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Human Medicines Division

Pharmacovigilance Risk Assessment Committee (PRAC) Minutes of the meeting on 05-08 July 2021

Chair: Sabine Straus – Vice-Chair: Martin Huber

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

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1. Introduction

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

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

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

Discussions, deliberations and voting took place in full respect of the restricted involvement of Committee members and experts in line with the relevant provisions of revision 2 of the Rules of Procedure ([EMA/PRAC/567515/2012 Rev.2](#)). All decisions taken at this meeting held under the conditions of an emergency situation, the Agency's BCP and in compliance with internal guidelines were made in the presence of a quorum of members (i.e. 18 or more members were present remotely). All decisions, recommendations and advice were agreed unanimously, unless otherwise specified.

The PRAC Chairperson welcomed Annalisa Capuano, Maria Teresa Herdeiro and Patricia McGettigan as new independent scientific experts nominated by the European Commission, with a mandate started as of 2 July 2021 for a period of three years. The PRAC Chairperson also noted that the mandate of Hedvig Marie Egeland Nordeng, Daniel Morales, Daniel-Milou Drici as independent scientific experts was prolonged for the same period of time. The Chair also announced that it was the last plenary meeting for Adrien Inoubli as the member for France.

At the organisational, regulatory and methodological matters (ORGAM) meeting held on 22 July 2021, the Chair announced that Krõõt Aab was the new alternate for Estonia replacing Katrin Kiisk, Polona Golmajer the new member for Slovenia and Petra Brina Kovacic the new alternate for Slovenia, replacing Jasmina Klopčič. The Chair also noted a swap of roles amongst the Hungarian delegation: Melinda Palfi becomes the member while Julia Pallos takes the role of alternate.

The Committee thanked the leaving members and alternates for their contribution to the work of PRAC.

Finally, PRAC welcomed the Slovenian presidency of the Council of the EU.

1.2. Agenda of the meeting on 05-08 July 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 07-10 June 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 07-10 June 2021 were published on the EMA website on 04 May 2022 ([EMA/PRAC/139868/2022](https://www.ema.europa.eu/en/press-room/news/2022/05/ema-prac-139868-2022)).

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

None

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](#).

Summary of recommendation(s)/conclusions

- PRAC discussed the assessment reports issued by the Rapporteurs.
- PRAC adopted a list of outstanding issues (LoOI), to be addressed by the MAHs in accordance with a revised timetable (EMA/PRAC/171547/2022 Rev.2).
- PRAC agreed on the need to convene an ad-hoc expert group (AHEG) meeting. PRAC adopted a list of questions (LoQ) to the AHEG.

3.3. Procedures for finalisation

3.3.1. Betibeglogene autotemcel – ZYNTGLO (CAP) – EMEA/H/A-20/1504

Applicant: Bluebird bio (Netherlands) B.V.; ATMP¹

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

Scope: Review of the benefit-risk balance following notification by the European Commission of a referral under Article 20 of Regulation (EC) No 726/2004 based on pharmacovigilance data

Background

A referral procedure under Article 20 of Regulation (EC) No 726/2004 for the review of Zynteglo (betibeglogene autotemcel) is to be concluded.

A final assessment of the data submitted was produced by the Rapporteurs according to the agreed timetable. For further background, see [PRAC minutes March 2021](#) and [PRAC minutes June 2021](#).

Discussion

PRAC discussed the conclusions reached by the Rapporteurs.

PRAC considered the totality of the data made available to the Committee on the use of Zynteglo (betibeglogene autotemcel) including the risk of developing acute myeloid leukaemia (AML) in a clinical trial in two sickle cell disease patients treated with investigational drug product bb1111 transduced with the same lentiviral vector as Zynteglo (betibeglogene autotemcel), and the responses submitted by the MAH in writing. PRAC also considered the views expressed by experts of the Committee for Advanced Therapies (CAT).

PRAC noted that based on the review of available information in one of the reported cases of AML, integration of the lentiviral vector at the vesicle associated membrane protein 4 (VAMP4) gene was observed. Since VAMP4 mutations are not known to be associated with oncogenicity, a causal association of the oncogenic event with the integration of the lentiviral vector at the VAMP4 site is considered unlikely.

PRAC also concluded that post-treatment mutations detected in a second AML patient treated with bb1111 in whom the leukaemic cells did not contain the lentiviral vector, are most likely to be related to the myeloablative conditioning. PRAC also considered based on the scientific knowledge about proliferative stress and its impact on patients that increased bone marrow stress due to the low cell number administered and lack of clinical response may have contributed to the development of AML in the reported cases.

¹ Advanced therapy medicinal product

Available non-clinical and quality data also did not point toward an increased tumorigenic risk through transduction of cells with the lentiviral vector used in Zynteglo (betibeglogene autotemcel) and bb1111.

Overall, PRAC concluded there is no evidence that the vector integration is involved in the development of AML events reported with bb1111, and as such, the risk of AML associated with Zynteglo (betibeglogene autotemcel) remains unchanged. As for other gene therapies, insertional oncogenesis remains an important potential risk also for Zynteglo (betibeglogene autotemcel) and PRAC recommended that patients should be monitored at least annually also for myelodysplasia in addition to leukaemia or lymphoma, including a complete blood count.

PRAC also agreed on revised key messages for the educational materials to strengthen the information on the risks associated with myeloablative conditioning and further emphasise the periodic monitoring of patients for malignancies post treatment with Zynteglo (betibeglogene autotemcel). PRAC also recommended amendments to the RMP to reflect these measures and clarify the frequencies for integration site analysis in long-term follow-up studies.

Summary of recommendation(s)/conclusions

- PRAC adopted a recommendation to vary² the terms of the marketing authorisation(s) for Zynteglo (betibeglogene autotemcel) to be considered by CHMP for an opinion – see EMA Press Release entitled 'EMA finds no evidence linking viral vector in Zynteglo to blood cancer' ([EMA/380481/2021](https://www.ema.europa.eu/en/press-room/2021/09/WGPR-21-0010)).

Post-meeting note 1: the press release 'CHMP endorses review finding no link between viral vector in Zynteglo and blood cancer' representing the opinion provided by CHMP ([EMA/546292/2021](https://www.ema.europa.eu/en/press-room/2021/09/WGPR-21-0010)) was published on the EMA website on 16 September 2021.

Post-meeting note 2: the PRAC assessment report ([EMA/418200/2021](https://www.ema.europa.eu/en/press-room/2021/07/WGPR-21-0008)) was published on 08 July 2021.

3.4. Re-examination procedures³

None

3.5. Others

None

4. Signals assessment and prioritisation⁴

4.1. New signals detected from EU spontaneous reporting systems

See also Annex I 14.1.

² Update of SmPC section 4.4. and Annex II. The package leaflet is updated accordingly

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

4.1.1. Coronavirus (COVID-19) mRNA⁵ vaccine (nucleoside-modified) - COMIRNATY (CAP)

Applicant(s): BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Signal of erythema multiforme

EPITT 19721 – New signal

Lead Member State(s): NL

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 16 years of age and older.

Based on routine signal detection activities and review of monthly summary safety reports (MSSR) for Comirnaty (COVID-19 mRNA vaccine (nucleoside-modified)), a signal of erythema multiforme was identified based on 72 cases retrieved from EudraVigilance. 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 22 July 2021, PRAC discussed the signal and adopted a recommendation.

Discussion

Having considered the available evidence from case reports in EudraVigilance and the literature, and taking into account the compatible time to onset (TTO), positive re-challenge and plausible causal relationship, PRAC agreed that further evaluation of the signal was warranted.

Summary of recommendation(s)

- The MAH for Comirnaty (COVID-19 mRNA vaccine (nucleoside-modified)) should submit to EMA, within 30 days, a cumulative review of cases of erythema multiforme, including spontaneous case reports, literature and clinical trials data. The MAH should include a causality assessment, together with a discussion on the possible biological mechanism and an observed/expected (O/E) analysis. The MAH should also make a proposal to update the product information and/or RMP as warranted. In addition, the MAH should consider providing recommendations for patients who experience erythema multiforme after the first dose and what action should be taken regarding administration of a second dose.
- A 30-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.1.2. Coronavirus (COVID-19) mRNA⁷ vaccine (nucleoside-modified) - COMIRNATY (CAP)

Applicant(s): BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

⁵ Messenger ribonucleic acid

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

⁷ Messenger ribonucleic acid

Scope: Signal of glomerulonephritis and nephrotic syndrome

EPITT 19722 – New signal

Lead Member State(s): NL

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 16 years of age and older.

Based on routine signal detection activities, a signal of glomerulonephritis and nephrotic syndrome was identified based on 9 cases retrieved from the literature. 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 22 July 2021, PRAC discussed the signal and adopted a recommendation.

Discussion

Having considered the available evidence from case reports in EudraVigilance and the literature, and taking into account the compatible time to onset (TTO), possible positive rechallenge and plausible causal relationship, PRAC agreed that further evaluation of the signal was warranted.

Summary of recommendation(s)

- The MAH for Comirnaty (COVID-19 mRNA vaccine (nucleoside-modified)) should submit to EMA, within 30 days, a cumulative review of cases of glomerulonephritis/nephrotic syndrome, including spontaneous case reports, literature and clinical trials data. The MAH should include a causality assessment, together with a discussion on the possible biological mechanism and an observed/expected (O/E) analysis. The MAH should also make a proposal to update the product information and/or RMP as warranted. In addition, the MAH should consider providing recommendations for patients who experience these events after the first dose and what action should be taken regarding administration of a second dose.
- A 30-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.1.3. Coronavirus (COVID-19) mRNA⁹ vaccine (nucleoside-modified) - SPIKEVAX (previously COVID-19 VACCINE MODERNA) (CAP)

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

PRAC Rapporteur: Hans Christian Siersted

Scope: Signal of erythema multiforme

EPITT 19720 – New signal

Lead Member State(s): DK

Background

⁸ Extended to specific COVID-19-related procedure(s) during EMA business continuity plan (BCP)

⁹ Messenger ribonucleic acid

Coronavirus disease 2019 (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 adults.

Based on routine signal detection activities and review of monthly summary safety reports (MSSR) for Spikevax (COVID-19 mRNA vaccine (nucleoside-modified)), a signal of erythema multiforme was identified based on 90 cases retrieved from EudraVigilance. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by PRAC. At the organisational, regulatory and methodological matters (ORGAM)¹⁰ meeting held on 22 July 2021, PRAC discussed the signal and adopted a recommendation.

Discussion

Having considered the available evidence from case reports in EudraVigilance and the literature, and taking into account the compatible time to onset (TTO) and positive re-challenge and plausible causal relationship, PRAC agreed that further evaluation of the signal was warranted.

Summary of recommendation(s)

- The MAH for Spikevax (COVID-19 mRNA vaccine (nucleoside-modified)) should submit to EMA, within 30 days, a cumulative review of cases of erythema multiforme, including spontaneous case reports, literature and clinical trials data. The MAH should include a causality assessment, together with a discussion on the possible biological mechanism and an observed/expected (O/E) analysis. The MAH should also make a proposal to update the product information and/or RMP as warranted. In addition, the MAH should consider providing recommendations for patients who experience erythema multiforme after the first dose and what action should be taken regarding administration of a second dose.
- A 30-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.1.4. Coronavirus (COVID-19) mRNA¹¹ vaccine (nucleoside-modified) - SPIKEVAX (previously COVID-19 VACCINE MODERNA) (CAP)

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

PRAC Rapporteur: Hans Christian Siersted

Scope: Signal of glomerulonephritis and nephrotic syndrome

EPITT 19724 – New signal

Lead Member State(s): DK

Coronavirus disease 2019 (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 adults.

Based on routine signal detection activities, a signal of glomerulonephritis and nephrotic

¹⁰ Extended to specific COVID-19-related procedure(s) during EMA business continuity plan (BCP)

¹¹ Messenger ribonucleic acid

syndrome was identified based on 14 cases retrieved from EudraVigilance and the literature. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by PRAC. At the organisational, regulatory and methodological matters (ORGAM)¹² meeting held on 22 July 2021, PRAC discussed the signal and adopted a recommendation.

Discussion

Having considered the available evidence from case reports in EudraVigilance and the literature, and taking into account the compatible time to onset (TTO), possible positive rechallenge and plausible causal relationship, PRAC agreed that further evaluation of the signal was warranted.

Summary of recommendation(s)

- The MAH for Spikevax (COVID-19 mRNA vaccine (nucleoside-modified)) should submit to EMA, within 30 days, a cumulative review of cases of glomerulonephritis/nephrotic syndrome, including spontaneous case reports, literature and clinical trials data. The MAH should include a causality assessment, together with a discussion on the possible biological mechanism and an observed/expected (O/E) analysis. The MAH should also make a proposal to update the product information and/or RMP as warranted. In addition, the MAH should consider providing recommendations for patients who experience these events after the first dose and what action should be taken regarding administration of a second dose.
- A 30-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.2. New signals detected from other sources

None

4.3. Signals follow-up and prioritisation

4.3.1. Coronavirus (COVID-19) mRNA¹³ vaccine (nucleoside-modified) - COMIRNATY (CAP) – EMEA/H/C/005735/SDA/032

Applicant(s): BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Signal of myocarditis and pericarditis

EPITT 19712 – Follow-up to June 2021

Background

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

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

Discussion

¹² Extended to specific COVID-19-related procedure(s) during EMA business continuity plan (BCP)

¹³ Messenger ribonucleic acid

PRAC considered the available evidence from EudraVigilance including data from clinical trials and post-marketing experience, the literature, observed to expected (O/E) analyses and additional data provided by the MAH both in writing and in an oral explanation, together with the Rapporteur's assessment. PRAC agreed that there is a reasonable possibility for a causal relationship between Comirnaty (COVID-19 mRNA vaccine (nucleoside-modified)) and myocarditis and pericarditis. Therefore, PRAC agreed that an update of the product information is warranted to add myocarditis and pericarditis as a warning and as undesirable effects with a frequency 'not known'.

Summary of recommendation(s)

- The MAH for Comirnaty (COVID-19 mRNA vaccine (nucleoside-modified)) should submit to EMA, within 4 days, a variation to amend¹⁴ the product information.
- PRAC agreed on the content of a joint direct healthcare professional communication ([DHPC](#)) for both mRNA vaccines along with a communication plan for its distribution. See also under 4.3.3.
- The MAH should submit to EMA, within 30 days, a causality assessment for myocarditis, pericarditis and Comirnaty (COVID-19 mRNA vaccine (nucleoside-modified)). Based on the available data, the MAH should provide a discussion on possible biological mechanism(s) that could explain the observation of higher O/E ratios for the second dose compared to first dose. In addition, the MAH should propose recommendations for administration of the second dose in case of myocarditis/pericarditis following the first dose.
- A 30-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.
- The MAH should submit to EMA an updated RMP to add myocarditis/pericarditis as an important identified risk at the next regulatory opportunity. The risk should be further characterised in the ongoing and/or planned studies of the pharmacovigilance plan.

See EMA Press Release entitled '[Comirnaty and Spikevax: possible link to very rare cases of myocarditis and pericarditis](#)'.

For the full PRAC recommendation, see [EMA/PRAC/380226/2021 Corr](#) published on 02 August 2021 on the EMA website.

4.3.2. Coronavirus (COVID-19) mRNA¹⁵ vaccine (nucleoside-modified) - SPIKEVAX (previously COVID-19 VACCINE MODERNA) (CAP) - EMEA/H/C/005791/SDA/026.1

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

PRAC Rapporteur: Hans Christian Siersted

Scope: Signal of immune thrombocytopenia

EPITT 19679 – Follow-up to May 2021

Background

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

¹⁴ Update of SmPC sections 4.4 and 4.8. The package leaflet is to be updated accordingly

¹⁵ Messenger ribonucleic acid

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

Discussion

Having considered the available evidence in EudraVigilance including data from spontaneous report and relevant clinical trial data, observed to expected (O/E) analyses and the literature together with the Rapporteur's assessment, PRAC agreed that there is not sufficient evidence at present to establish a causal relationship between ITP and the administration of Spikevax (COVID-19 mRNA vaccine (nucleoside-modified)). Therefore, PRAC concluded that no regulatory action is warranted at this stage.

Summary of recommendation(s)

- In the next PSUR¹⁶, the MAH for Spikevax (COVID-19 mRNA vaccine (nucleoside-modified)) should include a detailed review of cases of ITP including data from spontaneous case reports, clinical trials and relevant literature. The MAH should also provide an updated observed/expected (O/E) analysis. In addition, the MAH should include an overview of the possible exacerbation of disease in patients with autoimmune or inflammatory disorders together with a discussion on possible disease flare ups following administration of the vaccine.

4.3.3. Coronavirus (COVID-19) mRNA¹⁷ vaccine (nucleoside-modified) - SPIKEVAX (previously COVID-19 VACCINE MODERNA) (CAP) – EMEA/H/C/005791/SDA/033

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

PRAC Rapporteur: Hans Christian Siersted

Scope: Signal of myocarditis and pericarditis

EPITT 19713 – Follow-up to June 2021

Background

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

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

Discussion

PRAC considered the available evidence from EudraVigilance including data from clinical trials and post-marketing experience, the literature, observed to expected (O/E) analyses and additional data provided by the MAH, together with the Rapporteur's assessment. PRAC agreed that there is a reasonable possibility for a causal relationship between Spikevax (COVID-19 mRNA vaccine (nucleoside-modified)) and myocarditis and pericarditis. Therefore, PRAC agreed that an update of the product information is warranted to add myocarditis and pericarditis as a warning and as undesirable effects with a frequency 'not known'.

Summary of recommendation(s)

¹⁶ Data lock point (DLP): 17 June 2021

¹⁷ Messenger ribonucleic acid

- The MAH for Spikevax (COVID-19 mRNA vaccine (nucleoside-modified)) should submit to EMA, within 4 days, a variation to amend¹⁸ the product information.
- PRAC agreed on the content of a joint direct healthcare professional communication ([DHPC](#)) for both mRNA vaccines along with a communication plan for its distribution. See also under 4.3.1.
- The MAH should submit to EMA, within 30 days, proposed recommendations for administration of the second dose in case of myocarditis/pericarditis following the first dose.
- A 30-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.
- The MAH should submit to EMA an updated RMP to add myocarditis/pericarditis as an important identified risk at the next regulatory opportunity. The risk should be further characterised in the ongoing and/or planned studies of the pharmacovigilance plan.

See EMA Press Release entitled '[Comirnaty and Spikevax: possible link to very rare cases of myocarditis and pericarditis](#)'.

For the full PRAC recommendation, see [EMA/PRAC/380226/2021 Corr](#) published on 02 August 2021 on the EMA website.

4.3.4. [Coronavirus \(COVID-19\) vaccine \(ChAdOx1-S \[recombinant\]\) - VAXZEVRIA \(CAP\) - EMEA/H/C/005675/SDA/034.1](#)

Applicant(s): AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: Signal of immune thrombocytopenia

EPITT 19678 - Follow-up to May 2021

Background

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

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

Discussion

PRAC considered the available evidence including the further responses submitted by the MAH and the Rapporteur's assessment. PRAC agreed to add thrombocytopenia with or without associated bleeding to the RMP as important potential risk. PRAC also agreed to request further information from the MAH before drawing a final recommendation.

Summary of recommendation(s)

- The MAH should submit to EMA, within 30 days, a variation to include 'thrombocytopenia with or without associated bleeding' to the RMP as an important potential risk.

¹⁸ Update of sections 4.4 and 4.8 of the SmPC

- In order to further characterise this risk, the MAH should submit to EMA, within 7 days, an updated protocol for study D8111R00006¹⁹. See under 17.2.8.
- The MAH for Vaxzevria (COVID-19 vaccine (ChAdOx1-S [recombinant])) should submit to EMA, within 30 days, a causality assessment of cases of thrombocytopenia without thromboembolic events fulfilling Brighton Collaboration criteria (BCC) level 1 and level 2. The MAH should also provide a causality assessment of cases of thrombocytopenia without thromboembolic events and with a known medical history of thrombocytopenia/platelet count decreased. In addition, the MAH should perform a thorough analysis of literature publications by *Simpson CR et al*²⁰, *Pottegård A et al*²¹ and *Trogstad L et al*²². The MAH should also discuss the safety report regarding haemorrhages and COVID-19 vaccines published by the Paul-Ehrlich-Institut (PEI)²³. Based on the information provided, the MAH should propose to update the product information as warranted.
- In the next monthly summary safety report (MSSR), the MAH should provide an analysis of anti-platelet factor 4 (PF4) antibody test results in vaccinees who developed thrombocytopenia without a co-reported thromboembolic event.

4.3.5. Coronavirus (COVID-19) vaccine (ChAdOx1-S [recombinant]) - VAXZEVRIA (CAP) – EMEA/H/C/005675/SDA/065

Applicant(s): AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: Signal of acute macular outer retinopathy

EPITT 19703 - Follow-up to May 2021

Background

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

The MAH replied to the request for information on the signal of acute macular outer retinopathy and the responses were assessed by the Rapporteur.

Discussion

PRAC considered the available evidence from EudraVigilance, the literature, the review from the MAH together with the Rapporteur's assessment. Taking into account the seriousness of the condition and the close temporal association in all identified cases, PRAC agreed that acute macular neuroretinopathy (AMN) and paracentral acute middle maculopathy (PAMM) should be added to the list of adverse events of special interest (AESI) in the RMP.

¹⁹ A post-authorisation/post-marketing observational study using existing secondary health data sources to evaluate the association between exposure to COVID-19 vaccine (ChAdOx1-S [recombinant] (AZD1222 / Vaxzevria) and safety concerns

²⁰ Simpson CR et al. First-dose ChAdOx1 and BNT162b2 COVID-19 vaccines and thrombocytopenic, thromboembolic and hemorrhagic events in Scotland. *Nat Med.* 2021 Jun 9. doi: 10.1038/s41591-021-01408-4. Epub ahead of print. PMID: 34108714

²¹ Pottegård A et al. Arterial events, venous thromboembolism, thrombocytopenia, and bleeding after vaccination with Oxford-AstraZeneca ChAdOx1-S in Denmark and Norway: population-based cohort study. *BMJ.* 2021 May 5;373:n1114. doi: 10.1136/bmj.n1114. PMID: 33952445; PMCID: PMC8097496

²² Trogstad L et al. Association between ChAdOx1 nCoV-19 vaccination and bleeding episodes: large population-based cohort study. *Research Square*; 2021. DOI: 10.21203/rs.3.rs-484111/v1. (Preprint)

²³ Reports on suspected cases of adverse effects and vaccination complications following a vaccination for the protection against COVID-19 (reporting period 27 December 2020 to 31 May 2021) (German only) (https://www.pei.de/SharedDocs/Downloads/EN/newsroom-en/dossiers/safety-reports/safety-report-27-december-31-may-2021.pdf?__blob=publicationFile&v=7)

Summary of recommendation(s)

- The MAH for Vaxzevria (COVID-19 vaccine (ChAdOx1-S [recombinant])) should update the RMP to add AMN and PAMM to the list of AESI at the next regulatory opportunity.
- In the next monthly summary safety report (MSSR), the MAH should provide a detailed review of cases of AMN and PAMM.

4.3.6. Donepezil (NAP)

Applicant(s): various

PRAC Rapporteur: Martin Huber

Scope: Signal of cardiac conduction disorders including QT prolongation and Torsade de Pointes

EPITT 19667 – Follow-up to March 2021

Background

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

The MAH for the originator product containing donepezil replied to the request for information on the signal of cardiac conduction disorders including QT prolongation and Torsade de Pointes and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence in EudraVigilance and in the literature, the review from the MAH together with the Rapporteur's assessment, PRAC agreed that the causal relationship between donepezil and QT interval prolongation and Torsade de Pointes is at least a reasonable possibility. Therefore, PRAC agreed that an update of the product information is warranted to add polymorphic ventricular tachycardia including Torsade de Pointes and electrocardiogram QT interval prolonged as warnings and as undesirable effects with a frequency 'not known' and to reflect the drug-drug interaction between donepezil and other medicinal products known to prolong the QTc interval. In addition, fall is added to the existing undesirable effect of accidents with a frequency 'common'.

Summary of recommendation(s)

- The MAHs for donepezil-containing products should submit to relevant National Competent Authorities (NCAs) of the EU Member States, within 60 days, a variation to amend²⁴ the product information.
- PRAC agreed on key messages for a direct healthcare professional communication (DHPC) for implementation at the EU Member State levels as warranted.

For the full PRAC recommendation, see [EMA/PRAC/380226/2021 Corr](#) published on 02 August 2021 on the EMA website.

4.3.7. Immune checkpoint inhibitors: atezolizumab - TECENTRIQ (CAP) - EMEA/H/C/004143/SDA/021.1; avelumab - BAVENCIO (CAP) - EMEA/H/C/004338/SDA/007.1; cemiplimab - LIBTAYO (CAP) - EMEA/H/C/004844/SDA/007.1; durvalumab - IMFINZI (CAP) - EMEA/H/C/004771/SDA/007.1; ipilimumab - YERVOY (CAP) -

²⁴ Update of SmPC sections 4.4, 4.5 and 4.8. The package leaflet is to be updated accordingly

Applicant(s): AstraZeneca AB (Imfinzi), Bristol-Myers Squibb Pharma EEIG (Opdivo, Yervoy), Merck Europe B.V. (Bavencio), Merck Sharp & Dohme B.V. (Keytruda), Regeneron Ireland Designated Activity Company (DAC) (Libtayo), Roche Registration GmbH (Tecentriq)

PRAC Rapporteur: Menno van der Elst

Scope: Signal of immune-mediated cystitis

EPITT 19610 – Follow-up to May 2021

Background

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

The MAHs replied to the request for information on the signal of immune-mediated cystitis and the responses were assessed by the Rapporteur.

Discussion

Having considered the comments from the MAHs on the proposed wording together with the Rapporteur's assessment, PRAC confirmed there is sufficient evidence for a potential class effect of immune-mediated non-infectious cystitis induced by treatment with check point inhibitors (ICIs). Therefore, PRAC concluded on the update of the product information to add cystitis non-infective as a warning and as an undesirable effect.

Summary of recommendation(s)

- The MAHs for Tecentriq (atezolizumab), Bavencio (avelumab), Libtayo (cemiplimab), Imfinzi (durvalumab), Yervoy (ipilimumab), Keytruda (pembrolizumab) and Opdivo (nivolumab) should submit to EMA, within 60 days, a variation for amending²⁵ the product information.

For the full PRAC recommendation, see [EMA/PRAC/380226/2021 Corr](#) published on 02 August 2021 on the EMA website.

4.3.8. Octreotide (NAP)

Applicant(s): various

PRAC Rapporteur: Ronan Grimes

Scope: Signal of pancreatic exocrine insufficiency

EPITT 19661 – Follow-up to March 2021

Background

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

The MAH for the originator product containing octreotide replied to the request for information on the signal of pancreatic exocrine insufficiency (PEI) and the responses were assessed by the Rapporteur.

²⁵ Update of SmPC sections 4.4 and 4.8. The package leaflet is to be updated accordingly

Discussion

Having considered the available evidence from EudraVigilance, the literature and the Rapporteur's assessment, taking also into account the plausible biological mechanism of action of octreotide to cause PEI, PRAC agreed to make healthcare professionals (HCPs) aware of the risk of PEI in patients with gastro-entero-pancreatic endocrine tumours, since the symptoms of PEI may be misinterpreted as adverse reactions to octreotide or as lack of efficacy. Therefore, PRAC agreed that an update of the product information is warranted to add PEI as a warning in order to minimise the risk of underdiagnosis and delayed treatment of concomitant PEI which occurs frequently in patients receiving octreotide for neuroendocrine tumours.

Summary of recommendation(s)

- The MAHs for octreotide-containing products should submit to relevant National Competent Authorities (NCAs) of the EU Member States, within 60 days, a variation to amend²⁶ the product information.
- In the next PSUR²⁷, the MAHs for octreotide-containing products should provide an updated cumulative review of cases of PEI, including information on previous medical history of pancreatic function, data on pancreatic enzyme replacement therapy (PERT) and outcome, and stage of disease.

For the full PRAC recommendation, see [EMA/PRAC/380226/2021 Corr](#) published on 02 August 2021 on the EMA website.

4.3.9. [Olaparib – LYNPARZA \(CAP\) - EMEA/H/C/003726/SDA/017](#)

Applicant(s): AstraZeneca AB

PRAC Rapporteur: Ilaria Baldelli

Scope: Signal of *Pneumocystis jirovecii* pneumonia

EPITT 19651 – Follow-up to February 2021

Background

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

The MAH replied to the request for information on the signal of *Pneumocystis jirovecii* pneumonia (PJP) and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence from EudraVigilance, the literature, the review provided by the MAH together with the Rapporteur's assessment, PRAC agreed that there is insufficient evidence to establish a causal relationship between olaparib and the development of PJP. Therefore, PRAC concluded that an update of the product information is not warranted at present.

Summary of recommendation(s)

²⁶ Update of SmPC section 4.4. The package leaflet is to be updated accordingly

²⁷ Data lock point (DLP): 30 June 2023

- The MAH for Lynparza (olaparib) should continue to monitor cases of PJP as part of routine safety surveillance.
- In the next PSUR, the MAH should provide a review of cases of PJP.

4.4. Variation procedure(s) resulting from signal evaluation

4.4.1. Coronavirus (COVID-19) vaccine (Ad26.COVID-19, recombinant) - COVID-19 VACCINE JANSSEN (CAP) - EMEA/H/C/005737/II/0006/G

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Grouped variations consisting of: 1) update of section 4.4 of the SmPC to add a warning for individuals who have experienced a previous cerebral venous sinus thrombosis (CVST) with thrombocytopenia or heparin-induced thrombocytopenia (HIT) to outweigh the potential risks before the administration of COVID-19 Vaccine Janssen. The package leaflet and the RMP (version 2.1) are updated accordingly; 2) update to the RMP (version 2.1) for COVID-19 Vaccine Janssen to include thrombosis with thrombocytopenia syndrome (TTS) in the list of the safety concerns as an important identified risk as per the outcome adopted in May 2021 in the context of the signal procedure on embolic and thrombotic events (with COVID-19 Vaccine Janssen (Ad26.COVID-19 [recombinant]) (SDA 018.1). In addition, the MAH took the opportunity to update the RMP with the milestone date for the submission of the protocol for study VAC31518COV4003: a post-authorisation observational study to assess the safety of Ad26.COVID-19 using electronic health record (EHR) database(s) in Europe. Finally, the MAH proposed a revised frequency of data mining from the EudraVigilance database and to correct the long-term follow-up time in study VAC31518COV4001: a post-authorisation observational study to assess the safety of Ad26.COVID-19 using health insurance claims and/or EHR database(s) in the United States

Background

COVID-19 vaccine (Ad26.COVID-19 [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.

As per the final recommendation of a signal procedure concluded in May 2021 on embolic and thrombotic events (EPITT 19689) and COVID-19 vaccine Janssen (COVID-19 vaccine (Ad26.COVID-19 [recombinant])), the MAH submitted to EMA a variation to update the RMP to include thrombosis with thrombocytopenia syndrome (TTS) as an important identified risk and thrombocytopenia as an important potential risk. In addition, the MAH proposed to update the product information to add a warning for individuals who have experienced a previous cerebral venous sinus thrombosis (CVST) with thrombocytopenia or heparin-induced thrombocytopenia (HIT). 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 background information, see [PRAC minutes May 2021](#).

Summary of outcome(s)

- Based on the available data and the Rapporteur's assessment, PRAC supported the updates to the RMP, but did not support the proposed changes to the product information.
- PRAC also agreed on the content of a joint direct healthcare professional communication ([DHPC](#)) covering TTS and capillary leak syndrome (CLS) along with a communication plan for its distribution.

4.4.2. Coronavirus (COVID-19) vaccine (Ad26.COVID-19, recombinant) - COVID-19 VACCINE JANSSEN (CAP) - EMEA/H/C/005737/II/0010

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of section 4.3 of the SmPC in order to add a contraindication related to the administration of Ad26.COVID-19 to individuals with a history of capillary leak syndrome (CLS) reported following administration of this vaccine in the Global Medical Safety (GMS) and related to the signal procedure on CLS (with vaccine (ChAdOx1-S [recombinant])) (SDA 047) in June 2021. In addition, the company proposed to include CLS as an important potential risk in the EU-RMP

Background

COVID-19 vaccine (Ad26.COVID-19 [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.

In relation to the final recommendation of a signal procedure concluded in June 2021 on capillary leak syndrome (CLS) (EPITT 19672) with vaccine (ChAdOx1-S [recombinant]), and an emerging safety issue (ESI) sent to EMA mid-June 2021, the MAH for COVID-19 vaccine Janssen (COVID-19 vaccine (Ad26.COVID-19, recombinant)) submitted to EMA a variation to add a contraindication to the product information relating to the administration of the vaccine to individuals with a history of capillary leak syndrome (CLS). 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 background information, see [PRAC minutes June 2021](#).

Summary of outcome(s)

- Based on the available data and the Rapporteur's assessment, PRAC supported the updates²⁸ to the product information to add CLS as a contraindication in subjects who have a history of CLS, as a warning and as an undesirable effect with a frequency 'not known'.
- PRAC also agreed on the content of a joint direct healthcare professional communication ([DHPC](#)) covering thrombosis with thrombocytopenia syndrome (TTS) and CLS along with a communication plan for its distribution.

²⁸ Update of SmPC sections 4.3, 4.4 and 4.8. The package leaflet is updated accordingly

- In the next monthly summary safety report (MSSR), the MAH should discuss hypotheses for a mechanism leading to CLS following vaccination. Any potential relationship between the mechanism leading to CLS and the mechanism leading to TTS should be discussed. Finally, the MAH should discuss whether additional data are needed to document the inflammatory response following immunisation with the vaccine.

4.4.3. Coronavirus (COVID-19) vaccine (Ad26.COVID-19S, recombinant) - COVID-19 VACCINE JANSSEN (CAP) - EMEA/H/C/005737/II/0012

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of sections 4.4 and 4.8 of the SmPC in order to add a warning related to the possibility of developing Guillain-Barré syndrome (GBS) following the administration of COVID-19 vaccine (Ad26.COVID-19S, recombinant) and to add GBS as an adverse drug reaction (ADR). This is based on the information accumulated on cases of GBS reported to the vaccine adverse event reporting system (VAERS) in recipients of the COVID-19 vaccine Janssen and subsequently, on the analysis performed by the company on cases of GBS based on the available cumulative data from launch. In addition, the company took the opportunity to make some editorial changes. The package leaflet is updated accordingly

Background

COVID-19 vaccine (Ad26.COVID-19S [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.

Based on a review of cases of Guillain-Barré syndrome (GBS), the MAH for COVID-19 vaccine Janssen (COVID-19 vaccine (Ad26.COVID-19S, recombinant)) submitted to EMA a variation to add to the product information GBS as a warning and as an undesirable effect. 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. At the organisational, regulatory and methodological matters (ORGAM)²⁹ meeting on 22 July 2021, PRAC adopted its outcome. See also under 6.6.4.

Summary of outcome(s)

- Based on the available data and the Rapporteur's assessment, PRAC supported the updates³⁰ to the product information to add GBS as a warning and as an undesirable effect with a frequency 'very rare'.
- The MAH should submit to EMA, within 30 days, a variation to update the RMP accordingly.

²⁹ Extended to specific COVID-19-related procedure(s) during EMA business continuity plan (BCP)

³⁰ Update of SmPC sections 4.3, 4.4 and 4.8. The package leaflet is updated accordingly

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 (<https://www.ema.europa.eu/en/committees/chmp/chmp-agendas-minutes-highlights>).

See also Annex I 15.1.

5.1.1. Aducanumab - EMEA/H/C/005558

Scope: Treatment of Alzheimer's disease

5.1.2. Anifrolumab - EMEA/H/C/004975

Scope: Add-on therapy for the treatment of adult patients with moderate to severe systemic lupus erythematosus (SLE) despite standard therapy

5.1.3. Arachis hypogaea extract - EMEA/H/C/004810

Scope: Treatment of peanut allergy

5.1.4. Artesunate - EMEA/H/C/005718, Orphan

Applicant: B And O Pharm

Scope: Treatment of severe malaria

5.1.5. Avacopan - EMEA/H/C/005523, Orphan

Applicant: Vifor Fresenius Medical Care Renal Pharma France

Scope: Treatment of granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA)

5.1.6. Bamlanivimab - EMEA/H/C/005836

Scope: Treatment of coronavirus (COVID-19) in combination with etesevimab

5.1.7. Etesevimab - EMEA/H/C/005837

Scope: Treatment of coronavirus (COVID-19) in combination with bamlanivimab

5.1.8. Diroximel fumarate - EMEA/H/C/005437

Scope: Treatment of relapsing remitting multiple sclerosis

5.1.9. Lasmiditan - EMEA/H/C/005332

Scope: Acute treatment of migraine with or without aura in adults

5.1.10. Sotrovimab - EMEA/H/C/005676

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

5.1.11. Tecovirimat - EMEA/H/C/005248

Scope: Treatment of Orthopoxvirus disease

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

See Annex I 15.2.

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

See also Annex I 15.3.

5.3.1. Lomitapide - LOJUXTA (CAP) - EMEA/H/C/002578/II/0046

Applicant: Amryt Pharmaceuticals DAC

PRAC Rapporteur: Menno van der Elst

Scope: Submission of an alternative study: an evaluation of the effect of lomitapide treatment on major adverse cardiovascular events (MACE) in patients with homozygous familial hypercholesterolemia (LILITH) to the currently agreed protocol for study on the effects of lomitapide on carotid and aortic atherosclerosis in patients treated with lomitapide in usual care (CAPTURE) in order to propose an evaluation of the effect of lomitapide treatment on MACE in patients with homozygous familial hypercholesterolemia. As a consequence, Annex II-D on 'Conditions or restrictions with regard to the safe and effective use of the medicinal product' and the RMP (version 6.4) are updated accordingly. In addition, the MAH took the opportunity to bring the product information in line with the latest quality review of documents (QRD) template (version 10.2)

Background

Lomitapide is a lipid modifying agent indicated in adult patients with homozygous familial hypercholesterolaemia (HoFH), as an adjunct to a low-fat diet and other lipid-lowering medicinal products with or without low density lipoprotein (LDL) apheresis.

CHMP is evaluating a type II variation for Lojuxta, a centrally authorised product containing lomitapide, to include an alternative study (LILITH) to evaluate the effect of lomitapide treatment on major adverse cardiovascular events (MACE) in patients with homozygous familial hypercholesterolemia in replacement of the approved protocol for study (CAPTURE) on the effects of lomitapide on carotid and aortic atherosclerosis in patients treated with lomitapide. PRAC is responsible for providing advice to CHMP on the necessary updates to the RMP to support this type II variation. For further background, see [PRAC minutes April 2021](#).

Summary of advice

- The RMP for Lojuxta (lomitapide) in the context of the variation procedure under evaluation by PRAC and CHMP could be considered acceptable provided that an update to RMP version 6.6 and satisfactory responses to the request for supplementary information (RSI) are submitted.
- PRAC considered that 'interaction with statins' currently included as an important identified risk in the RMP should be changed to 'rhabdomyolysis with or without acute renal failure due to interaction with statins' to clearly specify the clinical effect of the interaction as part of the risk. This should be implemented throughout the RMP and the key elements of the educational materials. In addition, 'off-label use' no longer constitutes a safety concern based on data reviewed in the post-marketing phase. Therefore, it should be removed from the RMP and the key elements of the educational materials.

5.3.2. Posaconazole - NOXAFIL (CAP) - EMEA/H/C/000610/X/0063/G

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Adrien Inoubli

Scope: Grouped applications consisting of: 1) extension application to introduce a new pharmaceutical form (gastro-resistant powder and solvent for oral suspension); 2) extension of indication to the paediatric population. As a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2 of the SmPC are updated. The package leaflet and the RMP (version 17.1) are updated in accordance

Background

Posaconazole is a triazole derivative indicated for the treatment of several fungal infections in adults such as invasive aspergillosis, chromoblastomycosis and mycetoma, under certain conditions. It is also indicated for prophylaxis of invasive fungal infections, under specific conditions.

CHMP is evaluating a grouped extension application (line extension) for Noxafil, a centrally authorised product containing posaconazole, to introduce gastro-resistant powder and solvent for oral suspension as a new pharmaceutical form and to extend the current indication to the paediatric population. 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 March 2021](#).

Summary of advice

- The RMP for Noxafil (posaconazole) in the context of the variation procedure under evaluation by PRAC and CHMP could be considered acceptable provided that an update to RMP version 17.2 and satisfactory responses to the request for supplementary information (RSI) are submitted.
- PRAC agreed on the content of a direct healthcare professional communication (DHPC) as a one-time DHPC addressing the potential risk of medication error related to substitution between different formulations (oral suspension and gastro-resistant powder and solvent for oral suspension) marketed concomitantly as these two formulations are not interchangeable. PRAC also agreed on the DHPC recipients of a communication plan.

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. Rucaparib - RUBRACA (CAP) - PSUSA/00010694/202012

Applicant: Clovis Oncology Ireland Limited

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

Background

Rucaparib is an inhibitor of poly(ADP-ribose) polymerase (PARP) enzymes indicated, as Rubraca, for the maintenance treatment of adult patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy as monotherapy. It is also indicated, as monotherapy for the treatment of adult patients with platinum sensitive, relapsed or progressive, breast cancer gene (BRCA) mutated (germline and/or somatic), high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have been treated with two or more prior lines of platinum-based chemotherapy, and who are unable to tolerate further platinum-based chemotherapy.

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Rubraca, a centrally authorised medicine containing rucaparib 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 Rubraca (rucaparib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add hypersensitivity as an undesirable effect with a frequency 'common' for all grades according to common terminology criteria for adverse events (CTCAE), and with a frequency 'uncommon' for CTCAE grade 3 and above. Therefore, the current terms of the marketing authorisation(s) should be varied³¹.

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

6.1.2. Selexipag - UPTRAVI (CAP) - PSUSA/00010503/202012

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Adrien Inoubli

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

Scope: Evaluation of a PSUSA procedure

Background

Selexipag is a selective prostacyclin receptor agonist indicated, as Uptravi, for the long-term treatment of pulmonary arterial hypertension (PAH) in adult patients with World Health Organization (WHO) functional class (FC) II–III, either as combination therapy in patients insufficiently controlled with an endothelin receptor antagonist (ERA) and/or a phosphodiesterase type 5 (PDE-5) inhibitor, or as monotherapy in patients who are not candidates for these therapies.

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Uptravi, a centrally authorised medicine containing selexipag 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 Uptravi (selexipag) 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 of thrombocytopenia and platelet count decrease as well as of cases of angioedema. The MAH should provide 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.

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

See also Annex I 16.2.

6.2.1. Clofarabine - EVOLTRA (CAP); IVOZALL (CAP); NAP - PSUSA/00000805/202012

Applicants: Genzyme Europe BV (Evoltra), Orphelia Pharma SAS (Ivozall), various

PRAC Rapporteur: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

Background

Clofarabine is a purine nucleoside anti-metabolite indicated for the treatment of acute lymphoblastic leukaemia (ALL) in paediatric patients who have relapsed or are refractory after receiving at least two prior regimens and where there is no other treatment option anticipated to result in a durable response.

Based on the assessment of the PSURs, PRAC reviewed the benefit-risk balance of Evoltra and Ivozall, centrally authorised medicines containing clofarabine, and nationally authorised medicines containing clofarabine 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 clofarabine-containing medicinal products in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisations should be maintained.
- In the next PSUR, the MAHs should provide a cumulative review of cases of atrial fibrillation, including data from post-marketing sources, clinical trials and literature, and discuss whether an update of the product information is warranted.
- The MAH should submit to EMA, within 90 days, a variation to add a time period for contraception following the last dose of arsenic trioxide to the product information, taking into account the Safety Working Party ([SWP](#)) response document dated February 2020 on questions from CMDh on 'recommendations on the duration of contraception following the end of treatment with a genotoxic drug'. The MAH should propose an update of the product information as warranted. The variation should also include reviews on the need for pregnancy tests and on the time period for breastfeeding after the last dose of arsenic trioxide. The MAH should propose updates to 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. Submission of PSURs for products referred to in Articles 10(1), 10a, 14, 16a of Directive 2001/83/EC as amended is not required any longer. The list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC is updated accordingly.

6.2.2. Edotreotide - SOMAKIT TOC (CAP); NAP - PSUSA/00010552/202012

Applicants: Advanced Accelerator Applications (SomaKit TOC), various

PRAC Rapporteur: Ronan Grimes

Scope: Evaluation of a PSUSA procedure

Background

Edotreotide is a somatostatin analogue indicated, for diagnostic use only. After radiolabelling with gallium (^{68}Ga) chloride solution, the combined solution is indicated for positron emission tomography (PET) imaging of somatostatin receptor overexpression in adult patients with confirmed or suspected well-differentiated gastroenteropancreatic neuroendocrine tumours (GEP-NET) for localising primary tumours and their metastases. It is also indicated in imaging of meningioma.

Based on the assessment of the PSURs, PRAC reviewed the benefit-risk balance of Somakit Toc, a centrally authorised medicine containing edotreotide, and nationally authorised medicines containing edotreotide 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 edotreotide-containing medicinal products in the approved indication(s) remains unchanged.

- Nevertheless, the product information should be updated to amend the existing warning on the interpretation of gallium (⁶⁸Ga) edotreotide images and limitations of use to reflect that splenosis and accessory intrapancreatic spleen may be incidentally detected and could be misdiagnosed as neuroendocrine tumours. Therefore, the current terms of the marketing authorisations should be varied³².
- In the next PSUR, the MAHs should provide a cumulative review of cases of nausea and vomiting and a discussion on the need for updating the product information as warranted. In addition, the MAHs should provide a cumulative review of PET findings interpretation errors and discuss the need for further routine or additional risk minimisation measures to mitigate this risk. A critical analysis of relevant literature concerning PET findings interpretation errors with gallium (⁶⁸Ga) labelled somatostatin receptor targeted diagnostics should be included.

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

6.2.3. [Lenalidomide - LENALIDOMIDE ACCORD \(CAP\); LENALIDOMIDE MYLAN \(CAP\); REVLMID \(CAP\); NAP - PSUSA/00001838/202012](#)

Applicants: Accord Healthcare S.L.U. (Lenalidomide Accord), Bristol-Myers Squibb Pharma EEIG (Revlimid), Mylan Ireland Limited (Lenalidomide Mylan), various

PRAC Rapporteur: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

Background

Lenalidomide is an anti-neoplastic, anti-angiogenic, pro-erythropoietic and immunomodulatory agent indicated for the treatment of multiple myeloma, myelodysplastic syndromes, mantle cell lymphoma and follicular lymphoma, under certain conditions.

Based on the assessment of the PSURs, PRAC reviewed the benefit-risk balance of Lenalidomide Accord, Lenalidomide Mylan and Revlimid, centrally authorised medicines containing lenalidomide, and nationally authorised medicine(s) containing lenalidomide 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 lenalidomide-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the existing warning on tumour lysis syndrome to bring it in line with the current state of knowledge. Therefore, the current terms of the marketing authorisations should be varied³³.
- In the next PSUR, the MAHs should closely monitor the risk of coronavirus 2019 (COVID-19) infection.

³² Update of SmPC section 4.4. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion

³³ Update of SmPC section 4.4. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion

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

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

See also Annex I 16.3.

6.3.1. Benazepril (NAP) - PSUSA/00000313/202011

Applicant(s): various

PRAC Lead: Ronan Grimes

Scope: Evaluation of a PSUSA procedure

Background

Benazepril is an angiotensin-converting enzyme (ACE) inhibitor indicated primarily for the treatment of hypertension, congestive heart failure, and chronic renal insufficiency under certain conditions.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicinal products containing benazepril 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 benazepril-containing products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add psoriasis aggravation as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied³⁴.
- In the next PSUR, the MAH Mylan should continue to closely monitor the use of benazepril in pregnancy and propose to update the product information as warranted.

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

6.3.2. Ethanol extracts: Iberis amara L., planta tota recens; Angelica archangelica L., radix; Matricaria recutita L., flos; Carum carvi L., fructus; Silybum marianum (L.) Gaertn., fructus; Melissa officinalis L., folium; Mentha piperita L., folium; Chelidonium majus L., herba; Glycyrrhiza glabra L., radix (NAP) - PSUSA/00010800/202011

Applicant(s): various

PRAC Lead: Martin Huber

³⁴ Update of SmPC section 4.8. The package leaflet is updated accordingly The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position

Scope: Evaluation of a PSUSA procedure

Background

As a fixed combination of one aqueous ethanol fresh plant extract of *Iberis amara* total and eight further aqueous ethanolic drug extracts of *Angelica archangelica* L., radix / *Matricaria recutita* L., flos / *Carum carvi* L., fructus / *Silybum marianum* (L.) Gaertn., fructus / *Melissa officinalis* L., folium / *Mentha piperita* L., folium / *Chelidonium majus* L., herba / *Glycyrrhiza glabra* L., radix, it is indicated for the treatment of functional and motility-related gastrointestinal disorders such as functional dyspepsia and irritable bowel syndrome as well as supportive symptomatic treatment of gastritis, subject to certain conditions.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing ethanol extracts of *Iberis amara* L., planta tota recens / *Angelica archangelica* L., radix / *Matricaria recutita* L., flos / *Carum carvi* L., fructus / *Silybum marianum* (L.) Gaertn., fructus / *Melissa officinalis* L., folium / *Mentha piperita* L., folium / *Chelidonium majus* L., herba / *Glycyrrhiza glabra* L., radix 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 medicinal products containing ethanol extracts of *Iberis amara* L., planta tota recens / *Angelica archangelica* L., radix / *Matricaria recutita* L., flos / *Carum carvi* L., fructus / *Silybum marianum* (L.) Gaertn., fructus / *Melissa officinalis* L., folium / *Mentha piperita* L., folium / *Chelidonium majus* L., herba / *Glycyrrhiza glabra* L., radix in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add drug-induced liver injury (DILI) as a warning, as a contraindication for patients with higher risk for developing DILI and as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied³⁵.

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. Glatiramer (NAP) - PSUSA/00001529/202011

Applicant(s): various

PRAC Lead: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

Background

Glatiramer is an immunomodulator agent indicated for the treatment of patients with relapsing forms of multiple sclerosis, including patients who have experienced a first clinical episode and have magnetic resonance imaging (MRI) features consistent with multiple sclerosis.

³⁵ Update of SmPC sections 4.3, 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

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing glatiramer 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 glatiramer-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the existing warning on liver injury and to add liver injury and toxic hepatitis as undesirable effects with a frequency 'rare' and hepatic failure with a frequency 'not known'. In addition, the product information should be updated to remove abortion as an undesirable effect due to the unlikely causal relationship with glatiramer. Therefore, the current terms of the marketing authorisation(s) should be varied³⁶.
- In the next PSUR, all MAHs should provide a review of cases of reduced immune response, including malignancies, reduced response to vaccine and increased risk of infections. The MAH Teva should also provide a review on measuring the effectiveness of risk minimisation measures for the important identified of risk liver injury.

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

6.3.4. Hydroxycarbamide³⁷ (NAP) - PSUSA/00009182/202012

Applicant(s): various

PRAC Lead: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

Background

Hydroxycarbamide is an antineoplastic agent indicated for the treatment of leukaemia, myeloproliferative disorders like polycythemia vera, essential thrombocytosis and in sickle cell disease (SCD), subject to certain conditions.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing hydroxycarbamide 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 hydroxycarbamide³⁸-containing medicinal products in the approved indication(s) remains unchanged.

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

³⁷ Non-centrally authorised product(s) only

³⁸ Non-centrally authorised product(s) only

- Nevertheless, the product information should be updated to include add haemolytic anaemia as a warning and as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied³⁹.
- In the next PSUR, the MAHs should monitor cases of pancreatitis and hepatotoxicity including drug-induced liver injury (DILI) and perform an analysis for non-human immunodeficiency virus (HIV) infected patients, covering also cases of nodular regenerative hyperplasia. In addition, the MAHs should provide a review of cases of acute erythroid leukemia.

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. Indapamide (NAP) - PSUSA/00001731/202011

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Indapamide is a thiazide-like oral antihypertensive/diuretic indicated for the treatment of essential hypertension.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing indapamide 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 indapamide-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add erectile dysfunction as an undesirable effect with a frequency 'uncommon', hypomagnesaemia and hypochloraemia with a frequency 'rare'. The existing frequencies for hypokalaemia should be changed from 'not known' to 'common', and for hyponatremia from 'not known' to 'uncommon'. In addition, hypokalaemia and hypomagnesaemia should be added as warnings. Therefore, the current terms of the marketing authorisation(s) should be varied⁴⁰.
- In the next PSUR, the MAH should provide a cumulative review of cases of pemphigus and pemphigoid, together with a causality assessment and a discussion on the need to update the product information as warranted.

³⁹ 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

⁴⁰ Update of SmPC sections 4.4, 4.5 and 4.8. The package leaflet is updated accordingly The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position

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

6.4. Follow-up to PSUR/PSUSA procedures

6.4.1. Dexmedetomidine - DEXDOR (CAP) - EMEA/H/C/002268/LEG 016.3

Applicant: Orion Corporation

PRAC Rapporteur: Ulla Wändel Liminga

Scope: MAH's response to LEG 016.2 [analysis of available mortality data from controlled clinical trials in the dexmedetomidine development programme as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00000998/201903) adopted in November 2019] as per the request for supplementary information (RSI) adopted in May 2021

Background

Dexmedetomidine is a selective alfa-2 receptor agonist indicated, as Dexdor, a centrally authorised product, for sedation of adult intensive care unit (ICU) patients requiring a sedation level not deeper than arousal in response to verbal stimulation and for sedation of non-intubated adult patients prior to and/or during diagnostic or surgical procedures requiring sedation, i.e. procedural/awake sedation.

Following the evaluation of the most recently submitted PSUR(s) for the above-mentioned medicine(s), PRAC requested the MAH to submit further mortality data from controlled clinical trials in the dexmedetomidine development programme. For background, see [PRAC minutes November 2019](#)⁴¹, [PRAC minutes October 2020](#)⁴² and [PRAC minutes May 2021](#). The responses to the second request for supplementary information (RSI) adopted in May 2021 were assessed by the Rapporteur for further PRAC advice.

Summary of advice/conclusion(s)

- Based on the available data and the Rapporteur's assessment, PRAC considered there is sufficient evidence to warrant an update of the product information to add a warning statement relating to mortality in ICU patients <65 years old.
- The MAH should submit to EMA, within 60 days, a variation to update⁴³ the product information and update the RMP. In addition, the MAH should include a proposal for a direct healthcare professional communication (DHPC) together with a communication plan. Besides, the MAH should propose a strategy to study the impact of dexmedetomidine on 90-day mortality and effect-modification from relevant patient characteristics.

6.4.2. Fentanyl - EFFENTORA (CAP) - EMEA/H/C/000833/LEG 019

Applicant: Teva B.V.

PRAC Rapporteur: Martin Huber

⁴¹ Held 28-31 October 2019

⁴² Held 28 September - 01 October 2020

⁴³ Update of SmPC section 4.4. The package leaflet is to be updated accordingly

Scope: Review of the current labelling for fentanyl transmucosal route of administration regarding off-label use, misuse and accidental exposure as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00001369/202004) adopted in January 2021

Background

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

Following the evaluation of the most recently submitted PSUR(s) for the above-mentioned medicine(s), PRAC requested the MAH to submit a thorough review of their current labelling to ensure the risks for off-label use, misuse and accidental exposure are appropriately mitigated and to propose corrective actions as appropriate. For background, see [PRAC minutes January 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 the MAH should further propose a warning to inform patients that transmucosal fentanyl-containing product(s) must only be used by patients already taking other opioids for chronic cancer pain. The MAH should submit an update to the product information accordingly.

6.4.3. Fentanyl - INSTANYL (CAP) - EMEA/H/C/000959/LEG 030

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Tiphaine Vaillant

Scope: Review of the current labelling for fentanyl transmucosal route of administration regarding off-label use, misuse and accidental exposure as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00001369/202004) adopted in January 2021

Background

Fentanyl is an opioid indicated, as Instanyl, for the management of breakthrough pain in adults already receiving maintenance opioid therapy for chronic cancer pain.

Following the evaluation of the most recently submitted PSUR(s) for the above-mentioned medicine(s), PRAC requested the MAH to submit a thorough review of their current labelling to ensure the risks for off-label use, misuse and accidental exposure are appropriately mitigated and to propose corrective actions as appropriate. For background, see [PRAC minutes January 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 the MAH should further propose a warning to inform patients that transmucosal fentanyl-containing product(s) must only be used by patients already taking other opioids for chronic cancer pain. The MAH should submit an update to the product information accordingly.

6.4.4. Fentanyl - PECFENT (CAP) - EMEA/H/C/001164/LEG 021

Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Martin Huber

Scope: Review of the current labelling for fentanyl transmucosal route of administration regarding off-label use, misuse and accidental exposure as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00001369/202004) adopted in January 2021

Background

Fentanyl is an opioid indicated, as PecFent, for the management of breakthrough pain in adults already receiving maintenance opioid therapy for chronic cancer pain.

Following the evaluation of the most recently submitted PSUR(s) for the above-mentioned medicine(s), PRAC requested the MAH to submit a thorough review of their current labelling to ensure the risks for off-label use, misuse and accidental exposure are appropriately mitigated and to propose corrective actions as appropriate. For background, see [PRAC minutes January 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 the MAH should further propose a warning to inform patients that transmucosal fentanyl-containing product(s) must only be used by patients already taking other opioids for chronic cancer pain. The MAH should submit an update to the product information accordingly.

6.5. Variation procedure(s) resulting from PSUSA evaluation

See Annex I 16.5.

6.6. Expedited summary safety reviews⁴⁴

6.6.1. Coronavirus (COVID-19) mRNA⁴⁵ vaccine (nucleoside-modified) - COMIRNATY (CAP) - EMEA/H/C/005735/MEA 002.5

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

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

Background

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

PRAC assessed the sixth monthly summary safety report (MSSR) for Comirnaty (COVID-19

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

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 MSSR⁴⁶, the MAH should provide cumulative reviews and data. These include the results of the 'abnormal behaviour/mental disorder', 'acquired haemophilia', 'acute pancreatitis' and 'menstrual cycle abnormalities' reviews. With regard to thrombosis with thrombocytopenia syndrome (TTS), the MAH should provide a discussion on probable mechanism(s) of action for the occurrence of vaccine-associated TTS following administration of Comirnaty (COVID-19 mRNA vaccine (nucleoside-modified)) with an update on follow-up of TTS cases and a causality assessment. In addition, the MAH should provide age-stratified observed/expected (O/E) analyses regarding cases reporting a fatal outcome. Finally, the MAH should use ACCESS⁴⁷ background rates for the analysis of cases of acute disseminated encephalomyelitis (ADEM).

6.6.2. Coronavirus (COVID-19) mRNA⁴⁸ vaccine (nucleoside-modified) - SPIKEVAX (previously COVID-19 VACCINE MODERNA) (CAP) - EMEA/H/C/005791/MEA 011.4

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Hans Christian Siersted

Scope: Fifth expedited monthly summary safety report for Spikevax (previously COVID-19 Vaccine Moderna) (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 adults.

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

Summary of advice/conclusion(s)

- In the next MSSR⁴⁹, the MAH should provide cumulative reviews and data. These include the request to present observed/expected (O/E) analyses as overall, age-stratified, sex-stratified and age-and-sex-stratified analyses. With regard to Guillain-Barré syndrome (GBS) and multisystem inflammatory syndrome (MIS), the MAH should provide a review of cumulative cases stratified by age, gender, time-to-onset (TTO), history of COVID-19 infection and dose. In addition, the MAH should include a literature review as part of their review of 'use in pregnancy and while breastfeeding' and provide a detailed review of cases of lactation disorders and perform a pattern analysis. In addition, the MAH should provide a detailed review of cases of thrombosis with thrombocytopenia syndrome (TTS).

⁴⁶ Submission date on 15 July 2021

⁴⁷ vACCine Covid-19 monitoring readinESS

⁴⁸ Messenger ribonucleic acid

⁴⁹ Submission date on 15 July 2021

6.6.3. Coronavirus (COVID-19) vaccine (Ad26.COVID-19S, recombinant) - COVID-19 VACCINE JANSSEN (CAP) – EMEA/H/C/005737/MEA 014.2

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Ulla Wändel Liminga

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

Background

COVID-19 vaccine (Ad26.COVID-19S [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 third monthly summary safety report (MSSR) for COVID-19 vaccine Janssen (COVID-19 vaccine (Ad26.COVID-19S [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 for COVID-19 vaccine Janssen (COVID-19 vaccine (Ad26.COVID-19S [recombinant])) should submit to EMA, within 15 days, variation(s) to update⁵⁰ the product information to add diarrhoea lymphadenopathy, vomiting as undesirable effects with a frequency uncommon. The MAH should also include hypoesthesia and paraesthesia as an undesirable effect and propose a frequency accordingly.
- In the next MSSR⁵¹, the MAH should provide cumulative reviews and data. These include an in-depth cumulative review of cases of Guillain-Barré syndrome (GBS) with a proposal to update the product information and the RMP as warranted together with a discussion on the need for additional risk minimisation measures. The MAH should also include a comprehensive review of cases of immune thrombocytopenia with a proposal to update the product information as warranted. In addition, the MAH should include a comprehensive review of thromboembolic events with a proposal to update the product information as warranted together with a discussion on the need for further risk minimisation measures. Finally, the MAH should provide a review of cases of acute disseminated encephalomyelitis (ADEM), meningoencephalitis and immune thrombocytopenia (ITP).

6.6.4. Coronavirus (COVID-19) vaccine (ChAdOx1-S [recombinant]) - VAXZEVRIA (CAP) - EMEA/H/C/005675/MEA 027.3

Applicant: AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: Fourth expedited monthly summary safety report for Vaxzevria (COVID-19 vaccine

⁵⁰ Update of SmPC section 4.8. The package leaflet is to be updated accordingly

⁵¹ Submission date on 15 July 2021

(ChAdOx1-S [recombinant])) during the coronavirus disease (COVID-19) pandemic

Background

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

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

Summary of advice/conclusion(s)

- The MAH for Vaxzevria (COVID-19 vaccine (ChAdOx1-S [recombinant])) should submit to EMA, within 7 days, a variation to update⁵² the product information to add Guillain-Barré syndrome (GBS) as a warning.
- In the next MSSR⁵³, the MAH should provide cumulative reviews and data. These include an updated discussion of new and follow-up cases of GBS with an updated observed/expected (O/E) analysis. Regarding myocarditis, the MAH should provide a detailed review of cases of myocarditis and pericarditis with a discussion on the potential pathophysiological mechanism that lead to myocarditis and pericarditis respectively. The MAH should also consider multisystem inflammatory syndrome (MIS/MIS-C) as an alternative etiology when an on-going or recent COVID-19 infection is documented. In addition, the MAH should discuss the immunologic mechanism of MIS-induced myocarditis or pericarditis following COVID-19 infection. Finally, the MAH should include cumulative reviews of cases of acute disseminated encephalomyelitis (ADEM) and encephalitis.
- In the next PSUR, the MAH should provide a discussion on several signals identified in the population of vaccinees younger than 50 years of age. In addition, the MAH should provide a cumulative review of cases of severe cutaneous adverse reactions (SCARs), a discussion of the age and gender distribution of TTS cases as well as an analysis stratified by age for pulmonary embolism.

7. Post-authorisation safety studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)⁵⁴

See also Annex I 17.1.

7.1.1. Chlormadinone acetate, ethinylestradiol (NAP) – EMEA/H/N/PSA/J/0072

Applicant: Gedeon Richter PLC

PRAC Rapporteur: Martin Huber

⁵² Update of SmPC section 4.4. The package leaflet is to be updated accordingly

⁵³ Submission date on 15 July 2021

⁵⁴ In accordance with Article 107n of Directive 2001/83/EC

Scope: Substantial amendment to a protocol previously agreed in October 2018 (PSA/J/0030.1) for a case control study comparing levonorgestrel and chlormadinone acetate to compare the risk of venous thromboembolism (VTE) of combined hormonal contraceptives (COCs) containing chlormadinone (CMA) 2mg / ethinylestradiol (EE) 30 µg, compared to COCs containing levonorgestrel (LNG) 0.15 mg, both combined with 30 µg ethinylestradiol (EE) (RIVET-RCS)

Background

Chlormadinone acetate (CMA) is a steroidal synthetic progestin and ethinylestradiol an oestrogen. In combination, CMA/ethinylestradiol is used as a combined oral contraceptive (COC). The MAH submitted to EMA a substantial amendment to a protocol previously agreed in October 2018 for a retrospective cohort study on the risk of venous thromboembolism (VTE) associated with the use of COCs containing CMA/ethinylestradiol and levonorgestrel/ethinylestradiol (RIVET-RCS). The proposed study represents a meta-analysis using individual patient data to address the risk of VTE in women exposed to CMA-containing COCs. As a conclusion to a recent PRAC advice to the Member States in July 2020, PRAC supported that a meta-analysis based on data from previously conducted safety studies is an alternative approach to assess the VTE risk. For further background, see [PRAC minutes October 2018](#) and [PRAC minutes July 2020](#). The study is part of the conditions to the marketing authorisation(s) included in the EC decision [Annex IV](#) for the referral procedure under Article 31 of Directive 2001/83/EC ([EMA/607314/2013](#)) for COCs concluded in 2013.

Endorsement/Refusal of the protocol

- PRAC, having considered the protocol version 1.0 in accordance with Article 107n of Directive 2001/83/EC, 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.
- The MAH should ensure that the primary research question focus on COC combinations with fixed dose of 30 µg ethinylestradiol and clarify the inclusion/exclusion criteria in the setting. The MAH should also clarify whether only definite events or also probable events of VTE will be considered for the primary endpoint and check whether additional data sources may be included to enhance the number of study participants. Finally, the MAH should consider the conduct of a classical approach for data adjustment, whereas the propensity score (PS)-based approach should be considered in a sensitivity analysis.
- The MAH should submit a revised PASS protocol within 60 days to EMA. A 60 day-assessment timetable will be followed.

7.2. Protocols of PASS non-imposed in the marketing authorisation(s)⁵⁵

See also Annex I 17.2.

7.2.1. Coronavirus (COVID-19) mRNA⁵⁶ vaccine (nucleoside-modified) - SPIKEVAX (previously COVID-19 VACCINE MODERNA) (CAP) - EMEA/H/C/005791/MEA 004.2

Applicant: Moderna Biotech Spain, S.L.

⁵⁵ 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

⁵⁶ Messenger ribonucleic acid

PRAC Rapporteur: Hans Christian Siersted

Scope: Protocol for a study (listed as a category 3 study in the RMP): a post-authorisation active surveillance safety study using secondary data to monitor real-world safety of the COVID-19 mRNA-1273 vaccine in Europe [final clinical study report (CSR) expected in December 2023]

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 adults.

As stated in the [RMP](#) of Spikevax (COVID-19 mRNA vaccine (nucleoside-modified)), the MAH is requested to conduct a post-authorisation active surveillance safety study using secondary data to monitor real-world safety of the COVID-19 mRNA-1273 vaccine in Europe. The MAH Moderna Biotech Spain, S.L submitted to EMA a protocol for the study which was assessed by the Rapporteur. PRAC was requested to provide advice to CHMP on the protocol submitted by the MAH. At the organisational, regulatory and methodological matters (ORGAM)⁵⁷ meeting on 22 July 2021, PRAC adopted its outcome.

Summary of advice

- Based on the review of protocol and the assessment from the Rapporteur, PRAC considered the protocol for Spikevax (COVID-19 mRNA vaccine (nucleoside-modified)) could be acceptable provided that an updated protocol is submitted to EMA. The MAH should provide further data and clarifications.
- In particular, the MAH should explain the analytic principle underlying the signal detection phase and the necessity of a signal detection phase, rather than going directly to dedicated signal evaluation analyses for all adverse events of special interest (AESI). The MAH should also justify the use of a contemporary comparator in the evaluation phase and discuss the limitations of using historical cohorts. In addition, the MAH should ensure that comparative analyses are performed every six months and the results are reported in interim reports.

7.2.2. Coronavirus (COVID-19) mRNA⁵⁸ vaccine (nucleoside-modified) - SPIKEVAX (previously COVID-19 VACCINE MODERNA) (CAP) - EMEA/H/C/005791/MEA 034

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Hans Christian Siersted

Scope: Protocol for a study monitoring the safety of Spikevax (previously COVID-19 Vaccine Moderna) in pregnancy: an observational study using routinely collected health data in five European countries

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 adults.

⁵⁷ Extended to specific COVID-19-related procedure(s) during EMA business continuity plan (BCP)

⁵⁸ Messenger ribonucleic acid

As stated in the [RMP](#) of Spikevax (COVID-19 mRNA vaccine (nucleoside-modified)), the MAH is requested to conduct a study monitoring the safety of Spikevax in pregnancy: an observational study using routinely collected health data in five European countries. The MAH Moderna Biotech Spain, S.L submitted to EMA a protocol for the study which was assessed by the Rapporteur. PRAC was requested to provide advice to CHMP on the protocol submitted by the MAH. At the organisational, regulatory and methodological matters (ORGAM)⁵⁹ meeting on 22 July 2021, PRAC adopted its outcome.

Summary of advice

- Based on the review of protocol and the assessment from the Rapporteur, PRAC considered the protocol for Spikevax (COVID-19 mRNA vaccine (nucleoside-modified)) could be acceptable provided that an updated protocol is submitted to EMA. The MAH should provide further data and clarifications.
- In particular, the MAH should refine the research question and objectives of the study as well as the variables. For both study designs (prevalence study and cohort study), the MAH should also specify any comparison groups and the main measure of association. The MAH should describe methods for control of confounding and handling of missing data including imputation methods. Furthermore, a discussion on what confounder issues relate to the current labelling of the vaccine should be included.
- The MAH should update the RMP to include the study in the pharmacovigilance plan at the next regulatory opportunity.

7.3. Results of PASS imposed in the marketing authorisation(s)⁶⁰

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

Applicant: Theramex Ireland Limited

PRAC Rapporteur: Adrien Inoubli

Scope: 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

Background

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

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

⁵⁹ Extended to specific COVID-19-related procedure(s) during EMA business continuity plan (BCP)

⁶⁰ In accordance with Article 107p-q of Directive 2001/83/EC

safety of a monophasic oral contraceptive containing norgestrol acetate (2.5mg) and 17 β -estradiol (1.5mg)'. For further background, see [PRAC minutes June 2019](#).

PRAC discussed the final study results and adopted a recommendation.

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 a request for supplementary information (RSI) was necessary before a final recommendation could be issued.
- The MAH should provide further details on the low recruitment, sample size and number of event targets. The MAH should also discuss the representativeness of the cohort. In addition, the MAH should provide a discussion on the trainings of adjudicators and give clarifications on intra- and inter-variability assessments among adjudicators. The MAH should also perform further analyses by classifying venous thromboembolic events (VTEs) and arterial thromboembolic events (ATEs) as confirmed if at least one adjudicator has classified the event as confirmed.
- The MAH should submit responses to the RSI within 60 days to EMA. A 30 day-assessment timetable will be followed.

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

See also Annex I 17.4.

7.4.1. [Glycerol phenylbutyrate - RAVICTI \(CAP\) - EMEA/H/C/003822/II/0038/G, Orphan](#)

Applicant: Immedica Pharma AB

PRAC Rapporteur: Ilaria Baldelli

Scope: Grouped variations consisting of: 1) submission of the final report for study HPN-100-014: a non-interventional registry study - a long-term registry of patients with urea cycle disorders (UCDs) conducted in the United States (US); 2) submission of an updated RMP (version 7) to remove the important potential risks of carcinogenicity and peracetic acid (PAA) toxicity. The update to the RMP is based on the review of new and available data including the study report for HPN-100-014 and a new toxicological expert examination of pre-clinical carcinogenicity findings as well as a cumulative review of literature and post marketing data. In accordance with the proposed changes to the RMP, an update of Annex II is requested to waive the imposed condition related to the non-interventional PASS on 'European post-authorisation registry for Ravicti (glycerol phenylbutyrate) oral liquid in partnership with the European registry and network for intoxication type metabolic diseases (E-IMD)'. The SmPC and package leaflet have been updated to delete the information on additional monitoring (including the black triangle)

Background

Glycerol phenylbutyrate is a nitrogen-binding drug indicated, as Ravicti, a centrally authorised product, for use as adjunctive therapy for chronic management of patients with urea cycle disorders (UCDs) including deficiencies of carbamoyl phosphate synthetase I (CPS), ornithine carbamoyltransferase (OTC), argininosuccinate synthetase (ASS),

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

argininosuccinate lyase (ASL), arginase I (ARG) and ornithine translocase deficiency hyperornithinaemia-hyperammonaemia homocitrullinuria syndrome (HHH) who cannot be managed by dietary protein restriction and/or amino acid supplementation alone, subject to certain conditions.

As stated in the RMP and Annex II of Ravicti (glycerol phenylbutyrate), the MAH conducted a non-interventional study as a long-term registry of patients with UCDs conducted in the US (study HPN-100-014). The Rapporteur assessed the MAH's final study report together with the necessary updates to the RMP.

Summary of advice

- Based on the available data and the Rapporteur's review, PRAC considered that further information was necessary before the ongoing variation assessing the final study report can be recommended for approval. In addition, the RMP for Ravicti (glycerol phenylbutyrate) in the context of the grouped variation could be considered acceptable provided that an update to RMP version 7 is submitted.
- PRAC acknowledged the challenges in conducting study HZNP-RAV-401. Nevertheless, PRAC considered that the safety concerns should be sufficiently characterised and further evaluated to track long-term outcomes in patients with UCDs. In particular, 'carcinogenicity' and 'toxicity due to the active metabolite PAA (phenylacetic acid)' should be retained as important identified risks in the RMP at this stage. As a consequence, the MAH should address a request for supplementary for information (RSI) before a conclusion can be drawn.

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

See also Annex I 17.5.

7.5.1. Cabozantinib - CABOMETYX (CAP) - EMEA/H/C/004163/MEA 001.5

Applicant: Ipsen Pharma

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to MEA 001.4 [interim report for study F-FR-60000-001 (CASSIOPE): a prospective non-interventional study of the utilisation of cabozantinib tablets in adults with advanced renal cell carcinoma (RCC) following prior vascular endothelial growth factor (VEGF)-targeted therapy in real life settings in terms of dose modifications due to adverse events (AEs) when used as a second line therapy or third and later line therapy] as per the request for supplementary information (RSI) adopted in February 2021

Background

Cabozantinib is a receptor tyrosine kinase (RTK) inhibitor indicated, as Cabometyx a centrally authorised product, as monotherapy for advanced renal cell carcinoma as first-line treatment of adult patients with intermediate or poor and in adults following prior vascular endothelial growth factor (VEGF)-targeted therapy. In combination with nivolumab, it is indicated for the first-line treatment of advanced renal cell carcinoma in adults. It is also indicated as monotherapy for the treatment of hepatocellular carcinoma (HCC) in adults who have previously been treated with sorafenib.

As stated in the RMP of Cabometyx (cabozantinib), the MAH is requested to conduct a study entitled 'a prospective non-interventional study of the utilisation of cabozantinib tablets in adults with advanced renal cell carcinoma (RCC) following prior vascular endothelial growth factor (VEGF)-targeted therapy in real life settings' to evaluate drug dose modifications due to adverse events based on investigator's decision. An interim report for the study was assessed by the Rapporteur for PRAC review together with the MAH's responses to the request for supplementary information (RSI). For further background, see [PRAC minutes February 2021](#).

Summary of advice

- Based on the available data and the Rapporteur's review, PRAC agreed that the existing undesirable effect of haemorrhages should reflect that it includes epistaxis.
- The MAH should submit to EMA, within 60 days, a variation to update⁶² the product information accordingly.

7.6. Others

See Annex I 17.6.

7.7. New Scientific Advice

None

7.8. Ongoing Scientific Advice

None

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

None

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

8.1. Annual reassessments of the marketing authorisation

See Annex I 18.1.

8.2. Conditional renewals of the marketing authorisation

See Annex I 18.2.

8.3. Renewals of the marketing authorisation

See Annex I 18.2.

⁶² Update of section 4.8 of the SmPC

9. Product related pharmacovigilance inspections

9.1. List of planned pharmacovigilance inspections

None

9.2. Ongoing or concluded pharmacovigilance inspections

None

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.

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

11.1. Safety related variations of the marketing authorisation

None

11.2. Other requests

11.2.1. Fentanyl (NAP) - FR/H/PSUFU/00001369/202004

Applicants: Angelini farmaceutica S.A., Aurobindo, Gedeon Richter PLC, Grünenthal, Kyowa Mylan, Sandoz, Stada, Teva B.V., Yes Pharmaceuticals

PRAC Lead: Tiphaine Vaillant

Scope: PRAC consultation on a PSUR follow-up (PSU FU) procedure evaluating off-label use, misuse and accidental exposure, as discussed at PRAC and agreed by CMDh following the conclusion of the PSUR single assessment (PSUSA) procedure (PSUSA/00001369/202004) concluded in January 2021, on request of France

Background

Fentanyl is a potent opioid analgesic indicated for analgesia through various routes of administration and pharmaceutical forms. With respect to the transmucosal route of administration, fentanyl-containing products are indicated for the treatment of breakthrough pain (BTP) in adults with cancer who are already receiving maintenance opioid therapy for chronic cancer pain.

Based on the assessment of the recent PSUR single assessment (PSUSA) procedure for fentanyl for transmucosal route of administration (PSUSA/00001369/202004) concluded in January 2021, PRAC considered that a thorough review of the current labelling should be performed to ensure that the risks of off-label use, misuse and accidental exposure are appropriately mitigated. For further background, see [PRAC minutes January 2021](#).

On request of CMDh, MAH(s) for nationally approved fentanyl for transmucosal route of administration-containing product(s) submitted the requested 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/00001369/202004), France, as lead Member State (LMS), requested PRAC advice on its assessment.

Summary of advice

- Based on the available data and the LMS's assessment, PRAC supported requesting the MAHs to further propose a warning to inform patients that transmucosal fentanyl-containing product(s) must only be used by patients already taking other opioids for chronic cancer pain and to update their product information accordingly. Further consideration will be given in the context of the ongoing procedure.

12. Organisational, regulatory and methodological matters

12.1. Mandate and organisation of PRAC

12.1.1. Mandate of PRAC Chairperson - prolongation

In line with Article 3⁶³ of the Rules of Procedure of PRAC ([EMA/PRAC/567515/2012](#) Rev.2), and following confirmation of the current Chair's interest in prolonging her mandate, PRAC voted to prolong, for a further three years, the mandate of Sabine Straus as a Chair, taking effect as of September 2021.

12.1.2. PRAC working group - Best practice guide on using PRAC plenary time efficiently and effectively – update on the implementation of quantitative goals – Q2 2021

In line with the adopted PRAC best practice guidance (BPG) on Committee efficiency (see [PRAC minutes May 2016](#) and [PRAC minutes June 2018](#)) and the adopted implementation plan for the BPG including goals to measure compliance with the recommendations (see

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

[PRAC minutes June 2016](#) and [PRAC minutes June 2018](#)), the EMA secretariat informed PRAC about the quantitative measures collected for Q2 2021 of PRAC meetings. For previous update, see [PRAC minutes April 2021](#).

12.2. Coordination with EMA Scientific Committees or CMDh-v

None

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

12.3.1. Scientific Advice Working Party (SAWP)–PRAC interaction: process improvement - proposal

PRAC lead: Menno van der Elst, Adrien Inoubli, Martin Huber, Brigitte Keller-Stanislawski

At the organisational, regulatory and methodological matters (ORGAM) meeting on 22 July 2021, the EMA secretariat presented to PRAC an update on the process improvement for SAWP-PRAC interaction. A subgroup of PRAC members have proposed steps to improve the efficiency and clarity of the scientific advice procedure. This includes a PRAC peer-reviewer's comment template to facilitate the interaction with SAWP during the procedure. PRAC agreed with the new template and welcomed the clarifications on the procedure.

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. In addition, the EMA Secretariat also presented to PRAC an overview dated July 2021 on EMA-funded observational studies of COVID-19 vaccines.

At the organisational, regulatory and methodological matters (ORGAM)⁶⁴ meeting on 22 July 2021, the EMA secretariat presented an updated process for rolling review *ad hoc* procedures used in an emergency context to allow EMA to continuously assess the data for an upcoming highly promising application as they become available. PRAC endorsed the new proposal.

At the organisational, regulatory and methodological matters (ORGAM)⁶⁵ meeting on 22 July 2021, the EMA secretariat also presented the timetables for September-December 2021 to apply for upcoming monthly summary safety reports. PRAC endorsed the proposed timetables.

12.5. Cooperation with International Regulators

12.5.1. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)-E19 on 'optimisation of safety

⁶⁴ Extended to specific COVID-19-related procedure(s) during EMA business continuity plan (BCP)

⁶⁵ Extended to specific COVID-19-related procedure(s) during EMA business continuity plan (BCP)

In relation to the last discussion dated October 2019 (for background, see [PRAC minutes October 2019](#)), at the organisational, regulatory and methodological matters (ORGAM) meeting on 22 July 2021, the EMA Secretariat with EMA designated experts presented to PRAC, on behalf of the E19 Expert working group, the new version of the draft ICH E19 guideline on 'a selective approach to safety data collection in specific late-stage pre-approval or post-approval studies' following the public consultation dated 2019. PRAC members was invited to provide comments by 15 September 2021. Further update will be given in due course.

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 Q2 2021

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

12.8.2. PRAC workload statistics – Q2 2021

At the organisational, regulatory and methodological matters (ORGAM) meeting on 22 July 2021, the EMA secretariat presented to PRAC the quarterly and cumulative figures to estimate the evolution of the workload of PRAC for Q2 2021, by reflecting on the number of procedures and agenda items covered at each PRAC plenary meeting. For previous update, see [PRAC minutes April 2021](#).

12.9. Pharmacovigilance audits and inspections

12.9.1. Pharmacovigilance systems and their quality systems

None

12.9.2. Pharmacovigilance inspections

None

12.9.3. Pharmacovigilance audits

None

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

12.10.1. Periodic safety update reports

None

12.10.2. Granularity and Periodicity Advisory Group (GPAG)

None

12.10.3. PSURs repository

None

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

PRAC endorsed the draft revised EURD list, version July 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 July 2021, the updated EURD list was adopted by CHMP and CMDh at their July 2021 meetings and published on the EMA website on 28 July 2021, see:

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

12.10.5. Coronavirus (COVID-19) pandemic - Consideration on core requirements for PSURs of COVID-19 vaccines- corePSUR19 guidance

Action: For adoption

The EMA Secretariat presented to PRAC a draft document on 'Consideration on core requirements for PSURs of COVID19 vaccines - corePSUR19 guidance'. PRAC adopted the document.

Post-meeting note: On 09 July 2021, the coreRMP19 guidance version 3.0 ([EMA/362988/2021](#)) was published on the EMA website.

12.11. Signal management

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

PRAC lead: Menno van der Elst

At the organisational, regulatory and methodological matters (ORGAM) meeting on 22 July 2021, PRAC was updated on the progress from the signal management review technical (SMART) working group meeting on processes held on 22 June 2021. The meeting

focused on the approach for COVID-19 vaccine safety topics and use of signals vs. monthly summary safety reports (MSSRs) together with general considerations for criteria to apply. PRAC welcomed them. PRAC was also updated on the progress from SMART working group meeting on methods. The presentation focussed on vaccine targeted medical event, EVDAS dashboards and observed to expected (O/E) analyses. Further update will be planned in due course.

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

12.13. EudraVigilance database

12.13.1. Activities related to the confirmation of full functionality

None

12.14. Risk management plans and effectiveness of risk minimisations

12.14.1. Risk management systems

None

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

None

12.15. Post-authorisation safety studies (PASS)

12.15.1. Post-authorisation Safety Studies – imposed PASS

None

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

None

12.15.3. Post-authorisation Safety Studies - non-imposed non-interventional PASS protocol & protocol amendment - assessment report (AR) template

At the organisational, regulatory and methodological matters (ORGAM) meeting on 22 July 2021, the EMA secretariat presented to PRAC a revised assessment report (AR) template for non-imposed non-interventional (NINI) PASS protocol and protocol amendment. PRAC members were invited to send comments by 27 August 2021.

Post-meeting note: On 06 September 2021, the AR template for NINI protocol and protocol amendment was adopted by CHMP following PRAC endorsement in writing. The [template](#) was published on the EMA website accordingly.

12.16. Community procedures

12.16.1. Referral procedures for safety reasons

None

12.17. Renewals, conditional renewals, annual reassessments

None

12.18. Risk communication and transparency

12.18.1. Public participation in pharmacovigilance

None

12.18.2. Safety communication

None

12.18.3. Coronavirus disease 2019 (COVID-19) safety updates – revised proposal

The EMA Secretariat presented to PRAC to revise the current format of the COVID-19 safety updates to further improve the communication by providing high-level information about EudraVigilance data together with information on how to interpret these data. PRAC supported the new format.

12.18.4. PRAC communication – call for expression of interest to review communication strategy and materials

PRAC lead: Sabine Straus

At the organisational, regulatory and methodological matters (ORGAM) meeting on 22 July 2021, the EMA Secretariat presented to PRAC a call for expression of interest for new communication experts to replace Amelia Cupelli, Julia Pallos and Sofia Trantza.

Post-meeting note: Rhea Fitzgerald, Anette Kirstine Stark and Ulla Wändel Liminga were nominated as the new PRAC communication experts.

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 22 July 2021, the EMA Secretariat presented to PRAC as part of the PRAC Impact Strategy and follow-up to the discussion in December 2020 (for background, see [PRAC minutes December 2020](#)) the action relating to strengthening PRAC engagement with patients and healthcare professionals in relation to risk minimisation measures (RMM). A draft decision aid was presented for practical support to PRAC in determining the need and design of PRAC engagement events. PRAC members were invited to send comments. Further updates will be scheduled in September/October 2021.

12.20.2. Strategy on measuring the impact of pharmacovigilance – PRAC interest group (IG) Impact – study on codeine use and changes in alternative treatments for pain and cough in children after introduction of the risk minimisation measures following the completion of referral procedures for codeine-containing products

PRAC lead: David Olsen

At the organisational, regulatory and methodological matters (ORGAM) meeting on 22 July 2021, the EMA Secretariat presented to PRAC the results of the impact study ([EUPAS32021](#)) on codeine use and changes in alternative treatments for pain and cough in children after introduction of risk minimisation measures agreed as part of the conclusions of the referral procedures under Article 31 of Directive 2001/83/EC dated 2013 ([EMEA/H/A-31/1342](#)) and 2015 ([EMEA/H/A-31/1394](#)). PRAC noted the results of the study.

Post-meeting note: The study 'changes in alternative treatments for pain and cough in children after introduction of risk minimisation measures for codeine' is registered under [EUPAS32021](#) in the EU PAS register.

12.20.3. Strategy on measuring the impact of pharmacovigilance - impact of regulatory actions – impact study

PRAC lead: Liana Gross-Martirosyan

At the organisational, regulatory and methodological matters (ORGAM) meeting on 22 July 2021, the EMA Secretariat informed PRAC that the outcome of the signal was prioritised for impact research. As per the agreed prioritisation process, the EMA Secretariat presented to PRAC the methodological aspects and framework for an impact study. PRAC supported the research topic for an EMA funded study.

12.20.4. [Strategy on measuring the impact of pharmacovigilance – PRAC interest group \(IG\) Impact – qualitative impact study on COVID-19 vaccines regulatory actions for thrombosis with thrombocytopenia syndrome \(TTS\)](#)

The EMA Secretariat informed PRAC that the impact of regulatory actions on COVID-19 vaccines (Vaxzevria and COVID-19 vaccine Janssen) and thrombosis with thrombocytopenia syndrome (TTS) was prioritised for impact research. As per the agreed prioritisation process, the EMA Secretariat presented to PRAC the methodological aspects and framework for an impact study. PRAC supported the research topic for an EMA funded study and the proposed qualitative objectives.

At the organisational, regulatory and methodological matters (ORGAM) meeting on 22 July 2021, the EMA Secretariat presented to PRAC the technical specifications (TS). PRAC endorsed the TS.

Post-meeting note: A research contract was awarded. The study 'Impact of EU label changes and regulatory communication on SARS-CoV-2 adenovirus vector vaccines in context of thrombosis with thrombocytopenia syndrome (TTS): risk awareness and adherence' is registered under [EUPAS44970](#) in the EU PAS register.

12.21. Others

12.21.1. [EMA-funded study after vaccination against severe acute respiratory syndrome coronavirus 2 \(SARS-CoV-2\) – preliminary results](#)

The EMA-funded study investigator research group presented to PRAC the preliminary results of the study on thrombosis and thrombocytopenia (TTS) after vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). PRAC noted the preliminary results.

12.21.2. [Questions and answers \(Q&A\) document on 'complex clinical trials' - draft](#)

The EMA Secretariat presented to PRAC the project to develop a questions and answers (Q&A) document on 'complex clinical trials' initiated by the European Commission (EC) in collaboration with EMA and the Clinical Trials Facilitation group (CTFG). PRAC members were invited to express interest by 30 July 2021 to join the EC/EMA/CTFG drafting group to contribute to the next stage of drafting the Q&A.

13. Any other business

None

14. Annex I – Signals assessment and prioritisation⁶⁶

14.1. New signals detected from EU spontaneous reporting systems

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

14.1.1. Atezolizumab – TECENTRIQ (CAP)

Applicant(s): Roche Registration GmbH

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Signal of cholangitis sclerosing

EPITT 19708 – New signal

Lead Member State(s): PT

14.1.2. Ertapenem – INVANZ (CAP); NAP

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

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Signal of toxic encephalopathy in patients with renal impairment

EPITT 19498 – New signal

Lead Member State(s): PT

14.1.3. Propylthiouracil (NAP)

Applicant(s): various

PRAC Rapporteur: Maia Uusküla

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

EPITT 19692 – New signal

Lead Member State(s): EE

14.2. New signals detected from other sources

None

⁶⁶ Each signal refers to a substance or therapeutic class. The route of marketing authorisation is indicated in brackets (CAP for Centrally Authorised Products; NAP for Nationally Authorised Products including products authorised via Mutual Recognition Procedures and Decentralised Procedure). Product names are listed for reference Centrally Authorised Products (CAP) only. PRAC recommendations will specify the products concerned in case of any regulatory action required

⁶⁷ Cumulative review(s) requested as part of a 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 has been raised before the meeting

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. Adalimumab - EMEA/H/C/005548

Scope: Treatment of rheumatoid arthritis, psoriasis, hidradenitis suppurativa, Crohn's disease, paediatric Crohn's disease, ulcerative colitis, uveitis, paediatric uveitis, treatment of rheumatoid arthritis, juvenile idiopathic arthritis, axial spondyloarthritis, psoriatic arthritis, psoriasis, paediatric plaque psoriasis, hidradenitis suppurativa, Crohn's disease, paediatric Crohn's disease, ulcerative colitis, uveitis, paediatric uveitis

15.1.2. Adalimumab - EMEA/H/C/005947

Scope: Treatment of rheumatoid arthritis, juvenile idiopathic arthritis, axial spondyloarthritis, psoriatic arthritis, psoriasis, paediatric plaque psoriasis, hidradenitis suppurativa, Crohn's disease, paediatric Crohn's disease, ulcerative colitis, uveitis, paediatric uveitis

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

Applicant: Epitepoietic Research Corporation-Belgium (E.R.C.), ATMP⁶⁸

Scope: Treatment of glioma

15.1.4. Opicapone - EMEA/H/C/005782

Scope: Treatment of Parkinson's disease and motor fluctuations

15.1.5. Rivaroxaban - EMEA/H/C/005600

Scope: Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) and prevention of recurrent DVT and PE in adults; prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery

15.1.6. Sitagliptin fumarate - EMEA/H/C/005741

Scope: Treatment of type 2 diabetes mellitus (T2DM)

⁶⁸ Advanced therapy medicinal product

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. Atezolizumab - TECENTRIQ (CAP) - EMEA/H/C/004143/II/0061

Applicant: Roche Registration GmbH

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Submission of an updated RMP (version 20.0) in order to add severe cutaneous adverse reactions (SCARs) as an important identified risk and its associated risk minimisation measure: a dear healthcare professional communication (DHPC) following the addition of SCARs to the product information as an outcome of variation II/0054 finalised in February 2021. In addition, the MAH took the opportunity to update the due dates of final clinical study reports (CSR) of two post-authorisation efficacy studies (PAES)

15.2.2. 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

15.2.3. Brinzolamide, timolol - AZARGA (CAP) - EMEA/H/C/000960/II/0045

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Anette Kirstine Stark

Scope: Submission of an updated RMP (version 3.0) to remove important identified risks (respiratory disorders, cardiovascular disorders, corneal decompensation and metabolic acidosis), important potential risk (long term use of preserved eye drops) and missing information (use in paediatric patients)

15.2.4. Coronavirus (COVID-19) vaccine (ChAdOx1-S [recombinant]) - VAXZEVRIA (CAP) - EMEA/H/C/005675/II/0015

Applicant: AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: Submission of an updated RMP (version 3.1) in order to update the safety concerns to add 'thrombosis in combination with thrombocytopenia' as an important identified risk and 'thrombosis' as an important potential risk, with consequential changes in the RMP. Updates to the pharmacovigilance plan have also been implemented. These changes are implemented in line with the recommendation of the signal procedure on 'embolic and thrombotic events' (EPITT 19683) adopted in April 2021. The MAH took the opportunity to

further update the RMP to reclassify 'anaphylaxis' as an important identified risk, already reflected in the product information as an adverse drug reaction

15.2.5. [Emicizumab - HEMLIBRA \(CAP\) - EMEA/H/C/004406/II/0021](#)

Applicant: Roche Registration GmbH

PRAC Rapporteur: Ilaria Baldelli

Scope: Submission of an updated RMP (version 2.5) in order to add thromboembolic events without concomitant activated prothrombin complex concentrate (aPCC) as an important potential risk in the safety specifications and to update the milestones of study BO40853 (listed as a category 3 study in the RMP): a PASS based on healthcare professional (HCP) and patient/carer survey to evaluate awareness, knowledge and compliance of HCPs and patients/carers to additional risk minimisation measures (guide for HCPs, patient/carer guide, patient alert card), in relation to the safety concerns of thromboembolic events, thrombotic microangiopathy and life-threatening bleeding due to misinterpretation of the standard coagulation tests in line with the approved substantial amended protocol in December 2020 (MEA 002.2)

15.2.6. [Epoetin alfa - ABSEAMED \(CAP\) - EMEA/H/C/000727/WS2013/0092;](#) [BINOCRIT \(CAP\) - EMEA/H/C/000725/WS2013/0091;](#) [EPOETIN ALFA HEXAL \(CAP\) - EMEA/H/C/000726/WS2013/0091](#)

Applicant: Sandoz GmbH

PRAC Rapporteur: Tiphaine Vaillant

Scope: Submission of an updated RMP (version 18) for Abseamed, Binocrit, Epoetin Alfa Hexal (epoetin alfa) in line with the RMP of the medicinal product of reference consisting of: 1) replacement of the term 'tumour growth potential' with 'disease progression' and 'premature death' with 'survival impact'; 2) clinical study data on these two topics were shortened; 3) removal of TRIGONS study proposal (MEA18; HX575-502) as additional pharmacovigilance activity. The risks of disease progression and survival impact will be monitored by routine pharmacovigilance and continue to be reviewed in PSURs

15.2.7. [Ledipasvir, sofosbuvir - HARVONI \(CAP\) - EMEA/H/C/003850/WS2086/0097;](#) [sofosbuvir - SOVALDI \(CAP\) - EMEA/H/C/002798/WS2086/0071;](#) [sofosbuvir, velpatasvir - EPCLUSA \(CAP\) - EMEA/H/C/004210/WS2086/0059](#)

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Updated Annex II to revise the study milestone from 'Q2 2023' to 'Q3 2021' for the hepatocellular carcinoma (HCC) recurrence PASS as per the outcome of the imposed PASS protocol procedure (PSA/J/0055) adopted in June 2020. In addition, the MAH took the opportunity to update the list of local representatives and to bring the product information in line with the latest quality review of documents (QRD) template (version 10.2)

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. 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

15.3.2. Cabotegravir - VOCABRIA (CAP) - EMEA/H/C/004976/II/0004

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Martin Huber

Scope: Update of sections 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC based on week 124 results from the FLAIR study: a phase 3, randomized, open-label study to evaluate the efficacy, safety and tolerability of the combined treatment cabotegravir and rilpivirine. The package leaflet and the RMP (version 2) are updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet, to introduce editorial changes and corrections throughout the product information and to bring the product information in line with the latest quality review of documents (QRD) template (version 10.2)

15.3.3. Coronavirus (COVID-19) vaccine (ChAdOx1-S [recombinant]) - VAXZEVRIA (CAP) - EMEA/H/C/005675/II/0026

Applicant: AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: Update of sections 4.4, 4.8 and 5.1 of the SmPC in order to include updated efficacy and safety information based on primary analysis from study D8110C00001 (listed as a specific obligation in Annex II): a phase 3 randomised, double-blind, placebo-controlled, multicentre study in adults to determine the safety, efficacy and immunogenicity of Vaxzevria (COVID-19 vaccine). The package leaflet and Annex II are updated accordingly. The RMP (version 3 succession 2) is updated in accordance

15.3.4. Coronavirus (COVID-19) mRNA⁶⁹ vaccine (nucleoside-modified) - COMIRNATY (CAP) - EMEA/H/C/005735/II/0036

Applicant: BioNTech Manufacturing GmbH

⁶⁹ Messenger ribonucleic acid

PRAC Rapporteur: Menno van der Elst

Scope: Update of sections 4.8 and 5.1 of the SmPC to include new information based on updated interim results from study C4591001: a phase 1/2/3, placebo-controlled, observer-blind, interventional, dose-finding, study to evaluate the safety, tolerability, immunogenicity and efficacy of SARS-CoV-2 RNA vaccine candidates against COVID-19 in healthy individuals. The package leaflet and the RMP (version 2.1) are updated accordingly

15.3.5. Defibrotide - DEFITELIO (CAP) - EMEA/H/C/002393/II/0056, Orphan

Applicant: Gentium S.r.l.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of the final report from study 15-007 (listed as a specific obligation in Annex II): a phase 3, randomised, adaptive study of defibrotide vs. best supportive care in the prevention of hepatic veno-occlusive disease in adult and paediatric patients undergoing hematopoietic stem cell transplant (HSCT). The RMP (version 9) is updated accordingly. The MAH took the opportunity to bring the product information in line with the latest quality review of documents (QRD) (template 10.2). In addition, the MAH introduced some minor correction throughout the product information

15.3.6. Delamanid - DELTYBA (CAP) - EMEA/H/C/002552/X/0046/G, Orphan

Applicant: Otsuka Novel Products GmbH

PRAC Rapporteur: Laurence de Fays

Scope: Grouped applications consisting of: 1) extension application to introduce a new pharmaceutical form (dispersible tablets) associated with a new strength (25 mg); 2) extension of indication to include the treatment of children of at least 10 kg of body weight for Delytba (delamanid) 50 mg film-coated tablets. As a consequence, sections 3, 4.1, 4.2, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The package leaflet, labelling and the RMP (version 3.3) are updated accordingly. Annex II is updated to remove the specific obligation related to an in vitro study using the hollow fibre system model of tuberculosis (HFS-TB)

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

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Martin Huber

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

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

Applicant: EUSA Pharma (Netherlands) B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

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

15.3.9. Dupilumab - DUPIXENT (CAP) - EMEA/H/C/004390/X/0045/G

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Kimmo Jaakkola

Scope: Grouped applications consisting of: 1) extension of application to add a new strength (100 mg solution for injection) consisting of: one presentation containing 2 pre-filled syringes and one presentation containing 6 pre-filled syringes (multipack of 3 packs of 2); 2) extension of indication to include treatment of paediatric patients with severe asthma with type 2 inflammation aged 6 to 11 years old. The RMP (version 6.0) are updated accordingly

15.3.10. 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

15.3.11. 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

15.3.12. 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

15.3.13. Lenvatinib - LENVIMA (CAP) - EMEA/H/C/003727/II/0045

Applicant: Eisai GmbH

PRAC Rapporteur: Annika Folin

Scope: Update of section 5.1 of the SmPC with additional efficacy and safety data from study E7080-G000-211: a phase 2 multicentre, randomised, double-blind, non-inferiority trial in subjects with ¹³¹I-refractory differentiated thyroid cancer to evaluate whether an oral starting dose of 18 mg daily will provide comparable efficacy to a 24 mg starting dose with an improved safety profile. The RMP (version 12.3) is updated accordingly. In addition, the MAH took the opportunity to update the details of local representatives of Bulgaria, Croatia, Estonia, Hungary, Lithuania, Latvia, Malta, Poland, Romania, Slovenia

15.3.14. Lenvatinib - KISPLYX (CAP) - EMEA/H/C/004224/II/0048

Applicant: Eisai GmbH

PRAC Rapporteur: David Olsen

Scope: Submission of the final report from study E7080-G000-211 (listed as a category 3 study in the RMP): a multicentre, randomised, double-blind phase 2 trial of lenvatinib (E7080) in subjects with ¹³¹I-refractory differentiated thyroid cancer to evaluate whether an oral starting dose of 18 mg daily will provide comparable efficacy to a 24 mg starting dose, but have a better safety profile. The RMP (version 12.3) is updated accordingly

15.3.15. Mecasermin - INCRELEX (CAP) - EMEA/H/C/000704/II/0067

Applicant: Ipsen Pharma

PRAC Rapporteur: Kirsti Villikka

Scope: Update of the conditions of the non-interventional PASS (listed as a specific obligation in Annex II) by using different criteria of patient exposure and long term follow up to assess the relevant safety data, with consequential amendment of the study completion date. The RMP (version 13) is updated accordingly and submitted together with an amended global registry protocol (amendment 8). The package leaflet is updated

accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet and to bring the product information in line with the latest quality review of documents (QRD) template (version 10.2)

15.3.16. [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, 5.2 and 5.1 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, randomized, 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

15.3.17. [Paliperidone - PALIPERIDONE JANSSEN-CILAG INTERNATIONAL \(CAP\) - EMEA/H/C/005486/X/0002/G](#)

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Ulla Wändel Liminga

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

15.3.18. [Pandemic influenza vaccine \(H5N1\) \(split virion, inactivated, adjuvanted\) - ADJUPANRIX \(CAP\) - EMEA/H/C/001206/II/0074](#)

Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to include use in children from 6 months to <18 years for Adjupanrix (pandemic influenza vaccine (H5N1)) based on the results of the following studies: 1) study H5N1-013: a phase 2, non-randomised, open-label study to evaluate the safety and immunogenicity in children aged 6 to 35 months; 2) study H5N1-032: a phase 3, randomised, open, active-controlled study to evaluate the safety and immunogenicity in children aged 3 to 17 years. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 6.6 of the SmPC are updated. The package leaflet and the RMP (version 13) are updated in accordance. Further, the MAH proposed to update section 4.4 with information on sodium

and potassium content in line with the excipients guideline, as well as to add some wording on traceability. 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 10.2). Finally, the MAH introduced minor editorial changes throughout the product information

15.3.19. Posaconazole - NOXAFIL (CAP) - EMEA/H/C/000610/II/0062

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Adrien Inoubli

Scope: Extension of indication to include primary treatment of invasive aspergillosis in adults and adolescents from 13 years of age for Noxafil (posaconazole) gastroresistant tablet and concentrate for solution for infusion based on the results of study P069: a phase 3 randomized study of the efficacy and safety of posaconazole versus voriconazole for the treatment of invasive aspergillosis. 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 16.2) are updated in accordance

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

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Adrien Inoubli

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

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

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Liana Gross-Martirosyan

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

15.3.22. 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

15.3.23. Selinexor - NEXPOVIO (CAP) - EMEA/H/C/005127/II/0001/G

Applicant: Karyopharm Europe GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Grouped variations consisting of: 1) extension of indication for Nexpovio (selinexor) in combination with bortezomib and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy; 2) addition of a new pack size (8 tablets) to align with the dose modification guidance for the new indication. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 6.5 of the SmPC are updated accordingly. Annex II is updated to reflect the completion of the specific obligation. The labelling, package leaflet and RMP (version 1.1) are updated in accordance

15.3.24. Sofosbuvir, velpatasvir - EPCLUSA (CAP) - EMEA/H/C/004210/X/0056/G

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Grouped applications consisting of: 1) extension application to introduce a new pharmaceutical form (coated granules in sachet) associated with strengths 200mg/50mg and 150mg/37.5mg. The new presentations are indicated for the treatment of chronic hepatitis C virus (HCV) infection in patients 3 years of age and older; 2) inclusion of paediatric use in patients 3 years of age and older to the existing presentations of the film-coated tablets. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 7.1) are updated accordingly. In addition, the MAH took the opportunity to implement minor updates and corrections throughout the product information

15.3.25. Sofosbuvir, velpatasvir, voxilaprevir - VOSEVI (CAP) - EMEA/H/C/004350/X/0045/G

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Grouped application consisting of: 1) extension application to introduce a new strength (200 mg /50 mg /50 mg film-coated tablets). The new presentation is indicated for the treatment of chronic hepatitis C virus (HCV) infection in patients aged 12 years and older or weighing at least 30 kg. In addition, the MAH took the opportunity to implement minor editorial updates in module 3.2.P; 2) extension of indication to include paediatric use in patients aged 12 years and older or weighing at least 30 kg to the existing presentation. 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 3.2) are updated in accordance

15.3.26. Tenofovir alafenamide - VEMLIDY (CAP) - EMEA/H/C/004169/II/0030

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ilaria Baldelli

Scope: Submission of the final report from study GS-US-320-4018 (listed as a category 3 study in the RMP): a phase 3, randomised, double blind study to evaluate the efficacy and safety of switching from tenofovir disoproxil fumarate 300 mg once daily to tenofovir alafenamide 25 mg once daily in subjects with chronic hepatitis B who are virologically suppressed. The RMP (version 6.1) is updated accordingly

15.3.27. Tenofovir disoproxil - VIREAD (CAP) - EMEA/H/C/000419/II/0204

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Adrien Inoubli

Scope: Submission of final study report for study GS-US-174-0144 (listed as category 3 study in the RMP): a randomised, double-blind evaluation of the antiviral efficacy, safety and tolerability of tenofovir disoproxil fumarate. This application fulfils the Article 46 commitment to provide the final week 192 study results for clinical measure 'study 5' (study GS_US_174-0144) listed in the paediatric investigation plan (PIP). As a consequence, section 5.1 of the SmPC is updated accordingly. Additionally, the risk minimisation measures for paediatrics are removed from the RMP and Annex II of the product information. The package leaflet and the RMP (version 25.1) are updated accordingly. In addition, the MAH took the opportunity to implement minor linguistic amendments throughout the product information. Furthermore, the expression of lactose content in Annex I for the tablets was changed to refer to lactose base (not as monohydrate) in line with current practice

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

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

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

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. Angiotensin II - GIAPREZA (CAP) - PSUSA/00010785/202012

Applicant: Paion Deutschland GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.2. Betibeglogene autotemcel - ZYNTEGLO (CAP) - PSUSA/00010769/202011

Applicant: bluebird bio (Netherlands) B.V, ATMP⁷⁰

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.3. Blinatumomab - BLINCYTO (CAP) - PSUSA/00010460/202012

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

16.1.4. Cannabidiol⁷¹ - EPIDYOLEX (CAP) - PSUSA/00010798/202012

Applicant: GW Pharma (International) B.V.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.1.5. Cholera vaccine (recombinant, live, oral) - VAXCHORA (CAP) - PSUSA/00010862/202012

Applicant: Emergent Netherlands B.V.

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

16.1.6. Crisaborole - STAQUIS (CAP) - PSUSA/00010842/202012

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

⁷⁰ Advanced therapy medicinal product

⁷¹ Centrally authorised product(s) only

16.1.7. Darunavir - PREZISTA (CAP) - PSUSA/00000934/202012

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.8. Delafloxacin - QUOFENIX (CAP) - PSUSA/00010822/202012

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

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

16.1.9. Dengue tetravalent vaccine (live, attenuated) - DENGVAXIA (CAP) - PSUSA/00010740/202012

Applicant: Sanofi Pasteur

PRAC Rapporteur: Sonja Hrabcik

Scope: Evaluation of a PSUSA procedure

16.1.10. Elotuzumab - EMLICITI (CAP) - PSUSA/00010500/202011

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.11. Encorafenib - BRAFTOVI (CAP) - PSUSA/00010719/202012

Applicant: Pierre Fabre Medicament

PRAC Rapporteur: Rugile Pilviniene

Scope: Evaluation of a PSUSA procedure

16.1.12. Entrectinib - ROZLYTREK (CAP) - PSUSA/00010874/202012

Applicant: Roche Registration GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.13. Eribulin - HALAVEN (CAP) - PSUSA/00001254/202011

Applicant: Eisai GmbH

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

16.1.14. Follitropin delta - REKOVELLE (CAP) - PSUSA/00010554/202011

Applicant: Ferring Pharmaceuticals A/S

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.15. Formoterol fumarate dihydrate, glycopyrronium bromide, budesonide - TRIEXO AEROSPHERE (CAP) - PSUSA/00010908/202012

Applicant: AstraZeneca AB

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.1.16. Indacaterol, mometasone furoate - ATECTURA BREEZHALER (CAP); BEMRIST BREEZHALER (CAP) - PSUSA/00010850/202011

Applicant(s): Novartis Europharm Limited

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.1.17. Inotuzumab ozogamicin - BESPONSA (CAP) - PSUSA/00010659/202012

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.18. Levodopa - INBRIJA (CAP) - PSUSA/00107800/202012

Applicant: Acorda Therapeutics Ireland Limited

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

16.1.19. Luspatercept - REBLOZYL (CAP) - PSUSA/00010860/202012

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Laurence de Fays

Scope: Evaluation of a PSUSA procedure

16.1.20. Lutetium (¹⁷⁷Lu) oxodotreotide - LUTATHERA (CAP) - PSUSA/00010643/202012

Applicant: Advanced Accelerator Applications

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.21. Mexiletine⁷² - NAMUSCLA (CAP) - PSUSA/00010738/202012

Applicant: Lupin Europe GmbH

PRAC Rapporteur: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

16.1.22. Netarsudil - RHOKIINSA (CAP) - PSUSA/00107812/202012

Applicant: Aerie Pharmaceuticals Ireland Limited

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

16.1.23. Olaparib - LYNPARZA (CAP) - PSUSA/00010322/202012

Applicant: AstraZeneca AB

PRAC Rapporteur: Ilaria Baldelli

Scope: Evaluation of a PSUSA procedure

16.1.24. Pertuzumab, trastuzumab - PHESGO (CAP) - PSUSA/00010906/202012

Applicant: Roche Registration GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.25. Polatuzumab vedotin - POLIVY (CAP) - PSUSA/00010817/202012

Applicant: Roche Registration GmbH

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

16.1.26. Ponatinib - ICLUSIG (CAP) - PSUSA/00010128/202012

Applicant: Incyte Biosciences Distribution B.V.

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

16.1.27. Ravulizumab - ULTOMIRIS (CAP) - PSUSA/00010787/202012

Applicant: Alexion Europe SAS

PRAC Rapporteur: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

⁷² Centrally authorised product(s) only

16.1.28. Reteplase - RAPILYSIN (CAP) - PSUSA/00002623/202011

Applicant: Actavis Group PTC ehf
PRAC Rapporteur: Martin Huber
Scope: Evaluation of a PSUSA procedure

16.1.29. Rotavirus vaccine pentavalent (live, oral) - ROTATEQ (CAP) - PSUSA/00002666/202011

Applicant: MSD Vaccins
PRAC Rapporteur: Ulla Wändel Liminga
Scope: Evaluation of a PSUSA procedure

16.1.30. Saquinavir - INVIRASE (CAP) - PSUSA/00002684/202012

Applicant: Roche Registration GmbH
PRAC Rapporteur: Jan Neuhauser
Scope: Evaluation of a PSUSA procedure

16.1.31. Secukinumab - COSENTYX (CAP) - PSUSA/00010341/202012

Applicant: Novartis Europharm Limited
PRAC Rapporteur: Eva Segovia
Scope: Evaluation of a PSUSA procedure

16.1.32. Semaglutide - OZEMPIC (CAP); RYBELSUS (CAP) - PSUSA/00010671/202011

Applicant(s): Novo Nordisk A/S
PRAC Rapporteur: Annika Folin
Scope: Evaluation of a PSUSA procedure

16.1.33. Sofosbuvir - SOVALDI (CAP) - PSUSA/00010134/202012

Applicant: Gilead Sciences Ireland UC
PRAC Rapporteur: Ana Sofia Diniz Martins
Scope: Evaluation of a PSUSA procedure

16.1.34. Sonidegib - ODOMZO (CAP) - PSUSA/00010408/202012

Applicant: Sun Pharmaceutical Industries Europe B.V.
PRAC Rapporteur: Nikica Mirošević Skvrce
Scope: Evaluation of a PSUSA procedure

16.1.35. Treosulfan⁷³ - TRECONDI (CAP) - PSUSA/00010777/202012

Applicant: Medac Gesellschaft für klinische Spezialpräparate mbH

PRAC Rapporteur: Julia Pallos

Scope: Evaluation of a PSUSA procedure

16.1.36. Turoctocog alfa pegol - ESPEROCT (CAP) - PSUSA/00010782/202012

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.37. Venetoclax - VENCLYXTO (CAP) - PSUSA/00010556/202012

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

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

16.2.1. Human hepatitis B immunoglobulin - ZUTECTRA (CAP); NAP - PSUSA/00001631/202011

Applicants: Biotest Pharma GmbH (Zutectra), various

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.2.2. Lutetium (¹⁷⁷Lu) chloride - ENDOLUCINBETA (CAP); LUMARK (CAP); NAP - PSUSA/00010391/202012

Applicants: I.D.B. Holland B.V. (Lumark), ITM Medical Isotopes GmbH (EndolucinBeta), various

PRAC Rapporteur: Ronan Grimes

Scope: Evaluation of a PSUSA procedure

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

16.3.1. Ciprofloxacin hydrochloride, hydrocortisone (NAP) - PSUSA/00000774/202011

Applicant(s): various

PRAC Lead: Ilaria Baldelli

⁷³ Centrally authorised product(s) only

Scope: Evaluation of a PSUSA procedure

16.3.2. Diphtheria, tetanus, pertussis (acellular, component), poliomyelitis (inactivated), haemophilus type b conjugate vaccine (adsorbed) (NAP) - PSUSA/00001124/202011

Applicant(s): various

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.3.3. Methylprednisolone (NAP) - PSUSA/00002026/202011

Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.3.4. Phenylephrine, tropicamide (NAP) - PSUSA/00010430/202011

Applicant(s): various

PRAC Lead: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

16.3.5. Sultamicillin (NAP) - PSUSA/00002829/202011

Applicant(s): various

PRAC Lead: Maia Uusküla

Scope: Evaluation of a PSUSA procedure

16.3.6. Tafluprost, timolol (NAP) - PSUSA/00010324/202012

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.3.7. Vecuronium bromide (NAP) - PSUSA/00003102/202011

Applicant(s): various

PRAC Lead: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

16.3.8. Yellow fever vaccine (live) (NAP) - PSUSA/00003135/202012

Applicant(s): various

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.4. Follow-up to PSUR/PSUSA procedures

None

16.5. Variation procedure(s) resulting from PSUSA evaluation

16.5.1. Coronavirus (COVID-19) mRNA⁷⁴ vaccine (nucleoside-modified) - SPIKEVAX (previously COVID-19 VACCINE MODERNA) (CAP) - EMEA/H/C/005791/II/0015/G

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Hans Christian Siersted

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

16.5.2. 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

16.5.3. Fampridine - FAMPYRA (CAP) - EMEA/H/C/002097/II/0049

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Update of section 4.8 of SmPC to include new symptoms of trigeminal neuralgia as per the outcome of the last PSUR single assessment (PSUSA) procedure (PSUSA/00001352/202001) finalised in September 2020. The package leaflet is updated accordingly. The MAH introduced further editorial updates including an update of the product information in line with the latest quality review of documents (QRD) template (version 10.2) and an update of the contact details of the local representatives

⁷⁴ Messenger ribonucleic acid

16.5.4. 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 reviews⁷⁵

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 listed below without further plenary discussion.

17.1. Protocols of PASS imposed in the marketing authorisation(s)⁷⁶

17.1.1. Alemtuzumab – LEMTRADA (CAP) - EMEA/H/C/PSP/S/0087.2

Applicant: Sanofi Belgium

PRAC Rapporteur: Anette Kirstine Stark

Scope: MAH's response to PSP/S/0087.1 [protocol for a non-interventional PASS to investigate the risk of mortality in patients prescribed Lemtrada (alemtuzumab) relative to comparable patients using other disease modifying therapies: a cohort study] as per the request for supplementary information (RSI) adopted in February 2021

17.1.2. Alemtuzumab – LEMTRADA (CAP) - EMEA/H/C/PSP/S/0088.2

Applicant: Sanofi Belgium

PRAC Rapporteur: Anette Kirstine Stark

Scope: MAH's response to PSP/S/0088.1 [protocol for a non-interventional PASS to investigate drug utilisation and safety monitoring patterns for Lemtrada (alemtuzumab)] as per the request for supplementary information (RSI) adopted in February 2021

17.1.3. Cabotegravir – VOCABRIA (CAP); rilpivirine – REKAMBYS (CAP) - EMEA/H/C/PSP/J/0092.1

Applicant(s): Janssen-Cilag International N.V. (Rekambys), ViiV Healthcare B.V. (Vocabria)

⁷⁵ 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

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

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: MAH's response to PSP/J/0092 [protocol for a joint drug utilisation study (DUS) to assess adherence, effectiveness and resistance: a prospective observational cohort study in people living with human immunodeficiency virus (HIV) (PLWH) initiating antiretroviral (ARV) regimen of cabotegravir (CAB) + rilpivirine (RPV) long-acting (LA) in collaboration with EuroSIDA⁷⁷] as per the request for supplementary information (RSI) adopted in April 2021

17.1.4. Lenalidomide – REVLIMID (CAP) - EMEA/H/C/PSA/S/0067.1

Applicant: Bristol-Myers Squibb Pharma

PRAC Rapporteur: Tiphaine Vaillant

Scope: MAH's response to PSA/S/0067 [substantial amendment to a protocol previously agreed in September 2016 (PSP/0020.3) for study CC-5013-MM-034: a prospective non-interventional PASS of lenalidomide in previously untreated adult multiple myeloma patients who are not eligible for transplant (Revlimid TNE NDMM PASS)] as per the request for supplementary information (RSI) adopted in March 2021

17.1.5. Prasterone – INTRAROSA (CAP) - EMEA/H/C/PSA/S/0070

Applicant: Endoceutics S.A.

PRAC Rapporteur: Menno van der Elst

Scope: Substantial amendment to a protocol previously agreed for a non-interventional PASS: a drug utilisation study (DUS) to describe the baseline characteristics, utilisation patterns of EU postmenopausal women initiating treatment with Intrarosa (prasterone) and to assess whether EU prescribers abide by the contraindications stated in the EU SmPC

17.1.6. Valproate (NAP) - EMEA/H/N/PSA/J/0071

Applicant: Sanofi-Aventis Recherche & Développement (on behalf of a consortium)

PRAC Rapporteur: Jean-Michel Dogné

Scope: Substantial amendment to a protocol previously agreed for an observational study to evaluate and identify the best practices for switching of valproate in clinical practice

17.2. Protocols of PASS non-imposed in the marketing authorisation(s)⁷⁸

17.2.1. Autologous peripheral blood T cells CD⁷⁹4 and CD8 selected and CD3 and CD28 activated transduced with retroviral vector expressing anti-CD19 CD28/CD3-zeta chimeric antigen receptor and cultured - TECARTUS (CAP) - EMEA/H/C/005102/MEA 005

Applicant: Kite Pharma EU B.V., ATMP⁸⁰

⁷⁷ Prospective observational pan-European cohort study

⁷⁸ 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

⁷⁹ Cluster of differentiation

⁸⁰ Advanced therapy medicinal product

PRAC Rapporteur: Menno van der Elst

Scope: Protocol for study KT-EU-472-5966: a prescriber survey to assess prescribers' understanding of the risks of Tecartus (KTE-X19) to evaluate the effectiveness of risk minimisation activities, namely healthcare professional (HCP) educational materials and patient alert card (PAC) [final study report expected in September 2023] (from initial opinion/marketing authorisation(s) (MA))

17.2.2. [Beclometasone, formoterol, glycopyrronium bromide - TRIMBOW \(CAP\) - EMEA/H/C/004257/MEA 002](#)

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Jan Neuhauser

Scope: Protocol for study CLI-05993BA1-05 (TRIBE): a multinational database cohort study to assess adverse cardiovascular and cerebrovascular outcomes in patients with chronic obstructive pulmonary disease initiating a fixed triple therapy containing beclometasone dipropionate, formoterol fumarate and glycopyrronium administered via dry powder inhaler (DPI) compared to pressurised metered dose inhaler (pMDI)

17.2.3. [Canagliflozin - INVOKANA \(CAP\) - EMEA/H/C/002649/MEA 009.3](#)

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Martin Huber

Scope: MAH's response to MEA 009.2 consisting in an amended protocol for a drug utilisation study (DUS) to evaluate the drug utilisation patterns of canagliflozin-containing medicines including off-label usage in type 1 diabetes mellitus (T1DM) and the risk of diabetic ketoacidosis (DKA) using EU databases on market uptake and exposure within the European Union as per the request for supplementary information (RSI) adopted in October 2020

17.2.4. [Canagliflozin, metformin - VOKANAMET \(CAP\) - EMEA/H/C/002656/MEA 008.3](#)

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to MEA 008.2 consisting in an amended protocol for a drug utilisation study (DUS) to evaluate the drug utilisation patterns of canagliflozin-containing medicines including off-label usage in type 1 diabetes mellitus (T1DM) and the risk of diabetic ketoacidosis (DKA) using EU databases on market uptake and exposure within the European Union as per the request for supplementary information (RSI) adopted in October 2020

17.2.5. [Cannabidiol - EPIDYOLEX \(CAP\) - EMEA/H/C/004675/MEA 007.2](#)

Applicant: GW Pharma (International) B.V.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: MAH's response to MEA 007.1 [protocol for study GWEP19022 (listed as a category 3 study in the RMP): a prospective, observational cohort long-term safety study to assess

the potential for chronic liver injury in patients treated with Epidyolex (cannabidiol oral solution) when used under conditions of routine clinical care] as per the request for supplementary information (RSI) adopted in February 2021

17.2.6. [Coronavirus \(COVID-19\) vaccine \(Ad26.COV2-S, recombinant\) - COVID-19 VACCINE JANSSEN \(CAP\) - EMEA/H/C/005737/MEA 008](#)

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Protocol for study VAC31518COV4003 (listed as a category 3 study in the RMP): a post-authorisation, observational study to assess the safety of Ad26.COV2.S using electronic health record (EHR) database(s) in Europe (from initial opinion/marketing authorisation(s) (MA))

17.2.7. [Coronavirus \(COVID-19\) vaccine \(ChAdOx1-S \[recombinant\]\) - VAXZEVRIA \(CAP\) - EMEA/H/C/005675/MEA 007.1](#)

Applicant: AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: MAH's response to MEA 007 [protocol for study D8111R00006: a post-authorisation/post-marketing observational study using existing secondary health data sources to evaluate the association between exposure to COVID-19 vaccine (ChAdOx1-S [recombinant] (AZD1222 / Vaxzevria)) and safety concerns (from initial opinion/marketing authorisation)] as per the request for supplementary information (RSI) adopted in May 2021

17.2.8. [Coronavirus \(COVID-19\) vaccine \(ChAdOx1-S \[recombinant\]\) - VAXZEVRIA \(CAP\) - EMEA/H/C/005675/MEA 007.2](#)

Applicant: AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: MAH's response to MEA 007.1 [protocol for study D8111R00006: a post-authorisation/post-marketing observational study using existing secondary health data sources to evaluate the association between exposure to COVID-19 vaccine (ChAdOx1-S [recombinant] (AZD1222 / Vaxzevria)) and safety concerns (from initial opinion/marketing authorisation)] as per the request for supplementary information (RSI) adopted at the July 2021 plenary meeting

17.2.9. [Dabigatran etexilate - PRADAXA \(CAP\) - EMEA/H/C/000829/MEA 050](#)

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Anette Kirstine Stark

Scope: Protocol for a human factors study to assess effectiveness of a training video to mitigate potential medication errors during the reconstitution and dosing of the dabigatran etexilate paediatric oral solution [final clinical study report (CSR) expected in January 2022] (from X/0122/G)

17.2.10. Dimethyl fumarate - TECFIDERA (CAP) - EMEA/H/C/002601/MEA 008.6

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Martin Huber

Scope: MAH's response to MEA 008.5 [amendment to a protocol previously agreed in September 2020 for study 109MS402: Biogen multiple sclerosis (MS) pregnancy exposure registry to prospectively evaluate pregnancy outcomes in women with MS who were exposed to a registry-specified Biogen MS product during the eligibility window for that product] as per the request for supplementary information (RSI) adopted in March 2021

17.2.11. Dulaglutide - TRULICITY (CAP) - EMEA/H/C/002825/MEA 006.3

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Ilaria Baldelli

Scope: MAH's response to MEA 006.2 [protocol for study H9X-MC-B013 (listed as a category 3 study in the RMP): a non-interventional retrospective study to estimate the incidence rates of events of interest among type 2 diabetes mellitus (T2DM) patients treated with dulaglutide compared to other glucagon-like peptide 1 (GLP-1) receptor agonists in order to better characterise the safety profile of dulaglutide in terms of acute pancreatitis, pancreatic and thyroid malignancies] as per the request for supplementary information (RSI) adopted in February 2020

17.2.12. Esketamine - SPRAVATO (CAP) - EMEA/H/C/004535/MEA 002.2

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Kirsti Villikka

Scope: MAH's response to MEA 002.1 [protocol for a pregnancy registry study (listed as a category 3 study in the RMP) using the National Pregnancy Registry for Psychiatric Medications (NPRPM) in order to further characterise the impact of the missing information of use during pregnancy on the safety profile of esketamine nasal spray and obtain information on the frequency of major malformations (from initial opinion/marketing authorisation) [final report expected in Q4 2024]] as per the request for supplementary information (RSI) adopted in March 2021

17.2.13. Fremanezumab - AJOVY (CAP) - EMEA/H/C/004833/MEA 005.2

Applicant: Teva GmbH

PRAC Rapporteur: Kirsti Villikka

Scope: Substantial amendment to a protocol previously agreed in March 2020 for study TV48125-MH-50039: a long-term, prospective, phase 4, observational study to evaluate the safety, including cardiovascular safety, of fremanezumab in patients with migraine in routine clinical practice

17.2.14. Naloxegol - MOVENTIG (CAP) - EMEA/H/C/002810/MEA 006.10

Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: MAH's response to MEA 006.9 [substantial amendment to a protocol previously agreed in December 2018 for study D3820R00009 (previously study D2288R00084): an observational PASS of Moventig (naloxegol) among patients aged 18 years and older treated with opioids chronically] as per the request for supplementary information (RSI) adopted in March 2021

17.2.15. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/MEA 014.3

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: MAH's response to MEA 014.2 [protocol for study A3921321: a drug utilisation study (DUS) on the utilisation and prescribing patterns of Xeljanz (tofacitinib) in two European countries using administrative claims databases and national registries for assessment, as requested in the conclusions of the referral procedure under Article 20 of Regulation (EC) No 726/2004 (EMEA/H/A-20/1485) finalised in November 2019] as per the request for supplementary information (RSI) adopted in February 2021

17.2.16. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/MEA 047.2

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Rhea Fitzgerald

Scope: MAH's response to MEA 047.1 [protocol for study SWIBREG-UST UC: an observational PASS to describe the safety of ustekinumab and other ulcerative colitis treatments in a cohort of patients with ulcerative colitis using the Swedish Inflammatory Bowel Disease Register (SWIBREG) as requested in the conclusions of variation II/071 finalised in July 2019 [final clinical study report (CSR) expected in May 2027]] as per the request for supplementary information (RSI) adopted in February 2021

17.2.17. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/MEA 048.2

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Rhea Fitzgerald

Scope: MAH's response to MEA 048.1 [protocol for study SNDS-UST UC: an observational PASS to describe the safety of ustekinumab and other ulcerative colitis treatments in a cohort of patients with ulcerative colitis using the French administrative healthcare database (SNDS) as requested in the conclusions of variation II/071 finalised in July 2019 [final clinical study report (CSR) expected in May 2027]] as per the request for supplementary information (RSI) adopted in February 2021

17.3. Results of PASS imposed in the marketing authorisation(s)⁸¹

None

⁸¹ In accordance with Article 107p-q of Directive 2001/83/EC

17.4. Results of PASS non-imposed in the marketing authorisation(s)⁸²

17.4.1. Alglucosidase alfa - MYOZYME (CAP) - EMEA/H/C/000636/II/0079

Applicant: Genzyme Europe BV

PRAC Rapporteur: Adrien Inoubli

Scope: Submission of the final report from study ALGMYC07390: a prevalence study of immunology testing in patients treated with alglucosidase alfa with significant hypersensitivity/anaphylactic reactions to test the effectiveness of the approved safety information packet (SIP)

17.4.2. Aripiprazole - ABILIFY MAINTENA (CAP) - EMEA/H/C/002755/II/0040

Applicant: Otsuka Pharmaceutical Netherlands B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of the final report from study 15893N (listed as a category 3 study in the RMP): a non-interventional PASS related to extrapyramidal symptoms - a cohort study with a 2-year follow-up using European longitudinal electronic medical records or claims databases

17.4.3. Bazedoxifene - CONBRIZA (CAP) - EMEA/H/C/000913/II/0052

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Martin Huber

Scope: Submission of the final clinical study report (CSR) for study B1781044 (listed as a category 3 study in the RMP): a non-interventional cohort study to characterise the risk of venous thromboembolic events (VTE) and selected clinical endpoints of interest among a patient population prescribed bazedoxifene, raloxifene, or a bisphosphonate in Europe in usual clinical care setting

17.4.4. Daunorubicin, cytarabine - VYXEOS LIPOSOMAL (CAP) - EMEA/H/C/004282/II/0017, Orphan

Applicant: Jazz Pharmaceuticals Ireland Limited

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Submission of the final clinical study report (CSR) for a post-marketing observational study to assess the nature, incidence and severity of infusion-related reactions in adult patients treated with Vyxeos liposomal (daunorubicin/cytarabine)

17.4.5. Estrogens conjugated, bazedoxifene - DUAVIVE (CAP) - EMEA/H/C/002314/II/0030

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Martin Huber

⁸² 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

Scope: Submission of the final report from study B2311060 (listed as a category 3 study in the RMP): a non-interventional, post-authorisation safety study of conjugated estrogens/bazedoxifene (CE/BZA) in the US, with the aim to monitor the safety profile of Duavive (CE/BZA) in comparison to oestrogen and progestin combination hormone therapy (E+P HT)

17.4.6. Fingolimod - GILENYA (CAP) - EMEA/H/C/002202/II/0070/G

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Tiphaine Vaillant

Scope: Grouped variations consisting of: 1) submission of non-interventional final study report D2403: a long-term, prospective, multinational, parallel-cohort study monitoring safety in patients with multiple sclerosis (MS) newly started on fingolimod once daily or treated with another approved disease-modifying therapy; 2) submission of non-interventional final study report D2406/D2409: a long-term, prospective, non-interventional, multinational, parallel-cohort study monitoring safety in patients with MS newly initiated on fingolimod once daily or treated with another approved disease-modifying therapy (including cardiac sub-study D2409). As a consequence, Annex II-D on 'Conditions or restrictions with regard to the safe and effective use of the medicinal product' is updated to remove the obligation to perform study PASS D2409. The RMP (version 19.0) is updated accordingly. In addition, the MAH took the opportunity to implement some minor editorial changes

17.4.7. Isavuconazole - CRESEMBA (CAP) - EMEA/H/C/002734/II/0035/G, Orphan

Applicant: Basilea Pharmaceutica Deutschland GmbH

PRAC Rapporteur: Adam Przybylkowski

Scope: Grouped variations consisting of: 1) submission of the final report from study WSA-REG-001 (listed as a category 3 study in the RMP): a retrospective case-collection study, in which cases of invasive mucormycosis treated with isavuconazole were compared to cases treated with other systemic antifungals. The RMP (version 8.2) is updated accordingly; 2) remove study AK1820-301 (listed as a category 3 study in the RMP): a phase 3 multicentre, open-label study to evaluate safety and efficacy of 200 mg intravenous or oral isavuconazole for the treatment of adult Japanese patients with deep mycosis, with the primary endpoint of safety (proportion of patients with adverse events), and secondary endpoints of efficacy outcomes

17.4.8. Talimogene laherparepvec - IMLYGIC (CAP) - EMEA/H/C/002771/II/0044

Applicant: Amgen Europe B.V., ATMP⁸³

PRAC Rapporteur: Brigitte Keller-Stanislawski

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

⁸³ Advanced therapy medicinal product

17.4.9. Velaglucerase alfa - VPRIV (CAP) - EMEA/H/C/001249/II/0049, Orphan

Applicant: Shire Pharmaceuticals Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: Submission of final physician data study results for study EUPASS 14255: an evaluation of the effectiveness of risk minimisation measures - a survey among healthcare professionals (HCPs) and patient/caregivers to assess their knowledge and attitudes on prescribing and home administration conditions of velaglucerase alfa (Vpriv) in 6 European countries

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

17.5.1. Ataluren - TRANSLARNA (CAP) - EMEA/H/C/002720/MEA 002.7

Applicant: PTC Therapeutics International Limited

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Five-year interim report for study PTC124-GD-0250-DMD (listed as a category 3 study in the RMP): a post-approval registry observational study exploring the long-term of ataluren safety and effectiveness in usual care setting [final clinical study report (CSR) expected in April 2023] together with MAH's response to MEA 002.6 [four-year interim report for study PTC124-GD-0250-DMD] as per the request for supplementary information (RSI) adopted in January 2020

17.5.2. Baricitinib - OLUMIANT (CAP) - EMEA/H/C/004085/MEA 009.2

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: First interim report for study I4V-MC-B0166: a PASS to assess off-label use in paediatric patients in the United Kingdom (UK) using the Clinical Practice Research Datalink (CPRD) database

17.5.3. Belimumab - BENLYSTA (CAP) - EMEA/H/C/002015/MEA 003.15

Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Eighth annual interim report for study BEL116543/HGS1006-C1124 (SABLE): a long-term controlled safety registry evaluating the incidence of all-cause mortality and adverse events of special interest (AESIs) in patients with systemic lupus erythematosus followed for a minimum of 5 years

17.5.4. Cangrelor - KENGREXAL (CAP) - EMEA/H/C/003773/MEA 002.3

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Ilaria Baldelli

Scope: First interim report for study DFIDM-1801 (ARCANGELO (itAlIAn pRospective study on CANGrELOr)): a multicentre prospective observational study of acute coronary syndrome patients undergoing percutaneous coronary intervention (PCI) who receive cangrelor and transition to either clopidogrel, prasugrel or ticagrelor

17.5.5. Defibrotide - DEFITELIO (CAP) - EMEA/H/C/002393/LEG 011.1

Applicant: Gentium S.r.l.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Second interim report for a national, post-registration observational study of the long-term safety and health outcome of patients treated with Defitelio (defibrotide), including patients with severe hepatic veno-occlusive disease (VOD) after hematopoietic stem-cell transplantation (HSCT) (DEFIFRANCE registry)

17.5.6. Flutemetamol (¹⁸F) - VIZAMYL (CAP) - EMEA/H/C/002557/MEA 002.5

Applicant: GE Healthcare AS

PRAC Rapporteur: Martin Huber

Scope: Second recruitment report for study GE067-027 CPR: a post-authorisation study to assess the frequency of Vizamyl (flutemetamol (¹⁸F)) image classification errors in clinical practice in Europe and to evaluate the effectiveness of Vizamyl (flutemetamol (¹⁸F)) educational training programme/reader training in Europe [final study report expected in Q1 2021]

17.5.7. Pandemic influenza vaccine (H1N1) (split virion, inactivated, adjuvanted) - PANDEMRIX⁸⁴ - EMEA/H/C/000832/MEA 123.2

Applicant: GlaxoSmithKline Biologicals

PRAC Rapporteur: Menno van der Elst

Scope: Submission of a report on narcolepsy and Pandemrix (pandemic influenza vaccine (H1N1) (split virion, inactivated, adjuvanted)), including a review of publications

17.5.8. Rivastigmine - EXELON (CAP) - EMEA/H/C/000169/MEA 036.7

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Tiphaine Vaillant

Scope: Annual report (covering the period from 01 February 2020 to 31 January 2021) for a drug utilisation study (DUS) on the effectiveness of risk minimisation measures (RMM) for multiple patch use

17.5.9. Rivastigmine - PROMETAX (CAP) - EMEA/H/C/000255/MEA 037.7

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Tiphaine Vaillant

⁸⁴ Marketing authorisation expired on 13 August 2015

Scope: Annual report (covering the period from 01 February 2020 to 31 January 2021) for a drug utilisation study (DUS) on the effectiveness of risk minimisation measures (RMM) for multiple patch use

17.5.10. Romosozumab - EVENITY (CAP) - EMEA/H/C/004465/MEA 001.2

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Tiphaine Vaillant

Scope: First interim report for study OP0005: a European non-interventional PASS to study the adherence to the risk minimisation measures (RMMs) in the product information by estimating the compliance with contraindications and target indication(s) amongst incident romosozumab users, and analysing the utilisation pattern using the EU-adverse drug reactions (EU-ADR) Alliance [final study results expected in March 2026]

17.5.11. Romosozumab - EVENITY (CAP) - EMEA/H/C/004465/MEA 002.2

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Tiphaine Vaillant

Scope: Comparative interim report for study OP0004: a European non-interventional PASS to evaluate potential differences in terms of serious cardiovascular adverse events between romosozumab and currently available therapies used in comparable patients in real-world conditions using the EU-adverse drug reactions (EU-ADR) Alliance [final study results expected in December 2026]

17.5.12. Teduglutide - REVESTIVE (CAP) - EMEA/H/C/002345/ANX 003.8

Applicant: Shire Pharmaceuticals Ireland Limited

PRAC Rapporteur: Anette Kirstine Stark

Scope: MAH's response to MEA 003.6 [third biennial interim results for study TED-R-13-002: an international short bowel syndrome registry - a prospective, long-term observational cohort study of patients with short bowel syndrome] as per the request for supplementary information (RSI) adopted in March 2021

17.5.13. Tisagenlecleucel - KYMRIA (CAP) - EMEA/H/C/004090/ANX 003.6

Applicant: Novartis Europharm Limited, ATMP⁸⁵

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: MAH's response to ANX 003.4 [annual safety reports and first five-yearly interim report for a study based on disease registry CCTL019B2401 (listed as a category 1 study in Annex II and the RMP): a non-interventional PASS in acute lymphoblastic leukaemia (ALL) and diffuse large B-cell lymphoma (DLBCL) patients in order to further characterise the safety, including long-term safety, of Kymriah (tisagenlecleucel) [final study report expected in December 2038] as per the request for supplementary information (RSI) adopted in February 2021

⁸⁵ Advanced therapy medicinal product

17.5.14. Tisagenlecleucel - KYMRIAHA (CAP) - EMEA/H/C/004090/MEA 005.1

Applicant: Novartis Europharm Limited, ATMP⁸⁶

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: MAH's response to MEA 005 [first five-yearly interim report for study CCTL019A2205B (listed as a category 3 study in the RMP): a long-term follow-up of patients exposed to lentiviral-based CD19 directed chimeric antigen receptor T (CAR-T)-cell therapy in order to describe selected, delayed adverse events (AEs) suspected to be related to previous CD19 CAR-T-cell therapy as outlined in current Health Authority guidelines [final study report expected in December 2037] (from opinion/marketing authorisation (MA))] as per the request for supplementary information (RSI) adopted in February 2021

17.5.15. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/MEA 024.16

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Rhea Fitzgerald

Scope: MAH's response to MEA 024.15 [tenth annual interim report for study CNTO1275PSO4007 (Nordic pregnancy research initiative) (C0743T): exposure to ustekinumab during pregnancy in patients with psoriasis: a review and analysis of birth outcomes from the Swedish, Danish, and Finnish medical birth registers] as per the request for supplementary information (RSI) adopted in February 2021

17.6. Others

17.6.1. Avatrombopag - DOPTLET (CAP) - EMEA/H/C/004722/MEA 003

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Eva Segovia

Scope: Feasibility assessment for a study to further characterise the long-term safety profile of avatrombopag in patients with primary chronic immune thrombocytopenia in European patient registers and electronic health care databases as requested in the conclusions of variation II/0004/G finalised in December 2020

17.6.2. Fingolimod - GILENYA (CAP) - EMEA/H/C/002202/MEA 038.3

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Tiphaine Vaillant

Scope: MAH's response to MEA 038.2 [First interim report for open-label extension phase of study CFTY720D2311: a phase 3, two-year, double-blind, double dummy, randomised, multicentre, active controlled study evaluating efficacy and safety of fingolimod once daily versus interferon β -1a once weekly in paediatric patients with multiple sclerosis (MS) aged 10 to <18 years old] as per the request for supplementary information (RSI) adopted in March 2021

⁸⁶ Advanced therapy medicinal product

17.6.3. Rivaroxaban - XARELTO (CAP) - EMEA/H/C/000944/MEA 049

Applicant: Bayer AG

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Feasibility report on conducting a study in children from birth to less than 2 years diagnosed with VTE and treated with rivaroxaban in comparison to children with VTE treated with other anticoagulants (from X/074/G)

17.7. New Scientific Advice

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

17.8. Ongoing Scientific Advice

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

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

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

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

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

18.1. Annual reassessments of the marketing authorisation

18.1.1. Amifampridine - FIRDAPSE (CAP) - EMEA/H/C/001032/S/0071 (without RMP)

Applicant: SERB SA

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Annual reassessment of the marketing authorisation

18.1.2. 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

18.1.3. Idursulfase - ELAPRASE (CAP) - EMEA/H/C/000700/S/0092 (without RMP)

Applicant: Shire Human Genetic Therapies AB

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Annual reassessment of the marketing authorisation

18.2. Conditional renewals of the marketing authorisation

18.2.1. Brentuximab vedotin - ADCETRIS (CAP) - EMEA/H/C/002455/R/0090 (without RMP)

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Menno van der Elst

Scope: Conditional renewal of the marketing authorisation

18.2.2. Crizanlizumab - ADAKVEO (CAP) - EMEA/H/C/004874/R/0003 (without RMP)

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Laurence de Fays

Scope: Conditional renewal of the marketing authorisation

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

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Annika Folin

Scope: Conditional renewal of the marketing authorisation

18.3. Renewals of the marketing authorisation

18.3.1. Bezlotoxumab - ZINPLAVA (CAP) - EMEA/H/C/004136/R/0029 (without RMP)

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: 5-year renewal of the marketing authorisation

18.3.2. Darunavir - DARUNAVIR MYLAN (CAP) - EMEA/H/C/004068/R/0014 (without RMP)

Applicant: Mylan S.A.S

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: 5-year renewal of the marketing authorisation

18.3.3. Emtricitabine, tenofovir disoproxil - EMTRICITABINE/TENOFOVIR DISOPROXIL KRKA (CAP) - EMEA/H/C/004215/R/0018 (without RMP)

Applicant: Krka, d.d., Novo mesto

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: 5-year renewal of the marketing authorisation

18.3.4. Emtricitabine, tenofovir disoproxil - EMTRICITABINE/TENOFOVIR DISOPROXIL MYLAN (CAP) - EMEA/H/C/004050/R/0016 (without RMP)

Applicant: Mylan S.A.S

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: 5-year renewal of the marketing authorisation

18.3.5. Etelcalcetide - PARSABIV (CAP) - EMEA/H/C/003995/R/0017 (without RMP)

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ilaria Baldelli

Scope: 5-year renewal of the marketing authorisation

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

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Menno van der Elst

Scope: 5-year renewal of the marketing authorisation

18.3.7. Ivabradine - IVABRADINE ZENTIVA (CAP) - EMEA/H/C/004117/R/0008 (with RMP)

Applicant: Zentiva k.s.

PRAC Rapporteur: Menno van der Elst

Scope: 5-year renewal of the marketing authorisation

18.3.8. Mercaptamine - CYSTADROPS (CAP) - EMEA/H/C/003769/R/0022 (without RMP)

Applicant: Recordati Rare Diseases

PRAC Rapporteur: Eva Segovia

Scope: 5-year renewal of the marketing authorisation

18.3.9. Simoctocog alfa - VIHUMA (CAP) - EMEA/H/C/004459/R/0026 (without RMP)

Applicant: Octapharma AB

PRAC Rapporteur: Ulla Wändel Liminga

Scope: 5-year renewal of the marketing authorisation

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

Applicant: Mylan S.A.S

PRAC Rapporteur: Maria del Pilar Rayon

Scope: 5-year renewal of the marketing authorisation

18.3.11. 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

18.3.12. Teriparatide - MOVYMIA (CAP) - EMEA/H/C/004368/R/0024 (with RMP)

Applicant: Stada Arzneimittel AG

PRAC Rapporteur: Ronan Grimes

Scope: 5-year renewal of the marketing authorisation

18.3.13. Teriparatide - TERROSA (CAP) - EMEA/H/C/003916/R/0020 (with RMP)

Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Ronan Grimes

Scope: 5-year renewal of the marketing authorisation

19. Annex II – List of participants

including any restrictions with respect to involvement of members / alternates / experts following evaluation of declared interests for the 05-08 July 2021 meeting (marked as "a"), and for the 22 July 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

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
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	Member	Cyprus	No interests declared	Full involvement
Christina Sylvia Chrysostomou ^{a, b}	Alternate	Cyprus	No interests declared	Full involvement
Eva Jirsová ^{a, b}	Member	Czechia	No interests declared	Full involvement
Jana Lukacisinova ^a	Alternate	Czechia	No interests declared	Full involvement
Anette Kirstine Stark ^{a, b}	Member	Denmark	No interests declared	Full involvement
Maia Uusküla ^a	Member	Estonia	No interests declared	Full involvement
Krõõt Aab ^{a, b}	Alternate ⁸⁷	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
Adrien Inoubli ^a	Member	France	No interests declared	Full involvement
Tiphaine Vaillant ^{a, b}	Alternate	France	No interests declared	Full involvement
Martin Huber ^{a, b}	Member (Vice-Chair)	Germany	No interests declared	Full involvement
Brigitte Keller-Stanislawski ^a	Alternate	Germany	No interests declared	Full involvement
Julia Pallos ^{a, b}	Member (until 19/07/2021) Alternate (as of 19/07/2021)	Hungary	No restrictions applicable to this meeting	Full involvement
Guðrún Stefánsdóttir ^a	Member	Iceland	No participation in discussion, final	16.1.3. Blinatumomab – BLINCYTO (CAP),

⁸⁷ As of 19 July 2021

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			deliberations and voting on:	17.4.8. Talimogene laherparepvec - IMLYGIC (CAP), 18.3.5. Etelcalcetide - PARSABIV (CAP)
Rhea Fitzgerald ^{a, b}	Member	Ireland	No interests declared	Full involvement
Ilaria Baldelli ^{a, b}	Alternate	Italy	No interests declared	Full involvement
Zane Neikena ^{a, b}	Member	Latvia	No interests declared	Full involvement
Rugile Pilviniene ^{a, b}	Member	Lithuania	No interests declared	Full involvement
Nadine Petitpain ^a	Member	Luxembourg	No restrictions applicable to this meeting	Full involvement
Anne-Cécile Vuillemin ^{a, b}	Alternate	Luxembourg	No interests declared	Full involvement
John Joseph Borg ^a	Member	Malta	No interests declared	Full involvement
Benjamin Micallef ^a	Alternate	Malta	No interests declared	Full involvement
Menno van der Elst ^{a, b}	Member	Netherlands	No interests declared	Full involvement
Liana Gross-Martirosyan ^{a, b}	Alternate	Netherlands	No interests declared	Full involvement
David Olsen ^a	Member	Norway	No participation in final deliberations and voting on:	6.3.4. Ethanol extracts of: Iberis amara L.; planta tota recens, Angelica archangelica L.; radix, Matricaria recutita L.; flos, Carum carvi L.; fructus, Silybum marianum (L.) Gaertn.;

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				fructus, Melissa officinalis L.; folium, Mentha piperita L.; folium, Chelidonium majus L.; herba, Glycyrrhiza glabra L.; radix (NAP), 17.6.3. Rivaroxaban - XARELTO (CAP)
Karen Pernille Harg ^{a, b}	Alternate	Norway	No interests declared	Full involvement
Adam Przybylkowski ^a	Member	Poland	No interests declared	Full involvement
Katarzyna Ziolkowska ^{a, b}	Alternate	Poland	No interests declared	Full involvement
Ana Sofia Diniz Martins ^{a, b}	Member	Portugal	No interests declared	Full involvement
Marcia Silva ^{a, b}	Alternate	Portugal	No interests declared	Full involvement
Roxana Dondera ^a	Member	Romania	No interests declared	Full involvement
Alexandra - Maria Spurni ^{a, b}	Alternate	Romania	No interests declared	Full involvement
Marek Juracka ^{a, b}	Alternate	Slovakia	No interests declared	Full involvement
Polona Golmajer ^b	Alternate (18/07/2021 onwards)	Slovenia	No interests declared	Full involvement
Jasmina Klopčič ^a	Alternate (until 18/07/2021)	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

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Annika Folin ^{a, b}	Alternate	Sweden	No interests declared	Full involvement
Annalisa Capuano ^a	Member	Independent scientific expert	No interests declared	Full involvement
Milou Daniel Drici ^a	Member	Independent scientific expert	No restrictions applicable to this meeting	Full involvement
Maria Teresa Herdeiro ^a	Member	Independent scientific expert	No interests declared	Full involvement
Patricia McGettigan ^a	Member	Independent scientific expert	No interests declared	Full involvement
Daniel Morales ^a	Member	Independent scientific expert	No interests declared	Full involvement
Hedvig Nordeng ^a	Member	Independent scientific expert	No interests declared	Full involvement
Raymond Anderson ^a	Member	Healthcare Professionals' Representative	No interests declared	Full involvement
Roberto Frontini ^{a, b}	Alternate	Healthcare Professionals' Representative	No participation in final deliberations and voting on:	18.3.9. Simoctocog alfa - VIHUMA (CAP)
Cathalijne van Doorne ^{a, b}	Member	Patients' Organisation Representative	No interests declared	Full involvement
Els Beghein ^a	Expert - via Webex*	Belgium	No interests declared	Full involvement
Christelle Bizimungu ^{a, b}	Expert - via Webex*	Belgium	No restrictions applicable to this meeting	Full involvement
Ingrid Bourges ^a	Expert - via Webex*	Belgium	No interests declared	Full involvement
Inne Crevecoeur ^b	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

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Jamila Hamdani ^a	Expert - via Webex*	Belgium	No interests declared	Full involvement
Martine Sabbe ^{a, b}	Expert - via Webex*	Belgium	No interests declared	Full involvement
Nina Lalić ^a	Expert - via Webex*	Croatia	No restrictions applicable to this meeting	Full involvement
Ivana Ljubičić ^{a, b}	Expert - via Webex*	Croatia	No restrictions applicable to this meeting	Full involvement
Lara Miletić ^a	Expert - via Webex*	Croatia	No restrictions applicable to this meeting	Full involvement
Livia Puljak ^a	Expert - via Webex*	Croatia	No interests declared	Full involvement
Magdalena Fabiánová ^a	Expert - via Webex*	Czechia	No interests declared	Full involvement
Karin Erneholm ^a	Expert - via Webex*	Denmark	No restrictions applicable to this meeting	Full involvement
Kirsten Egebjerg Juul ^a	Expert - via Webex*	Denmark	No interests declared	Full involvement
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
Moritz Sander ^b	Expert - via Webex*	Denmark	No interests declared	Full involvement
Emma Louise Nautrup Ravn Stadsbjerg ^{a, b}	Expert - via Webex*	Denmark	No interests declared	Full involvement
Josiane Uwera ^a	Expert - via Webex*	Denmark	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
Krõõt Aab ^a	Expert - via Webex*	Estonia	No interests declared	Full involvement
Karima Adamo ^a	Expert - via Webex*	France	No restrictions applicable to this meeting	Full involvement
Sarah Bendahou ^a	Expert - via Webex*	France	No restrictions applicable to this meeting	Full involvement
Violaine Closson-Carella ^a	Expert - via Webex*	France	No interests declared	Full involvement
Emmanuel Doyen ^a	Expert - via Webex*	France	No interests declared	Full involvement
Stéphanie Hueber ^a	Expert - via Webex*	France	No restrictions applicable to this meeting	Full involvement
Alexis Jacquet ^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
Dennis Lex ^{a, b}	Expert – via Webex*	Germany	No restrictions applicable to this meeting	Full involvement
Jelena Katic ^a	Expert – via Webex*	Germany	No interests declared	Full involvement
Tania Meier ^a	Expert – via Webex*	Germany	No interests declared	Full involvement
Susanne Müller ^a	Expert – via Webex*	Germany	No interests declared	Full involvement
Nerina Pflanz ^a	Expert – via Webex*	Germany	No interests declared	Full involvement
Wiebke Seeman ^a	Expert – via Webex*	Germany	No interests declared	Full involvement
Gabriele Schwarz ^b	Expert – via Webex*	Germany	No interests declared	Full involvement
Grainne Kirwan ^a	Expert – via Webex*	Ireland	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Alessandro Aiuti ^a	Expert – via Webex*	Italy	No restrictions applicable to this meeting	Full involvement
Amelia Cupelli ^{a, b}	Expert – via Webex*	Italy	No interests declared	Full involvement
Ineke Crijns ^a	Expert – via Webex*	The Netherlands	No restrictions applicable to this meeting	Full involvement
Esther de Vries ^b	Expert – via Webex*	The Netherlands	No interests declared	Full involvement
Carla Herberts ^a	Expert – via Webex*	The Netherlands	No restrictions applicable to this meeting	Full involvement
Johann Lodewijk Hillege ^a	Expert – via Webex*	The Netherlands	No interests declared	Full involvement
Carla Jonker ^a	Expert – via Webex*	The Netherlands	No interests declared	Full involvement
Peter Mol ^b	Expert – via Webex*	The Netherlands	No interests declared	Full involvement
Viktoriia Starokozhko ^a	Expert – via Webex*	The Netherlands	No restrictions applicable to this meeting	Full involvement
Maria Vanenburg ^b	Expert – via Webex*	The Netherlands	No interests declared	Full involvement
Eleonora Wijnans ^a	Expert – via Webex*	The Netherlands	No interests declared	Full involvement
Sol Ruiz ^a	Expert – via Webex*	Spain	No interests declared	Full involvement
Helena Back ^a	Expert – via Webex*	Sweden	No interests declared	Full involvement
Charlotte Backman ^{a, b}	Expert – via Webex*	Sweden	No interests declared	Full involvement
Rolf Gedeberg ^a	Expert – via Webex*	Sweden	No restrictions applicable to this meeting	Full involvement
Jessica Mwinyi ^a	Expert – via Webex*	Sweden	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
Daniel Prieto Alhambra	Expert – via Webex*	United Kingdom	Expert witness for:	4.3.1 – COVID-19 mRNA vaccine (nucleoside-modified) - COMIRNATY (CAP) 4.3.3 - COVID-19)mRNA vaccine (nucleoside-modified) - SPIKEVAX (CAP)
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, the EMA is requested to conduct a scientific assessment of a particular medicine or class of medicines on behalf of the European Union (EU). For further detailed information on safety related referrals please see:

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

Signals assessment and prioritisation

(Item 4 of the PRAC minutes)

A safety signal is information on a new or incompletely documented adverse event that is potentially caused by a medicine and that warrants further investigation. Signals are generated from several sources such as spontaneous reports, clinical studies and the scientific literature. The evaluation of safety signals

is a routine part of pharmacovigilance and is essential to ensuring that regulatory authorities have a comprehensive knowledge of a medicine's benefits and risks.

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

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

Risk Management Plans (RMPs)

(Item 5 of the PRAC minutes)

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

Assessment of Periodic Safety Update Reports (PSURs)

(Item 6 of the PRAC minutes)

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

Post-authorisation Safety Studies (PASS)

(Item 7 of the PRAC minutes)

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

Product related pharmacovigilance inspections

(Item 9 of the PRAC minutes)

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

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

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