second annual update for an observational study (listed as a category 3 study in the RMP) using EU registries (Spanish drug-induced liver injury (DILI) registry and Prospective European DILI Network (Pro-Euro DILI registry)) 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 (EMEA/H/A-20/1460)

17.5.26. Ulipristal acetate - ESMYA (CAP) - EMEA/H/C/002041/MEA 027.3

Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Annika Folin

Scope: Second annual update for a genetic analysis (HLA) study (listed as a category 3 study in the RMP) from EU registries (Spanish drug-induced liver injury (DILI) registry and Prospective European DILI Network (Pro-Euro DILI registry)) with biomarker data in patients with severe DILI, 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)

17.5.27. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/MEA 045.6

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Rhea Fitzgerald

Scope: Second interim report for study RRA-20745: an observational PASS to describe the safety of ustekinumab and other Crohn's disease treatments in a cohort of patients with Crohn's disease

17.6. Others

17.6.1. Cabazitaxel - CABAZITAXEL ACCORD (CAP) - EMEA/H/C/005178/MEA 001

Applicant: Accord Healthcare S.L.U.

PRAC Rapporteur: Tiphaine Vaillant

Scope: Six-monthly review of cases of 'medication error' for cabazitaxel reported during routine signal management activities

17.6.2. Radium (²²³Ra) dichloride - XOFIGO (CAP) - EMEA/H/C/002653/MEA 016

Applicant: Bayer AG

PRAC Rapporteur: Rugile Pilviniene

Scope: Interim status report for study NCT03574571 (DoRA) (listed as a category 3 study in the RMP): a phase 3 open-label, 1:1 randomised trial of docetaxel vs. docetaxel and radium-223 dichloride for metastatic castration-resistant prostate cancer (mCRPC) sponsored by the prostate Cancer Clinical Trials Consortium (PCCTC) to address the important identified risk of bone fractures [final clinical study report (CSR) expected in Q4 2023] as requested in the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 (EMEA/H/A-20/1459) completed in 2018

17.6.3. Ulipristal acetate - ESMYA (CAP) - EMEA/H/C/002041/MEA 024.3

Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Annika Folin

Scope: Second yearly report on the 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, as requested in the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 completed in 2018 (EMEA/H/A-20/1460)

17.7. New Scientific Advice

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

17.8. Ongoing Scientific Advice

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

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

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

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

Based on the review of the available pharmacovigilance data for the medicines listed below and the CHMP Rapporteur's assessment report, 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. Zanamivir - DECTOVA (CAP) - EMEA/H/C/004102/S/0011 (without RMP)

Applicant: GlaxoSmithKline Trading Services Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Annual reassessment of the marketing authorisation

18.2. Conditional renewals of the marketing authorisation

18.2.1. Autologous peripheral blood T cells CD¹⁰³⁴ and CD8 selected and CD3 and CD28 activated transduced with retroviral vector expressing anti-CD19 CD28/CD3-zeta chimeric antigen receptor and cultured - TECARTUS (CAP) - EMEA/H/C/005102/R/0010 (without RMP)

Applicant: Kite Pharma EU B.V., ATMP¹⁰⁴

PRAC Rapporteur: Menno van der Elst

Scope: Conditional renewal of the marketing authorisation

18.2.2. Coronavirus (COVID-19) mRNA¹⁰⁵ vaccine (nucleoside-modified) - COMIRNATY (CAP) - EMEA/H/C/005735/R/0046 (without RMP)

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Conditional renewal of the marketing authorisation

¹⁰³ Cluster of differentiation

¹⁰⁴ Advanced therapy medicinal product

¹⁰⁵ Messenger ribonucleic acid

18.2.3. Coronavirus (COVID-19) mRNA¹⁰⁶ vaccine (nucleoside-modified) - SPIKEVAX (CAP) - EMEA/H/C/005791/R/0025 (without RMP)

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Hans Christian Siersted

Scope: Conditional renewal of the marketing authorisation

18.2.4. Ixazomib - NINLARO (CAP) - EMEA/H/C/003844/R/0030 (without RMP)

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Annika Folin

Scope: Conditional renewal of the marketing authorisation

18.2.5. Obeticholic acid - OCALIVA (CAP) - EMEA/H/C/004093/R/0027 (without RMP)

Applicant: Intercept Pharma International Limited

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Conditional renewal of the marketing authorisation

18.2.6. Polatuzumab vedotin - POLIVY (CAP) - EMEA/H/C/004870/R/0008 (without RMP)

Applicant: Roche Registration GmbH

PRAC Rapporteur: Annika Folin

Scope: Conditional renewal of the marketing authorisation

18.2.7. Trastuzumab deruxtecan - ENHERTU (CAP) - EMEA/H/C/005124/R/0006 (without RMP)

Applicant: Daiichi Sankyo Europe GmbH

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Conditional renewal of the marketing authorisation

18.3. Renewals of the marketing authorisation

18.3.1. Baricitinib - OLUMIANT (CAP) - EMEA/H/C/004085/R/0025 (without RMP)

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: 5-year renewal of the marketing authorisation

18.3.2. Chlormethine - LEDAGA (CAP) - EMEA/H/C/002826/R/0030 (with RMP)

Applicant: Helsinn Birex Pharmaceuticals Limited

¹⁰⁶ Messenger ribonucleic acid

PRAC Rapporteur: Tiphaine Vaillant

Scope: 5-year renewal of the marketing authorisation

18.3.3. Daptomycin - DAPTOMYCIN HOSPIRA (CAP) - EMEA/H/C/004310/R/0018 (without RMP)

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Pernille Harg

Scope: 5-year renewal of the marketing authorisation

18.3.4. Edotreotide - SOMAKIT TOC (CAP) - EMEA/H/C/004140/R/0019 (with RMP)

Applicant: Advanced Accelerator Applications

PRAC Rapporteur: Ronan Grimes

Scope: 5-year renewal of the marketing authorisation

18.3.5. Insulin glargine, lixisenatide - SULIQUA (CAP) - EMEA/H/C/004243/R/0022 (with RMP)

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Menno van der Elst

Scope: 5-year renewal of the marketing authorisation

18.3.6. Methotrexate - JYLAMVO (CAP) - EMEA/H/C/003756/R/0015 (without RMP)

Applicant: Therakind (Europe) Limited

PRAC Rapporteur: Jan Neuhauser

Scope: 5-year renewal of the marketing authorisation

18.3.7. Miglustat - YARGESA (CAP) - EMEA/H/C/004016/R/0011 (with RMP)

Applicant: Piramal Critical Care B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: 5-year renewal of the marketing authorisation

18.3.8. Pregabalin - PREGABALIN ZENTIVA K.S. (CAP) - EMEA/H/C/004277/R/0019 (with RMP)

Applicant: Zentiva k.s.

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: 5-year renewal of the marketing authorisation

18.3.9. Rituximab - TRUXIMA (CAP) - EMEA/H/C/004112/R/0047 (without RMP)

Applicant: Celltrion Healthcare Hungary Kft.

PRAC Rapporteur: Anette Kirstine Stark

Scope: 5-year renewal of the marketing authorisation

18.3.10. Tadalafil - TADALAFIL LILLY (CAP) - EMEA/H/C/004666/R/0008 (without RMP)

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Maria del Pilar Rayon

Scope: 5-year renewal of the marketing authorisation

18.3.11. Tadalafil - TALMANCO (CAP) - EMEA/H/C/004297/R/0011 (without RMP)

Applicant: Mylan S.A.S

PRAC Rapporteur: Maria del Pilar Rayon

Scope: 5-year renewal of the marketing authorisation

18.3.12. Umeclidinium - ROLUFTA ELLIPTA (CAP) - EMEA/H/C/004654/R/0019 (without RMP)

Applicant: GlaxoSmithKline Trading Services Limited

PRAC Rapporteur: Ilaria Baldelli

Scope: 5-year renewal of the marketing authorisation

19. Annex II – List of participants

including any restrictions with respect to involvement of members / alternates / experts following evaluation of declared interests for the 30 August – 02 September 2021 meeting (marked as 'a') and for the 16 September 2021 ORGAM teleconference (marked as 'b').

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Sabine Straus ^{a, b}	Chair	The Netherlands	No interests declared	Full involvement
Jan Neuhauser ^{a, b}	Member	Austria	No interests declared	Full involvement
Sonja Hrabcik ^a	Alternate	Austria	No interests declared	Full involvement
Jean-Michel Dogné ^a	Member	Belgium	No interests declared	Full involvement
Laurence de Fays ^{a, b}	Alternate	Belgium	No interests declared	Full involvement
Maria Popova-Kiradjieva ^{a, b}	Member	Bulgaria	No interests declared	Full involvement
Nikica Mirošević Skvrce ^{a, b}	Member	Croatia	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
Panagiotis Psaras ^{a, b}	Member	Cyprus	No interests declared	Full involvement
Christina Sylvia Chrysostomou ^{a, b}	Alternate	Cyprus	No interests declared	Full involvement
Eva Jirsová ^{a, b}	Member	Czechia	No interests declared	Full involvement
Jana Lukacisinova ^b	Alternate	Czechia	No interests declared	Full involvement
Anette Kirstine Stark ^{a, b}	Member	Denmark	No interests declared	Full involvement
Hans Christian Siersted ^{a, b}	Alternate	Denmark	No participation in discussion, final deliberations and voting on:	15.3.28. Mepolizumab - NUCALA (CAP) - EMEA/H/C/003 860/II/0036/G 15.3.29. Mepolizumab - NUCALA (CAP) - EMEA/H/C/003 860/II/0037 15.3.30. Mepolizumab - NUCALA (CAP) - EMEA/H/C/003 860/X/0042
Maia Uusküla ^{a, b}	Member	Estonia	No interests declared	Full involvement
Kroot Aab ^{a, b}	Alternate	Estonia	No interests declared	Full involvement
Kirsti Villikka ^{a, b}	Member	Finland	No interests declared	Full involvement
Kimmo Jaakkola ^{a, b}	Alternate	Finland	No interests declared	Full involvement
Tiphaine Vaillant ^{a, b}	Member	France	No interests declared	Full involvement
Martin Huber ^{a, b}	Member (Vice-Chair)	Germany	No interests declared	Full involvement
Brigitte Keller-Stanislawski ^a	Alternate	Germany	No interests declared	Full involvement
Agni Kapou ^b	Member	Greece	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
Melinda Palfi ^{a, b}	Member	Hungary	No interests declared	Full involvement
Julia Pallos ^{a, b}	Alternate	Hungary	No participation in final deliberations and voting on:	14.1.3. Pregabalin – LYRICA (CAP); NAP 16.3.22. Dapoxetine (NAP) – PSUSA/000009 28/202012
Guðrún Stefánsdóttir ^a	Member	Iceland	No participation in final deliberations and voting on:	5.1.13. Sotorasib - EMEA/H/C/005 522 14.1.3. Pregabalin – LYRICA (CAP); NAP 17.4.9. Pegfilgrastim - NEULASTA (CAP) - EMEA/H/C/000 420/II/0116 17.4.10. Talimogene laherparepvec - IMLYGIC (CAP) - EMEA/H/C/002 771/II/0044 17.5.5. Apremilast - OTEZLA (CAP) - EMEA/H/C/003 746/MEA 008.1
Rhea Fitzgerald ^{a, b}	Member	Ireland	No interests declared	Full involvement
Ronan Grimes ^b	Alternate	Ireland	No interests declared	Full involvement
Ilaria Baldelli ^{a, b}	Alternate	Italy	No interests declared	Full involvement
Zane Neikena ^{a, b}	Member	Latvia	No interests declared	Full involvement
Rugile Pilviniene ^{a, b}	Member	Lithuania	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
Anne-Cécile Vuillemin ^{a, b}	Alternate	Luxembourg	No interests declared	Full involvement
John Joseph Borg ^{a, b}	Member (CHMP member)	Malta	No interests declared	Full involvement
Benjamin Micallef ^a	Alternate	Malta	No interests declared	Full involvement
Menno van der Elst ^a	Member	The Netherlands	No interests declared	Full involvement
Liana Gross-Martirosyan ^{a, b}	Alternate	The Netherlands	No interests declared	Full involvement
David Olsen ^{a, b}	Member	Norway	No participation in final deliberations and voting on:	<p>4.3.4. Fluoroquinolones: ciprofloxacin (NAP); delafloxacin - QUOFENIX (CAP); levofloxacin - QUINSAIR (CAP), NAP; lomefloxacin (NAP); moxifloxacin (NAP); norfloxacin (NAP); ofloxacin (NAP); pefloxacin (NAP); prulifloxacin (NAP); rufloxacin (NAP)</p> <p>5.1.6. Finerenone - EMEA/H/C/005200</p> <p>7.1.2. Levonorgestrel (NAP) - EMEA/H/N/PSA/S/0073</p> <p>7.3.2. Iron (NAP) - EMEA/H/N/PSR/J/0026</p>

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				14.1.3. Pregabalin – LYRICA (CAP); NAP 15.2.1. Aflibercept - EYLEA (CAP) - EMEA/H/C/002 392/II/0075 16.1.18. Darolutamide - NUBEQA (CAP) - PSUSA/000108 43/202101 16.3.33. Lormetazepam (NAP) - PSUSA/000019 10/202012 17.5.23. Octocog alfa - KOVALTRY (CAP) - EMEA/H/C/003 825/MEA 005.3 17.6.2. Radium (223Ra) dichloride - XOFIGO (CAP) - EMEA/H/C/002 653/MEA 016
Karen Pernille Harg ^{a, b}	Alternate	Norway	No interests declared	Full involvement
Adam Przybylkowski ^a	Member	Poland	No interests declared	Full involvement
Katarzyna Ziolkowska ^{a, b}	Alternate	Poland	No interests declared	Full involvement
Ana Sofia Diniz Martins ^{a, b}	Member	Portugal	No interests declared	Full involvement
Marcia Silva ^{a, b}	Alternate	Portugal	No interests declared	Full involvement
Roxana Dondera ^b	Member	Romania	No interests declared	Full involvement
Alexandra - Maria Spurni ^{a, b}	Alternate	Romania	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
Marek Juracka ^{a, b}	Alternate	Slovakia	No interests declared	Full involvement
Polona Golmajer ^{a, b}	Alternate	Slovenia	No interests declared	Full involvement
Eva Segovia ^{a, b}	Member	Spain	No interests declared	Full involvement
Maria del Pilar Rayon ^{a, b}	Alternate	Spain	No interests declared	Full involvement
Ulla Wändel Liminga ^{a, b}	Member	Sweden	No interests declared	Full involvement
Annika Folin ^{a, b}	Alternate	Sweden	No interests declared	Full involvement
Annalisa Capuano ^a	Member	Independent scientific expert	No interests declared	Full involvement
Milou Daniel Drici ^a	Member	Independent scientific expert	No restrictions applicable to this meeting	Full involvement
Maria Teresa Herdeiro ^a	Member	Independent scientific expert	No interests declared	Full involvement
Patricia McGettigan ^{a, b}	Member	Independent scientific expert	No interests declared	Full involvement
Daniel Morales ^a	Member	Independent scientific expert	No interests declared	Full involvement
Hedvig Nordeng ^a	Member	Independent scientific expert	No interests declared	Full involvement
Annalisa Capuano ^a	Member	Independent scientific expert	No interests declared	Full involvement
Milou Daniel Drici ^{a, b}	Member	Independent scientific expert	No restrictions applicable to this meeting	Full involvement
Maria Teresa Herdeiro ^{a, b}	Member	Independent scientific expert	No interests declared	Full involvement
Raymond Anderson ^a	Member	Healthcare Professionals' Representative	No interests declared	Full involvement
Roberto Frontini ^{a, b}	Alternate	Healthcare Professionals' Representative	No participation in final deliberations and voting on:	14.1.3. Pregabalin – LYRICA (CAP); NAP 15.2.8. Simoctocog alfa - NUWIQ (CAP)

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				- EMA/H/C/002813/WS2064/0043; VIHUMA (CAP) - EMA/H/C/004459/WS2064/0024 16.1.42. Simoctocog alfa - NUWIQ (CAP); VIHUMA (CAP) - PSUSA/00010276/202101 16.3.6. Antithrombin III (NAP) - PSUSA/00003159/202012
Cathalijne van Doorne ^{a, b}	Member	Patients' Organisation Representative	No interests declared	Full involvement
Virginie Hivert	Alternate	Patients' Organisation Representative	No restrictions applicable to this meeting	Full involvement
Evelien De Clercq ^a	Expert - via Webex*	Belgium	No interests declared	Full involvement
Tom Lams ^a	Expert - via Webex*	Belgium	No interests declared	Full involvement
Stephan Lehr ^a	Expert - via Webex*	Belgium	No interests declared	Full involvement
Jo Robays ^a	Expert - via Webex*	Belgium	No interests declared	Full involvement
Martine Sabbe ^a	Expert - via Webex*	Belgium	No interests declared	Full involvement
Flora Musuamba Tshinanu ^a	Expert - via Webex*	Belgium	No restrictions applicable to this meeting	Full involvement
Françoise Wuillaume ^a	Expert - via Webex*	Belgium	No interests declared	Full involvement
Nina Lalić ^a	Expert - via Webex*	Croatia	No restrictions	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			applicable to this meeting	
Ivana Ljubičić ^{a, b}	Expert - via Webex*	Croatia	No restrictions applicable to this meeting	Full involvement
Petra Kaftanová ^b	Expert - via Webex*	Czechia	No interests declared	Full involvement
Karin Erneholm ^a	Expert - via Webex*	Denmark	No restrictions applicable to this meeting	Full involvement
Kirsten Egebjerg Juul ^a	Expert - via Webex*	Denmark	No interests declared	Full involvement
Andreas James Schaeffer Senders ^a	Expert - via Webex*	Denmark	No interests declared	Full involvement
Aynur Sert ^a	Expert - via Webex*	Denmark	No interests declared	Full involvement
Emma Louise Nautrup Ravn Stadsbjerg ^a	Expert - via Webex*	Denmark	No interests declared	Full involvement
Josiane Uwera ^a	Expert - via Webex*	Denmark	No restrictions applicable to this meeting	Full involvement
Maija Kaukonen ^b	Expert - via Webex*	Finland	No restrictions applicable to this meeting	Full involvement
Hanna Leskinen ^b	Expert - via Webex*	Finland	No interests declared	Full involvement
Nicolas Beix ^a	Expert - via Webex*	France	No interests declared	Full involvement
Vincent Gazin ^a	Expert - via Webex*	France	No interests declared	Full involvement
Leo Lambert ^a	Expert - via Webex*	France	No restrictions applicable to this meeting	Full involvement
Youssef Shaim ^a	Expert - via Webex*	France	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
Christine Diesinger ^a	Expert – via Webex*	Germany	No interests declared	Full involvement
Dennis Lex ^a	Expert – via Webex*	Germany	No restrictions applicable to this meeting	Full involvement
Kerstin Löschcke ^a	Expert – via Webex*	Germany	No interests declared	Full involvement
Karin Seifert ^a	Expert – via Webex*	Germany	No interests declared	Full involvement
Sun Yuansheng ^a	Expert – via Webex*	Germany	No interests declared	Full involvement
Georgia Gkegka ^b	Expert – via Webex*	Greece	No interests declared	Full involvement
Grainne Kirwan ^a	Expert – via Webex*	Ireland	No interests declared	Full involvement
Eamon O'Murchu ^a	Expert – via Webex*	Ireland	No interests declared	Full involvement
Amelia Cupelli ^{a, b}	Expert – via Webex*	Italy	No interests declared	Full involvement
Marcel Kwa ^a	Expert – via Webex*	The Netherlands	No interests declared	Full involvement
Evelyn Mulder-Olthof ^a	Expert – via Webex*	The Netherlands	No interests declared	Full involvement
Fakhredin Sayed Tabatabaei ^a	Expert – via Webex*	The Netherlands	No interests declared	Full involvement
Rosana Sibug ^a	Expert – via Webex*	The Netherlands	No interests declared	Full involvement
Justine van Tongeren ^a	Expert – via Webex*	The Netherlands	No interests declared	Full involvement
Maria Vanenburg ^a	Expert – via Webex*	The Netherlands	No interests declared	Full involvement
Linnea Asp ^a	Expert – via Webex*	Sweden	No restrictions applicable to this meeting	Full involvement
Helena Back ^a	Expert – via Webex*	Sweden	No interests declared	Full involvement
Charlotte Backman ^a	Expert – via Webex*	Sweden	No interests declared	Full involvement
Sofia Bosdotter Enroth ^a	Expert – via Webex*	Sweden	No interests declared	Full involvement
A representative from the European Commission attended the meeting				

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
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Meeting run with support from relevant EMA staff

* Experts were 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>