29 April 2022
EMA/PRAC/244588/2022
Human Medicines Division

Pharmacovigilance Risk Assessment Committee (PRAC)

Minutes for the meeting on 27-30 September 2021

Chair: Sabine Straus – Vice-Chair: Martin Huber

Disclaimers

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

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

Note on access to documents

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

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1. Introduction

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

The Chairperson opened the 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.

1.2. Agenda of the meeting on 27-30 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 meeting on 30 August – 02 September 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 30 August – 02 September 2021 were published on the EMA website on 20 July 2022 (EMA/PRAC/233544/2022).

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

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

3.1. Newly triggered procedures

3.1.1. Chlormadinone (NAP); chlormadinone, ethinylestradiol (NAP); nomegestrol (NAP); nomegestrol, estradiol – ZOELY (CAP), NAP - EMEA/H/A-31/1510

Applicants: Theramex Ireland Limited (Zoely), various

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

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

Background

Nomegestrol and chlormadinone are progestin derivatives indicated alone for different gynaecological disorders such as amenorrhea, breast tenderness, hormone replacement therapy (HRT), menorrhagia and uterine bleedings with or without fibromas, menstrual cycle abnormal, menstrual disorder, metrorrhagia, oligomenorrhea, polymenorrhea, premenstrual syndrome and primary dysmenorrhea. Nomegestrol is also indicated for the treatment of endometriosis. In combination with ethinylestradiol, an oestrogen derivative, nomegestrol/ethinylestradiol is indicated, as Zoely, a centrally authorised product, for hormonal contraception. Nomegestrol/ethinylestradiol is also indicated in other medicinal product(s) for the treatment of menopausal symptoms.

The French Medicines Agency (ANSM)[1] sent a letter of notification dated 22 September 2021 of a referral under Article 31 of Directive 2001/83/EC for the review of nomegesterol- and chlormadinone-containing product(s) following new data from two epidemiological studies carried out in France in women taking these medicines to investigate the risk of meningioma. Although the risk is known since 2018 and the product information of nomegestrol-containing product(s) was updated in line with the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00002181/201801) adopted in October 2018 to add contraindication and warnings relating to meningioma (for background, see PRAC minutes October 2018), France observed in the studies an increase of reported cases of meningioma with dose and duration of treatment and may be greater in women taking nomegestrol or chlormadinone for several years. The studies also showed that after women had stopped taking nomegestrol or chlormadinone for one year or more, the risk of developing these tumours was reduced and comparable to the risk in people who never used these medicines.

In view of the above and the necessity to take an action at the EU level, France considered that it is in the interest of the Union to refer to the matter to PRAC and to request that it gives its recommendation as to whether marketing authorisations of these medicinal product(s) should be maintained, varied, suspended or revoked.

Discussion

[1] Agence nationale de sécurité du médicament et des produits de santé

PRAC noted the notification letter from ANSM.

PRAC appointed Martin Huber as Rapporteur and Željana Margan Koletić as Co-Rapporteur for the procedure.

PRAC discussed a list of questions (LoQ) to be addressed during the procedure together with a timetable for conducting the review. PRAC also discussed the need for a public hearing.

Summary of recommendation(s)/conclusions

- The Committee adopted a LoQ to the MAHs for chlormadinone-, chlormadinone/ethinylestradiol-, nomegestrol- and nomegestrol/estradiol-containing products (EMA/PRAC/522593/2021) and a timetable for the procedure (EMA/PRAC/522598/2021).
- PRAC also discussed the option to conduct a public hearing in the context of the current procedure according to the pre-defined criteria set out in the rules of procedure[2] (EMA/363479/2015). It was agreed by the Committee that at this stage of the procedure, in light of the currently available data and the need to determine the suitable approach to stakeholder engagement, a public hearing would not be appropriate. PRAC can reconsider this at a later stage of the procedure, as needed.

See EMA press release (EMA/538480/2021) entitled 'EMA starts review of meningioma risk with nomegestrol- and chlormadinone-containing medicines'.

3.2. Ongoing procedures

3.2.1. Amfepramone (NAP) - EMEA/H/A-31/1501

Applicant(s): Artegodan GmbH, Temmler Pharma GmbH

PRAC Rapporteur: Anette Kirstine Stark; PRAC Co-rapporteur: Eva Jirsová

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

Background

A referral procedure under Article 31 of Directive 2001/83/EC is ongoing for amfepramone-containing products reviewing the benefit-risk balance, in light of the known serious safety concerns related to the therapeutic class of anorexigens, the reported cases of cardiac-related adverse drug reactions, cases of pulmonary hypertension, and the off-label use despite the risk minimisation measures in place, and taking into account the uncertainties as to clinical relevance of this treatment. For further background, see PRAC minutes February 2021 and PRAC minutes July 2021.

Summary of recommendation(s)/conclusions

- In the context of the agreement to convene an ad-hoc expert group (AHEG) meeting, PRAC adopted the list of experts (LoE) for the AHEG to be held on 11 October 2021.

3.3. Procedures for finalisation

None

[2] Rules of procedure on the organisation and conduct of public hearings at PRAC

3.4. Re-examination procedures[3]

None

3.5. Others

None

4. Signals assessment and prioritisation[4]

4.1. New signals detected from EU spontaneous reporting systems

See Annex I 14.1.

4.2. New signals detected from other sources

See also Annex I 14.2.

4.2.1. Coronavirus (COVID-19) mRNA[5] vaccine (nucleoside-modified) - COMIRNATY (CAP)

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Signal of myocarditis and pericarditis

Action: For adoption of PRAC recommendation

EPITT 19712 – Related to September 2021

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.

Based on the preliminary results from a study entitled: 'SARS-CoV-2 vaccination and risk of pericarditis and myocarditis: Nordic nationwide cohort study of 20 million individuals' consisting in a meta-analysis of data from Denmark, Finland, Norway and Sweden, Sweden reopened the signal on myocarditis and pericarditis for which a recommendation was last adopted in September 2021. For further background, see PRAC minutes September 2021.

The Rapporteur confirmed that the signal needed initial analysis and prioritisation by PRAC. At the organisational, regulatory and methodological matters (ORGAM)[6] meeting held on 14 October 2021, PRAC discussed the signal and adopted a recommendation.

Discussion

[3] Re-examination of PRAC recommendation under Article 32 of Directive 2001/83/EC
[4] Each signal refers to a substance or therapeutic class. The route of marketing authorisation is indicated in brackets (CAP for Centrally Authorised Products; NAP for Nationally Authorised Products including products authorised via Mutual Recognition Procedures and Decentralised Procedure). Product names are listed for reference Centrally Authorised Products (CAP) only. PRAC recommendations will specify the products concerned in case of any regulatory action required
[5] Messenger ribonucleic acid
[6] Extended to specific COVID-19-related procedure(s) during EMA business continuity plan (BCP)

Having considered the new data from the preliminary study results on the known risk of myocarditis and pericarditis, PRAC agreed to perform an in-depth evaluation of the preliminary report.

Summary of recommendation(s)

- The Rapporteur will perform an in-depth evaluation of the preliminary report within 15 days for discussion at the November 2021 PRAC meeting. EMA will provide an updated observed to expected (O/E) analysis considering the most recent data from EudraVigilance.
- The MAH for Comirnaty (COVID-19 mRNA vaccine (nucleoside-modified)) should continue to monitor any emerging evidence on myocarditis and pericarditis arising from all available sources.

4.2.2. Coronavirus (COVID-19) mRNA[7] vaccine (nucleoside-modified) - SPIKEVAX (CAP)

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Hans Christian Siersted

Scope: Signal of myocarditis and pericarditis

Action: For adoption of PRAC recommendation

EPITT 19713 – Related to September 2021

Lead Member State(s): DK

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.

Based on the preliminary results from a study entitled: 'SARS-CoV-2 vaccination and risk of pericarditis and myocarditis: Nordic nationwide cohort study of 20 million individuals' consisting in a meta-analysis of data from Denmark, Finland, Norway and Sweden, Sweden reopened the signal on myocarditis and pericarditis for which a recommendation was last adopted in September 2021. For further background, see PRAC minutes September 2021. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by PRAC. At the organisational, regulatory and methodological matters (ORGAM)[8] meeting held on 14 October 2021, PRAC discussed the signal and adopted a recommendation.

Discussion

Having considered the new data from the preliminary study results on the known risk of myocarditis and pericarditis, PRAC agreed to perform an in-depth evaluation of the preliminary report.

Summary of recommendation(s)

- The Rapporteur will perform an in-depth evaluation of the preliminary report within 15 days for discussion at the November 2021 PRAC meeting. EMA will provide an updated

[7] Messenger ribonucleic acid
[8] Extended to specific COVID-19-related procedure(s) during EMA business continuity plan (BCP)

observed to expected (O/E) analysis considering the most recent data from EudraVigilance.

- The MAH for Spikevax (COVID-19 mRNA vaccine (nucleoside-modified)) should continue to monitor any emerging evidence on myocarditis and pericarditis arising from all available sources.

4.3. Signals follow-up and prioritisation

4.3.1. Coronavirus (COVID-19) mRNA[9] vaccine (nucleoside-modified) - COMIRNATY (CAP) – EMEA/H/C/005735/SDA/034

Applicant(s): BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Signal of erythema multiforme

EPITT 19721 – Follow-up to July 2021

Background

For background information, see PRAC minutes July 2021.

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

Discussion

Having considered the available evidence from EudraVigilance, the responses from the MAH including observed to expected (O/E) analyses and the literature together with the Rapporteur's assessment, PRAC agreed that a causal role of the vaccine is at least a reasonable possibility in the occurrence of cases of erythema multiforme. Therefore, PRAC agreed that erythema multiforme should be added to the product information as an undesirable effect with a frequency 'not known'.

Summary of recommendation(s)

- The MAH for Comirnaty (COVID-19 mRNA vaccine (nucleoside-modified)) should submit to EMA, within 30 days, a variation to amend[10] the product information.
- The MAH should continue to closely monitor any new cases of erythema multiforme as part of routine safety surveillance.

For the full PRAC recommendation, see EMA/PRAC/540066/2021 published on 26 October 2021 on the EMA website.

4.3.2. Coronavirus (COVID-19) mRNA[11] vaccine (nucleoside-modified) - COMIRNATY (CAP) – EMEA/H/C/005735/SDA/035

Applicant(s): BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

[9] Messenger ribonucleic acid
[10] Update of section 4.8 of the SmPC. The package leaflet is to be updated accordingly
[11] Messenger ribonucleic acid

Scope: Signal of glomerulonephritis and nephrotic syndrome

EPITT 19722 – Follow-up to July 2021

Background

For background information, see PRAC minutes July 2021.

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

Discussion

Having considered the available evidence from EudraVigilance, the literature, the responses from the MAH including observed to expected (O/E) analyses together with the Rapporteur's assessment, PRAC agreed that there is insufficient evidence to establish a causal relationship at present.

Summary of recommendation(s)

- The MAH for Comirnaty (COVID-19 mRNA vaccine (nucleoside-modified)) should continue to closely monitor any new cases of glomerulonephritis/nephrotic syndrome, including exacerbations as part of routine safety surveillance.
- In the next PSUR, the MAH should include a cumulative review of cases of glomerulonephritis/nephrotic syndrome from all sources and relevant literature.

4.3.3. Coronavirus (COVID-19) mRNA[12] vaccine (nucleoside-modified) - SPIKEVAX (CAP) - EMEA/H/C/005791/SDA/036

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

PRAC Rapporteur: Hans Christian Siersted

Scope: Signal of erythema multiforme

EPITT 19720 – Follow-up to July 2021

Background

For background information, see PRAC minutes July 2021.

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

Discussion

Having considered the available evidence from EudraVigilance, the responses from the MAH including observed to expected (O/E) analyses together with the Rapporteur's assessment, PRAC agreed that a causal role of the vaccine is at least a reasonable possibility in the occurrence of cases of erythema multiforme. Therefore, PRAC agreed that erythema multiforme should be added to the product information as an undesirable effect with a frequency 'not known'.

Summary of recommendation(s)

[12] Messenger ribonucleic acid

- The MAH for Spikevax (COVID-19 mRNA vaccine (nucleoside-modified)) should submit to EMA, within 30 days, a variation to amend[13] the product information.
- The MAH should continue to closely monitor any new cases of erythema multiforme as part of routine safety surveillance.

For the full PRAC recommendation, see EMA/PRAC/540066/2021 published on 26 October 2021 on the EMA website.

4.3.4. Coronavirus (COVID-19) mRNA[14] vaccine (nucleoside-modified) - SPIKEVAX (CAP) - EMEA/H/C/005791/SDA/037

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

PRAC Rapporteur: Hans Christian Siersted

Scope: Signal of glomerulonephritis and nephrotic syndrome

EPITT 19724 – Follow-up to July 2021

Background

For background information, see PRAC minutes July 2021.

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

Discussion

Having considered the available evidence from EudraVigilance, the literature, the responses from the MAH including observed to expected (O/E) analyses together with the Rapporteur's assessment, PRAC agreed that there is insufficient evidence to establish a causal relationship at present.

Summary of recommendation(s)

- The MAH for Spikevax (COVID-19 mRNA vaccine (nucleoside-modified)) should continue to closely monitor any new cases of glomerulonephritis/nephrotic syndrome, including exacerbations as part of routine safety surveillance.
- In the next PSUR, the MAH should include a cumulative review of cases of glomerulonephritis/nephrotic syndrome from all sources and relevant literature.

4.3.5. Coronavirus (COVID-19) vaccine (ChAdOx1-S [recombinant]) - VAXZEVRIA (CAP) - EMEA/H/C/005675/SDA/034.2

Applicant(s): AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: Signal of immune thrombocytopenia

EPITT 19678 - Follow-up to July 2021

Background

For background information, see PRAC minutes July 2021.

[13] Update of section 4.8 of the SmPC. The package leaflet is to be updated accordingly
[14] Messenger ribonucleic acid

The MAH replied to a further request for information on the signal of immune thrombocytopenia and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence from EudraVigilance, the literature, the responses provided by the MAH together with the Rapporteur's assessment, PRAC agreed that there is at least a reasonable possibility that vaccination with Vaxzevria (COVID-19 vaccine (ChAdOx1-S [recombinant])) may be associated with cases of thrombocytopenia including immune thrombocytopenia and that healthcare professionals (HCPs) should be aware of this risk, in particular in patients with a history of a thrombocytopenic disorder. Therefore, PRAC agreed that thrombocytopenia should be added to the product information as a warning and immune thrombocytopenia as an undesirable effect with a frequency 'not known'. PRAC also agreed that the risk should be communicated to HCPs via a direct healthcare professional communication (DHPC) to raise awareness on the risk of thrombocytopenia, including immune thrombocytopenia, with or without associated bleeding.

Summary of recommendation(s)

- The MAH for Vaxzevria (COVID-19 vaccine (ChAdOx1-S [recombinant])) should submit to EMA, within 15 days, a variation to amend[15] the product information.
- PRAC agreed on the content of a DHPC along with a communication plan for its distribution.
- In future monthly summary safety report(s) (MSSR), the MAH should evaluate any new cases of cases of thrombocytopenia without co-reported thrombotic events in vaccinees with a known history of ITP or related disorders. It should comprise a cumulative review of cases, including a causality assessment and a discussion of any possible exacerbation of patients' condition. In addition, the MAH should continue to evaluate cases of bleeding with/without thrombocytopenia.

For the full PRAC recommendation, see EMA/PRAC/540066/2021 published on 26 October 2021 on the EMA website.

4.3.6. Piperacillin (NAP); piperacillin, tazobactam (NAP)

Applicant(s): various

PRAC Rapporteur: Marek Juračka

Scope: Signal of hemophagocytic lymphohistiocytosis (HLH)

EPITT 19676 – Follow-up to April 2021

Background

For background information, see PRAC minutes April 2021.

The MAHs Fresenius Kabi, Mylan, Novartis, Pfizer, and Teva for piperacillin and/or piperacillin/tazobactam-containing product(s) replied to the request for information on the signal of hemophagocytic lymphohistiocytosis (HLH) and the responses were assessed by the Rapporteur.

Discussion

[15] Update of sections 4.4 and 4.8 of the SmPC. The package leaflet is to be updated accordingly

Having considered the available evidence from EudraVigilance, the literature, data provided by the MAHs together with the Rapporteur's assessment, and taking into account the seriousness of the condition, PRAC agreed that healthcare professionals and patients should be aware of a potential risk of HLH during treatment with both piperacillin/tazobactam and piperacillin alone. Therefore, PRAC agreed that HLH should be added to the product information as a warning.

Summary of recommendation(s)

- The MAH(s) for piperacillin- and piperacillin/tazobactam-containing product(s) should submit to the relevant National Competent Authorities (NCAs) of the Member States, within 60 days, a variation for amending[16] the product information.
- In the next PSUR, the MAH(s) should add HLH as a PSUR important potential risk. The MAH(s) should continue to monitor cases of HLH as part of the routine pharmacovigilance.

For the full PRAC recommendation, see EMA/PRAC/540066/2021 published on 26 October 2021 on the EMA website.

4.3.7. Warfarin (NAP)

Applicant(s): various

PRAC Rapporteur: Anette Kirstine Stark

Scope: Signal of anticoagulant-related nephropathy

EPITT 19652 – Follow-up to May 2021

Background

For background information, see PRAC minutes May 2021.

The MAH Bristol-Myers Squibb for the originator warfarin-containing product(s) replied to a further request for information on the signal of anticoagulant-related nephropathy and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence from EudraVigilance, the literature, clinical trial data and data provided by the MAH Bristol-Myers Squibb as well as the Rapporteur's assessment, PRAC agreed that there is sufficient evidence to add anticoagulant-related nephropathy to the product information of warfarin-containing product(s) as part of refined warning on acute kidney injury and as an undesirable effect with a frequency 'not known'.

Summary of recommendation(s)

- The MAH(s) for warfarin-containing product(s) should submit to the relevant National Competent Authorities (NCAs) of the Member States, within 60 days, a variation for amending[17] the product information.
- In the next PSUR, the MAH(s) should provide a literature review of anticoagulant-related nephropathy and warfarin, with a specific focus on 'potential increased mortality' and

[16] Update of section 4.4 of the SmPC. The package leaflet is to be updated accordingly. Any existing wording should be adjusted to the recommended product information changes
[17] Update of sections 4.4 and 4.8 of the SmPC. The package leaflet is to be updated accordingly. Any existing wording should be adjusted to the recommended product information changes

'decreased renal function' as a consequence of anticoagulant-related nephropathy and warfarin treatment. The review should also explore any new information published regarding possible risk factors of developing anticoagulant-related nephropathy from warfarin treatment.

For the full PRAC recommendation, see EMA/PRAC/540066/2021 published on 26 October 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.

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. Coronavirus (COVID-19) vaccine (recombinant) – EMEA/H/C/005754

Scope: Active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2 virus), in individuals 18 years of age and older

5.1.2. Semaglutide - EMEA/H/C/005422

Scope: Treatment for weight loss and weight maintenance

5.1.3. Voxelotor - EMEA/H/C/004869, Orphan

Applicant: Global Blood Therapeutics Netherlands

Scope: Treatment of haemolytic anaemia in adults and paediatric patients 12 years of age and older with sickle cell disease (SCD)

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

See also Annex I 15.2.

5.2.1. Coronavirus (COVID-19) mRNA[18] vaccine (nucleoside-modified) - COMIRNATY (CAP) - EMEA/H/C/005735/II/0059

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Submission of an updated RMP (version 2.3) in order to add myocarditis/pericarditis as an important identified risk as per the outcome of the signal procedure (SDA/032) (EPITT: 19712) dated July 2021. This includes an update of the risk minimisation measures related to myocarditis/pericarditis. The MAH took the opportunity to update the RMP in line with exposure data, information on planned/ongoing safety studies and inclusion of two new non-interventional US PASS, namely study C4591009: a non-interventional post-approval safety study of COVID-19 mRNA vaccine (Comirnaty) in the United States, and study C4591036: a prospective cohort study with at least 5 years of follow-up for potential long-term sequelae of myocarditis after vaccination (Pediatric Heart Network)

Background

Nucleoside-modified messenger ribonucleic acid (mRNA) vaccine is indicated, as Comirnaty, a centrally authorised vaccine, 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 is evaluating a type II variation procedure for Comirnaty, a centrally authorised medicine as a nucleoside-modified messenger ribonucleic acid (mRNA) vaccine, to update the RMP to reflect the addition of myocarditis and pericarditis as important identified risks as per the outcome of the signal procedure (SDA/032) (EPITT: 19712) dated July 2021. The MAH took the opportunity to add further information on planned/ongoing safety studies and to include two new non-interventional US PASS. PRAC is responsible for adopting an outcome based on the assessment report from the PRAC Rapporteur, to be further considered at the level of CHMP, responsible for adopting an opinion on this variation. For further background, see PRAC minutes July 2021.

Summary of advice

- The RMP version 2.3 for Comirnaty (COVID-19 mRNA vaccine (nucleoside-modified)) in the context of the variation procedure under evaluation by PRAC is acceptable.

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

See also Annex I 15.3.

5.3.1. Anakinra - KINERET (CAP) - EMEA/H/C/000363/II/0086

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Anette Kirstine Stark

Scope: Extension of indication to include treatment of coronavirus disease 2019 (COVID-19) in adult patients with pneumonia who are at risk of developing severe respiratory failure. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 5.7) are updated in accordance

[18] Messenger ribonucleic acid

Background

For background information on substance(s) and indication(s) of centrally authorised product(s) identified as 'CAP', see Human medicine European public assessment report (EPAR) on the EMA website.

CHMP is evaluating a type II variation as an extension of indication for Kineret, a centrally authorised product containing anakinra, to include the treatment of coronavirus disease 2019 (COVID-19) in adult patients with pneumonia who are at risk of developing severe respiratory failure. PRAC is responsible for providing advice to CHMP on the necessary updates to the RMP to support this procedure.

Summary of advice

- The RMP for Kineret (anakinra) in the context of the variation procedure under evaluation by PRAC and CHMP could be considered acceptable provided that an update to RMP version 5.7 and satisfactory responses to the request for supplementary information (RSI) are submitted.
- PRAC agreed that there is no need for additional pharmacovigilance studies nor any additional risk minimisations measures (aRMM) in light of the current knowledge. In addition, the MAH should update the information within the safety specifications in line with the proposed indication. In addition, the MAH should update the 'populations not studied in clinical trials' with regard to exclusion criteria for the SAVE-MORE[19] study, including limitations to detect adverse reactions and exposure of special populations in the COVID-19 indication.

5.3.2. Baricitinib - OLUMIANT (CAP) - EMEA/H/C/004085/II/0028

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Extension of indication to include treatment of coronavirus disease 2019 (COVID-19) in hospitalised adult and paediatric patients aged 10 years and older who require low-flow oxygen or non-invasive ventilation/high flow oxygen. As a consequence, sections 4.1, 4.2, 4.4, 4.6, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated. Annex II, the package leaflet and the RMP (version 11.1) are updated in accordance

Background

For background information on substance(s) and indication(s) of centrally authorised product(s) identified as 'CAP', see Human medicine European public assessment report (EPAR) on the EMA website.

CHMP is evaluating a type II variation as an extension of indication for Olumiant, a centrally authorised product containing baricitinib, to include the treatment of coronavirus disease 2019 (COVID-19) in hospitalised adult and paediatric patients aged 10 years and older who require low-flow oxygen or non-invasive ventilation/high flow oxygen. PRAC is responsible for providing advice to CHMP on the necessary updates to the RMP to support this procedure. For further background, see PRAC minutes July 2021.

[19] A pivotal, confirmatory, phase 3 randomised clinical trial (RCT) aiming to evaluate the efficacy and safety of early start of anakinra guided by soluble urokinase plasminogen activator receptor (suPAR) in patients with lower respiratory tract infection (LRTI) by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in improving the clinical state of COVID-19 over 28 days as measured by the ordinal scale of the 11-point World Health Organization (WHO) clinical progression scale (CPS)

Summary of advice

- The RMP for Olumiant (baricitinib) in the context of the variation procedure under evaluation by PRAC and CHMP could be considered acceptable provided that an update to RMP version 11.2 and satisfactory responses to the request for supplementary information (RSI) are submitted.
- PRAC agreed that there is no need for additional pharmacovigilance studies nor any additional risk minimisations measures (aRMM) in light of the current knowledge. In addition, the MAH should reclassify venous thromboembolism as an important identified risk. The MAH should also further comment on the exclusion criteria for the ACTT-2[20] and KHAA[21] studies and conclude on the clinical safety relevance of each COVID-19 exclusion criteria for treatment in the proposed COVID-19 indication.

5.3.3. Deferiprone - FERRIPROX (CAP) - EMEA/H/C/000236/X/0145

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Tiphaine Vaillant

Scope: Extension application to introduce a new pharmaceutical form (gastro-resistant tablets). The RMP (version 14.0) is updated in accordance

Background

For background information on substance(s) and indication(s) of centrally authorised product(s) identified as 'CAP', see Human medicine European public assessment report (EPAR) on the EMA website.

CHMP is evaluating an extension application (line extension) for Ferriprox, a centrally authorised product containing deferiprone, to introduce gastro-resistant tablets as a new pharmaceutical form as modified release (MR). PRAC is responsible for providing advice to CHMP on the necessary updates to the RMP to support this procedure. For further background, see PRAC minutes September 2020, PRAC minutes February 2021 and PRAC minutes June 2021.

Summary of advice

- The RMP for Ferriprox (deferiprone) in the context of the variation procedure under evaluation by PRAC could be considered acceptable provided that an update to RMP version 14.2 and satisfactory responses to the request for supplementary information (RSI) are submitted.
- The MAH should develop a distinct colour between the immediate release (IR) and MR tablets to mitigate the risk of confusion between both formulations. Together with all the existing risk minimisation measures in place, the MAH should also provide a summary of proposed mitigation measures and associated timelines.
- PRAC agreed on the content of a direct healthcare professional communication (DHPC) along with a communication plan for its distribution.

[20] A multicentre, adaptive, randomised blinded controlled trial of the safety and efficacy of investigational therapeutics for the treatment of COVID-19 in hospitalized adults
[21] A pharmacokinetic (PK) study in adult COVID-19 patients on mechanical ventilation

5.3.4. Tocilizumab - ROACTEMRA (CAP) - EMEA/H/C/000955/II/0101

Applicant: Roche Registration GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include the treatment of coronavirus disease 2019 (COVID-19) in hospitalised adults who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation. As a consequence, sections 4.1, 4.2, 4.3, 4.4, 4.8, 5.1 and 5.2 of the SmPC for RoActemra (tocilizumab) 20 mg/mL concentrate for solution for infusion are updated. The package leaflet and the RMP (version 27.0) are updated in accordance. Furthermore, the product information is brought in line with the latest quality review of documents (QRD) template (version 10.2 rev. 1)

Background

For background information on substance(s) and indication(s) of centrally authorised product(s) identified as 'CAP', see Human medicine European public assessment report (EPAR) on the EMA website.

CHMP is evaluating a type II variation as an extension of indication for Roactemra, a centrally authorised product containing tocilizumab, to include the treatment of coronavirus disease 2019 (COVID-19) in hospitalised adults who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation. PRAC is responsible for providing advice to CHMP on the necessary updates to the RMP to support this procedure.

Summary of advice

- The RMP for Roactemra (tocilizumab) in the context of the variation procedure under evaluation by PRAC and CHMP could be considered acceptable provided that an update to RMP version 27.0 and satisfactory responses to the request for supplementary information (RSI) are submitted.
- PRAC agreed that there is no need for additional pharmacovigilance studies nor any additional risk minimisations measures (aRMM) in light of the current knowledge. In addition, the MAH should review the safety specifications to ensure all identified risks are consistent between the existing chronic indications and the indication in COVID-19 patients. The MAH should remove 'hypersensitivity' as an important risk.

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. Baricitinib - OLUMIANT (CAP) - PSUSA/00010578/202102

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

Background

For background information on substance(s) and indication(s) of centrally authorised product(s) identified as 'CAP', see Human medicine European public assessment report (EPAR) on the EMA website.

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Olumiant, a centrally authorised medicine containing baricitinib 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 Olumiant (baricitinib) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAH should provide cumulative reviews of cases for malignancies excluding non-melanoma skin cancer (NMSC), major adverse cardiovascular events (MACE) and of all-cause mortality. In this respect, the MAH discuss the need for further need for further risk minimisation measures and updates to the product information as warranted. In addition, the MAH should discuss the relevance of findings for tofacitinib from the ORAL[22] surveillance study considering similarity of mechanism of action of JAK inhibitors as well as similar treated population. The MAH should propose appropriate risk minimisation measures as warranted.
- The MAH should submit to EMA, within 30 days, the interim results from study I4V-MC-B023[23] and discuss the need to update the product information is warranted.

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

6.1.2. Brentuximab vedotin - ADCETRIS (CAP) - PSUSA/00010039/202102

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

Background

For background information on substance(s) and indication(s) of centrally authorised product(s) identified as 'CAP' in relevant entries, see Human medicine European public assessment report (EPAR) on the EMA website.

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

[22] 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 (A3921133).
[23] A retrospective observational study to compare baricitinib relative to the standard of care.

- Nevertheless, the product information should be updated to add drug reaction with eosinophilia and systemic symptoms (DRESS) as a warning and as an undesirable effect with a frequency 'not known'. In addition, the risk of infusion site extravasation should be added to the product information as a warning and the existing undesirable effect on extravasation should be updated to reflect that it may result in exfoliation or cellulitis at or surrounding the infusion site. Therefore, the current terms of the marketing authorisation(s) should be varied[24].
- In the next PSUR, the MAH should provide a cumulative review of cases of Guillain-Barré syndrome (GBS) and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) and discuss the need for an update of the product information as warranted. In addition, the MAH should provide a review of cases of neurological deterioration leading to coma.

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

6.1.3. Cabotegravir - VOCABRIA (CAP) - PSUSA/00010900/202103

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

For background information on substance(s) and indication(s) of centrally authorised product(s) identified as 'CAP', see Human medicine European public assessment report (EPAR) on the EMA website.

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Vocabria, a centrally authorised medicine containing cabotegravir 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 Vocabria (cabotegravir) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add suicide attempt and suicidal ideation as undesirable effects with a frequency 'uncommon'. Therefore, the current terms of the marketing authorisation(s) should be varied[25].
- In the next PSUR, the MAH should closely monitor cases of weight gain, sleep disorders, anxiety, depression, suicide ideation and behaviour, bipolar disorder, psychosis and mood disorders, injection site reactions, rash, rhabdomyolysis, seizure and hyperglycaemia.

[24] Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion
[25] 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

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

6.1.4. Dabigatran - PRADAXA (CAP) - PSUSA/00000918/202103

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

Background

For background information on substance(s) and indication(s) of centrally authorised product(s) identified as 'CAP', see Human medicine European public assessment report (EPAR) on the EMA website.

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Pradaxa, a centrally authorised medicine containing dabigatran 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 Pradaxa (dabigatran) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add anticoagulant-related nephropathy as an undesirable effect part of the bleeding reactions. Therefore, the current terms of the marketing authorisation(s) should be varied[26].

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

6.1.5. Fremanezumab - AJOVY (CAP) - PSUSA/00010758/202103

Applicant: Teva GmbH

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

Background

For background information on substance(s) and indication(s) of centrally authorised product(s) identified as 'CAP', see Human medicine European public assessment report (EPAR) on the EMA website.

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

Summary of recommendation(s) and conclusions

[26] Update of SmPC section 4.8. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Ajovi (fremanezumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add anaphylactic reaction as a warning and as an undesirable effect with a frequency 'rare'. Therefore, the current terms of the marketing authorisation(s) should be varied[27].
- In the next PSUR, the MAH should provide a cumulative review of cases of arthralgia, including data from clinical trials, post-marketing setting, along with a causality assessment. The MAH should provide a discussion on the plausible mechanism(s) based on literature data and on the need for an update of the product information as warranted.

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

6.1.6. Guanfacine - INTUNIV (CAP) - PSUSA/00010413/202103

Applicant: Shire Pharmaceuticals Ireland Limited

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

Background

For background information on substance(s) and indication(s) of centrally authorised product(s) identified as 'CAP' in relevant entries, see Human medicine European public assessment report (EPAR) on the EMA website.

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Intuniv, a centrally authorised medicine containing guanfacine 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 Intuniv (guanfacine) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the existing warning on suicidal ideation and to add aggression as a warning and as an undesirable effect with a frequency 'uncommon'. Therefore, the current terms of the marketing authorisation(s) should be varied[28].
- In the next PSUR, the MAH should provide a cumulative review of cases of tinnitus from all sources and discuss the potential underlying mechanisms, as well as the need for an update of the product information as warranted. In addition, the MAH should provide cumulative reviews of cases of epilepsy, convulsions and seizures and should continue to monitor cases of suicidal events as an important potential risk. Moreover, the MAH

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

should closely monitor cases of angina pectoris and deafness as well as Raynaud's syndrome.

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.

6.1.7. Nalmefene - SELINCRO (CAP) - PSUSA/00010120/202102

Applicant: H. Lundbeck A/S

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

For background information on substance(s) and indication(s) of centrally authorised product(s) identified as 'CAP' in relevant entries, see Human medicine European public assessment report (EPAR) on the EMA website.

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Selincro, a centrally authorised medicine containing nalmefene 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 Selincro (nalmefene) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add visual impairment as an undesirable effect with a frequency 'not known' and leading to effects on ability to drive and use machines. Therefore, the current terms of the marketing authorisation(s) should be varied[29].
- In the next PSUR, the MAH should provide a cumulative review of cases of hypersensitivity reactions, with a specific focus on anaphylactic reactions. The MAH should also include a cumulative review of cases of suicide/self-injury from all sources and discuss the need to update the product information as warranted.

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

6.1.8. Pirfenidone - ESBRIET (CAP) - PSUSA/00002435/202102

Applicant: Roche Registration GmbH

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

Background

[29] Update of SmPC sections 4.7 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion

For background information on substance(s) and indication(s) of centrally authorised product(s) identified as 'CAP', see Human medicine European public assessment report (EPAR) on the EMA website.

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Esbriet, a centrally authorised medicine containing pirfenidone 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 Esbriet (pirfenidone) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add Stevens Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) as undesirable effects with a frequency 'not known' and to include a warning on permanent discontinuation of pirfenidone treatment in case these adverse reactions occur. Therefore, the current terms of the marketing authorisation(s) should be varied[30].
- In the next PSUR, the MAH should continue to monitor cases of severe skin reaction and provide a comprehensive analysis of all cases together with any other relevant data.

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.

6.1.9. Pomalidomide - IMNOVID (CAP) - PSUSA/00010127/202102

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

Background

For background information on substance(s) and indication(s) of centrally authorised product(s) identified as 'CAP', see Human medicine European public assessment report (EPAR) on the EMA website.

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Imnovid, a centrally authorised medicine containing pomalidomide 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 Imnovid (pomalidomide) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add solid organ transplant rejection as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[31].

[30] Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion
[31] 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

- In the next PSUR, the MAH should provide a review of cases of severe infections due to neutropenia and pancytopenia and of progressive multifocal leukoencephalopathy (PML).

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

6.1.10. Upadacitinib - RINVOQ (CAP) - PSUSA/00010823/202102

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

Background

For background information on substance(s) and indication(s) of centrally authorised product(s) identified as 'CAP', see Human medicine European public assessment report (EPAR) on the EMA website.

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Rinvoq, a centrally authorised medicine containing upadacitinib 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 Rinvoq (upadacitinib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add diverticulitis as a warning and as an undesirable effect with a frequency 'uncommon'. Therefore, the current terms of the marketing authorisation(s) should be varied[32].
- In the next PSUR, the MAH should include cumulative reviews of cases reporting off-label use, cataract, fractures, sepsis with positive de-challenge and hypertension. In addition, the MAH should provide time adjusted analyses for malignancies excluding non-melanoma skin cancer (NMSC), for major adverse cardiovascular events (MACE) and for all-cause mortality. In this respect, the MAH discuss the need for further need for further risk minimisation measures and updates to the product information as warranted. Finally, the MAH should discuss the relevance of findings for tofacitinib from the ORAL[33] surveillance study considering similarity of mechanism of action of these JAK inhibitors as well as similar treated population. The MAH should propose appropriate risk minimisation measures 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.

[32] Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion
[33] 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 (A3921133)

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. Dexmedetomidine - DEXDOR (CAP); NAP - PSUSA/00000998/202103 (with RMP)

Applicants: Orion Corporation (Dexdor), various

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Background

Dexmedetomidine is a selective alfa-2 receptor agonist indicated for the sedation of adult intensive care unit (ICU) patients requiring a sedation level not deeper than arousal in response to verbal stimulation (corresponding to Richmond agitation-sedation scale (RASS) 0 to -3) and for the sedation of non-intubated adult patients prior to and/or during diagnostic or surgical procedures requiring sedation, i.e. procedural/awake sedation.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of Dexdor, a centrally authorised medicine containing dexmedetomidine, and nationally authorised medicines containing dexmedetomidine 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 dexmedetomidine-containing products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add diabetes insipidus as a warning and as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisations should be varied[34].
- The MAHs with an RMP in place should update it in order to remove ischemic heart disease and respiratory depression as safety concerns and to add rhabdomyolysis as an important potential risk at the next regulatory opportunity and no later than in 180 days.

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.

6.2.2. Estradiol, nomegestrol acetate - ZOELY (CAP); NAP - PSUSA/00002182/202101

Applicants: Theramex Ireland Limited (Zoely), various

PRAC Rapporteur: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

[34] 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

Nomegestrol is a progestogen and estradiol an oestrogen. In combination, nomegestrol/estradiol is indicated, as Zoely, a centrally authorised medicine, for oral contraception.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of Zoely, a centrally authorised medicine(s) containing estradiol/nomegestrol acetate, and nationally authorised medicine(s) containing estradiol/nomegestrol acetate 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 estradiol/nomegestrol acetate-containing products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include exacerbation of symptoms of hereditary and acquired angioedema as a warning, as well as to add a warning on the drug-drug interaction with glecaprevir/pibrentasvir in patients with hepatitis C. Therefore, the current terms of the marketing authorisations should be varied[35].
- In the next PSUR, the MAH for Zoely (estradiol/nomegestrol acetate) should provide a review of cases of off-label use in menopause.

Additionally, PRAC considered that the warning on exacerbation of symptoms of hereditary and acquired angioedema and the warning relating to the drug-drug interaction with glecaprevir/pibrentasvir is also relevant for estradiol-containing products as a single agent or in fixed-dose combinations. Further consideration will be given at the level of CMDh.

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

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

See also Annex I 16.3.

6.3.1. Baclofen[36] (NAP) - PSUSA/00000293/202101

Applicant(s): various

PRAC Lead: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

Background

Baclofen is a muscle relaxant indicated, for intrathecal use, for the treatment of adult patients with severe chronic spasticity resulting from trauma, multiple sclerosis or other spinal cord disorders, who are unresponsive to oral baclofen or other orally administered

[35] Update of SmPC sections 4.4 and 4.5. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of a position
[36] Intrathecal use only

antispastic medicinal products and/or those patients who experience unacceptable side-effects at effective oral doses. In children, it is indicated for severe chronic spasticity of spinal or cerebral origin who are unresponsive to orally administered antispastics and/or who experience unacceptable undesirable effects at effective oral doses.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing baclofen for intrathecal 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 baclofen-containing product(s) for intrathecal use in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, all MAHs should provide a cumulative review of cases of drug-drug interaction with dalfampridine or fampridine, including post-marketing, clinical trials and literature data, along with a causality assessment. The MAH(s) should also discuss the need for an update of the risk minimisation measures as warranted. In addition, the MAHs should closely monitor cases of baclofen infusion effect in paediatric patients with cerebral palsy (CP) caused by significant changes in the atmospheric pressure and provide a cumulative review of cases of akinetic mutism, along with a discussion on the need for an update of risk minimisation measures 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. Dexamethasone[37] (NAP) - PSUSA/00000973/202101

Applicant(s): various

PRAC Lead: Ilaria Baldelli

Scope: Evaluation of a PSUSA procedure

Background

Dexamethasone is a corticosteroid indicated for the treatment of inflammatory and autoimmune diseases, allergic and inflammatory conditions of the conjunctiva, cornea and anterior part of the eye as well as for the treatment of seborrheic dermatitis and atopical eczema in children.

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

Summary of recommendation(s) and conclusions

[37] Non-centrally authorised product(s) only

- Based on the review of the data on safety and efficacy, the benefit-risk balance of dexamethasone[38]-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information of parenteral dexamethasone-containing products should be updated to add hypertrophic cardiomyopathy in preterm infants as a warning and as an undesirable effect with a frequency 'not known'. Also, the product information for parenteral use should be updated to add a warning on neonatal hypoglycaemia following antenatal use of dexamethasone. Therefore, the current terms of the marketing authorisation(s) should be varied[39].

Due to different pharmaceutical forms, indications and safety profiles, the existing EURD list entry should be split into two separate entries, respectively for systemic formulations and for all formulations apart from systemic use. 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. Lanthanum (NAP) - PSUSA/00003175/202103

Applicant(s): various

PRAC Lead: Roxana Dondera

Scope: Evaluation of a PSUSA procedure

Background

Lanthanum is a phosphate binding agent indicated for the control of hyperphosphatemia in chronic renal failure patients on dialysis and in adult patients with chronic kidney disease not on dialysis with serum phosphate levels ≥1.78 mmol/L (≥5.5 mg/dL) in whom a low phosphate diet alone is insufficient to control serum phosphate levels.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing lanthanum 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 lanthanum-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the existing warning on lanthanum deposition in the gastrointestinal mucosa and to add product residue present as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[40].
- In the next PSUR, the MAHs Takeda Pharmaceutical Company Limited and Viatris should provide a cumulative review of cases of gastritis, gastritis erosive, gastric mucosal lesion and gastric ulcer and other MedDRA PTs[41] relevant for gastrointestinal mucosal injury, including histopathological changes, The review should include relevant information from

[38] Non-centrally authorised product(s) only
[39] 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 CMDh for adoption of a position
[40] 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
[41] Medical dictionary for regulatory activities – Preferred term

all sources. The MAHs should discuss the need for an update of the product information as warranted.

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.

6.3.4. Nafarelin (NAP) - PSUSA/00002105/202102

Applicant(s): various

PRAC Lead: Karen Pernille Harg

Scope: Evaluation of a PSUSA procedure

Background

Nafarelin is a potent agonistic analogue of gonadotropin-releasing hormone (GnRH) indicated for hormonal management of endometriosis, including pain relief and reduction of endometriotic lesions; hormonal management of symptomatic uterine fibroids prior to planned myomectomy or hysterectomy, including the relief of clinical symptoms and the reduction of uterine and fibroid volume for the treatment of central precocious puberty (gonadotropin-dependent precocious puberty) in children of both sexes and for controlled ovarian stimulation prior to in-vitro fertilisation.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing nafarelin 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 nafarelin-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add a warning on ovarian hyperstimulation syndrome. Therefore, the current terms of the marketing authorisation(s) should be varied[42].

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

6.3.5. Valproic acid (NAP); sodium valproate (NAP); valproate pivoxil (NAP); valproate semisodium (NAP); valpromide (NAP); valproate bismuth (NAP); calcium valproate (NAP); valproate magnesium (NAP) - PSUSA/00003090/202101

Applicant(s): various

PRAC Lead: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

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

Background

Valproic acid and related substances: sodium valproate, valproate pivoxil, valproate semisodium, valpromide, valproate bismuth, calcium valproate and valproate magnesium, are indicated for the treatment of epilepsy and for the treatment of manic episodes when lithium is contraindicated or not tolerated. Valproate is also indicated in some EU Member States in prophylaxis of migraine attacks.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicines containing valproic acid, sodium valproate, valproate pivoxil, valproate semisodium, valpromide, valproate bismuth, calcium valproate and valproate magnesium 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 valproic acid-, sodium valproate-, valproate pivoxil-, valproate semisodium-, valpromide-, valproate bismuth-, calcium valproate- and valproate magnesium-containing products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include eye malformation as a consequence of in utero exposure and to include a warning regarding lack of efficacy in patients with renal insufficiency undergoing haemodialysis. In addition, the product information should be updated to include information on testicular findings following valproate use from non-clinical data. Therefore, the current terms of the marketing authorisation(s) should be varied[43].
- In the next PSUR, the MAHs should provide a cumulative review of cases of colour blindness including non-clinical, clinical, post-marketing and literature data and discuss a possible biological mechanism. In addition, the MAHs should provide the number of exposed pregnancy cases, namely the number of exposed pregnancies reported annually and in the context of valproate exposure. The MAHs should discuss the compliance to the pregnancy prevention programme (PPP) elements amongst valproate exposed pregnancy cases. Finally, MAH Sanofi should revaluate the signals of 'effect of iron salts on valproate leading to a decreased efficacy of valproate' and 'sleep apnoea'.

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

6.4. Follow-up to PSUR/PSUSA procedures

See also Annex I 16.4.

6.4.1. Leflunomide - ARAVA (CAP) - EMEA/H/C/000235/LEG 058

Applicant: Sanofi-Aventis Deutschland GmbH

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Cumulative review of cases of skin ulcer in line with the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00001837/202009) adopted in May 2021

[43] Update of SmPC sections 4.2, 4.6 and 5.3. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position

Background

For background information on substance(s) and indication(s) of centrally authorised product(s) identified as 'CAP', see Human medicine European public assessment report (EPAR) on the EMA website.

Following the evaluation of the most recently submitted PSUR(s) for the above-mentioned medicine(s), PRAC requested the MAH to submit a cumulative review of skin ulcer, including a review of data from clinical trials and literature. For background, see PRAC minutes May 2021. The responses were assessed by the Rapporteur for PRAC advice.

Summary of advice/conclusion(s)

- Based on the available data and the Rapporteur's assessment, PRAC agreed that a causal relationship between leflunomide and skin ulcer is established. Therefore, PRAC concluded that an update of the product information is warranted to add skin ulcer as an undesirable effect and to add a warning to consider treatment discontinuation together with a washout procedure as a recommendation to healthcare professionals (HCPs).
- The MAH should propose a frequency for skin ulcer as an undesirable effect, based on clinical study data.

6.4.2. Leflunomide - LEFLUNOMIDE MEDAC (CAP) - EMEA/H/C/001227/LEG 010

Applicant: medac Gesellschaft fur klinische Spezialpraparate mbH

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Cumulative review of cases of skin ulcer in line with the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00001837/202009) adopted in May 2021

Background

For background information on substance(s) and indication(s) of centrally authorised product(s) identified as 'CAP', see Human medicine European public assessment report (EPAR) on the EMA website.

Following the evaluation of the most recently submitted PSUR(s) for the above-mentioned medicine(s), PRAC requested the MAH to submit a cumulative review of skin ulcer, including a review of data from clinical trials and literature. For background, see PRAC minutes May 2021. The responses were assessed by the Rapporteur for PRAC advice.

Summary of advice/conclusion(s)

- Based on the available data and the Rapporteur's assessment, PRAC agreed that a causal relationship between leflunomide and skin ulcer is established. Therefore, PRAC concluded that an update of the product information is warranted to add skin ulcer as an undesirable effect and to add a warning to consider treatment discontinuation together with a washout procedure as a recommendation to healthcare professionals (HCPs).
- The MAH should propose a frequency for skin ulcer as an undesirable effect, based on clinical study data.

6.4.3. Leflunomide - LEFLUNOMIDE ZENTIVA (CAP) - EMEA/H/C/001129/LEG 026

Applicant: Zentiva, k.s.

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Cumulative review of cases of skin ulcer in line with the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00001837/202009) adopted in May 2021

Background

For background information on substance(s) and indication(s) of centrally authorised product(s) identified as 'CAP', see Human medicine European public assessment report (EPAR) on the EMA website.

Following the evaluation of the most recently submitted PSUR(s) for the above-mentioned medicine(s), PRAC requested the MAH to submit a cumulative review of skin ulcer, including a review of data from clinical trials and literature. For background, see PRAC minutes May 2021. The responses were assessed by the Rapporteur for PRAC advice.

Summary of advice/conclusion(s)

- Based on the available data and the Rapporteur's assessment, PRAC agreed that a causal relationship between leflunomide and skin ulcer is established. Therefore, PRAC concluded that an update of the product information is warranted to add skin ulcer as an undesirable effect and to add a warning to consider treatment discontinuation together with a washout procedure as a recommendation to healthcare professionals (HCPs).
- The MAH should propose a frequency for skin ulcer as an undesirable effect, based on clinical study data.

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/0020

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of sections 4.4 and 4.8 of the SmPC to add a new warning on immune thrombocytopenia (ITP) and to add dizziness and ITP to the list of adverse drug reactions with frequencies 'uncommon' and 'not known' as per the conclusions of post-authorisation measure MEA 014.3 (monthly summary safety report (MSSR)) finalised in August 2021. The package leaflet is updated accordingly

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 the fourth monthly summary safety report (MSSR) for the above-mentioned medicine(s), PRAC requested the MAH to submit a variation to update the product information to add immune thrombocytopenia (ITP) as a warning and as an undesirable

effect with a frequency 'not known', and to add dizziness as an undesirable effect with a frequency 'uncommon'. For background information, see PRAC minutes August 2021. PRAC is responsible for adopting an outcome based on the assessment report from the PRAC Rapporteur, to be further considered at the level of CHMP, responsible for adopting an opinion on this variation.

Summary of conclusion(s)

- Based on the available data and the Rapporteur's assessment, PRAC further confirmed the changes to the product information in ITP and dizziness following adjustments to the proposed text.
- PRAC agreed on the content of a direct healthcare professional communication (DHPC) common for both ITP and venous thromboembolism (VTE) along with a communication plan for its distribution. See under 6.6.4.

6.6. Expedited summary safety reviews[44]

6.6.1. Coronavirus (COVID-19) mRNA[45] vaccine (nucleoside-modified) - COMIRNATY (CAP) - EMEA/H/C/005735/MEA 002.8

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Ninth 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 ninth 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)

- The MAH should submit to EMA, a variation[46] to add hypoesthesia and paraesthesia to the product information as undesirable effects. The MAH should propose a frequency accordingly.
- In the next MSSR[47], the MAH should provide cumulative reviews and data. In particular, the MAH should provide a cumulative review of cases of uveitis and a causality assessment of cases of relapse of rheumatoid arthritis, an updated cumulative review of cases of rhabdomyolysis together with a causality assessment and a review of the publication by *Faissner et al*[48] as well as an updated review of cases of thrombosis with

[44] 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
[45] Messenger ribonucleic acid
[46] Update of section 4.8 of the SmPC. The package leaflet is to be updated accordingly
[47] Submission date on 15 October 2021
[48] Faissner, S., Richter, D., Ceylan, U. et al. COVID-19 mRNA vaccine induced rhabdomyolysis and fasciitis. J Neurol (2021). https://doi.org/10.1007/s00415-021-10768-3

thrombocytopenia syndrome (TTS). With regard to myopericarditis, the MAH should review the publication by *Li. C et al*[49]*.* Regarding cases of myocarditis and/or pericarditis, the MAH should provide more detailed information including age-stratified data regarding time to onset, outcome and number of vaccine doses administered. Furthermore, the MAH should provide a detailed review relating to the increased frequency of flare up of autoimmune disorders as well as updated review of cases of myasthenia gravis. Finally, a detailed review of cases of capillary leak syndrome (CLS) ad CLS flare should be included.

- In the next PSUR, the MAH should provide an estimate of 'third dose' exposure.

6.6.2. Coronavirus (COVID-19) mRNA[50] vaccine (nucleoside-modified) - SPIKEVAX (CAP) - EMEA/H/C/005791/MEA 011.7

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Hans Christian Siersted

Scope: Eigth 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 eight 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 MSSR[51], the MAH should provide cumulative reviews and data. In particular, the MAH should include further cumulative reviews of cases of acute disseminated encephalomyelitis (ADEM) including a review of cases of encephalitis, neuralgic amyotrophy as well as a detailed review of cases of Guillain-Barré syndrome (GBS). The MAH should also provide updated cumulative reviews of cases of rhabdomyolysis and myositis. In addition, the MAH should present reviews of cases of capillary leak syndrome (CLS), herpes zoster, stroke and thromboembolism. Finally, with regard to myopericarditis, the MAH should review the publication by *Li. C et al*[52]*.*
- In the next PSUR, the MAH should provide updated cumulative reviews of cases of flare up of rheumatoid arthritis and myasthenia gravis. The MAH should propose to update the product information as warranted.

[49] Li, C. et al. (2021). Intravenous injection of coronavirus disease 2019 (COVID-19) mRNA vaccine can induce acute myopericarditis in mouse model clinical infectious diseases, ciab707, https://doi.org/10.1093/cid/ciab707
[50] Messenger ribonucleic acid
[51] Submission date on 15 October 2021
[52] Li, C. et al. (2021). Intravenous injection of coronavirus disease 2019 (COVID-19) mRNA vaccine can induce acute myopericarditis in mouse model clinical infectious diseases, ciab707, https://doi.org/10.1093/cid/ciab707

6.6.3. Coronavirus (COVID-19) vaccine (Ad26.COV2-S, recombinant) - COVID-19 VACCINE JANSSEN (CAP) – EMEA/H/C/005737/MEA 014.5

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Sixth expedited monthly summary safety report (MSSR) for COVID-19 Vaccine Janssen (COVID-19 vaccine (Ad26.COV2-S, recombinant)) during the coronavirus disease (COVID-19) pandemic

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.

PRAC assessed the sixth monthly summary safety report (MSSR) for COVID-19 vaccine Janssen (COVID-19 vaccine (Ad26.COV2-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 60 days, a variation to add transverse myelitis to the product information as an undesirable effect with a frequency 'not known'. The MAH should discuss the inclusion of a warning as warranted.
- The MAH should submit to EMA, within 60 days, a variation to amend the existing wording on thrombotic and thrombocytogenic syndrome (TTS) to reflect the even gender distribution of reported cases.
- In the next MSSR[53], the MAH should provide cumulative reviews and data. In particular, the MAH should include cumulative reviews of cases with cardiomyopathy, myocarditis and pericarditis, encephalitis including a review of cases of acute disseminated encephalomyelitis (ADEM) and neuromyelitis optica. The MAH should also provide updated reviews of cases of menstrual disorders and post-menopausal bleeding and new cases of nephrotic syndrome and minimal change disease.

6.6.4. Coronavirus (COVID-19) vaccine (Ad26.COV2-S, recombinant) - COVID-19 VACCINE JANSSEN (CAP) – EMEA/H/C/005737/MEA 032

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Interim data from clinical study COV3009: a randomised, double-blind, placebo-controlled phase 3 study to assess the efficacy and safety of Ad26.COV2.S (COVID-19 Vaccine Janssen) for the prevention of SARS-CoV-2-mediated COVID-19 in adults aged 18 years and older; and study COV3001: a randomised, double-blind, placebo-controlled phase 3 study to assess the efficacy and safety of Ad26.COV2.S for the prevention of SARS-CoV-2-mediated COVID-19 in adults aged 18 years and older, to assess the potential for a

[53] Submission date on 15 October 2021

causal relationship between COVID-19 Vaccine Janssen (COVID-19 vaccine) and venous thromboembolism (VTE), as requested in the conclusions of post-authorisation measure MEA 014.4 (fifth monthly summary safety report (MSSR)) finalised in September 2021

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 the fifth monthly summary safety report (MSSR) for the above-mentioned medicine(s), PRAC requested the MAH to submit to EMA further data from ongoing clinical trials, namely study COV3009[54] and study COV3001[55], with respect to venous thromboembolism (VTE) together with an in-depth discussion on the overall potential for a causal relationship between the vaccine and VTE. For background information, see PRAC minutes September 2021. At the plenary meeting, following the review of the data provided by the MAH both in writing and in an oral explanation, PRAC adopted its conclusions.

Summary of advice/conclusion(s)

- The MAH should submit to EMA, within 7 days, a variation to add VTE to the product information as a warning and as an undesirable effect with a frequency 'rare'.
- PRAC agreed on the content of a direct healthcare professional communication (DHPC) common for both VTE and immune thrombocytopenia (ITP) along with a communication plan for its distribution. See under 6.5.1.

7. Post-authorisation safety studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)[56]

See also Annex I 17.1.

7.1.1. Afamelanotide - SCENESSE (CAP) - EMEA/H/C/PSA/S/0076

Applicant: Clinuvel Europe Limited

PRAC Rapporteur: Martin Huber

Scope: Substantial amendment to a protocol previously agreed in March 2016 (PSP/0022.1.A.1 (PSA/0002)) for study CUV-PA001: a post-authorisation disease registry safety study to generate data on long-term safety and clinical effectiveness of Scenesse (afamelanotide) in patients with erythropoietic protoporphyria (EPP)

[54] Study COV3009: a randomised, double-blind, placebo-controlled phase 3 study to assess the efficacy and safety of Ad26.COV2.S (COVID-19 Vaccine Janssen) for the prevention of SARS-CoV-2-mediated COVID-19 in adults aged 18 years and older
[55] Study COV3001: a randomised, double-blind, placebo-controlled phase 3 study to assess the efficacy and safety of Ad26.COV2.S for the prevention of SARS-CoV-2-mediated COVID-19 in adults aged 18 years and older
[56] In accordance with Article 107n of Directive 2001/83/EC

Background

For background information on substance(s) and indication(s) of centrally authorised product(s) identified as 'CAP', see Human medicine European public assessment report (EPAR) on the EMA website.

In order to fulfil the specific obligation to conduct a PASS (Annex II-E) imposed in the marketing authorisation(s) of Scenesse (afamelanotide), the MAH Clinuvel Europe Limited submitted to EMA substantial amendment version 9 to a protocol previously agreed for a study entitled: 'a post-authorisation disease registry safety study to generate data on long-term safety and clinical effectiveness of Scenesse (afamelanotide) in patients with erythropoietic protoporphyria (EPP)' for review by PRAC. PRAC is responsible for evaluating the PASS protocol and any substantial amendments.

Endorsement/Refusal of the protocol

- Having considered the draft protocol version 9 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 all centres should take part in the registry. Therefore, the MAH should ensure to get all accredited centres engaged with the registry by proposing measures fostering centres participation.
- The MAH should submit a revised PASS protocol within 60 days to EMA. A 60 day-assessment timetable will be followed.

7.1.2. Fenfluramine - FINTEPLA (CAP) - EMEA/H/C/PSP/S/0093.1

Applicant: Zogenix ROI Limited

PRAC Rapporteur: Martin Huber

Scope: MAH's response to PSP/S/0093 [protocol for an observational registry to provide data on long-term safety of fenfluramine in routine practice, with a focus on characterising and quantifying the important potential risks of valvular heart disease (VHD) and pulmonary arterial hypertension (PAH) (primary objective), and growth retardation (secondary objective). In addition, data on the frequency of echocardiographic monitoring contribute to assess the effectiveness of risk minimisation measures] as per the request for supplementary information (RSI) adopted in May 2021

Background

For background information on substance(s) and indication(s) of centrally authorised product(s) identified as 'CAP', see Human medicine European public assessment report (EPAR) on the EMA website.

In order to fulfil the specific obligation to conduct a PASS (Annex II-D) imposed in accordance with Article 107n(3) of Directive 2001/83/EC, the MAH Zogenix ROI Limited submitted to EMA a protocol version 1.0 for a study entitled: 'a registry of subjects with Dravet syndrome treated with fenfluramine' for review by PRAC in order to assess long-term cardiac safety of fenfluramine prescribed in routine practice. PRAC is responsible for evaluating the PASS protocol and the responses from the MAH to a request for

supplementary information adopted in May 2021. For further background, see PRAC minutes May 2021.

Endorsement/Refusal of the protocol

- Having considered the protocol version 2.0 in accordance with Article 107n of Directive 2001/83/EC, PRAC confirmed that the study is non-interventional and the PASS protocol is endorsed.
- PRAC agreed that the length of the follow-up period for subjects enrolled in the study should not be shortened. PRAC also agreed with the proposed delay to provide the final study report in Q1 2033.
- The MAH should submit to EMA a variation to update the requirements of the condition to the marketing authorisation(s) of Fintepla (Fenfluramine) to amend the due date for the final study report.

7.2. Protocols of PASS non-imposed in the marketing authorisation(s)[57]

See Annex I 17.2.

7.3. Results of PASS imposed in the marketing authorisation(s)[58]

See also Annex I 17.3.

7.3.1. Hydroxyethyl starch (HES) (NAP) - EMEA/H/N/PSR/J/0031

Applicant(s): Fresenius Kabi Deutschland GmbH (Volulyte, Voluven), B. Braun Melsungen AG (Tetraspan, Venofundin)

PRAC Rapporteur: Tiphaine Vaillant

Scope: MAH's response to PSR/J/0031 [results for a joint retrospective, multinational, drug utilisation study (DUS) to assess the non-adherence of physicians in hydroxyethyl starch (HES) accredited hospitals to the approved European product information [regarding indication for use, contraindications and posology (dosage)] for HES 130-containing medicinal products in clinical routine after implementation of a set of risk minimisation measures as required in the outcome of the referral procedure under Article 107i of Directive 2001/83/EC for HES completed in 2018 (EMEA/H/A-107i/1457)] as per the request for supplementary information (RSI) adopted in May 2021

Background

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

In line with the conclusions of the referral procedures under Article 31 of Directive 2001/83/EC (EMEA/H/A-31/1348) and Article 107i of Directive 2001/83/EC (EMEA/H/A-107i/1376) in 2013 for HES-containing medicines as well as a further referral procedure under Article 107i of Directive 2001/83/EC (EMEA/H/A-107i/1457) concluded in 2018, MAHs

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

were required as a condition of the marketing authorisations (Annex IV) to implement additional risk minimisation measures.

The MAHs Fresenius Kabi Deutschland GmbH and B. Braun Melsungen AG submitted to EMA the results of the required drug utilisation study (DUS) entitled 'a retrospective, multinational, DUS to investigate the routine use of HES-containing Infusion solutions in HES-accredited European (EU) hospitals after implementation of a set of risk minimisation measures'. For further background, see PRAC minutes January 2019, PRAC minutes June 2019, PRAC minutes September 2020[59] and PRAC minutes December 2020[60].

PRAC discussed the final study report for the DUS. PRAC is responsible for evaluating the PASS final results together with the responses from the MAH(s) to the request for supplementary information (RSI) adopted in May 2021. For further background, see PRAC minutes May 2021.

Summary of recommendation(s) and conclusions

- Based on the review of the final report of the DUS and the assessment from the Rapporteur, PRAC considered that a further RSI is necessary before a final recommendation can be made based on the PASS final report and the responses to the RSI.
- The MAH(s) should provide further clarifications on the high non-adherence rates observed in some EU Member States. In addition, the MAH(s) should calculate the impact of non-adherence to the product information and estimate the proportion of patients for whom fatal or other serious outcomes could be expected with regards to the non-adherence to the product information based on knowledge of the general safety profile of HES including clinical studies and the results of the DUS. The MAH(s) should provide a discussion on the current additional risk minimisation measures (aRMM) in place and propose further aRMM as warranted, discuss their feasibility and the timeframe needed for their implementation.
- The MAH(s) should submit responses to the further RSI to EMA within 30 days. A 60 day-assessment timetable will be followed.

7.3.2. Nomegestrol, estradiol - ZOELY (CAP) - EMEA/H/C/PSR/S/0032

Applicant: Theramex Ireland Limited

PRAC Rapporteur: Tiphaine Vaillant

Scope: MAH's response to PSR/S/0032 [results for a prospective observational study to assess in particular the risk of venous thromboembolic events (VTE) and arterial thromboembolic events (ATE) in nomegestrel/oestradiol users compared with the VTE risk in users of combined oral contraceptives (COCs)-containing levonorgestrel] as per the request for supplementary information (RSI) adopted in July 2021

Background

For background information on substance(s) and indication(s) of centrally authorised product(s) identified as 'CAP', see Human medicine European public assessment report (EPAR) on the EMA website.

[59] Held 31 August - 03 September 2020
[60] Held 23-26 November 2020

Further to the conclusions dated 2013 of the referral procedure under Article 31 of Directive 2001/83/EC (EMEA/H/A-31/1356) for combined oral contraceptives, the MAH for Zoely (nomegestrol/estradiol) was required to conduct a PASS to further assess the risk of thromboembolic events (TE) as reflected in Annex II-D on 'Conditions or restrictions with regard to the safe and effective use of the medicinal product' of the marketing authorisation(s). The MAH for Zoely (nomegestrol/estradiol) submitted to EMA the final results version 1.0 of study PRO-E2 entitled: 'prospective controlled cohort study on the safety of a monophasic oral contraceptive containing nomegestrol acetate (2.5mg) and 17β-estradiol (1.5mg)'. For further background, see PRAC minutes June 2019.

PRAC discussed the final study results of the cohort study. PRAC is responsible for evaluating the PASS final results together with the responses from the MAH(s) to the request for supplementary information (RSI) adopted in July 2021. For further background, see PRAC minutes July 2021.

Summary of recommendation(s) and conclusions

- Based on the review of the final report of the prospective observational study and the assessment from the Rapporteur, PRAC considered that the obligation to perform the PASS is fulfilled.
- PRAC recommended to vary the terms of the marketing authorisation(s) by reflecting the study results in the product information[61] by amending the existing warning on the risk of venous thromboembolism (VTE) to state that Zoely (nomegestrol/estradiol) may have a risk of VTE in the same range as observed with combined oral contraceptive containing levonorgestrel (COC_{LNG}). In addition, the requirement for the back triangle should be removed from the list of additional monitoring. Moreover, the study should be removed from the conditions on 'the safe and effective use of the medicinal product'.
- The MAH should retain the follow-up questionnaires (FUQ) regarding VTE and arterial thromboembolism (ATE) in the RMP.

7.3.3. Radium (Ra^{223}) – XOFIGO (CAP) - EMEA/H/C/PSR/S/0034

Applicant: Bayer AG

PRAC Rapporteur: Rugile Pilviniene

Scope: Results for study PRECISE: an observational, non-randomised, retrospective study evaluating the rates of bone fractures and survival in metastatic castration-resistant prostate cancer (mCRPC) patients treated with radium-223 in routine clinical practice in Sweden, as required in the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 completed in 2018 (EMEA/H/A-20/1459)

Background

For background information on substance(s) and indication(s) of centrally authorised product(s) identified as 'CAP', see Human medicine European public assessment report (EPAR) on the EMA website.

Further to the conclusions dated 2018 of the referral procedure Article 20 of Regulation (EC) No 726/2004 (EMEA/H/A-20/1459) for Xofigo (radium (Ra^{223})), the MAH was required to

[61] Update of sections 4.3 and 4.4 of the SmPC and Annex II-D. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion

conduct a PASS to investigate if the use of radium (Ra^{223}) increases the risk of bone fractures, the risk of death or prostate cancer-specific death compared with other treatments for metastatic castration-resistant prostate cancer (mCRPC) in routine clinical practice as reflected in Annex II-D on 'Conditions or restrictions with regard to the safe and effective use of the medicinal product' of the marketing authorisation(s). The MAH for Xofigo (radium (Ra^{223})) submitted to EMA the final results version 1.0 of study PRECISE as 'an observational, non-randomised, retrospective study evaluating the rates of bone fractures and survival in mCRPC patients treated with radium-223 in routine clinical practice in Sweden.

PRAC discussed the final study results of the observational study. PRAC is responsible for evaluating the PASS final results.

Summary of recommendation(s) and conclusions

- Based on the review of the final report of the observational study and the assessment from the Rapporteur, PRAC considered that the obligation to perform the PASS is fulfilled.
- PRAC recommended to vary the terms of the marketing authorisation(s)[62] by removing the study requirement from the conditions with regard to the safe and effective use of the medicinal product.

7.4. Results of PASS non-imposed in the marketing authorisation(s)[63]

See also Annex I 17.4.

7.4.1. Brolucizumab - BEOVU (CAP) - EMEA/H/C/004913/II/0008

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of section 4.8 of the SmPC in order to include the description of intraocular inflammation, based on the final results from a non-interventional retrospective real-world evidence study conducted in patients with neovascular (wet) age-related macular degeneration (nAMD) to better understand the incidence of adverse events/safety signal after initiating treatment with brolucizumab for up to 6 months

Background

For background information on substance(s) and indication(s) of centrally authorised product(s) identified as 'CAP', see Human medicine European public assessment report (EPAR) on the EMA website.

As stated in the RMP of Beovu (brolucizumab), the MAH conducted a retrospective observational study regarding the association between prior intraocular inflammation (IOI) including retinal vasculitis (RV) and/or retinal vascular occlusion (RO) within 12 months prior to the first brolucizumab injection and the occurrence of any form of IOI including RV and/or RO in patients with neovascular (wet) age-related macular degeneration (nAMD) for up to 6 months after initiation of treatment with brolucizumab. The Rapporteur assessed the MAH's final study report and the responses from the MAH to a request for supplementary

[62] Update of Annex II-D. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion
[63] 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

information (RSI) adopted in May 2021. For further background, see PRAC minutes June 2021.

Summary of advice

- Based on the available data and the assessment of the Rapporteur, PRAC considered that the ongoing variation assessing the final study report can be recommended for approval.
- PRAC agreed to maintain retinal vein occlusion (RVO) and RV as undesirable effects with a frequency 'not known' and to implement a warning on intraocular inflammation including RV and/or RVO.

7.4.2. Teriflunomide - AUBAGIO (CAP) - EMEA/H/C/002514/II/0038

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Martin Huber

Scope: Submission of the final study report for study OBS12753 (listed as a category 3 study in the RMP): a prospective cohort study of long-term safety of teriflunomide in multiple sclerosis patients in Europe. The RMP (version 7.1) is updated accordingly

Background

For background information on substance(s) and indication(s) of centrally authorised product(s) identified as 'CAP', see Human medicine European public assessment report (EPAR) on the EMA website.

As stated in the RMP of Aubagio (teriflunomide), the MAH conducted a prospective cohort study of long-term safety of teriflunomide in multiple sclerosis patients in Europe. The Rapporteur assessed the MAH's final study report.

Summary of advice

- Based on the available data and the assessment of the Rapporteur, PRAC considered that further information is necessary before the ongoing variation assessing the final study report can be recommended for approval. In addition, the RMP for Aubagio (teriflunomide) in the context of the variation could be considered acceptable provided that an update to RMP version 7.1 is submitted.
- The MAH should remove from the RMP interstitial lung disease (ILD) and peripheral neuropathy as important identified risks. Further on, the MAH should discuss if cardiovascular effect should be removed as an important potential risk. In addition, the MAH should further elaborate on the data leading to its proposal to remove teratogenicity as an important potential risk.

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 also Annex I 18.3.

8.3.1. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/R/0040 (without RMP)

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: 5-year renewal of the marketing authorisation

Background

For background information on substance(s) and indication(s) of centrally authorised product(s) identified as 'CAP', see Human medicine European public assessment report (EPAR) on the EMA website.

Xeljanz, a centrally authorised medicine containing tofacitinib, was authorised in 2017.

The MAH submitted an application for renewal of the marketing authorisation for opinion by CHMP. PRAC is responsible for providing advice to CHMP on this renewal with regard to safety and risk management aspects.

The MAH submitted an application for renewal of the marketing authorisation(s) for opinion by CHMP. PRAC is responsible for providing advice to CHMP on this renewal with regard to safety and risk management aspects.

Summary of advice

- Based on the review of the available pharmacovigilance data for Xeljanz (tofacitinib) and the CHMP Rapporteur's assessment report, PRAC considered that a second five-year renewal of the marketing authorisation(s) is warranted on the basis of pharmacovigilance grounds including the signal of increased all-cause mortality identified by the MAH in completed study A3921133[64].

9. Product related pharmacovigilance inspections

9.1. List of planned pharmacovigilance inspections

None

9.2. Ongoing or concluded pharmacovigilance inspections

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

9.3. Others

None

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

10.1. Safety related variations of the marketing authorisation

None

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

None

10.3. Other requests

None

10.4. Scientific Advice

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

[64] 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

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

11.1. Safety related variations of the marketing authorisation

11.1.1. Fluconazole (NAP) - DE/H/xxxx/WS/926

Applicant(s): Pfizer Pharma PFE GmbH

PRAC Lead: Martin Huber

Scope: PRAC consultation on a worksharing variation procedure (DE/H/xxxx/WS/926) for fluconazole-containing medicinal products on the product information wording on congenital malformations and low-dose fluconazole treatment, related to the wording agreed in the recommendation of PSUR single assessment (PSUSA) procedure (PSUSA/00001404/202003) concluded in November 2020, on request of Germany

Background

Fluconazole is an antifungal agent indicated for the treatment of cryptococcosis, systemic candidiasis, mucosal candidiasis, genital candidiasis, prevention of fungal infections in patients with malignancy, and deep endemic mycoses in immunocompetent patients.

In relation to the most recent PSUR single assessment (PSUSA) procedure for fluconazole (PSUSA/00002014/201910) concluded in November 2020, MAH Pfizer for nationally approved fluconazole-containing product(s) submitted a worksharing variation relating to the agreed wording on congenital malformations and low-dose fluconazole treatment. For further background, see to PRAC minutes November 2020[65].

In the context of the ongoing evaluation of the worksharing variation (DE/H/xxxx/WS/926), Germany, as Reference Member State (RMS), requested PRAC advice on its assessment.

Summary of advice

- Based on the review of the available data and the assessment from Germany, PRAC agreed that no new data had been provided which could justify an amendment to the previously agreed product information regarding congenital malformations and low-dose fluconazole treatment.

11.2. Other requests

11.2.1. Irinotecan[66] (NAP) - FR/H/PSUFU/00001783/202005

Applicant(s): Pfizer Healthcare Ireland (Campto), Sun Pharmaceutical Industries Europe B.V (Irinotecan), Aurovitas Spain, S.A.U (Irinotecan Aurovitas)

PRAC Lead: Tiphaine Vaillant

Scope: PRAC consultation on a PSUR follow-up (PSU FU) procedure evaluating analyses relating to irinotecan starting dose in patients with reduced uridine diphosphate glucuronosyltransferase (UGT1A1) activity and possible risk minimisation measures, as discussed at PRAC and agreed by CMDh following the conclusion of the PSUR single

[65] Held 26-29 October 2020
[66] Except liposomal formulation(s)

assessment (PSUSA) procedure (PSUSA/00001783/202005) concluded in January 2021, on request of France

Background

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

Based on the assessment of the most recent PSUR single assessment (PSUSA) procedure for irinotecan for all formulations except liposomal formulation(s) (PSUSA/00001783/202005) concluded in January 2021, PRAC considered that analyses relating to irinotecan starting dose in patients with reduced uridine diphosphate glucuronosyltransferase (UGT1A1) activity and possible risk minimisation measures should be further assessed. For further background, see PRAC minutes January 2021.

On request of CMDh, MAH(s) for nationally approved methotrexate-containing product(s) submitted the requested safety reviews for evaluation within a worksharing periodic safety update follow-up (PSU FU) procedure. In the context of the ongoing evaluation of the PSU FU procedure (FR/H/PSUFU/00001783/202005), France, as lead Member State (LMS), requested PRAC advice on its assessment.

Summary of advice

- Based on the review of the available evidence and the LMS's assessment, PRAC agreed that no specific recommendations with regard to dose reduction in patients with reduced UGT1A1 can be made in the product information at present. Nevertheless, PRAC agreed with making further recommendation as warnings in relation to UGT1A1 poor metabolisers, especially patients who are administered doses >180 mg/m² or frail patients without specifying the level of the required dose reduction. PRAC also discussed uncertainties regarding utility of pre-treatment UGT1A1 genotyping and supported reflecting it in the product information. PRAC also agreed that a direct healthcare professional communication (DHPC) could be helpful to increase awareness of healthcare professionals (HCPs) about patients with UGT1A1 reduced activity and the need to reduce the starting dose in these patients. The need for a DHPC should be agreed at the national levels.

12. Organisational, regulatory and methodological matters

12.1. Mandate and organisation of PRAC

12.1.1. PRAC membership

The Chair announced that Amelia Cupelli has been appointed as the new member for Italy[67]. At the organisational, regulatory and methodological matters (ORGAM) meeting on 14 October 2021, the Chair also announced that Nathalie Gault has been appointed as the new alternate for France[68].

[67] Mandate effective as of 22 September 2021
[68] Mandate effective as of 11 October 2021

12.1.2. Vote by proxy

None

12.2. Coordination with EMA Scientific Committees or CMDh-v

None

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

None

12.4. Cooperation within the EU regulatory network

12.4.1. Coronavirus (COVID-19) pandemic - update

The EMA Secretariat updated 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. Coronavirus (COVID-19) pandemic - EMA lessons learned

The EMA Secretariat presented to PRAC considerations identified in the ongoing exercise of EMA lessons learned from the coronavirus 2019 (COVID-19) pandemic, with a view to present them at the EMA Management Board (MB) meeting scheduled on 07 October 2021. The exercise is conducted in cooperation with the Heads of Medicines Agencies (HMA), with an intention to ultimately draw EU regulatory network's lessons learned. As future steps, joint EMA-European Medical medicines network (EMRN) workshops will be organised.

12.5. Cooperation with International Regulators

None

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

None

12.7. PRAC work plan

None

12.8. Planning and reporting

12.8.1. Marketing authorisation applications (MAA) forecast for 2021 – planning update dated Q3 2021

The EMA Secretariat presented to PRAC for information a quarterly updated report on marketing authorisation applications (MAA) planned for submission (the business 'pipeline'). For previous update, see PRAC minutes July 2021.

12.9. Pharmacovigilance audits and inspections

12.9.1. Pharmacovigilance systems and their quality systems

None

12.9.2. Pharmacovigilance audits

None

12.9.3. Pharmacovigilance inspections

None

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

12.10.1. Periodic safety update reports

None

12.10.2. Granularity and Periodicity Advisory Group (GPAG)

PRAC lead: Menno van der Elst, Maia Uusküla

PRAC was updated on the activities of the Granularity and Periodicity Advisory Group (GPAG) focussing on harmonising and streamlining the EURD list and noted the GPAG progress highlights.

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 October 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 October 2021, the updated EURD list was

adopted by CHMP and CMDh at their October 2021 meetings and published on the EMA website: 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

None

12.12. Adverse drug reactions reporting and additional monitoring

12.12.1. Management and reporting of adverse reactions to medicinal products

None

12.12.2. Additional monitoring

None

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

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: Home>Human Regulatory>Post-authorisation>Pharmacovigilance>Medicines under additional monitoring>List of medicines under additional monitoring

12.13. EudraVigilance database

12.13.1. Activities related to the confirmation of full functionality

None

12.14. Risk management plans and effectiveness of risk minimisations

12.14.1. Risk management systems

None

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

None

12.15. Post-authorisation safety studies (PASS)

12.15.1. Post-authorisation Safety Studies – imposed PASS

None

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

None

12.16. Community procedures

12.16.1. Referral procedures for safety reasons

None

12.17. Renewals, conditional renewals, annual reassessments

None

12.18. Risk communication and transparency

12.18.1. Public participation in pharmacovigilance

None

12.18.2. Safety communication

None

12.19. Continuous pharmacovigilance

12.19.1. Incident management

None

12.20. Impact of pharmacovigilance activities

12.20.1. Strategy on measuring the impact of pharmacovigilance – PRAC interest group (IG) Impact – draft decision aid for PRAC stakeholder engagement

PRAC lead: Daniel Morales

At the organisational, regulatory and methodological matters (ORGAM) meeting on 14 October 2021, the EMA Secretariat presented to PRAC, on behalf of the PRAC interest group (IG) Impact, the activities of one of the PRAC impact strategy objectives, aiming at strengthening PRAC engagement with patients and healthcare professionals in relation to risk minimisation measures (RMM). So far, three building blocks have been established, namely conceptualisation and definition of pharmacovigilance engagement, proposals for PRAC engagement based on an implementation science-based analysis of stakeholder input for the valproate referral, and a proposal for a framework relating types of engagement to types of risk scenarios. For further background, see PRAC minutes December 2020[69]. The IG engagement workstream consolidated the three building blocks into a draft decision aid for practical support to PRAC in determining the need and design of PRAC engagement events, in view to start a pilot exercise in 2022-2023. Following comments from PRAC, the pilot will

[69] Held 23-26 November 2020

focus on engaging patient and healthcare professional representatives in RMM and the draft document will be refined in light of the pilot experience. Further update will be given in due course.

12.21. Others

12.21.1. EMA new emergency notification system

The EMA Secretariat presented to PRAC the new emergency notification system for EMA to send out emergency alerts to Committee members and alternates in the event of a crisis situation, disruption to business-critical infrastructure or other emergency event. PRAC noted the new system.

12.21.2. EU pharmaceutical legislation – revision of Directive 2001/83/EC and Regulation (EC) No 726/2004

At the organisational, regulatory and methodological matters (ORGAM) meeting on 14 October 2021, the EMA Secretariat presented to PRAC the European Commission (EC) request to HMA/CMDh and EMA to prepare concept papers to support the upcoming revision of Directive 2001/83/EC and Regulation (EC) No 726/2004. For background, see the EC roadmap for Revision of the EU general pharmaceuticals legislation. Status updates will be given on a regular basis.

12.21.3. Good Pharmacovigilance Practice (GVP) – planning for 2022

PRAC lead: Sabine Straus

As a follow-up to the presentation made in June 2021 (for background, see PRAC minutes June 2021), PRAC was provided with a refined overview of the GVP modules/chapters status, including an update on the ongoing or planned work on new or revised GVP modules/chapters and their addenda together with their scope, proposed timelines for PRAC discussion and adoption. PRAC agreed with the plan. This will be used for the consolidation of the work plan 2022.

13. Any other business

None

14. Annex I – Signals assessment and prioritisation[70]

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 timetables[71].

14.1.1. Enzalutamide – XTANDI (CAP)

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Eva Segovia

Scope: Signal of erythema multiforme

EPITT 19734 – New signal

Lead Member State(s): ES

14.2. New signals detected from other sources

14.2.1. Sorafenib – NEXAVAR (CAP)

Applicant: Bayer AG

PRAC Rapporteur: Annika Folin

Scope: Signal of tumour lysis syndrome (TLS)

EPITT 19733 – New signal

Lead Member State(s): SE

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. Metformin hydrochloride, sitagliptin hydrochloride monohydrate - EMEA/H/C/005678

Scope: Treatment of type 2 diabetes mellitus (T2DM)

[70] 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

[71] 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

15.1.2. Sapropterin - EMEA/H/C/005646

Scope: Treatment of hyperphenylalaninemia (HPA)

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. Benralizumab - FASENRA (CAP) - EMEA/H/C/004433/II/0036

Applicant: AstraZeneca AB

PRAC Rapporteur: David Olsen

Scope: Submission of an updated RMP (version 4.0) to remove long term use of benralizumab, serious hypersensitivity, loss of/reduction of long-term efficacy as safety concerns and to change the risk categorisation of helminth infection from an important identified risk to an important potential one, as requested in the conclusions of the last PSUR single assessment (PSUSA) procedure (PSUSA/00010661/202005) finalised in May 2021 and variation II/031 finalised in July 2021

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

Applicant: Merck Europe B.V.

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Submission of an updated RMP (version 1.5.2) in order to bring it in line with revision 2.0.1 of the guidance on the format of RMP in the EU (template). In addition, the MAH took the opportunity to include long-term safety data from the completed PREMIERE registry: a prospective observational long-term safety registry of multiple sclerosis patients who have participated in cladribine clinical studies; and to remove it from the pharmacovigilance plan. Furthermore, the status of the post-approval safety study MS 700568-0002: a long term, prospective, observational cohort study evaluating the safety profile in patients with highly active relapsing multiple sclerosis (RMS) newly started on oral cladribine (CLARION); and study MS 700568-0004: pregnancy outcomes in women exposed to oral cladribine: a multi-country cohort database study (CLEAR) are updated. Finally, the RMP is updated in line with the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00010634/201907) adopted in January 2020

15.2.3. Coronavirus (COVID-19) vaccine (Ad26.COV2-S, recombinant) - COVID-19 VACCINE JANSSEN (CAP) - EMEA/H/C/005737/II/0018

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of an updated RMP (version 2.2) in order to include thrombocytopenia as an important potential risk as per the outcome of the signal procedure on embolic and thrombotic events (SDA/018.1 - EPITT 19689) in May 2021 and the outcome of variation II/0006/G dated July 2021, to propose studies aimed at further characterisation of

thrombosis with thrombocytopenia syndrome (TTS) and thrombocytopenia, following the outcome of the signal procedure on embolic and thrombotic events (SDA/018.1 - EPITT 19689) in May 2021, to include Guillain-Barré syndrome as an important identified risk as per the outcome of variation II/0012 dated July 2021. In addition, the MAH took the opportunity to update in the RMP to include the submission milestone dates for study VAC31518COV4001: a post-authorisation, observational study to assess the safety of Ad26.COV2.S (COVID-19 Vaccine Janssen) using health insurance claims and/or electronic health record (EHR) database(s) in the United States, and study VAC31518COV4002: a post-authorisation, observational study to assess the effectiveness of Ad26.COV2.S (COVID-19 Vaccine Janssen) using health insurance claims and/or electronic health record (EHR) database(s) in the United States

15.2.4. Emtricitabine, tenofovir disoproxil - TRUVADA (CAP) - EMEA/H/C/000594/II/0173

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Submission of an updated RMP (version 17.2) to remove the additional risk minimisation measures (aRMMs) for the pre-exposure prophylaxis (PrEP) indication risks. Annex II of the product information is updated accordingly

15.2.5. Fentanyl - EFFENTORA (CAP) - EMEA/H/C/000833/WS2127/0058; NAP

Applicant: Teva B.V.

PRAC Rapporteur: Martin Huber

Scope: Submission of an updated RMP (version 5.0) to bring it in line with revision 2 of GVP module V on 'Risk management systems' and to update the list of safety concerns in line with the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00001369/201704) adopted in February 2018. In addition, the key messages of the educational materials are updated in line with the conclusions of the PSUSA procedure (PSUSA/00001369/202004) adopted in January 2021

15.2.6. Filgrastim - NIVESTIM (CAP) - EMEA/H/C/001142/II/0063

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Kirsti Villikka

Scope: Submission of an updated RMP (version 10.0) in order to update the RMP in accordance with revision 2 of GVP module V on 'Risk management systems' and revision 2.0.1 of the guidance on the format of RMP in the EU (template) and to propose deletion of selected safety concerns listed as important identified risks, important potential risks and missing information

15.2.7. Ivabradine - CORLENTOR (CAP) - EMEA/H/C/000598/WS2050/0056/G; PROCORALAN (CAP) - EMEA/H/C/000597/WS2050/0055/G

Applicant: Les Laboratoires Servier

PRAC Rapporteur: Menno van der Elst

Scope: Grouped variations consisting of: 1) submission of an updated RMP (version 7.0) in line with the changes approved for Ivabradine Anpharm (R/0014) finalised in March 2020; 2) product information is brought in line with the latest quality review of documents (QRD) template (version 10.2)

15.2.8. Ledipasvir, sofosbuvir - HARVONI (CAP) - EMEA/H/C/003850/WS2157/0102; sofosbuvir - SOVALDI (CAP) - EMEA/H/C/002798/WS2157/0076; sofosbuvir, velpatasvir - EPCLUSA (CAP) - EMEA/H/C/004210/WS2157/0062; sofosbuvir, velpatasvir, voxilaprevir - VOSEVI (CAP) - EMEA/H/C/004350/WS2157/0049

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Update of Annex II-D on 'Conditions or restrictions with regard to the safe and effective use of the medicinal product' to amend the study milestone due date from 'Q3 2021' to 'Q4 2021' for the PASS to evaluate the recurrence of hepatocellular carcinoma (HCC)

15.2.9. Obeticholic acid - OCALIVA (CAP) - EMEA/H/C/004093/II/0026, Orphan

Applicant: Intercept Pharma International Limited

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Submission of an updated RMP (version 1.2) in order to bring it in line with revision 2.0.1 of the guidance on the format of RMP in the EU (template) and to add clinical studies (listed as specific obligations in Annex II-E on 'Specific obligation to complete post-authorisation measures for the conditional marketing authorisation') to the pharmacovigilance plan, namely study 747-302: a phase 4, double-blind, randomised, placebo-controlled, multicentre study evaluating the effect of obeticholic acid on clinical outcomes in patients with primary biliary cholangitis; and study 747-401: a phase 4, double-blind, randomised, placebo-controlled study evaluating the pharmacokinetics and safety of obeticholic acid in patients with primary biliary cholangitis and moderate to severe hepatic impairment; as agreed in the conclusions of the conditional renewal procedure (R/0023) finalised in November 2020. Other changes also include an update to the exposure data from clinical studies, addition of data on post-marketing experience and addition of some specific relevant SmPC wording in the risk minimisation measures

15.2.10. Tivozanib - FOTIVDA (CAP) - EMEA/H/C/004131/II/0018

Applicant: EUSA Pharma (Netherlands) B.V.

PRAC Rapporteur: Rugile Pilviniene

Scope: Submission of an updated RMP (version 4.0) in order to include data from study TIVO-3: a randomised, controlled, multicentre, open-label phase 3 study to compare tivozanib with sorafenib in subjects with advanced renal cell carcinoma. Additional updates to the RMP include new information from clinical studies and post-marketing exposure

15.2.11. Vildagliptin - GALVUS (CAP) - EMEA/H/C/000771/WS1970/0067; JALRA (CAP) - EMEA/H/C/001048/WS1970/0069; XILIARX (CAP) - EMEA/H/C/001051/WS1970/0067; vildagliptin, metformin hydrochloride - EUCREAS (CAP) - EMEA/H/C/000807/WS1970/0081; ICANDRA (CAP) -

EMEA/H/C/001050/WS1970/0084; ZOMARIST (CAP) - EMEA/H/C/001049/WS1970/0083

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Annika Folin

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

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

As per agreed criteria, 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. Atezolizumab - TECENTRIQ (CAP) - EMEA/H/C/004143/II/0064

Applicant: Roche Registration GmbH

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Extension of indication to include adjuvant treatment of non-small cell lung cancer (NSCLC) following resection and platinum-based chemotherapy for adult patients whose tumours have programmed death-ligand 1 (PD-L1) expression on ≥ 1% of tumour cells (TC) for Tecentriq (atezolizumab) as monotherapy based on the results from pivotal study GO29527 (IMpower010): a phase 3, open-label, randomised study to investigate the efficacy and safety of atezolizumab compared with best supportive care following adjuvant cisplatin-based chemotherapy in patients with completely resected stage IB-IIIA NSCLC. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of Tecentriq (atezolizumab) 840 mg concentrate for solution for infusion SmPC and Tecentriq (atezolizumab) 1,200 mg concentrate for solution for infusion SmPC are updated. The package leaflet and the RMP (version 21.0) are updated. The MAH took the opportunity to introduce minor editorial updates throughout the product information

15.3.2. Beclometasone dipropionate, formoterol fumarate dihydrate, glycopyrronium - TRYDONIS (CAP) - EMEA/H/C/004702/X/0015

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Jan Neuhauser

Scope: Extension application to add a new pharmaceutical form (inhalation powder) associated with new strength (88 µg / 5 µg / 9 µg). The RMP (version 7.1) is updated in accordance

15.3.3. Bictegravir, emtricitabine, tenofovir alafenamide - BIKTARVY (CAP) - EMEA/H/C/004449/X/0040/G

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Grouped application consisting of: 1) extension application to introduce a new strength 30/120/15 mg; 2) extension of indication to include a paediatric indication by adding the use in patients of 2 years of age and older and weighing at least 14 kg. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC and the Package Leaflet are updated to support the extended indication. The RMP (version 3.1) is updated in accordance

15.3.4. Brentuximab vedotin - ADCETRIS (CAP) - EMEA/H/C/002455/II/0093, Orphan

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Menno van der Elst

Scope: Update of sections 4.2, 4.8, 5.1, 5.2, and 6.6 of the SmPC based on results from study C25004: an open-label study in order to assess the safety and tolerability, of brentuximab vedotin when combined with multiagent chemotherapy regimen for first-line treatment of advanced-stage Hodgkin lymphoma in paediatric patients. The RMP (version 16.0) is updated in accordance

15.3.5. Brigatinib - ALUNBRIG (CAP) - EMEA/H/C/004248/II/0037

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Update of section 5.1 of the SmPC in order to update efficacy information based on final results from study AP26113-13-301 (listed as a post-authorisation efficacy study (PAES) in Annex II): a randomised, open-label, multicentre phase 3 study comparing brigatinib versus crizotinib in patients with advanced anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC) who have not previously received ALK-directed therapy. The RMP (version 5.4) is updated in accordance

15.3.6. Ceftolozane, tazobactam - ZERBAXA (CAP) - EMEA/H/C/003772/II/0036

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Extension of indication to include treatment of paediatric patients aged from birth to less than 18 years based on final results from: 1) study MK-7625A-034: a phase 2, randomised, active comparator-controlled, double-blind clinical trial to study the safety and efficacy of ceftolozane/tazobactam versus meropenem in paediatric subjects with complicated urinary tract infection, including pyelonephritis; 2) study MK-7625A-035: a phase 2, randomised, active comparator-controlled, double-blind clinical trial to study the safety and efficacy of ceftolozane/tazobactam plus metronidazole versus meropenem in paediatric subjects with complicated intra-abdominal infection. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated. The package leaflet and the RMP (version 3.1) are updated in accordance. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet

15.3.7. Coronavirus (COVID-19) mRNA[72] vaccine (nucleoside-modified) - COMIRNATY (CAP) - EMEA/H/C/005735/X/0044/G

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Extension application to add a new pharmaceutical form (dispersion for injection) with a new strength (0.1 mg/mL). The RMP (version 2.4) is updated accordingly

15.3.8. Dapagliflozin - EDISTRIDE (CAP) - EMEA/H/C/004161/WS1952/0042; FORXIGA (CAP) - EMEA/H/C/002322/WS1952/0060

Applicant: AstraZeneca AB

PRAC Rapporteur: Annika Folin

Scope: Extension of indication for Forxiga and Edistride (dapagliflozin) to include treatment of children aged 10 years and adolescents with type 2 diabetes mellitus (T2DM) based on the results from studies: 1) study MB10209/D1690C000016: a randomised, multicentre, parallel, single-dose study to explore the pharmacokinetics and pharmacodynamics of dapagliflozin in children, 10 to less than 18 years of age with T2DM receiving one of three dose levels of dapagliflozin: 2.5, 5 or 10 mg; 2) study MB102-138/D1690C00017: a randomised, double-blind, placebo-controlled, 24-week efficacy and safety study of dapagliflozin 10 mg as compared to placebo with a 28-week open label safety extension phase, in patients aged from 10 to less than 18 years (and young adults from 18 to less than 25 years) with T2DM who have inadequate glycaemic control on diet and exercise with: either metformin only, or insulin only or with metformin and insulin. 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 21.0) are updated in accordance

15.3.9. Evolocumab - REPATHA (CAP) - EMEA/H/C/003766/II/0049/G

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Kimmo Jaakkola

Scope: Grouped variations consisting of: 1) extension of indication to include a new paediatric indication in paediatric patients aged 10 years and over with heterozygous familial hypercholesterolaemia as an adjunct to diet, alone or in combination with other lipid-lowering therapy, to reduce low-density lipoprotein cholesterol (LDL-C) based on results of study 20120123 (HAUSER-RCT): a randomised, multicentre, placebo-controlled, double blind, parallel group, 24-week trial in 158 paediatric patients aged 10 to > 18 years with heterozygous familial hypercholesterolaemia. As a consequence, sections 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; 2) extension of indication to modify the existing indication for treatment of adults and paediatric patients aged 10 years and over with homozygous familial hypercholesterolaemia in combination with other lipid-lowering therapies based on interim results from study 20120124 (HAUSER-OLE): an open label, single arm, multicentre, 80-week trial to evaluate the safety, tolerability and efficacy of Repatha (evolocumab) for LDL-C reduction in paediatric patients from aged ≥ 10 to < 18 years of age with homozygous familial hypercholesterolaemia. As a consequence, sections 4.1, 4.2,

[72] Messenger ribonucleic acid

4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet is updated accordingly

15.3.10. Febuxostat - ADENURIC (CAP) - EMEA/H/C/000777/II/0061

Applicant: Menarini International Operations Luxembourg S.A.

PRAC Rapporteur: Jan Neuhauser

Scope: Update of sections 4.4, 4.8 and 5.1 of the SmPC based on the final results from study FAST (Febuxostat versus Allopurinol Streamlined Trial) (listed as a category 3 study in the RMP): an interventional study investigating the cardiovascular safety of febuxostat in comparison with allopurinol in patients with chronic symptomatic hyperuricaemia. The package leaflet and the RMP (version 8.0) are updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet and to update the warning relevant to the content of sodium according to the Annex to the European Commission guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use'.

15.3.11. 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, randomised, 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, randomised, 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 randomised 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

15.3.12. Human normal immunoglobulin - HIZENTRA (CAP) - EMEA/H/C/002127/II/0129

Applicant: CSL Behring GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication in order to expand the approved secondary immunodeficiencies (SID) indications to any symptomatic SID in accordance with the 'guideline on core SmPC for human normal immunoglobulin for intravenous administration' (EMA/CHMP/BPWP/94038/ 2007 Rev 5; CHMP, 2018). As a consequence, sections 4.1 and 4.2 of the SmPC are updated. The package leaflet and the RMP (version 4.6) are updated in accordance. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet

15.3.13. Ibalizumab - TROGARZO (CAP) - EMEA/H/C/004961/II/0015

Applicant: Theratechnologies Europe Limited

PRAC Rapporteur: David Olsen

Scope: Updated timelines for the post-authorisation efficacy study (PAES) to further characterise the efficacy of ibalizumab in combination with other anti-retroviral medicinal products, for the treatment of adults infected with multidrug resistant human immunodeficiency virus-1 (HIV-1) infection for whom it is otherwise not possible to construct a suppressive antiviral regimen (PROMISE study) to provide the final study report from October 2025 to October 2026. Annex II of the product information is updated accordingly. The RMP (version 2.0) is updated accordingly and in line with the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00010797/202009) adopted in April 2021

15.3.14. Ibrutinib - IMBRUVICA (CAP) - EMEA/H/C/003791/II/0068, Orphan

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Update of section 4.4 of the SmPC in order to add baseline monitoring in in addition to the current warnings for periodic monitoring of cardiac failure and cardiac arrhythmias in patients receiving ibrutinib. The package leaflet and the RMP (version 18.1) are updated accordingly

15.3.15. Insulin lispro - LYUMJEV (CAP) - EMEA/H/C/005037/X/0010

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Annika Folin

Scope: Extension application to change the insulin lispro master cell bank (MCB) and related process steps. The RMP is updated (version 11.1) accordingly

15.3.16. Ivacaftor - KALYDECO (CAP) - EMEA/H/C/002494/II/0096, Orphan

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Extension of indication for Kalydeco (ivacaftor) tablets in combination regiment with Kaftrio (ivacaftor/tezacaftor/elexacaftor) to include the treatment of adults, adolescents and children aged 6 years and older with cystic fibrosis who are homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene or heterozygous for F508del and have a minimal function (MF) mutation in the CFTR gene. This application is based on the results of study VX18-445-106: a phase 3, open-label, multicentre study in subjects 6 through 11 years of age, with F/MF and F/F genotypes. As a consequence, sections 4.1, 4.2, 5.1, and 5.2 of the SmPC are updated. The package leaflet is updated in accordance. The RMP (version 12.0) are updated in accordance

15.3.17. Ivacaftor - KALYDECO (CAP) - EMEA/H/C/002494/WS2048/0101; tezacaftor, ivacaftor - SYMKEVI (CAP) - EMEA/H/C/004682/WS2048/0030

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Update of sections 4.2, 4.5, 4.8 and 5.1 of the SmPC to reflect the final clinical study report (CSR) part A of study VX17-661-116: a phase 3, open-label, rollover study to evaluate the safety and efficacy of long-term treatment with tezacaftor in combination with ivacaftor in subjects with cystic fibrosis aged 6 years and older, homozygous or heterozygous for the F508del-cystic fibrosis transmembrane conductance regulator (CFTR) mutation. The package leaflet and the RMP (version 3.1 for Symkevi) are updated accordingly

15.3.18. Ivacaftor, tezacaftor, elexacaftor - KAFTRIO (CAP) - EMEA/H/C/005269/X/0008/G, Orphan

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Martin Huber

Scope: Grouped applications consisting of: 1) extension application to introduce a new strength of 37.5 mg/25 mg/50 mg film-coated tablets; 2) extension of indication to include paediatric use aged from 6 to 11 years. The RMP (version 3.0) is updated accordingly

15.3.19. Lipegfilgrastim - LONQUEX (CAP) - EMEA/H/C/002556/II/0058/G

Applicant: Teva B.V.

PRAC Rapporteur: Kirsti Villikka

Scope: Grouped variations consisting of an extension of indication to include treatment of the paediatric population and introduction of an age-appropriate presentation in vials. 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 12.0) are updated in accordance. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet. Furthermore, the product information is brought in line with the latest quality review of documents (QRD) template (version 10.1)

15.3.20. Migalastat - GALAFOLD (CAP) - EMEA/H/C/004059/II/0034, Orphan

Applicant: Amicus Therapeutics Europe Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of sections 4.8, 5.1 and 5.2 of the SmPC based on final results from study AT1001-020 (listed as category 3 in the RMP): a phase 3b, 2-stage, open-label, uncontrolled, multicentre study to evaluate the safety, pharmacokinetic, pharmacodynamic and efficacy of migalastat treatment in paediatric subjects 12 to < 18 years of age and weighing ≥ 45 kg with Fabry disease and with amenable galactosidase alfa (GLA) variants. The RMP (version 7.0) is updated accordingly (in fulfilment of Article 46 of Regulation 1901/2006 as amended). In addition, the MAH took the opportunity to introduce some minor editorial changes to the SmPC and package leaflet and to bring the product

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

15.3.21. Niraparib - ZEJULA (CAP) - EMEA/H/C/004249/X/0029, Orphan

Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Jan Neuhauser

Scope: Extension application to introduce a new pharmaceutical form (100 mg film-coated tablet). The RMP (version 5.1) is updated in accordance

15.3.22. Nitisinone - NITISINONE MDK (CAP) - EMEA/H/C/004281/X/0007

Applicant: MendeliKABS Europe Limited

PRAC Rapporteur: Ilaria Baldelli

Scope: Extension application to add a new strength of 20 mg (hard capsule). The RMP (version 2.0) is updated accordingly

15.3.23. Ospemifene - SENSHIO (CAP) - EMEA/H/C/002780/II/0041

Applicant: Shionogi B.V.

PRAC Rapporteur: Kirsti Villikka

Scope: Extension of indication to delete information on specific subset of patients, based on the final study report of the imposed non-interventional PASS (listed in Annex II-D on 'Conditions or restrictions with regard to the safe and effective use of the medicinal product'): an observational retrospective cohort study of ospemifene to assess the incidence of venous thromboembolism (VTE) and other safety concerns as agreed in the RMP in vulvar and vaginal atrophy (VVA) patients treated with ospemifene compared to: 1) patients newly prescribed selective estrogen receptor modulators (SERMs) for oestrogen-deficiency conditions or breast cancer prevention, and 2) the incidence in untreated VVA patients. As a consequence, sections 4.1 and 4.4 of the SmPC are updated. The package leaflet and Annex II-D are updated in accordance. The RMP (version 2) is updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet

15.3.24. Ozanimod - ZEPOSIA (CAP) - EMEA/H/C/004835/II/0002/G

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Grouped variation consisting of: 1) extension of indication 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 for Zeposia (ozanimod). As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC and Annex II-D on 'Conditions or restrictions with regard to the safe and effective use of the medicinal product' are updated. The package leaflet and the RMP (version 1.1) are updated in accordance. In addition, the MAH took the opportunity to implement editorial changes throughout the product information; 2) update of sections 4.4

and 4.5 of the SmPC in order to update the current SmPC description about pharmacokinetic (PK) interaction with breast cancer resistance protein (BCRP) inhibitors based on study RPC-1063-CP-001: a phase 1, randomised, parallel-group, open-label study to evaluate the effect of cyclosporine on the single-dose pharmacokinetics of ozanimod and major active metabolites in healthy adult subjects

15.3.25. Padeliporfin - TOOKAD (CAP) - EMEA/H/C/004182/II/0015

Applicant: STEBA Biotech S.A

PRAC Rapporteur: Maia Uusküla

Scope: Submission of the clinical study report for study CLIN1001 PCM301FU5 (listed as a post-authorisation efficacy study (PAES), category 1 study in Annex II): a European randomised phase 3 study to assess the efficacy and safety of Tookad (padeliporfin) soluble for localised prostate cancer compared to active surveillance. Annex II is updated to remove reference to this study. The RMP (version 8.0) is updated accordingly

15.3.26. Pembrolizumab - KEYTRUDA (CAP) - EMEA/H/C/003820/II/0108

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to include the adjuvant treatment in monotherapy of adults with renal cell carcinoma (RCC) at intermediate-high or high risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions. As a consequence, sections 4.1, 4.2 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 35.1) are updated accordingly

15.3.27. Pembrolizumab - KEYTRUDA (CAP) - EMEA/H/C/003820/II/0109

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication for Keytruda (pembrolizumab) as monotherapy in the treatment of unresectable or metastatic microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR) colorectal, endometrial, gastric, small intestine, biliary, or pancreatic cancer in adults who have received prior therapy, based on the results from: 1) study KEYNOTE-164 (KN164): a phase 2 study of pembrolizumab as monotherapy in subjects with previously treated locally advanced unresectable or metastatic (stage IV) dMMR or MSI-H colorectal carcinoma; 2) study KEYNOTE-158 (KN158): a clinical trial of pembrolizumab evaluating predictive biomarkers in subjects with advanced solid tumours. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 34.1) are updated in accordance

15.3.28. Risankizumab - SKYRIZI (CAP) - EMEA/H/C/004759/II/0014

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Extension of indication to include the treatment of active psoriatic arthritis in adults.

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 3.0) are updated accordingly. Additionally, Annex II is also updated

15.3.29. Secukinumab - COSENTYX (CAP) - EMEA/H/C/003729/II/0079

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Eva Segovia

Scope: Extension of indication to include treatment of juvenile idiopathic arthritis (enthesitis-related arthritis and juvenile psoriatic arthritis) in patients 2 years and older whose disease has responded inadequately to, or who cannot tolerate, conventional therapy. 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 10.0) are updated in accordance

15.3.30. Semaglutide - OZEMPIC (CAP) - EMEA/H/C/004174/X/0021

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Annika Folin

Scope: Extension application to add a new strength of 2 mg solution for injection. The RMP (version 6.0) is updated accordingly

15.3.31. Somapacitan - SOGROYA (CAP) - EMEA/H/C/005030/X/0001/G, Orphan

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Martin Huber

Scope: Grouped application consisting of extension application to add a new strength of 5 mg/1.5 mL (3.3 mg/mL). The RMP is updated (version 2.0) accordingly; alignment of the endotoxin release acceptance for Sogroya (somapacitan) 10 mg, to the narrower limit proposed limit for the 5 mg strength (<16 EU/mL). At the same time, the units for endotoxin are changed from EU/mg to EU/mL

15.3.32. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/II/0035

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Extension of indication to include treatment of adult patients with active ankylosing spondylitis (AS) who have responded inadequately to conventional therapy for Xeljanz (tofacitinib) film-coated tablets. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 17.1) are updated in accordance

15.3.33. Vedolizumab - ENTYVIO (CAP) - EMEA/H/C/002782/II/0061

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Adam Przybylkowski

Scope: Extension of indication to add treatment of adult patients with pouchitis, who have undergone proctocolectomy and ileal pouch anal anastomosis for ulcerative colitis, and have had an inadequate response with, lost response to, or were intolerant to antibiotic therapy for Entyvio (vedolizumab) 300 mg powder for concentrate for solution for infusion, based on final results from study Vedolizumab-4004 (ERNEST): an interventional, randomised, double-blind, placebo-controlled, multicentre study to evaluate the efficacy and safety of Entyvio intravenous (vedolizumab) in the treatment of chronic pouchitis. As a consequence, sections 4.1, 4.2, 4.5, 5.1 and 5.2 of the SmPC for Entyvio (vedolizumab) 300 mg are updated. The package leaflet and the RMP (version 7.0) are updated in accordance

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 procedures listed below were finalised at the PRAC level without further plenary discussion.

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

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

16.1.1. Agomelatine - THYMANAX (CAP); VALDOXAN (CAP) - PSUSA/00000071/202102 (with RMP)

Applicant(s): Les Laboratoires Servier (Valdoxan), Servier (Ireland) Industries Ltd. (Thymanax)

PRAC Rapporteur: Pernille Harg

Scope: Evaluation of a PSUSA procedure

16.1.2. Apalutamide - ERLEADA (CAP) - PSUSA/00010745/202102

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

16.1.3. Baloxavir marboxil - XOFLUZA (CAP) - PSUSA/00010895/202102

Applicant: Roche Registration GmbH

PRAC Rapporteur: Sonja Hrabcik

Scope: Evaluation of a PSUSA procedure

16.1.4. Belimumab - BENLYSTA (CAP) - PSUSA/00009075/202103

Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.5. Bempedoic acid - NILEMDO (CAP); bempedoic acid, ezetimibe - NUSTENDI (CAP) - PSUSA/00010841/202102

Applicant(s): Daiichi Sankyo Europe GmbH

PRAC Rapporteur: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

16.1.6. Bevacizumab - AVASTIN (CAP); AYBINTIO (CAP); EQUIDACENT (CAP); MVASI (CAP); ONBEVZI (CAP); ZIRABEV (CAP) - PSUSA/00000403/202102

Applicant(s): Amgen Technology (Ireland) Unlimited Company (Mvasi), Centus Biotherapeutics Europe Limited (Equidacent), Pfizer Europe MA EEIG (Zirabev), Roche Registration GmbH (Avastin), Samsung Bioepis NL B.V. (Aybintio, Onbevzi)

PRAC Rapporteur: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

16.1.7. Bosutinib - BOSULIF (CAP) - PSUSA/00010073/202103

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.8. Brimonidine[73] - MIRVASO (CAP) - PSUSA/00010093/202102

Applicant: Galderma International

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

16.1.9. Burosumab - CRYSVITA (CAP) - PSUSA/00010669/202102

Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.10. Caplacizumab - CABLIVI (CAP) - PSUSA/00010713/202102

Applicant: Ablynx NV

[73] Centrally authorised product(s) only

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.1.11. Ceftazidime, avibactam - ZAVICEFTA (CAP) - PSUSA/00010513/202102

Applicant: Pfizer Ireland Pharmaceuticals

PRAC Rapporteur: Rugile Pilviniene

Scope: Evaluation of a PSUSA procedure

16.1.12. Elosulfase alfa - VIMIZIM (CAP) - PSUSA/00010218/202102

Applicant: BioMarin International Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

16.1.13. Eravacycline - XERAVA (CAP) - PSUSA/00010718/202102

Applicant: Paion Deutschland GmbH

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.14. Esketamine[74] - SPRAVATO (CAP) - PSUSA/00010825/202103

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

16.1.15. Ex vivo expanded autologous human corneal epithelial cells containing stem cells - HOLOCLAR (CAP) - PSUSA/00010352/202102

Applicant: Holostem Terapie Avanzate s.r.l., ATMP[75]

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

16.1.16. Ferric maltol - FERACCRU (CAP) - PSUSA/00010476/202102

Applicant: Norgine B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

[74] Centrally authorised product(s) only
[75] Advanced therapy medicinal product

16.1.17. Fluticasone furoate, umeclidinium, vilanterol - ELEBRATO ELLIPTA (CAP); TEMYBRIC ELLIPTA (CAP); TRELEGY ELLIPTA (CAP) - PSUSA/00010653/202103

Applicant(s): GlaxoSmithKline Trading Services Limited

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

16.1.18. Gimeracil, oteracil monopotassium, tegafur - TEYSUNO (CAP) - PSUSA/00002875/202101

Applicant: Nordic Group B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.19. Human coagulation factor X - COAGADEX (CAP) - PSUSA/00010481/202103

Applicant: BPL Bioproducts Laboratory GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.20. Ibalizumab - TROGARZO (CAP) - PSUSA/00010797/202103

Applicant: Theratechnologies Europe Limited

PRAC Rapporteur: David Olsen

Scope: Evaluation of a PSUSA procedure

16.1.21. Imlifidase - IDEFIRIX (CAP) - PSUSA/00010870/202102

Applicant: Hansa Biopharma AB

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.22. Influenza vaccine (surface antigen, inactivated, prepared in cell cultures) - FLUCELVAX TETRA (CAP) - PSUSA/00010737/202103

Applicant: Seqirus Netherlands B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.23. Isatuximab - SARCLISA (CAP) - PSUSA/00010851/202103

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

16.1.24. Lefamulin - XENLETA (CAP) - PSUSA/00010872/202102

Applicant: Nabriva Therapeutics Ireland DAC

PRAC Rapporteur: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

16.1.25. Lenvatinib - KISPLYX (CAP); LENVIMA (CAP) - PSUSA/00010380/202102

Applicant(s): Eisai GmbH

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

16.1.26. Meropenem, vaborbactam - VABOREM (CAP) - PSUSA/00010727/202102

Applicant: Menarini International Operations Luxembourg S.A.

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

16.1.27. Obiltoxaximab - OBILTOXAXIMAB SFL (CAP) - PSUSA/00010885/202103

Applicant: SFL Pharmaceuticals Deutschland GmbH

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.28. Ospemifene - SENSHIO (CAP) - PSUSA/00010340/202102

Applicant: Shionogi B.V.

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

16.1.29. Plasmodium falciparum and hepatitis B vaccine (recombinant, adjuvanted) - MOSQUIRIX (Art 58[76]) - EMEA/H/W/002300/PSUV/0056

Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Jean-Michel Dogné

[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).

Scope: Evaluation of a PSUR procedure

16.1.30. Prasugrel - EFIENT (CAP) - PSUSA/00002499/202102

Applicant: Daiichi Sankyo Europe GmbH

PRAC Rapporteur: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

16.1.31. Pretomanid - DOVPRELA (CAP) - PSUSA/00010863/202102

Applicant: Mylan IRE Healthcare Limited

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.32. Ranolazine - RANEXA (CAP) - PSUSA/00002611/202101

Applicant: Menarini International Operations Luxembourg S.A.

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

16.1.33. Reslizumab - CINQAERO (CAP) - PSUSA/00010523/202102

Applicant: Teva B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.34. Ribociclib - KISQALI (CAP) - PSUSA/00010633/202103 (with RMP)

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

16.1.35. Rilpivirine[77] - REKAMBYS (CAP) - PSUSA/00010901/202103

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.36. Ropeginterferon alfa-2b - BESREMI (CAP) - PSUSA/00010756/202102

Applicant: AOP Orphan Pharmaceuticals AG

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

[77] Intramuscular use only

Scope: Evaluation of a PSUSA procedure

16.1.37. Ruxolitinib - JAKAVI (CAP) - PSUSA/00010015/202102

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

16.1.38. Telotristat - XERMELO (CAP) - PSUSA/00010639/202102

Applicant: Ipsen Pharma

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.39. Tisagenlecleucel - KYMRIAH (CAP) - PSUSA/00010702/202102

Applicant: Novartis Europharm Limited, ATMP[78]

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.40. Tivozanib - FOTIVDA (CAP) - PSUSA/00010636/202102

Applicant: EUSA Pharma (Netherlands) B.V.

PRAC Rapporteur: Rugile Pilviniene

Scope: Evaluation of a PSUSA procedure

16.1.41. Trastuzumab emtansine - KADCYLA (CAP) - PSUSA/00010136/202102

Applicant: Roche Registration GmbH

PRAC Rapporteur: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

16.1.42. Ulipristal acetate[79] - ESMYA (CAP); ULIPRISTAL ACETATE GEDEON RICHTER[80] - PSUSA/00009325/202102

Applicant(s): Gedeon Richter Plc.

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

[78] Advanced therapy medicinal product
[79] Indication(s) for the treatment of moderate to severe symptoms of uterine fibroids only
[80] European Commission (EC) decision on the marketing authorisation (MA) withdrawal of Ulipristal acetate Gedeon Richter dated 13 July 2021

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

16.2.1. Atosiban - TRACTOCILE (CAP); NAP - PSUSA/00000264/202101

Applicants: Ferring Pharmaceuticals A/S (Tractocile), various

PRAC Rapporteur: Ilaria Baldelli

Scope: Evaluation of a PSUSA procedure

16.2.2. Cladribine[81] - LITAK (CAP); NAP - PSUSA/00000787/202102

Applicants: Lipomed GmbH (Litak), various

PRAC Rapporteur: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

16.2.3. Dexrazoxane - SAVENE (CAP); NAP - PSUSA/00001001/202102

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

PRAC Rapporteur: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

16.2.4. Fingolimod - FINGOLIMOD ACCORD (CAP); GILENYA (CAP); NAP - PSUSA/00001393/202102

Applicants: Accord Healthcare S.L.U. (Fingolimod Accord), Novartis Europharm Limited (Gilenya), various

PRAC Rapporteur: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

16.2.5. Influenza vaccine (surface antigen, inactivated, adjuvanted) - FLUAD TETRA (CAP); NAP - PSUSA/00010300/202103

Applicants: Seqirus Netherlands B.V. (Fluad Tetra), various

PRAC Rapporteur: Ilaria Baldelli

Scope: Evaluation of a PSUSA procedure

16.2.6. Nitisinone - NITISINONE MDK (CAP); NITYR (CAP); ORFADIN (CAP); NAP - PSUSA/00002169/202102

Applicants: Cycle Pharmaceuticals (Europe) Limited (Nityr), MendeliKABS Europe Limited (Nitisinone MDK), Swedish Orphan Biovitrum International AB (Orfadin), various

PRAC Rapporteur: Ilaria Baldelli

[81] Apart from medicinal product(s) with indication(s) for the treatment of multiple sclerosis

Scope: Evaluation of a PSUSA procedure

16.2.7. Pemetrexed - ALIMTA (CAP); ARMISARTE (CAP); PEMETREXED ACCORD (CAP); PEMETREXED FRESENIUS KABI (CAP); NAP - PSUSA/00002330/202102

Applicants: Accord Healthcare S.L.U. (Pemetrexed Accord), Actavis Group PTC ehf (Armisarte), Eli Lilly Nederland B.V. (Alimta), Fresenius Kabi Deutschland GmbH (Pemetrexed Fresenius Kabi), various

PRAC Rapporteur: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

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

16.3.1. Alprostadil[82] (NAP) - PSUSA/00000110/202101

Applicant(s): various

PRAC Lead: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

16.3.2. Amitriptyline hydrochloride, chlordiazepoxide (NAP) - PSUSA/00000171/202102

Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.3.3. Argatroban (NAP) - PSUSA/00009057/202101

Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.3.4. Cilazapril (NAP); cilazapril, hydrochlorothiazide (NAP) - PSUSA/00000749/202102

Applicant(s): various

PRAC Lead: Ronan Grimes

Scope: Evaluation of a PSUSA procedure

16.3.5. Cytomegalovirus immunoglobulin (NAP) - PSUSA/00000914/202101

Applicant(s): various

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

[82] Erectile dysfunction indication(s) only

16.3.6. Eletriptan (NAP) - PSUSA/00001204/202102

Applicant(s): various

PRAC Lead: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

16.3.7. Granisetron[83] (NAP) - PSUSA/00001568/202102

Applicant(s): various

PRAC Lead: Marek Juracka

Scope: Evaluation of a PSUSA procedure

16.3.8. Human coagulation factor VIII[84] (NAP) - PSUSA/00009174/202102

Applicant(s): various

PRAC Lead: Sonja Hrabcik

Scope: Evaluation of a PSUSA procedure

16.3.9. Hydroxyethyl starch (HES) (NAP) - PSUSA/00001694/202103

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.3.10. Iloprost[85] (NAP) - PSUSA/00009190/202101

Applicant(s): various

PRAC Lead: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

16.3.11. Influenza vaccine[86] (split virion, inactivated) (NAP) - PSUSA/00010298/202103

Applicant(s): various

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.3.12. Influenza vaccine (surface antigen, inactivated) (NAP) - PSUSA/00001744/202103

Applicant(s): various

PRAC Lead: Ilaria Baldelli

[83] All formulation(s) except transdermal patch
[84] Inhibitor bypassing fraction only
[85] Intravenous (IV) use only
[86] Non-centrally authorised product(s) only

Scope: Evaluation of a PSUSA procedure

16.3.13. Lisdexamfetamine (NAP) - PSUSA/00010289/202102

Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.3.14. Nomegestrol (NAP) - PSUSA/00002181/202101

Applicant(s): various

PRAC Lead: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.3.15. Propafenone (NAP) - PSUSA/00002550/202101

Applicant(s): various

PRAC Lead: Polona Golmajer

Scope: Evaluation of a PSUSA procedure

16.4. Follow-up to PSUR/PSUSA procedures

16.4.1. Leflunomide - ARAVA (CAP) - EMEA/H/C/000235/LEG 054

Applicant: Sanofi-Aventis Deutschland GmbH

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Cumulative review of cases of serious infections, including opportunistic infections and varicella-zoster infections when leflunomide is used in combination with other immunosuppressant therapies in line with the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00001837/202009) adopted in May 2021

16.5. Variation procedure(s) resulting from PSUSA evaluation

16.5.1. Dupilumab - DUPIXENT (CAP) - EMEA/H/C/004390/II/0046

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Kimmo Jaakkola

Scope: Update of section 4.8 of the SmPC to introduce facial rash with a frequency 'uncommon' related to the outcome of the PSUR single assessment (PSUSA) procedure (PSUSA/00010645/201909) finalised in April 2020. The package leaflet is updated accordingly

16.5.2. Ravulizumab - ULTOMIRIS (CAP) - EMEA/H/C/004954/II/0016

Applicant: Alexion Europe SAS

PRAC Rapporteur: Kimmo Jaakkola

Scope: Update of sections 4.4 and 4.8 of the SmPC to add anaphylactic reaction, hypersensitivity and infusion-related reactions following the outcome of the last PSUR single assessment (PSUSA) procedure (PSUSA/00010787/202006) finalised in January 2021. The patient leaflet is updated accordingly

16.6. Expedited summary safety reviews[87]

None

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

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

17.1. Protocols of PASS imposed in the marketing authorisation(s)[88]

17.1.1. Valproate (NAP) - EMEA/H/N/PSP/J/0075.5

Applicant: Sanofi-Aventis Recherche & Développement

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: MAH's response to PSP/J/0075.4 [interim report and substantial amendment to a protocol previously agreed in February 2020 for a joint drug utilisation study (DUS) to assess the effectiveness of the new risk minimisation measures (RMMs) and to further characterise the prescribing patterns for valproate as required in the outcome of the referral procedure under Article 31 of Directive 2001/83/EC on valproate-containing products completed in February 2018 (EMEA/H/A-31/1454] as per the request for supplementary information (RSI) adopted in May 2021

17.2. Protocols of PASS non-imposed in the marketing authorisation(s)[89]

17.2.1. Berotralstat - ORLADEYO (CAP) - EMEA/H/C/005138/MEA 002

Applicant: BioCryst Ireland Limited

PRAC Rapporteur: Julia Pallos

Scope: Protocol for study BCX7353-401: a non-interventional post-authorisation study to evaluate safety, tolerability and effectiveness of berotralstat for patients with hereditary angioedema in a real-world setting (from initial opinion/marketing authorisation (MA))

[87] 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
[88] In accordance with Article 107n of Directive 2001/83/EC
[89] 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

17.2.2. Coronavirus (COVID-19) vaccine (Ad26.COV2-S, recombinant) - COVID-19 VACCINE JANSSEN (CAP) - EMEA/H/C/005737/MEA 010

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Protocol for study VAC31518COV4001 (listed as a category 3 study in the RMP): a post-authorisation, observational study to assess the safety of Ad26.COV2.S (COVID-19 Vaccine Janssen) using health insurance claims and/or electronic health record (EHR) database(s) in the United States [final study report expected in December 2024]

17.2.3. Dabigatran etexilate - PRADAXA (CAP) - EMEA/H/C/000829/MEA 051

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Anette Kirstine Stark

Scope: Protocol for study 1160.307: a European non-interventional cohort study based on new data collection to measure the safety of dabigatran etexilate for the treatment of venous thromboembolism (VTE) and prevention of recurrent VTE in paediatric patients from birth to less than 2 years of age [final clinical study report (CSR) expected in Q2 2025] (from X/0122/G)

17.2.4. Fenfluramine - FINTEPLA (CAP) - EMEA/H/C/003933/MEA 005.1

Applicant: Zogenix ROI Limited

PRAC Rapporteur: Martin Huber

Scope: MAH's response to MEA 005 [protocol for study ZX008-2102: a drug utilisation study (DUS) in Europe to describe fenfluramine use in routine clinical practice [final report expected in August 2025] (from initial opinion/marketing authorisation)] as per the request for supplementary information (RSI) adopted in May 2021

17.2.5. Fenfluramine - FINTEPLA (CAP) - EMEA/H/C/003933/MEA 006

Applicant: Zogenix ROI Limited

PRAC Rapporteur: Martin Huber

Scope: Protocol for study ZX008-2104: a European study of the effectiveness of risk minimisation measures for fenfluramine in Dravet syndrome [final report expected in October 2023] (from initial opinion/marketing authorisation (MA))

17.2.6. Ivacaftor, tezacaftor, elexacaftor - KAFTRIO (CAP) - EMEA/H/C/005269/MEA 002.2

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Martin Huber

Scope: MAH Response to MEA 002.1 [protocol for study VX20-445-120: a five year-registry based study to assess real-world effects and utilisation patterns of elexacaftor/tezacaftor/ivacaftor combination therapy (ELX/TEZ/IVA) in patients with cystic fibrosis (CF)] as per the request for supplementary information (RSI) adopted in June 2021

17.2.7. Risdiplam - EVRYSDI (CAP) - EMEA/H/C/005145/MEA 007

Applicant: Roche Registration GmbH

PRAC Rapporteur: Jan Neuhauser

Scope: Protocol for study BN42833 - Risdiplam pregnancy surveillance study: a phase 4, non-interventional surveillance study [final study report expected in Q4/2031] (from initial opinion/marketing authorisation (MA))

17.2.8. Sotagliflozin - ZYNQUISTA (CAP) - EMEA/H/C/004889/MEA 004.4

Applicant: Guidehouse Germany GmbH

PRAC Rapporteur: Martin Huber

Scope: MAH's response to MEA 004.3 [protocol for study LX4211.1-401-MAL: a nested, case-control study to evaluate the risk of malignancies (bladder, renal, breast, Leydig cell, pancreatic, thyroid and prostate cancers) in adult patients with type 1 diabetes mellitus (T1DM) using sotagliflozin in existing healthcare databases in Europe and in the United States [final clinical study report (CSR) expected in April 2030] as per the request for supplementary information (RSI) adopted in April 2021

17.2.9. Tacrolimus - ADVAGRAF (CAP) - EMEA/H/C/000712/MEA 030.2

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Ronan Grimes

Scope: MAH's response to MEA 030.1 [protocol for study F506-PV-0001: a non-interventional PASS on outcomes associated with the use of tacrolimus around conception, or during pregnancy or lactation using data from the Transplant Pregnancy Registry International (TPRI) registry] as per the request for supplementary information (RSI) adopted in May 2021

17.2.10. Tacrolimus - MODIGRAF (CAP) - EMEA/H/C/000954/MEA 022.2

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: MAH's response to MEA 022.1 [protocol for study F506-PV-0001: a non-interventional PASS on outcomes associated with the use of tacrolimus around conception, or during pregnancy or lactation using data from the Transplant Pregnancy Registry International (TPRI) registry] as per the request for supplementary information (RSI) adopted in May 2021

17.2.11. Vonicog alfa - VEYVONDI (CAP) - EMEA/H/C/004454/MEA 001.4

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Amendment to a protocol previously agreed in June 2019 for study ON (BAX0111) VWF-500 COL (also called ATHN-9 study) (listed as a category 3 study in the RMP): a real-

world safety and effectiveness study of factor replacement for clinically severe von Willebrand disease (VWD)

17.3. Results of PASS imposed in the marketing authorisation(s)[90]

17.3.1. Rivaroxaban – XARELTO (CAP) - EMEA/H/C/PSR/S/0027

Applicant: Bayer AG

PRAC Rapporteur: Ulla Wändel Liminga

Scope: MAH's response to PSR/S/0027 [final study report comprising the pharmaco-epidemiological study programme of rivaroxaban use and potential adverse outcomes in routine clinical practice in the UK, Germany, the Netherlands and Sweden] as per the request for supplementary information (RSI) adopted in March 2021

17.4. Results of PASS non-imposed in the marketing authorisation(s)[91]

17.4.1. Apremilast - OTEZLA (CAP) - EMEA/H/C/003746/II/0038

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Eva Segovia

Scope: Submission of the final study report (CSR) from PsOBest registry (listed as a category 3 study in the RMP): an observational study to assess the long-term safety and effectiveness of apremilast in routine clinical practice in Germany. The RMP (version 14.0) is updated accordingly.

17.4.2. Apremilast - OTEZLA (CAP) - EMEA/H/C/003746/II/0039

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Eva Segovia

Scope: Submission of the final study report (CSR) from the UK Clinical Practice Research Database (CPRD) (listed as a category 3 study in the RMP): an observational study to assess the long-term data of apremilast in patients with psoriasis and psoriatic arthritis. The RMP (version 14.0) is updated accordingly

17.4.3. Dabigatran etexilate - PRADAXA (CAP) - EMEA/H/C/000829/II/0126/G

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Anette Kirstine Stark

Scope: Grouped variation consisting of: 1) submission of the final report from drug utilisation study 1160.129 (GLORIA AF): a three-phase, international, multicentre, prospective, observational registry programme in patients with newly diagnosed non-valvular atrial fibrillation (NV AF) at risk for stroke in order to investigate patient characteristics influencing the choice of antithrombotic treatment for the prevention of

[90] In accordance with Article 107p-q of Directive 2001/83/EC
[91] 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

stroke in NV AF patients globally and to collect data from clinical practice settings on important outcome events of antithrombotic treatments for the prevention of stroke; 2) submission of the final report from drug utilisation study 1160.136 (EU GLORIA AF) (listed as a category 3 study in the RMP): a three-phase, international, multicentre, prospective, observational registry programme in patients with newly diagnosed non-valvular atrial fibrillation (NV AF) at risk for stroke in order to investigate patient characteristics influencing the choice of antithrombotic treatment for the prevention of stroke in NV AF patients from participating countries in EU/EEA Member States and to collect data from clinical practice settings on important outcome events of antithrombotic treatments for the prevention of stroke. The RMP (version 39) is updated accordingly

17.4.4. Edoxaban - LIXIANA (CAP) - EMEA/H/C/002629/WS2078/0034; ROTEAS (CAP) - EMEA/H/C/004339/WS2078/0020

Applicant: Daiichi Sankyo Europe GmbH

PRAC Rapporteur: Tiphaine Vaillant

Scope: Submission of the final report from study ETNA-VTE-EUROPE (DSE-EDO-05-14-EU), (listed as a category 3 study in the RMP): a non-interventional study on edoxaban treatment in routine clinical practice in patients with venous thromboembolism in Europe. The RMP (version 12.0) is updated accordingly

17.4.5. Infliximab - INFLECTRA (CAP) - EMEA/H/C/002778/II/0100/G

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Kimmo Jaakkola

Scope: Grouped variations consisting of the submission of the final clinical study reports (CSRs) for CT-P13 registry studies in inflammatory bowel disease (IBD), ankylosing spondylitis (AS) and rheumatoid arthritis (RA) initiated with the objective of assessing long-term safety in these indications, namely: 1) study CT-P13 4.3: EU and Korean IBD registry; 2) CT-P13 4.4: EU and Korean AS registry; 3) study from the British Society for Rheumatology Biologicals Register (BSRBR)-RA; 4) study from the German Register for Rheumatoid Arthritis Observation of Biologic Therapy (RABBIT)

17.4.6. Infliximab - REMSIMA (CAP) - EMEA/H/C/002576/II/0103/G

Applicant: Celltrion Healthcare Hungary Kft.

PRAC Rapporteur: Kimmo Jaakkola

Scope: Grouped variations consisting of the submission of the final clinical study reports (CSRs) for CT-P13 registry studies in inflammatory bowel disease (IBD), ankylosing spondylitis (AS) and rheumatoid arthritis (RA) initiated with the objective of assessing long-term safety in these indications, namely: 1) study CT-P13 4.3: EU and Korean IBD registry; 2) CT-P13 4.4: EU and Korean AS registry; 3) study from the British Society for Rheumatology Biologicals Register (BSRBR)-RA; 4) study from the German Register for Rheumatoid Arthritis Observation of Biologic Therapy (RABBIT)

17.4.7. Insulin glargine, lixisenatide - SULIQUA (CAP) - EMEA/H/C/004243/II/0024

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Menno van der Elst

Scope: Submission of the final clinical study report (CSR) of study INSLIC08571 (listed as a category 3 study in the RMP): a survey to evaluate the knowledge and understanding of the key safety messages in the healthcare professional guide and the patient guide (in fulfilment of MEA 002). The RMP (version 6.0) is updated accordingly

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

17.5.1. Alglucosidase alfa - MYOZYME (CAP) - EMEA/H/C/000636/MEA 024.15

Applicant: Genzyme Europe BV

PRAC Rapporteur: Tiphaine Vaillant

Scope: MAH's response to MEA 024.14 [annual report 2020 on adverse events and/or lack of efficacy, immunological data, follow-up growth disturbances in children and data on urinary hexose tetrasaccharide (Hex4) from the Pompe registry: a global, multicentre, observational and voluntary programme designed to collect uniform and meaningful clinical data related to the onset, progression, and treated course of patients with Pompe disease irrespective of treatment status [final clinical study report expected in Q4 2021]] as per the request for supplementary information (RSI) adopted in March 2021

17.5.2. Alglucosidase alfa - MYOZYME (CAP) - EMEA/H/C/000636/MEA 025.15

Applicant: Genzyme Europe BV

PRAC Rapporteur: Tiphaine Vaillant

Scope: MAH's response to MEA 025.14 [annual report 2020 on data on patients with renal or hepatic insufficiency from the Pompe registry: a global, multicentre, observational and voluntary programme designed to collect uniform and meaningful clinical data related to the onset, progression, and treated course of patients with Pompe disease irrespective of treatment status [final clinical study report expected in Q4 2021]] as per the request for supplementary information (RSI) adopted in March 2021

17.5.3. Alirocumab - PRALUENT (CAP) - EMEA/H/C/003882/MEA 019.7

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: MAH's response to MEA 019.6 [second interim report for drug utilisation survey OBS14697: a drug utilisation study to assess the effectiveness of dosing recommendation of Praluent (alirocumab) as per the product information to avoid very low-density lipoprotein (LDL)-C levels [final results expected in Q3 2021]] as per the request for supplementary information (RSI) adopted in May 2021

17.5.4. Coronavirus (COVID-19) mRNA[92] vaccine (nucleoside-modified) - SPIKEVAX (CAP) - EMEA/H/C/005791/MEA 003.2

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Hans Christian Siersted

Scope: Interim report for an enhanced pharmacovigilance study (listed as a category 3 study in the RMP) to provide additional evaluation of adverse events of special interest (AESI) and emerging validated safety signals - post authorisation safety of SARS-CoV-2 mRNA-1273 vaccine in the US [final clinical study report (CSR) expected in June 2023] (from initial opinion/marketing authorisation (MA))

17.5.5. Coronavirus (COVID-19) mRNA[93] vaccine (nucleoside-modified) - SPIKEVAX (CAP) - EMEA/H/C/005791/MEA 005.2

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Hans Christian Siersted

Scope: Interim report for a study (listed as a category 3 study in the RMP): Moderna mRNA-1273 observational pregnancy outcome study to evaluate outcomes of pregnancies in females exposed to mRNA-1273 vaccine (Spikevax) during pregnancy [final clinical study report (CSR) expected in June 2024]

17.5.6. Elosulfase alfa - VIMIZIM (CAP) - EMEA/H/C/002779/ANX 005.6

Applicant: BioMarin International Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Seventh annual report (reporting period: 14 February 2020 to 12 February 2021) for the multicentre, multinational, observational Morquio A registry study (MARS): a voluntary observational registry study to characterise and describe the mucopolysaccharidosis IV type A (MPS IVA) population and to evaluate the long-term effectiveness and safety of Vimizim (elosulfase alfa) [final clinical study report (CSR) expected by March 2025]

17.5.7. Empagliflozin - JARDIANCE (CAP) - EMEA/H/C/002677/MEA 010.4

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Eva Segovia

Scope: Fifth monitoring interim report for study 1245.97: a non-interventional PASS assessing the risk of urinary tract malignancies in relation to empagliflozin exposure in patients with type 2 diabetes mellitus (T2DM): a multi-database European study [final clinical study report (CSR) expected in June 2021]

17.5.8. Empagliflozin, metformin - SYNJARDY (CAP) - EMEA/H/C/003770/MEA 006.6

Applicant: Boehringer Ingelheim International GmbH

[92] Messenger ribonucleic acid
[93] Messenger ribonucleic acid

PRAC Rapporteur: Eva Segovia

Scope: Fifth monitoring interim report for study 1245.97: a non-interventional PASS assessing the risk of urinary tract malignancies in relation to empagliflozin exposure in patients with type 2 diabetes mellitus (T2DM): a multi-database European study [final clinical study report (CSR) expected in June 2021]

17.5.9. Eribulin - HALAVEN (CAP) - EMEA/H/C/002084/MEA 024.1

Applicant: Eisai GmbH

PRAC Rapporteur: Annika Folin

Scope: MAH's response to MEA 024 [interim results for study E7389-M044-504 (IRENE): an observational, post-authorisation, single-arm, prospective, multicentre cohort study to characterise and determine the incidence of eribulin-induced peripheral neuropathy (PN), and the frequency and time to resolution of eribulin-induced PN in adult patients treated with eribulin in a real-life setting with locally advanced or metastatic breast cancer who have progressed after at least one chemotherapeutic regimen for advanced disease] as per the request for supplementary information (RSI) adopted in March 2020

17.5.10. Plasmodium falciparum and hepatitis B vaccine (recombinant, adjuvanted) - MOSQUIRIX (Art 58[94]) - EMEA/H/W/002300/MEA 003.5

Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Jean-Michel Dogné

Scope: Fourth annual progress report for study EPI-MAL-003 (listed as a category 3 study in the RMP): a phase 4 prospective observational study to evaluate the safety, effectiveness and impact of Mosquirix (plasmodium falciparum and hepatitis B vaccine (recombinant, adjuvanted)) in young children in sub-Saharan Africa in order to estimate the incidence of potential adverse events of special interest (AESI) and other adverse events leading to hospitalisation or death, in children vaccinated with the vaccine, together with MAH's response to MEA 003.4 [third annual progress report] as per the request for supplementary information (RSI) adopted in March 2021

17.5.11. Umeclidinium - ROLUFTA ELLIPTA (CAP) - EMEA/H/C/004654/ANX 003.1

Applicant: GlaxoSmithKline Trading Services Limited

PRAC Rapporteur: Ilaria Baldelli

Scope: MAH's response to ANX 003 [interim report for study 201038 (EU PASS 10316): non-interventional post-authorisation safety (PAS) observational cohort study to quantify the incidence and comparative safety of selected cardiovascular and cerebrovascular events in chronic obstructive pulmonary disease (COPD) patients with umeclidinium/vilanterol (UMEC/VI) combination, or inhaled UMEC versus tiotropium] as per the request for supplementary information (RSI) adopted in June 2021

[94] 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)

17.5.12. Umeclidinium, vilanterol - ANORO ELLIPTA (CAP) - EMEA/H/C/002751/ANX 001.3

Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Ilaria Baldelli

Scope: MAH's response to ANX 001.2 [interim report for study 201038 (EU PASS 10316): non-interventional post-authorisation safety (PAS) observational cohort study to quantify the incidence and comparative safety of selected cardiovascular and cerebrovascular events in chronic obstructive pulmonary disease (COPD) patients with umeclidinium/vilanterol (UMEC/VI) combination, or inhaled UMEC versus tiotropium] as per the request for supplementary information (RSI) adopted in June 2021

17.5.13. Umeclidinium, vilanterol - LAVENTAIR ELLIPTA (CAP) - EMEA/H/C/003754/ANX 001.3

Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Ilaria Baldelli

Scope: MAH's response to ANX 001.2 [interim report for study 201038 (EU PASS 10316): non-interventional post-authorisation safety (PAS) observational cohort study to quantify the incidence and comparative safety of selected cardiovascular and cerebrovascular events in chronic obstructive pulmonary disease (COPD) patients with umeclidinium/vilanterol (UMEC/VI) combination, or inhaled UMEC versus tiotropium] as per the request for supplementary information (RSI) adopted in June 2021

17.5.14. Umeclidinium bromide - INCRUSE ELLIPTA (CAP) - EMEA/H/C/002809/ANX 001.3

Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Ilaria Baldelli

Scope: MAH's response to ANX 001.2 [interim report for study 201038 (EU PASS 10316): non-interventional post-authorisation safety (PAS) observational cohort study to quantify the incidence and comparative safety of selected cardiovascular and cerebrovascular events in chronic obstructive pulmonary disease (COPD) patients with umeclidinium/vilanterol (UMEC/VI) combination, or inhaled UMEC versus tiotropium] as per the request for supplementary information (RSI) adopted in June 2021

17.5.15. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/MEA 022.23

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Rhea Fitzgerald

Scope: MAH's response to MEA 022.22 [tenth annual report for study C0168Z03 (PSOLAR: PSOriasis Longitudinal Assessment and Registry): an international prospective cohort study/registry programme designed to collect data on psoriasis (PSO) patients that are eligible to receive systemic therapies, including generalised phototherapy and biologics] as per the request for supplementary information (RSI) adopted in May 2021

17.6. Others

17.6.1. Acalabrutinib - CALQUENCE (CAP) - EMEA/H/C/005299/MEA 002.1

Applicant: AstraZeneca AB

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: MAH's response to MEA 002 [protocol for study D8220C00008 (listed as a category 3 study in the RMP): a phase 3b, multicentre, open-label, single-arm study in subjects with chronic lymphocytic leukaemia (ASSURE) to address missing information around moderate to severe cardiac impaired patients in subjects treated with Calquence (acalabrutinib)] as per the request for supplementary information (RSI) adopted in April 2021

17.6.2. Plasmodium falciparum and hepatitis B vaccine (recombinant, adjuvanted) - MOSQUIRIX (Art 58[95]) - EMEA/H/W/002300/MEA 019

Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Jean-Michel Dogné

Scope: Statistical report on the results of the 'Malaria Vaccine Program Evaluation' (MVPE) led by WHO[96] - Mosquirix (plasmodium falciparum and hepatitis B vaccine - RTS,S/AS01) MVPE 24 months after the vaccination with Mosquirix (plasmodium falciparum and hepatitis B vaccine) was introduced by national immunisation programmes

17.6.3. Sacubitril, valsartan - ENTRESTO (CAP) - EMEA/H/C/004062/MEA 004.10

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Anette Kirstine Stark

Scope: Statistical analysis plan for CLCZ696B2015 (PASS 3) (listed as a category 3 study in the RMP): a non-interventional post-authorisation European multi-database safety study to assess the risk of myotoxicity, hepatotoxicity and acute pancreatitis in statin-exposed heart failure patients with or without concomitant use of Entresto/Neparvis (sacubitril/valsartan) [final study report expected in December 2022]

17.6.4. Sacubitril, valsartan - NEPARVIS (CAP) - EMEA/H/C/004343/MEA 003.7

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Anette Kirstine Stark

Scope: Statistical analysis plan for CLCZ696B2015 (PASS 3) (listed as a category 3 study in the RMP): a non-interventional post-authorisation European multi-database safety study to assess the risk of myotoxicity, hepatotoxicity and acute pancreatitis in statin-exposed heart failure patients with or without concomitant use of Entresto/Neparvis (sacubitril/valsartan) [final study report expected in December 2022]

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

17.6.5. Tacrolimus - ADVAGRAF (CAP) - EMEA/H/C/000712/MEA 032

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Ronan Grimes

Scope: Submission of a critical analysis of the feasibility of using alternative data sources to complement the Transplantation Pregnancy Registry International (TPRI) study outcomes on pregnancy and breastfeeding

17.6.6. Tacrolimus - MODIGRAF (CAP) - EMEA/H/C/000954/MEA 024

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of a critical analysis of the feasibility of using alternative data sources to complement the Transplantation Pregnancy Registry International (TPRI) study outcomes on pregnancy and breastfeeding

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 below-listed 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. Chenodeoxycholic acid - CHENODEOXYCHOLIC ACID LEADIANT (CAP) - EMEA/H/C/004061/S/0017 (without RMP)

Applicant: Leadiant GmbH

PRAC Rapporteur: Adam Przybylkowski

Scope: Annual reassessment of the marketing authorisation

18.1.2. Dinutuximab beta - QARZIBA (CAP) - EMEA/H/C/003918/S/0028 (without RMP)

Applicant: EUSA Pharma (Netherlands) B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Annual reassessment of the marketing authorisation

18.1.3. Ebola vaccine (rDNA[97], replication-incompetent) - MVABEA (CAP) - EMEA/H/C/005343/S/0006 (without RMP)

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Jean-Michel Dogné

Scope: Annual reassessment of the marketing authorisation

18.1.4. Ebola vaccine (rDNA[98], replication-incompetent) - ZABDENO (CAP) - EMEA/H/C/005337/S/0005 (without RMP)

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Jean-Michel Dogné

Scope: Annual reassessment of the marketing authorisation

18.2. Conditional renewals of the marketing authorisation

18.2.1. Burosumab - CRYSVITA (CAP) - EMEA/H/C/004275/R/0026 (without RMP)

Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Conditional renewal of the marketing authorisation

18.2.2. Coronavirus (COVID-19) mRNA[99] 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

18.2.3. Coronavirus (COVID-19) vaccine (ChAdOx1-S [recombinant]) - VAXZEVRIA (CAP) - EMEA/H/C/005675/R/0037 (without RMP)

Applicant: AstraZeneca AB

[97] Ribosomal deoxyribonucleic acid
[98] Ribosomal deoxyribonucleic acid
[99] Messenger ribonucleic acid

PRAC Rapporteur: Jean-Michel Dogné

Scope: Conditional renewal of the marketing authorisation

18.2.4. Ex vivo expanded autologous human corneal epithelial cells containing stem cells - HOLOCLAR (CAP) - EMEA/H/C/002450/R/0039 (without RMP)

Applicant: Holostem Terapie Avanzate s.r.l., ATMP[100]

PRAC Rapporteur: Rhea Fitzgerald

Scope: Conditional renewal of the marketing authorisation

18.2.5. 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

18.2.6. Selpercatinib - RETSEVMO (CAP) - EMEA/H/C/005375/R/0008 (without RMP)

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Conditional renewal of the marketing authorisation

18.3. Renewals of the marketing authorisation

18.3.1. Adalimumab - AMGEVITA (CAP) - EMEA/H/C/004212/R/0029 (without RMP)

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: 5-year renewal of the marketing authorisation

18.3.2. Chenodeoxycholic acid - CHENODEOXYCHOLIC ACID LEADIANT (CAP) - EMEA/H/C/004061/R/0018 (without RMP)

Applicant: Leadiant GmbH

PRAC Rapporteur: Adam Przybylkowski

Scope: 5-year renewal of the marketing authorisation

18.3.3. Edoxaban - ROTEAS (CAP) - EMEA/H/C/004339/R/0021 (with RMP)

Applicant: Berlin Chemie AG

PRAC Rapporteur: Tiphaine Vaillant

Scope: 5-year renewal of the marketing authorisation

[100] Advanced therapy medicinal product

18.3.4. Tenofovir alafenamide - VEMLIDY (CAP) - EMEA/H/C/004169/R/0035 (without RMP)

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ilaria Baldelli

Scope: 5-year renewal of the marketing authorisation

18.3.5. 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 27-30 September 2021 meeting (marked as "a"), and for the 14 October 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, b]	Member	Belgium	No interests declared	Full involvement
Laurence de Fays [a]	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
Panagiotis Psaras [a, b]	Member	Cyprus	No interests declared	Full involvement
Christina Sylvia Chrysostomou [a]	Alternate	Cyprus	No interests declared	Full involvement
Eva Jirsová [a]	Member	Czechia	No interests declared	Full involvement
Jana Lukacisinova [a, b]	Alternate	Czechia	No interests declared	Full involvement
Anette Kirstine Stark [a, b]	Member	Denmark	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Hans Christian Siersted [a]	Alternate	Denmark	No restrictions applicable to this meeting	Full involvement
Maia Uusküla [b]	Member	Estonia	No interests declared	Full involvement
Krõõt Aab [a, b]	Alternate	Estonia	No interests declared	Full involvement
Kirsti Villikka [a, b]	Member	Finland	No interests declared	Full involvement
Kimmo Jaakkola [a]	Alternate	Finland	No interests declared	Full involvement
Tiphaine Vaillant [a, b]	Member	France	No interests declared	Full involvement
Nathalie Gault [b]	Alternate (mandate as alternate for France started on 11/10/2022)	France	No interests declared	Full involvement
Martin Huber [a, b]	Member (Vice-Chair)	Germany	No interests declared	Full involvement
Brigitte Keller-Stanislawski [a, b]	Alternate	Germany	No interests declared	Full involvement
Melinda Palfi [a]	Member	Hungary	No interests declared	Full involvement
Julia Pallos [a, b]	Alternate	Hungary	No participation in final deliberations and voting on:	18.3.3. Edoxaban - ROTEAS (CAP) - EMEA/H/C/004339/R/0021 (with RMP)
Guðrún Stefánsdóttir [a, b]	Member	Iceland	No participation in final deliberations and voting on:	15.3.8. Evolocumab - REPATHA (CAP) - EMEA/H/C/003766/II/0049/G

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				16.1.6. Bevacizumab - AVASTIN (CAP); AYBINTIO (CAP); EQUIDACENT (CAP); MVASI (CAP); ONBEVZI (CAP); ZIRABEV (CAP) - PSUSA/00000403/202102 17.4.1. Apremilast - OTEZLA (CAP) - EMEA/H/C/003746/II/0038 17.4.2. Apremilast - OTEZLA (CAP) - EMEA/H/C/003746/II/0039 18.3.1. Adalimumab - AMGEVITA (CAP) - EMEA/H/C/004212/R/0029 (without RMP)
Ronan Grimes [a, b]	Alternate	Ireland	No interests declared	Full involvement
Amelia Cupelli [a, b]	Member	Italy	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
Nadine Petitpain [a]	Member	Luxembourg	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
Anne-Cécile Vuillemin [b]	Alternate	Luxembourg	No interests declared	Full involvement
John Joseph Borg [a]	Member (CHMP member)	Malta	No interests declared	Full involvement
Menno van der Elst [a, b]	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:	3.1.1. Chlormadinone (NAP); chlormadinone, ethinylestradiol (NAP); nomegestrol (NAP); nomegestrol, estradiol (CAP) – ZOELY (CAP), NAP - EMEA/H/A-31/1510 7.3.3. Radium (Ra223) – XOFIGO (CAP) - EMEA/H/C/PSR/S/0034 14.2.1. Sorafenib – NEXAVAR (CAP) 16.3.10. Iloprost (NAP) - PSUSA/00009190/202101 17.3.1. Rivaroxaban – XARELTO (CAP) - EMEA/H/C/PSR/S/0027

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Karen Pernille Harg [a]	Alternate	Norway	No interests declared	Full involvement
Adam Przybylkowski [a]	Member	Poland	No interests declared	Full involvement
Katarzyna Ziolkowska [b]	Alternate	Poland	No interests declared	Full involvement
Ana Sofia Diniz Martins [a, b]	Member	Portugal	No interests declared	Full involvement
Marcia Sofia Sanches de Castro Lopes Silva [a, b]	Alternate	Portugal	No interests declared	Full involvement
Roxana Dondera [a, b]	Member	Romania	No interests declared	Full involvement
Alexandra - Maria Spurni [a, b]	Alternate	Romania	No interests declared	Full involvement
Michal Radik [b]	Member	Slovakia	No interests declared	Full involvement
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, 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
Patricia McGettigan [a]	Member	Independent scientific expert	No interests declared	Full involvement
Daniel Morales [a]	Member	Independent scientific expert	No interests declared	Full involvement

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Hedvig Nordeng [a]	Member	Independent scientific expert	No interests declared	Full involvement
Raymond Anderson [a]	Member	Healthcare Professionals' Representative	No interests declared	Full involvement
Roberto Frontini [a]	Alternate	Healthcare Professionals' Representative	No restrictions applicable to this meeting	Full involvement
Cathalijne van Doorne [a]	Member	Patients' Organisation Representative	No interests declared	Full involvement
Virginie Hivert [a]	Alternate	Patients' Organisation Representative	No restrictions applicable to this meeting	Full involvement
Christelle Bizimungu [a]	Expert - via Webex*	Belgium	No restrictions applicable to this meeting	Full involvement
Evelien De Clercq [a]	Expert - via Webex*	Belgium	No interests declared	Full involvement
Jamila Hamdani [a]	Expert - via Webex*	Belgium	No interests declared	Full involvement
Piush Jain [a]	Expert - via Webex*	Belgium	No restrictions applicable to this meeting	Full involvement
Tom Lams [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
Jo Robays [a]	Expert - via Webex*	Belgium	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
Martine Sabbe [a]	Expert - via Webex*	Belgium	No interests declared	Full involvement
Françoise Wuillaume [a]	Expert - via Webex*	Belgium	No interests declared	Full involvement
Melita Dumančić [a]	Expert - via Webex*	Croatia	No restrictions applicable to this meeting	Full involvement
Barbara Kovačić [a]	Expert - via Webex*	Croatia	No interests declared	Full involvement
Nina Lalić [a]	Expert - via Webex*	Croatia	No restrictions applicable to this meeting	Full involvement
Ivana Ljubičić [a]	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, b]	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
Helle Esbjørn Kristensen [a]	Expert - via Webex*	Denmark	No interests declared	Full involvement
Kristina Laursen [a]	Expert - via Webex*	Denmark	No interests declared	Full involvement
Helle Gerda Olsen [a]	Expert - via Webex*	Denmark	No interests declared	Full involvement
Peter Horskjær Rose [a]	Expert - via Webex*	Denmark	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Moritz Sander [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
Päivi Susanna Worsøe [a]	Expert - via Webex*	Denmark	No interests declared	Full involvement
Helve Vestman [b]	Expert - via Webex*	Estonia	No interests declared	Full involvement
Maija Kaukonen [b]	Expert - via Webex*	Finland	No interests declared	Full involvement
Karima Adamo [a]	Expert - via Webex*	France	No restrictions applicable to this meeting	Full involvement
Anissa Benlazar [a]	Expert - via Webex*	France	No restrictions applicable to this meeting	Full involvement
Samuel Crommelynck [b]	Expert - via Webex*	France	No restrictions applicable to this meeting	Full involvement
Pauline Dayani [a]	Expert - via Webex*	France	No interests declared	Full involvement
Pierre Demolis [a]	Expert - via Webex*	France	No interests declared	Full involvement
Vincent Gazin [a]	Expert - via Webex*	France	No interests declared	Full involvement
Leo Lambart [a, b]	Expert – via Webex*	France	No restrictions applicable to this meeting	Full involvement
Marie-Caroline Pesquidous [a]	Expert – via Webex*	France	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	
Youssef Shaim [b]	Expert – via Webex*	France	No restrictions applicable to this meeting	Full involvement
Nicole Bick [a]	Expert – via Webex*	Germany	No interests declared	Full involvement
Jelena Katic [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
Tania Meier [a]	Expert – via Webex*	Germany	No interests declared	Full involvement
Wiebke Seeman [a]	Expert – via Webex*	Germany	No interests declared	Full involvement
Eleanor Carey [a]	Expert – via Webex*	Ireland	No restrictions applicable to this meeting	Full involvement
Grainne Kirwan [a]	Expert – via Webex*	Ireland	No interests declared	Full involvement
Marcel Kwa [a, b]	Expert – via Webex*	The Netherlands	No interests declared	Full involvement
Petrus Luijsterburg [a]	Expert – via Webex*	The Netherlands	No interests declared	Full involvement
Lotte Minnema [a]	Expert – via Webex*	The Netherlands	No interests declared	Full involvement
Peter Mol [a]	Expert – via Webex*	The Netherlands	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
Maria Vanenburg [a]	Expert – via Webex*	The Netherlands	No interests declared	Full involvement
Ulrike Jüse [a]	Expert – via Webex*	Norway	No interests declared	Full involvement
Silvia de Orbe [a]	Expert – via Webex*	Spain	No interests declared	Full involvement
Lourdes Fernández Martn [a]	Expert – via Webex*	Spain	No restrictions applicable to this meeting	Full involvement
Consuelo Mejias Pavon [a]	Expert – via Webex*	Spain	No interests declared	Full involvement
Miguel del Rey [a]	Expert – via Webex*	Spain	No interests declared	Full involvement
Charlotte Backman [a, b]	Expert – via Webex*	Sweden	No interests declared	Full involvement
Sofia Bosdotter Enroth [a]	Expert – via Webex*	Sweden	No interests declared	Full involvement
Jessica Mwinyi [a]	Expert – via Webex*	Sweden	No interests declared	Full involvement
Elina Rönnemaa [a]	Expert – via Webex*	Sweden	No interests declared	Full involvement
A representative from the European Commission attended the meeting				
Meeting run with support from relevant EMA staff				

* Experts were 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, EMA is requested to conduct a scientific assessment of a particular medicine or class of medicines on behalf of the European Union (EU). For further detailed information on safety related referrals please see:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000150.jsp&mid=WC0b01ac05800240d0

Signals assessment and prioritisation

(Item 4 of the PRAC minutes)

A safety signal is information on a new or incompletely documented adverse event that is potentially caused by a medicine and that warrants further investigation. Signals are generated from several sources such as spontaneous reports, clinical studies and the scientific literature. The evaluation of safety signals is a routine part of pharmacovigilance and is essential to ensuring that regulatory authorities have a comprehensive knowledge of a medicine's benefits and risks.
The presence of a safety signal does not mean that a medicine has caused the reported adverse event. The adverse event could be a symptom of another illness or caused by another medicine taken by the patient. The evaluation of safety signals is required to establish whether or not there is a causal relationship between the medicine and the reported adverse event.
The evaluation of safety signals may not necessarily conclude that the medicine caused the adverse event in question. In cases where a causal relationship is confirmed or considered likely, regulatory action may be necessary and this usually takes the form of an update of the summary of product characteristics and the package leaflet.

Risk Management Plans (RMPs)

(Item 5 of the PRAC minutes)

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

Assessment of Periodic Safety Update Reports (PSURs)

(Item 6 of the PRAC minutes)

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

Post-authorisation Safety Studies (PASS)

(Item 7 of the PRAC minutes)

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

Product related pharmacovigilance inspections
(Item 9 of the PRAC minutes)

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

More detailed information on the above terms can be found on the EMA website:
http://www.ema.europa.eu/ema/