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Human Medicines Division

Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC minutes on 08-11 March 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.

1.2. Agenda of the meeting on 08-11 March 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 08-11 February 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 08-11 February 2021 were published on the EMA website on 20 December 2021 ([EMA/PRAC/696693/2021](#)).

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

2.1. Newly triggered procedures

None

2.2. Ongoing procedures

None

2.3. Procedures for finalisation

None

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

3.1. Newly triggered procedures

3.1.1. 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

The European Commission (EC) sent a letter of [notification](#) dated 18 February 2021 triggering a procedure under Article 20 of Regulation (EC) No 726/2004 for the review of Zynteglo (betibeglogene autotemcel), a centrally authorised advanced therapy medicinal product (ATMP), indicated for the treatment of patients 12 years and older with transfusion-dependent β -thalassaemia (TDT) who do not have a β^0/β^0 genotype, for whom haematopoietic stem cell transplantation (HSCT) is appropriate but a human leukocyte antigen (HLA)-matched related HSC donor is not available.

The review was initiated following the report of a case of acute myeloid leukaemia (AML) in a patient treated for sickle cell disease with a related investigational drug, bb1111. This investigational drug uses the same lentiviral vector as Zynteglo (betibeglogene autotemcel) to transduce CD²³⁴⁺ cells. However, bb1111 is under development to treat sickle cell disease rather than thalassaemia. Some of the characteristics of the patient's adverse event raised concerns regarding a possible causal association between the lentiviral vector or other aspects related to the therapy and the event. In addition, two other patients who were administered bb1111 developed another type of blood disorder entitled myelodysplastic syndrome which progressed to leukaemia in one of them. Therefore, it was considered necessary to review all available data to investigate the potential causal relationship between the use of the lentiviral vector of bb1111 and Zynteglo (betibeglogene autotemcel) and the occurrence of clonal disorders, other aspects related to the therapy and the potential impact for patients receiving Zynteglo (betibeglogene autotemcel).

As a consequence, the EC requested EMA to assess the above concerns and their impact on the benefit risk balance for Zynteglo (betibeglogene autotemcel) and to give its opinion whether the marketing authorisation(s) for this medicinal product should be maintained, varied, suspended or revoked. In addition, the EC requested EMA to give its opinion as to whether provisional measures were necessary to ensure the safe and effective use of the medicinal product.

¹ Advanced therapy medicinal product

² Cluster of differentiation

Discussion

The PRAC noted the notification letter from the EC.

The PRAC appointed Brigitte Keller-Stanislawski as Rapporteur and Menno van der Elst as Co-Rapporteur for the procedure.

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

Summary of recommendation(s)/conclusions

- The Committee adopted a LoQ ([EMA/PRAC/104560/2021](#)) to the MAH and a timetable for the procedure ([EMA/PRAC/104559/2021](#)).
- The PRAC also discussed the option to conduct a public hearing in the context of the current procedure according to the pre-defined criteria set out in the rules of procedure³ ([EMA/363479/2015](#)). It was agreed by the Committee that at this stage of the procedure, in light of the currently available data and the need to determine the suitable approach to stakeholder engagement, a public hearing would not be appropriate. The PRAC can come back to reconsider this at a later stage of the procedure as needed.

See EMA press release ([EMA/127031/2021](#)) entitled 'Review of thalassaemia medicine Zynteglo started'.

3.2. Ongoing procedures

None

3.3. Procedures for finalisation

3.3.1. Ifosfamide⁴ (NAP) - EMEA/H/A-31/1495

Applicant(s): various

PRAC Rapporteur: Martin Huber; PRAC Co-rapporteur: Nikica Mirošević Skvrce

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

Background

A referral procedure under Article 31 of Directive 2001/83/EC for the review of the risk of encephalopathy associated to ifosfamide-containing solutions is to be concluded.

This review was initiated following two epidemiological studies suggesting an increased risk of ifosfamide-induced encephalopathy (IIE) with Ifosfamide EG solution for infusion (ifosfamide) compared with ifosfamide powder for solution. A final assessment of the data submitted was produced by the Rapporteurs according to the agreed timetable. For further background, see [PRAC minutes March 2020](#), [PRAC minutes July 2020](#) and [PRAC minutes November 2020](#)⁵.

³ Rules of procedure on the organisation and conduct of public hearings at the PRAC

⁴ Solution, concentrate for solution

⁵ Held 26-29 October 2020

Discussion

The PRAC discussed the conclusions reached by the Rapporteurs.

The PRAC reviewed the totality of data made available to the Committee on ifosfamide-containing solutions and the risk of encephalopathy, including data provided by the MAH(s) both in writing and in an oral explanation as well data available in EudraVigilance, in the literature, and from studies performed in France to investigate this matter.

Whilst some retrospective studies suggest an increased risk for encephalopathies in patients treated with ifosfamide-containing solutions compared to the powder formulation, the PRAC considered that such increased risk with the solution formulations could neither be confirmed nor excluded. The PRAC further considered that in order for the known risk of IIE to be appropriately minimised, existing warnings should be revised to take into account the latest available information with regards to the characteristics, associated risk factors and possible treatment, as well as the need for patients to be closely monitored. In view of the observed out-of-specification results in so-called worst-case studies, the PRAC recommended as a condition to the marketing authorisation(s) that the MAH(s) shall perform in-use stability studies and submit the results to the relevant National Competent Authorities (NCAs) of the Member State(s) for assessment within an agreed timeframe.

As a consequence, the PRAC considered that the benefit-risk balance of ifosfamide-containing solutions remains favourable subject to the agreed condition to the marketing authorisation(s) and to the agreed amendments to the product information.

Summary of recommendation(s)/conclusions

- The PRAC adopted, by majority, a recommendation to vary⁶ the terms of the marketing authorisation(s) for ifosfamide-containing medicinal product(s) authorised as solution for infusion and concentrate for solution for infusion and adopted a recommendation to be considered by CMDh for a position – see EMA Press Release entitled 'Benefits of ifosfamide solutions continue to outweigh risks' ([EMA/140127/2021](#)).

Thirty-one members voted in favour of the recommendation whilst one member⁷ had a divergent view. The Icelandic and Norwegian PRAC members agreed with the recommendation.

Post-meeting note 1: the press release 'Benefits of ifosfamide solutions continue to outweigh risk' representing the CMDh position ([EMA/219444/2021](#)) was published on the EMA website on 23 April 2021.

Post-meeting note 2: the PRAC assessment report ([EMA/159195/2021](#)) was published on 29 June 2021.

3.4. Re-examination procedures⁸

None

3.5. Others

None

⁶ Update of SmPC section 4.4. The package leaflet is updated accordingly

⁷ Adrien Inoubli

⁸ Re-examination of PRAC recommendation under Article 32 of Directive 2001/83/EC

4. Signals assessment and prioritisation⁹

4.1. New signals detected from EU spontaneous reporting systems

See also Annex I 14.1.

4.1.1. Coronavirus (COVID-19) mRNA¹⁰ vaccine (nucleoside-modified) - COMIRNATY (CAP)

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Signal of localised swelling in persons with history of dermal filler injections

EPITT 19674 – New signal

Lead Member State(s): NL

Background

Coronavirus (COVID-19) mRNA¹¹ vaccine is a nucleoside-modified messenger RNA vaccine formulated in lipid nanoparticles which enable delivery of the non-replicating RNA into host cells to direct transient expression of the SARS-CoV-2 S antigen. It is indicated, as Comirnaty, a centrally authorised vaccine, for active immunisation to prevent coronavirus-19 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus in individuals 16 years of age and older.

Based on a case of skin reactions related to the use of dermal fillers reported in Norway, EMA performed further analysis in EudraVigilance and a signal of localised swelling in persons with history of dermal filler injections was identified. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

Having considered the available evidence from case reports in EudraVigilance, PRAC agreed that despite the limited number of cases and sometimes scarce information, a causal relationship between the reaction and Comirnaty (COVID-19 mRNA vaccine) is plausible based on the reported time to onset (TTO) of the reported cases and taking into account the current labeling for another COVID-19 mRNA vaccine. The 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 the signal, including an analysis based on spontaneous reports studies and the literature. The MAH should make a proposal to update the product information/RMP as warranted.

⁹ 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

¹⁰ Messenger ribonucleic acid

¹¹ Messenger ribonucleic acid

- A 30-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.1.2. Coronavirus (COVID-19) mRNA¹² vaccine (nucleoside-modified) - COMIRNATY (CAP)

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Signal of immune thrombocytopenia

EPITT 19680 – New signal

Lead Member State(s): NL

Background

Coronavirus (COVID-19) mRNA¹³ vaccine is a nucleoside-modified messenger RNA vaccine formulated in lipid nanoparticles which enable delivery of the non-replicating RNA into host cells to direct transient expression of the SARS-CoV-2 S antigen. It is indicated, as Comirnaty a centrally authorised vaccine, for active immunisation to prevent coronavirus-19 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus, in individuals 16 years of age and older.

During routine signal detection activities, a signal of immune thrombocytopenia (ITP) was identified by EMA, based on 63 cases retrieved from EudraVigilance. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the available evidence from case reports in EudraVigilance. Taking into account the conclusions from the evaluation of the second monthly summary safety review (MSSR) adopted in February 2021 (MEA 002.1), the PRAC confirmed the signal required further investigation. For background, see [PRAC minutes February 2021](#).

Summary of recommendation(s)

- In the next MSSR¹⁴, the MAH for Comirnaty (COVID-19 mRNA vaccine (nucleoside-modified)) should provide a cumulative review of cases of ITP and related terms, including spontaneous case reports, literature and clinical trials data. The MAH should include a discussion on the possible biological mechanism together with a proposal to update the product information and/or RMP as warranted.
- In the following MSSR¹⁵, the MAH for Comirnaty (COVID-19 mRNA vaccine) should provide a cumulative review of cases of embolic and thrombotic events, including all available data from spontaneous cases, clinical trials and literature. The MAH should include a discussion on the possible biological mechanism together with a proposal to update the product information and/or RMP as warranted.

¹² Messenger ribonucleic acid

¹³ Messenger ribonucleic acid

¹⁴ Third MSSR due for submission on 15 March 2021

¹⁵ Fourth MSSR due for submission on 15 April 2021

4.1.3. Coronavirus (COVID-19) vaccine (ChAdOx1-S [recombinant]) - COVID-19 VACCINE ASTRAZENECA (CAP)

Applicant: AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: Signal of anaphylactic reaction

EPITT 19668 – New signal

Lead Member State(s): BE

Background

Coronavirus (COVID-19) (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 COVID-19 Vaccine AstraZeneca, a centrally authorised vaccine, for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in individuals 18 years of age and older.

During routine signal detection activities, a signal of anaphylactic reaction and anaphylactic shock was identified by EMA, based on 41 cases retrieved from EudraVigilance. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

Having considered the case reports in EudraVigilance, PRAC agreed that there is sufficient evidence that anaphylaxis and other types of hypersensitivity reactions may occur following administration of COVID-19 Vaccine AstraZeneca (COVID-19 vaccine (ChAdOx1-S [recombinant])). Therefore, PRAC recommended that anaphylaxis is added to the product information as a warning and anaphylaxis/hypersensitivity as undesirable effects with a 'frequency not known'.

Summary of recommendation(s)

- The MAH for COVID-19 Vaccine AstraZeneca (COVID-19 vaccine (ChAdOx1-S [recombinant])) should submit to EMA, within 30 days, a variation to amend¹⁶ the product information.
- The MAH should submit to EMA, within 15 days, a thorough analysis of cases of hypersensitivity.

For the full PRAC recommendation, see [EMA/PRAC/146285/2021](#) published on 06 April 2021 on the EMA website.

4.1.4. Coronavirus (COVID-19) vaccine (ChAdOx1-S [recombinant]) - COVID-19 VACCINE ASTRAZENECA (CAP)

Applicant: AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: Signal of immune thrombocytopenia

¹⁶ Update of SmPC sections 4.4 and 4.8. The package leaflet is to be updated accordingly

EPITT 19678 – New signal

Lead Member State(s): BE

Background

Coronavirus (COVID-19) (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 COVID-19 Vaccine AstraZeneca a centrally authorised vaccine, for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in individuals 18 years of age and older.

During routine signal detection activities, a signal of immune thrombocytopenia (ITP) was identified by EMA, based on 19 cases retrieved from EudraVigilance. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

Having considered the available evidence from case reports in EudraVigilance and the literature, and considering a possible immune related mechanism, PRAC agreed that further evaluation of the signal was warranted.

Summary of recommendation(s)

- The MAH for COVID-19 Vaccine AstraZeneca (COVID-19 vaccine (ChAdOx1-S [recombinant])) should submit to EMA, within 15 days, a cumulative review of cases of ITP and related terms, including spontaneous case reports, literature and clinical trials data. The MAH should include a discussion on the possible biological mechanism and an observed/expected analysis. The MAH should also make a proposal to update the product information and/or RMP as warranted.
- A 30-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.1.5. Coronavirus (COVID-19) vaccine (ChAdOx1-S [recombinant]) - COVID-19 VACCINE ASTRAZENECA (CAP)

Applicant: AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: Signal of embolic and thrombotic events

EPITT 19683 – New signal

Lead Member State(s): BE

Background

Coronavirus (COVID-19) (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 COVID-19 Vaccine AstraZeneca, a centrally authorised vaccine, for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in individuals 18 years of age and older.

A signal of embolic and thrombotic events was identified by EMA, based on 269 cases retrieved from EudraVigilance. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

At an extraordinary meeting convened remotely on 18 March 2021, the PRAC reviewed the signal. The PRAC is responsible for adopting a recommendation.

Discussion

The PRAC reviewed the available evidence on the occurrence of thromboembolic events following administration of COVID-19 Vaccine AstraZeneca (COVID-19 vaccine (ChAdOx1-S [recombinant])) using a wide range of sources including spontaneous case reports in EudraVigilance, quality/clinical/pre-clinical and literature data as well as additional data provided by the MAH both in writing and in an oral explanation. The PRAC also explored possible pathophysiological explanations for the observed cases. The PRAC concluded that there may be a risk of rare thrombotic events accompanied by thrombocytopenia following receipt of COVID-19 Vaccine AstraZeneca (COVID-19 vaccine (ChAdOx1-S [recombinant])) that needs to be reflected in the product information, while further evidence is being collected.

The PRAC recommended, by majority, that the product information is amended to add thrombocytopenia and coagulation disorders as a warning.

Thirty-two members voted in favour of the recommendation whilst one member¹⁷ had a divergent view. The Icelandic member agreed with the recommendation while the Norwegian member had a divergent view.

Summary of recommendation(s)

- The MAH for COVID-19 Vaccine AstraZeneca (COVID-19 vaccine (ChAdOx1-S [recombinant])) should submit to EMA, within 1 day, a variation to amend¹⁸ the product information.
- The PRAC agreed on the content of a direct healthcare professional communication ([DHPC](#)) along with a communication plan for its distribution.
- The PRAC agreed on the need to convene an ad-hoc expert group (AHEG) meeting to further discuss possible hypotheses, pathophysiological mechanisms and possible underlying risk factors.

See EMA Press Release entitled '[COVID-19 Vaccine AstraZeneca: benefits still outweigh the risks despite possible link to rare blood clots with low blood platelets](#)'.

For the full PRAC recommendation, see [EMA/PRAC/146285/2021](#) published on 06 April 2021 on the EMA website.

Post-meeting note: On 24 March 2021, PRAC adopted by written procedure the list of questions (LoQ) for the AHEG meeting scheduled on 29 March 2021. On 28 March 2021, PRAC also adopted by written procedure the list of experts (LoE) for the meeting.

¹⁷ Milou-Daniel Drici

¹⁸ Update of SmPC section 4.4. The package leaflet is to be updated accordingly

4.1.6. Coronavirus (COVID-19) mRNA¹⁹ vaccine (nucleoside-modified) - COVID-19 VACCINE MODERNA (CAP)

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Hans Christian Siersted

Scope: Signal of immune thrombocytopenia

EPITT 19679 – New signal

Lead Member State(s): DK

Background

COVID-19 Vaccine Moderna contains mRNA encapsulated in lipid nanoparticles and is indicated, as COVID-19 Vaccine Moderna, for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older.

During routine signal detection activities, a signal of immune thrombocytopenia (ITP) was identified by EMA, based on 12 cases retrieved from EudraVigilance. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

Having considered the available evidence from case reports in EudraVigilance and the literature, and taking into account the plausible temporal relationship, PRAC agreed that further evaluation of the signal was warranted.

Summary of recommendation(s)

- The MAH for COVID-19 Vaccine Moderna (COVID-19) mRNA vaccine (nucleoside-modified)) should submit to EMA, within 15 days, a cumulative review of cases of ITP and related terms, including spontaneous case reports, literature and clinical trials data. The MAH should include a discussion on the possible biological mechanism and an observed/expected analysis. The MAH should also make a proposal to update the product information and/or RMP as warranted.
- A 30-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.
- In the third MSSR²⁰, the MAH for COVID-19 Vaccine Moderna ((COVID-19) mRNA vaccine (nucleoside-modified)) should provide a cumulative review of cases of embolic and thrombotic events, including all available data from spontaneous cases, clinical trials and literature. The MAH should include a discussion on the possible biological mechanism together with a proposal to update the product information and/or RMP as warranted.

4.2. New signals detected from other sources

4.2.1. Tofacitinib – XELJANZ (CAP)

Applicant(s): Pfizer Europe MA EEIG

¹⁹ Messenger ribonucleic acid

²⁰ Third MSSR due for submission on 15 April 2021

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Signal of major adverse cardiovascular events (MACE) and malignancies excluding non-melanoma skin cancer (NMSC) from a clinical trial²¹

EPITT 19673 – New signal

Lead Member State(s): NL

Background

Tofacitinib is a potent selective Janus kinase (JAK) inhibitor. Xeljanz (tofacitinib) is a centrally authorised product indicated, in combination with methotrexate (MTX), for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying antirheumatic drugs and as monotherapy in case of intolerance to MTX or when treatment with MTX is inappropriate. It is also indicated in combination with MTX for the treatment of active psoriatic arthritis (PsA) in adult patients who have had an inadequate response or who have been intolerant to a prior disease-modifying antirheumatic drug (DMARD) therapy. As monotherapy, Xeljanz (tofacitinib) is indicated for 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.

The exposure for Xeljanz (tofacitinib) is estimated to have been more than 391,640 patient-years worldwide, in the period from first authorisation in 2012 to 2020.

Following the preliminary review of the results²² of post-authorisation safety study A3921133, signals of major adverse cardiovascular events (MACE) and malignancies excluding non-melanoma skin cancer (NMSC) was identified by the MAH and an emerging safety issue (ESI) notification was submitted to EMA. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the preliminary data from the completed post-authorisation safety study with tofacitinib and available evidence to date on cases of MACE and malignancies excluding NMSC. The PRAC agreed that further analyses for the risks of myocardial infarction (MI) and malignancies with tofacitinib is necessary before a final recommendation can be made. Therefore, PRAC adopted a list of questions (LoQ) to the MAH and agreed on the need to communicate to healthcare professionals (HCP) while the evaluation continues.

Summary of recommendation(s)

- The PRAC agreed on the content of the direct healthcare professional communication ([DHPC](#)) along with a communication plan for its distribution.
- The MAH for Xeljanz (tofacitinib) should submit to EMA, within 30 days, a response to LoQ.
- A 60-day timetable was recommended for the assessment of the response leading to a further PRAC recommendation.

²¹ Study A3921133: a phase 3b/4 randomised safety endpoint study of 2 doses of tofacitinib in comparison to a tumour necrosis fibrosis (TNF) inhibitor in subjects with rheumatoid arthritis

²² Final study report planned submission in August 2021

4.3. Signals follow-up and prioritisation

4.3.1. Anakinra - KINERET (CAP) - EMEA/H/C/000363/SDA/032.1; canakinumab - ILARIS (CAP) - EMEA/H/C/001109/SDA/054.1

Applicant(s): Novartis Europharm Limited (Ilaris), Swedish Orphan Biovitrum AB (publ) (Kineret)

PRAC Rapporteur: Anette Kirstine Stark

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

EPITT 19566 – Follow-up to November 2020

Background

For background information, see PRAC minutes of [PRAC minutes November 2020](#)²³.

The MAHs for Kineret (anakinra) and Ilaris (canakinumab) replied to the request for information on the signal of drug reaction with eosinophilia and systemic symptoms (DRESS). The authors of the publication *Saper et al.* 2019²⁴ also provided further evidence. The responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence from EudraVigilance, literature, the responses from the authors of the publication *Saper et al.* 2019 and the cumulative reviews provided by the MAHs, PRAC agreed that the potential association between the use of interleukin-1 (IL-1) inhibitors and DRESS cannot be excluded. In view of the uncertainties, rarity and severity of DRESS including potentially fatal outcomes, particularly in the paediatric population with systemic juvenile idiopathic arthritis (sJIA), PRAC concluded that an update of the product information is warranted to add DRESS as a warning.

Summary of recommendation(s)

- The MAHs for Kineret (anakinra) and Ilaris (canakinumab) should submit to EMA, within 90 days, a variation to amend²⁵ the product information.

For the full PRAC recommendation, see [EMA/PRAC/146285/2021](#) published on 06 April 2021 on the EMA website.

4.3.2. Efavirenz - SUSTIVA (CAP) - EMEA/H/C/000249/SDA/084; STOCRIN (CAP) - EMEA/H/C/000250/SDA/073; NAP

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

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Signal of microcephaly

EPITT 19595 – Follow-up to October 2020

²³ Held 26-29 October 2020

²⁴ Saper VE, Chen G, Deutsch GH, et al. Emergent high fatality lung disease in systemic juvenile arthritis. *Ann Rheum Dis.* 2019;78(12):1722-1731

²⁵ Update of SmPC section 4.4. The package leaflet is to be updated accordingly

Background

For background information, see PRAC minutes of [PRAC minutes October 2020](#)²⁶.

The MAHs for Sustiva and Stocrin (efavirenz) replied to the request for information on the signal of microcephaly and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence, including the data provided by the MAHs, the PRAC agreed that there is insufficient evidence at this stage to confirm a causal association between in utero exposure to efavirenz and the occurrence of microcephaly, neurologic or neurodevelopmental disorders.

Summary of recommendation(s)

- The MAHs for Sustiva and Stocrin (efavirenz) should continue to monitor the events of microcephaly, neurologic and neurodevelopmental disorders as part of routine safety surveillance.

4.3.3. [Trastuzumab emtansine - KADCYLA \(CAP\) - EMEA/H/C/002389/SDA/022](#)

Applicant: Roche Registration GmbH

PRAC Rapporteur: Anette Kirstine Stark

Scope: Signal of extravasation and epidermal necrosis

EPITT 19611 – Follow-up to November 2020

Background

For background information, see [PRAC minutes November 2020](#)²⁷.

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

Discussion

Having considered the available evidence, including the data provided by the MAH as well as published literature, spontaneous reports and data from clinical trials, the PRAC considered that there is sufficient evidence for a causal relationship between trastuzumab emtansine and extravasation with epidermal necrosis and trastuzumab emtansine. Therefore, PRAC agreed that an update of the product information is warranted to add epidermal necrosis following extravasation as a warning and as an undesirable effect.

Summary of recommendation(s)

- The MAH for Kadcyla (trastuzumab emtansine) should submit to EMA, within 60 days, a variation to amend²⁸ the product information.

For the full PRAC recommendation, see [EMA/PRAC/146285/2021](#) published on 06 April 2021 on the EMA website.

²⁶ Held 28 September – 01 October 2020

²⁷ Held 26-29 October 2020

²⁸ Update of SmPC sections 4.2, 4.4 and 4.8. The package leaflet is to be updated accordingly

4.4. Variation procedure(s) resulting from signal evaluation

None

5. Risk management plans (RMPs)

5.1. Medicines in the pre-authorisation phase

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

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

See also Annex I 15.1.

5.1.1. Coronavirus (COVID-19) vaccine (Ad26.COV2-S, recombinant) - EMEA/H/C/005737

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

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

5.1.2. Eflornithine, sulindac - EMEA/H/C/005043, Orphan

Applicant: Cancer Prevention Pharma (Ireland) Limited

Scope: Treatment of adults patients with familial adenomatous polyposis (FAP)

5.1.3. Obeticholic acid - EMEA/H/C/005249

Scope: Improvement of liver fibrosis and resolution of steatohepatitis in adult patients with significant liver fibrosis due to non-alcoholic steatohepatitis (NASH)

5.1.4. Vericiguat - EMEA/H/C/005319

Scope: Treatment of symptomatic chronic heart failure

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. 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 and 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, as Noxafil, for the treatment of several fungal infections in adults such as invasive aspergillosis, fusariosis, chromoblastomycosis and mycetoma, coccidioidomycosis oropharyngeal candidiasis and chromoblastomycosis, under specific conditions. It is also indicated for prophylaxis of invasive fungal infections under specific conditions.

The CHMP is evaluating a grouped application for Noxafil, a centrally authorised product containing posaconazole, consisting of an extension application to introduce a new pharmaceutical form and of an extension of indication to the paediatric population. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this variation.

Summary of advice

- The RMP for Noxafil (posaconazole) in the context of the procedure under evaluation by the CHMP could be considered acceptable provided that an update to RMP version 17.1 is submitted.
- The MAH should add 'medication errors related to substitution between different formulations (oral suspension and powder for oral suspension)' as an important potential risk to the list of safety concerns. In addition, the MAH should amend the existing risk minimisation measures in accordance with this safety concern. Finally, the MAH should propose a direct healthcare professional communication (DHPC) for review by the PRAC in order to inform healthcare professionals about the new pharmaceutical form and the associated risk of medication error with existing form(s).

6. Periodic safety update reports (PSURs)

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

See also Annex I 16.1.

6.1.1. Baricitinib - OLUMIANT (CAP) - PSUSA/00010578/202008

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

Background

Baricitinib is a Janus kinase (JAK)1 and JAK2 inhibitor indicated, as Olumiant, in monotherapy or in combination with methotrexate for the treatment of moderate to severe active rheumatoid arthritis in adult patients who have responded inadequately to, or who are

intolerant to one or more disease-modifying anti-rheumatic drugs. It is also indicated for the treatment of moderate to severe atopic dermatitis in adult patients who are candidates for systemic therapy.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Olumiant (baricitinib) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAH should provide data on a potential increase of immunosuppression-related serious infections, opportunistic infections and varicella-zoster infections following the use of baricitinib in combination with synthetic glucocorticoids (sGCS) in the atopic dermatitis indication. Also, the MAH should provide an updated analysis of immunosuppression-related serious infections, opportunistic infections and varicella-zoster infections following the use of baricitinib in combination with other immunosuppressive drugs, especially leflunomide and synthetic glucocorticoids (sGCS) in the rheumatoid arthritis indication. In addition, the MAH should provide a cumulative review of cases of hypoglycaemia and discuss whether an update of product information is warranted.

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

6.1.2. Cobicistat, elvitegravir, emtricitabine, tenofovir disoproxil - STRIBILD (CAP) - PSUSA/00010082/202008

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

Background

Cobicistat is a mechanism-based inhibitor of cytochrome P450 of the CYP3A²⁹ subfamily, elvitegravir a human immunodeficiency virus-1 (HIV-1) integrase strand transfer inhibitor (INSTI), emtricitabine a nucleoside analogue of cytidine and tenofovir a nucleoside monophosphate (nucleotide) analogue of adenosine monophosphate. In combination, it is indicated, as Stribild, for the treatment of HIV-1 infection in adults aged 18 years and over who are antiretroviral treatment-naïve or are infected with HIV-1 without known mutations associated with resistance to any of the antiretroviral agents. It is also indicated for the treatment of HIV-1 infection in adolescents aged 12 to < 18 years weighing ≥ 35 kg who are infected with HIV-1 without known mutations associated with resistance to any of the three antiretroviral agents in Stribild (cobicistat/elvitegravir/emtricitabine/tenofovir disoproxil) and who have experienced toxicities which preclude the use of other regimens that do not contain tenofovir disoproxil fumarate.

²⁹ Cytochrome P450 3A4

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Stribild, a centrally authorised medicine containing cobicistat/elvitegravir/emtricitabine/tenofovir disoproxil, 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 Stribild (cobicistat/elvitegravir/emtricitabine/tenofovir disoproxil) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the existing warning on bone effects associated with tenofovir disoproxil in light of the current knowledge. Therefore, the current terms of the marketing authorisation(s) should be varied³⁰.
- In the next PSUR, the MAH should continue to monitor cases of chronic progressive external ophthalmoplegia (CPEO) and discuss whether there is an increase of the incidence of this condition in neonates.

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

6.1.3. Natalizumab - TYSABRI (CAP) - PSUSA/00002127/202008

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

Background

Natalizumab is a humanised monoclonal antibody that binds to the $\alpha 4$ chain of the $\alpha 4\beta 1$ and $\alpha 4\beta 7$ integrins. It is indicated, as Tysabri, as single disease modifying therapy (DMT) in adults with highly active relapsing remitting multiple sclerosis (RRMS) in patients with highly active disease despite a full and adequate course of treatment with at least one DMT and patients with rapidly evolving severe relapsing remitting multiple sclerosis defined by 2 or more disabling relapses in one year, and with 1 or more gadolinium enhancing lesions on brain magnetic resonance imaging (MRI) or a significant increase in T2 lesion load as compared to a previous recent MRI.

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

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

- Nevertheless, the product information should be updated to add thrombocytopenia and as undesirable effects with a frequency 'uncommon' and thrombocytopenia including ITP immune thrombocytopenic purpura (ITP) as a warning. 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.

6.1.4. Palbociclib - IBRANCE (CAP) - PSUSA/00010544/202008

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

Background

Palbociclib is an inhibitor of cyclin-dependent kinases (CDK) 4 and 6. It is indicated, as Ibrance, for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer in combination with an aromatase inhibitor or in combination with fulvestrant in women who have received prior endocrine therapy under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Ibrance, a centrally authorised medicine containing palbociclib, 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 Ibrance (palbociclib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add cutaneous lupus erythematosus as an undesirable effect with a frequency 'uncommon'. Therefore, the current terms of the marketing authorisation(s) should be varied³².
- In the next PSUR, the MAH should provide an updated cumulative review of cases of severe cutaneous adverse reactions (SCARs), particularly Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) from clinical trials, post-marketing reports and literature. In addition, the MAH should provide cumulative reviews of cases of autoimmune diseases, including cases of lupus and immunological thrombocytopenic purpura, of cases reporting renal effects and of cases reporting a potential association between palbociclib and a risk of radiation injuries from clinical trials, post-marketing reports and literature. Moreover, the MAH should provide a cumulative review of cases of secondary primary malignancies, including haematological effects other than myelosuppression. For all these reviews, the MAH should discuss whether a need to update the product information and/or RMP is warranted. Finally, the MAH should discuss non-clinical data and any other information regarding the carcinogenic potential

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

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

of palbociclib and should also provide a discussion on the class effect of CDK4/6 inhibitors and mechanisms of action that could be involved in a tumorigenic potential.

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

6.1.5. [Sacubitril, valsartan - ENTRESTO \(CAP\); NEPARVIS \(CAP\) - PSUSA/00010438/202007](#)

Applicant(s): Novartis Europharm Limited

PRAC Rapporteur: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

Background

Sacubitril is a neprilysin inhibitor prodrug and valsartan is an angiotensin receptor antagonist. In combination, sacubitril/valsartan is indicated, as Entresto and Neparvis, for the treatment of symptomatic chronic heart failure with reduced ejection fraction in adult patients.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Entresto and Neparvis, centrally authorised medicines containing sacubitril/valsartan, 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 Entresto and Neparvis (sacubitril/valsartan) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add psychiatric disorders as a warning, hallucinations and sleep disorders as undesirable effects with a frequency 'rare' and paranoia with a frequency 'very rare'. In addition, the product information should be updated to add information on the correct administration of the medicine, with a recommendation not to split or crush tablets as well as to amend the existing information on toxicity relating to drug-drug interaction with lithium. Therefore, the current terms of the marketing authorisation(s) should be varied³³.

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

6.1.6. [Sitagliptin - JANUVIA \(CAP\); RISTABEN \(CAP\); TESAVEL \(CAP\); XELEVIA \(CAP\); sitagliptin, metformin hydrochloride - EFFICIB \(CAP\); JANUMET \(CAP\); RISTFOR \(CAP\); VELMETIA \(CAP\) - PSUSA/00010673/202008 \(with RMP\)](#)

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

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

³³ Update of SmPC sections 4.2, 4.4, 4.5 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

Background

Sitagliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor and metformin is a biguanide oral anti-diabetic. Januvia, Ristaben, Tesavel and Xelevia (sitagliptin) and Efficib, Janumet, Ristofofor and Velmetia (sitagliptin/metformin) are indicated for the treatment of adult patients with type 2 diabetes mellitus (T2DM) to improve glycaemic control subject to certain conditions.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of Januvia, Ristaben, Tesavel and Xelevia (sitagliptin) and Efficib, Janumet, Ristofofor and Velmetia (sitagliptin/metformin), centrally authorised medicines, 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 Januvia, Ristaben, Tesavel and Xelevia (sitagliptin) and Efficib, Janumet, Ristofofor and Velmetia (sitagliptin/metformin) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- The MAH should submit to EMA, within 90 days, a detailed review of the risk of malignancies/neoplasms in particular of pancreatic carcinoma from clinical trials, literature and post-marketing data.

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

6.1.7. Upadacitinib - RINVOQ (CAP) - PSUSA/00010823/202008

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

Background

Upadacitinib is a Janus kinase (JAK)1-selective inhibitor indicated, as Rinvoq, for the treatment of moderate to severe active rheumatoid arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drugs (DMARDs) and for the treatment of active psoriatic arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more DMARDs, as monotherapy or in combination with methotrexate. It is also indicated for the treatment of active ankylosing spondylitis in adult patients who have responded inadequately to conventional therapy.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Rinvoq (upadacitinib) in the approved indication(s) remains unchanged.

- Nevertheless, the product information should be updated to amend the existing warning on viral reactivation to state that the risk of herpes zoster is higher in Japanese patients treated with upadacitinib. Therefore, the current terms of the marketing authorisation(s) should be varied³⁴.
- In the next PSUR, the MAH should provide cumulative reviews of cases of diverticulitis and of cases of hypersensitivity reactions, including literature and data from clinical trials. Also, the MAH should provide a comprehensive analysis of new cases of anaphylaxis and angioedema.

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

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

See also Annex I 16.2.

6.2.1. Buprenorphine³⁵ - BUVIDAL (CAP); NAP - PSUSA/00000459/202007

Applicants: Camurus AB (Buvidal), various

PRAC Rapporteur: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

Background

Buprenorphine is a partial agonist/antagonist of opioid μ -receptors indicated³⁶ for the treatment of opioid dependence within a framework of medical, social and psychological treatment, in adults and adolescents aged 16 years or over.

Based on the assessment of the PSURs, the PRAC reviewed the benefit-risk balance of Buvidal, a centrally authorised medicine containing buprenorphine, and nationally authorised medicines containing buprenorphine³⁷, 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 buprenorphine³⁸-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include sleep-related breathing disorders such as sleep apnoea and sleep related hypoxemia as a warning. In addition, the product information for medicinal products for transdermal use should be updated to add application site discolouration and dermatitis contact as undesirable

³⁴ Update of SmPC section 4.4. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

³⁵ All formulation(s) except implant(s)

³⁶ All formulation(s) except implant(s)

³⁷ All formulation(s) except implant(s)

³⁸ All formulation(s) except implant(s)

effects with a frequency 'not known'. Therefore, the current terms of the marketing authorisations should be varied³⁹.

- In the next PSUR, the MAHs should provide a comprehensive review of all current risk minimisation measures in the EU related to the risk of abuse/misuse/dependence/off-label use/accidental exposure and discuss the need to update the product information in order to enhance the warning on these risks. In addition, the MAHs should provide an analysis of cases of hyperaesthesia, including a literature review and a discussion on a possible mechanism of action together with the need to update the product information as warranted. Moreover, MAHs are requested to investigate the signal of limb malformation with data from the literature and cases reported during clinical trials and in post-marketing setting. Also, MAHs of medicinal products for subcutaneous use should closely monitor cases of skin reaction site such as hyper- and hypopigmentation, application site burn, application site ulcer and blister. A comprehensive analysis, including a discussion on a possible mechanism of action should be provided, as well as a discussion on the need to update the product information as warranted.

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

6.2.2. Ribavirin⁴⁰ - REBETOL (CAP); NAP - PSUSA/00010007/202007

Applicants: Merck Sharp & Dohme B.V. (Rebetol), various

PRAC Rapporteur: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

Background

Ribavirin is a synthetic nucleoside analogue indicated in combination for the treatment of chronic hepatitis C (CHC) in adults and paediatric patients, subject to certain conditions.

Based on the assessment of the PSURs, the PRAC reviewed the benefit-risk balance of Rebetol, a centrally authorised medicine containing ribavirin, and nationally authorised medicine(s) containing ribavirin⁴¹, 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 ribavirin⁴²-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a statement summarising the most common undesirable effects associated with ribavirin in combination with direct antiviral agents, along those associated with ribavirin and

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 the CHMP for adoption of an opinion

⁴⁰ Oral formulation(s) only

⁴¹ Oral formulation(s) only

⁴² Oral formulation(s) only

interferons. Therefore, the current terms of the marketing authorisations should be varied⁴³.

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.

Additionally, PRAC agreed that MAH(s) should be requested to amend their product information on the duration of contraception following the end of treatment with ribavirin, taking into account the Safety Working Party ([SWP](#)) response document dated February 2020 on questions from CMDh on 'recommendations on the duration of contraception following the end of treatment with a genotoxic drug'. Further consideration should be given at the level of CHMP and CMDh.

6.2.3. Temozolomide - TEMODAL (CAP); NAP - PSUSA/00002886/202007

Applicants: Merck Sharp & Dohme B.V. (Temodal), various

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Temozolomide is a triazene indicated for the treatment of adult patients with newly diagnosed glioblastoma multiforme concomitantly with radiotherapy (RT) and subsequently as monotherapy treatment. It is also indicated for the treatment of children from the age of three years, adolescents and adult patients with malignant glioma, such as glioblastoma multiforme or anaplastic astrocytoma, showing recurrence or progression after standard therapy.

Based on the assessment of the PSURs, the PRAC reviewed the benefit-risk balance of Temodal, a centrally authorised medicine containing temozolomide, and nationally authorised medicine(s) containing temozolomide, 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 temozolomide-containing medicinal product(s) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisations should be maintained.

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.

Additionally, PRAC agreed that the MAH for the originator product containing temozolomide should be requested to amend their product information on the duration of contraception following the end of treatment with temozolomide, taking into account the Safety Working Party ([SWP](#)) response document dated February 2020 on questions from CMDh on

⁴³ Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

'recommendations on the duration of contraception following the end of treatment with a genotoxic drug'. Further consideration should be given at the level of CHMP.

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

See also Annex I 16.3.

6.3.1. Cisatracurium (NAP) - PSUSA/00000777/202007

Applicant(s): various

PRAC Lead: Jana Lukacisinova

Scope: Evaluation of a PSUSA procedure

Background

Cisatracurium is a non-depolarising neuromuscular blocking agent (NMBA) for intravenous (IV) administration. It is indicated for use during surgical procedures and in intensive care, as an adjunct to general anaesthesia, or sedation in intensive care units (ICU), to relax skeletal muscles, and to facilitate tracheal intubation and mechanical ventilation.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing cisatracurium 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 cisatracurium-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to add anaphylactic shock as an undesirable effect with a frequency 'very rare'. In addition, the product information should be updated to amend information regarding the potential influence of cisatracurium on breastfed infants. Therefore, it is recommended to abstain from breastfeeding for five elimination half-lives.
- Therefore, the current terms of the marketing authorisation(s) should be varied⁴⁴.

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC. Submission of PSURs for products referred to in Articles 10(1), 10a, 14, 16a of Directive 2001/83/EC is not required any longer and the EURD list should be updated accordingly.

6.3.2. Ezetimibe, rosuvastatin (NAP) – PSUSA/00010271/202007

Applicant(s): various

PRAC Lead: Nikica Mirošević Skvrce

⁴⁴ Update of SmPC sections 4.6 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

Scope: Evaluation of a PSUSA procedure

Background

Ezetimibe is a lipid modifying agent and rosuvastatin is a selective, competitive inhibitor of 3-hydroxy 3-methylglutaryl coenzyme A (HMG-CoA) reductase. In combination, ezetimibe/rosuvastatin is indicated as a substitution for adjunctive therapy to diet and other non-pharmacological treatments (e.g. exercise, weight reduction) for use in adult patients with primary hypercholesterolaemia (heterozygous familial and non-familial) or homozygous familial hypercholesterolaemia, which are already treated and adequately controlled on the combination of ezetimibe and rosuvastatin. It is also indicated to reduce the risk of cardiovascular events as substitution therapy in patients with coronary heart disease (CHD) and a history of acute coronary syndrome (ACS), who are adequately controlled with the individual substances given concurrently at the same dose level as in the fixed dose combination, but as separate medicinal products.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing ezetimibe/rosuvastatin 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 ezetimibe/rosuvastatin-containing medicinal product(s) in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include drug reaction with eosinophilia and systemic symptoms (DRESS) as a warning and as an undesirable effect with a frequency 'not known'. Also, the product information should be updated to add information on the interaction between ticagrelor and rosuvastatin due to ticagrelor that can cause renal insufficiency. Therefore, the current terms of the marketing authorisation(s) should be varied⁴⁵.
- In the next PSUR, MAHs should perform a detailed review of cases of cataract and provide a causality assessment. In addition, MAHs should perform detailed reviews of cases of Merkel cell carcinoma and non-melanoma skin cancer as well as of cases of lichenoid eruptions and provide a detailed analysis. In addition, MAHs should provide detailed analysis of cases of myasthenia gravis and to add myasthenia gravis as a PSUR potential risk.

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

Additionally, PRAC agreed that the above updates of the product information are also relevant for medicinal products containing rosuvastatin alone or in fixed-dose combinations (others than ezetimibe) for DRESS. In addition, PRAC considered that the above update of the product information regarding rosuvastatin and ticagrelor is also relevant for ticagrelor-containing product(s). Further consideration should be given at the level of CMDh.

⁴⁵ Update of SmPC sections 4.4, 4.5 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

6.3.3. Fluocinolone acetonide⁴⁶ (NAP) - PSUSA/00010224/202008

Applicant(s): various

PRAC Lead: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Evaluation of a PSUSA procedure

Background

Fluocinolone acetonide is a fluorinated synthetic corticosteroid indicated, as intravitreal implant in applicator, for the treatment of vision impairment associated with chronic diabetic macular oedema considered insufficiently responsive and for the prevention of relapse in recurrent non-infectious uveitis affecting the posterior segment of the eye.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing fluocinolone acetonide⁴⁷ 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 fluocinolone acetonide⁴⁸-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the existing warning on device dislocation and to add corneal oedema as an undesirable effect associated to the device dislocation with a frequency 'uncommon'. Therefore, the current terms of the marketing authorisation(s) should be varied⁴⁹.
- In the next PSUR, the MAH(s) should provide a detailed review of cases of aphakic eyes with ruptured/torn posterior capsule and of pseudophakic eyes with anterior chamber lenses and ruptured/torn posterior capsule.

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. Fosphenytoin (NAP) - PSUSA/00001476/202008

Applicant(s): various

PRAC Lead: Ronan Grimes

Scope: Evaluation of a PSUSA procedure

Background

Fosphenytoin is a water-soluble prodrug formulation of phenytoin, an anticonvulsant. It is indicated in adults and children aged 5 years and older for the control of status epilepticus of tonic-clonic (grand mal) type, for the prevention and treatment of seizures occurring in

⁴⁶ Intravitreal implant(s) in applicator only

⁴⁷ Intravitreal implant(s) in applicator only

⁴⁸ Intravitreal implant(s) in applicator only

⁴⁹ Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

connection with neurosurgery and/or head trauma and as a substitute for oral phenytoin if oral administration is not possible and/or contraindicated.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing fosphenytoin 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 fosphenytoin-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning on the increased risk of severe cutaneous adverse reactions (SCARs) in carriers of the CYP2C9⁵⁰*3 allele and the risk of increased toxicity in intermediate or poor metabolisers of CYP2C9 substrates. Also, the product information should be updated to add urticaria as an undesirable effect with a frequency 'not known' and to add information regarding the interaction between fosphenytoin and tenofovir alafenamide and afatinib respectively. Therefore, the current terms of the marketing authorisation(s) should be varied⁵¹.
- In the next PSUR, the MAH Pfizer should provide a literature review of information regarding genetic factors, including human leukocyte antigens (HLA) and cytochrome polymorphisms which can influence the risk of SCARs and discuss whether an update of the product information is warranted. In addition, the MAH should provide a discussion on cases of medication errors including a root cause analysis and discuss whether there is a need to implement further risk minimisation measures.

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

6.3.5. Ibuprofen, levomenthol (NAP) - PSUSA/00001708/202007

Applicant(s): various

PRAC Lead: Jana Lukacisinova

Scope: Evaluation of a PSUSA procedure

Background

Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID) and levomenthol is an essential oil extract. Their combination is indicated in adults and adolescents for anti-inflammatory effect and local treatment of rheumatic pain, muscular pain, pain and swellings such as strains, sprains and sports injuries.

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

⁵⁰ Cytochrome P450 family 2 subfamily C member 9

⁵¹ Update of SmPC sections 4.4, 4.5 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of ibuprofen/levomenthol-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add photosensitivity reaction as undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied⁵².

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

6.3.6. Ifosfamide (NAP) - PSUSA/00001723/202007

Applicant(s): various

PRAC Lead: Annika Folin

Scope: Evaluation of a PSUSA procedure

Background

Ifosfamide is an alkylating agent indicated in the treatment of various malignancies in oncology and haematology for children and adults.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing ifosfamide 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 ifosfamide-containing medicinal product(s) in the approved indications remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained in the context of the current procedure. This recommendation is without prejudice to the final conclusions of the procedure (EMA/H/A-31/1495) assessed under Article 31 of Directive 2001/83/EC. See under 3.3.1.

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

6.3.7. Indometacin (NAP) - PSUSA/00001738/202007

Applicant(s): various

PRAC Lead: Eva Segovia

Scope: Evaluation of a PSUSA procedure

Background

⁵² Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

Indometacin is a non-steroidal anti-inflammatory drug (NSAID) indicated for symptomatic treatment of pain and inflammation accompanying acute arthritis, chronic arthritis, rheumatoid arthritis, ankylosing spondylitis, degenerative joint disease of the hip, acute musculoskeletal disorders and low back pain, as well as other inflammatory, rheumatoid conditions of the spine, irritative conditions arising from arthrosis and spondylarthrosis, inflammatory soft-tissue rheumatic diseases and painful swelling or inflammation due to injuries, periarticular disorders such as bursitis, tendinitis, synovitis, tenosynovitis and capsulitis, inflammation, pain and oedema following orthopaedic procedures. It is also indicated for oral use for the treatment of pain and associated symptoms of primary dysmenorrhoea. It is also indicated for topical use for external and symptomatic treatment of pain and swelling after blunt injuries, muscle tensions and lumbago as well as in inflammatory, soft-tissue rheumatism such as tendinitis and tendovaginitis in adults. As intravenous use, it is indicated for the symptomatic treatment of acute pain due to inflammatory conditions of the musculoskeletal apparatus. As ocular use, it is indicated for inhibition of miosis during surgical interventions, prevention of non-infectious inflammation linked to surgery for cataracts and of the anterior segment of the eye, post-operative treatment for eye pain during the first few days following photorefractive keratectomy and for the treatment of possibly painful inflammatory states, not on an infectious basis, affecting the anterior segment of the eye in particular for cataract surgery.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing indometacin 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 indometacin-containing medicinal product(s) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAHs of systemic formulations should provide a cumulative review of cases of haemorrhagic stroke, including literature and post marketing data and discuss whether an update of the product information is warranted.

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

6.3.8. Naftifine (NAP) - PSUSA/00002109/202008

Applicant(s): various

PRAC Lead: Maia Uusküla

Scope: Evaluation of a PSUSA procedure

Background

Naftifine is an allylamine derivative antifungal indicated in adult patients for the topical treatment of skin infections like mycoses of the skin or skin folds, interdigital mycoses or as a second line treatment for the treatment of cutaneous candidiasis.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing naftifine 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 naftifine-containing medicinal product(s) in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to add contact dermatitis and erythema as undesirable effects with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied⁵³.

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

6.3.9. Naproxen (NAP) - PSUSA/00002125/202008

Applicant(s): various

PRAC Lead: Ilaria Baldelli

Scope: Evaluation of a PSUSA procedure

Background

Naproxen is a propionic acid derivative and non-steroidal anti-inflammatory non-selective cyclooxygenase 1-2 (COX-1-2) inhibitor drug (NSAID) indicated for the symptomatic treatment of pain and inflammation of conditions that include rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, gouty arthropathy, and various forms of extra-articular rheumatism and in the treatment of painful events due to musculoskeletal disorders or surgery and dental surgery. It is also indicated in dysmenorrhea and migraine. In addition, it is indicated in the treatment of inflammatory syndromes of female genital tract and in the pre-and postoperative prophylaxis in gynaecological surgery. The gel formulation is in particular indicated for the treatment of myalgia, back pain, stiff neck, fibromyalgia, bursitis, tendonitis, tenosynovitis, peri-arthritis, bruises, muscle strains, sprains, bruises, swelling and infiltration traumatic phlebitis and as adjuvant for orthopaedic and rehabilitative therapies.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing naproxen 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 naproxen-containing medicinal product(s) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAHs should provide cumulative reviews of cases of low amniotic fluid levels or kidney problems following exposure during pregnancy, including literature

⁵³ Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

data and discuss whether an update of the product information is warranted. In addition, the MAHs for systemic use should provide cumulative reviews of cases of fixed drug eruption (FDE).

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

6.3.10. Oxymetazoline (NAP) - PSUSA/00002258/202008

Applicant(s): various

PRAC Lead: Maia Uusküla

Scope: Evaluation of a PSUSA procedure

Background

Oxymetazoline is an imidazole derivative and α -adrenergic agonist indicated for the topical symptomatic treatment of nasal or sinus congestion and for diagnostic purposes for reduction of mucosal oedema.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing oxymetazoline 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 oxymetazoline-containing medicinal product(s) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.

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

6.3.11. Quetiapine (NAP) - PSUSA/00002589/202007

Applicant(s): various

PRAC Lead: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

Background

Quetiapine is an atypical antipsychotic indicated for the treatment of schizophrenia, of moderate to severe manic episodes in bipolar disorder, of major depressive episodes in bipolar disorder and for the prevention of recurrence of manic or depressed episodes in patients with bipolar disorder who previously responded to quetiapine treatment. Prolonged release quetiapine-containing medicinal products are also indicated for add-on treatment of major depressive episodes in patients with major depressive disorder (MDD) who have had sub-optimal response to antidepressant monotherapy.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing quetiapine 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 quetiapine-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the existing warning on cardiomyopathy and myocarditis and to add cardiomyopathy and myocarditis as undesirable effects with a frequency 'not known'. In addition, the product information should be updated to add cutaneous vasculitis with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied⁵⁴.
- In the next PSUR, the MAH for the originator quetiapine-containing product should provide cumulative reviews of cases of pericarditis and of cases of serotonin syndrome, including data from EudraVigilance, literature and clinical trials and discuss the need for an update of the product information as warranted. The MAH should also provide a comprehensive analysis regarding abuse and misuse, including a discussion on the need to update the product information as warranted. Finally, the MAH should provide a detailed analysis regarding off-label use, including a literature review and discuss whether there are any new identified risk factors.

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

6.4. Follow-up to PSUR/PSUSA procedures

See Annex I 16.4.

6.5. Variation procedure(s) resulting from PSUSA evaluation

6.5.1. Coronavirus (COVID-19) mRNA⁵⁵ vaccine (nucleoside-modified) - COMIRNATY (CAP) - EMEA/H/C/005735/II/0016/G

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Grouped variation consisting of: 1) update of section 4.8 SmPC to add 'diarrhea' and 'vomiting' as adverse drug reactions (ADRs) with frequencies and update the ADR 'pain in extremity' in order to fulfil MEA 002.1 (monthly summary safety review (MSSR)) concluded in February 2021; 2) update of section 4.8 SmPC to update the ADR 'hypersensitivity reactions' in more detail with the relevant frequency categories in order to fulfil LEG 022.1. The package leaflet is updated accordingly. In addition, the MAH took the opportunity to perform editorial changes in section 6.6 of the SmPC

Background

⁵⁴ Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

⁵⁵ Messenger ribonucleic acid

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.

Following the evaluation of the most recently submitted monthly summary safety review (MSSR) for the above-mentioned medicine(s) (MEA 002.1) and of a review on anaphylaxis and hypersensitivity reactions (LEG 022), the PRAC requested the MAH to submit further analyses and proposals to update the product information. For background information, see [PRAC minutes February 2021](#). The PRAC is responsible for adopting an outcome based on the assessment report from the PRAC Rapporteur, to be further considered at the level of the CHMP, responsible for adopting an opinion on this variation. At the organisational, regulatory and methodological matters (ORGAM)⁵⁶ meeting on 25 March 2021, the PRAC adopted its conclusions.

Summary of advice/conclusion(s)

- Based on the available data and the Rapporteur's assessment, PRAC considered that the MAH should provide further clarifications before the procedure can be concluded. In particular, the MAH should propose relevant frequency(ies) for 'hypersensitivity reactions' as undesirable effects.

6.5.2. Pegfilgrastim - NEULASTA (CAP) - EMEA/H/C/000420/II/0114

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Update of section 6.6 of the SmPC in order to add a new warning that the medicine should be allowed to reach room temperature before use, based on cumulative reviews of post-marketing reports of medication errors with the on-body injector (OBI) following the conclusions of MEA 060.3 adopted in September 2020

Background

Pegfilgrastim is a covalent conjugate of recombinant human granulocyte colony-stimulating factor (G-CSF) indicated, as Neulasta, a centrally authorised product, for the reduction in the duration of neutropenia and the incidence of febrile neutropenia in adult patients treated with cytotoxic chemotherapy for malignancy under certain conditions.

Following the evaluation of the most recently submitted reviews of medication error events reported with the on-body injector (OBI) in the EU market for the above mentioned medicine(s), the MAH submitted a variation to update the product information in line with the conclusions of a post-authorisation measure (MEA 060.3) adopted in September 2020. For background, see [PRAC minutes September 2020](#).

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

Summary of advice/conclusion(s)

⁵⁶ Extended to specific COVID-19-related procedure(s) during EMA business continuity plan (BCP)

- Based on the available data and the Rapporteur's assessment, the PRAC agreed to amend⁵⁷ the product information to add a new warning to ensure the medicine reaches room temperature before use to avoid medication errors with the OBI.

6.6. Expedited summary safety reviews⁵⁸

6.6.1. Coronavirus (COVID-19) mRNA⁵⁹ vaccine (nucleoside-modified) - COMIRNATY (CAP) - EMEA/H/C/005735/MEA 002.2

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Third 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.

The PRAC assessed the third monthly summary safety report (MSSR) for Comirnaty ((COVID-19) mRNA vaccine (nucleoside-modified)) as part of the safety monitoring of the vaccine. At the organisational, regulatory and methodological matters (ORGAM)⁶⁰ meeting on 25 March 2021, the PRAC adopted its conclusions.

Summary of advice/conclusion(s)

- The PRAC agreed that the MAH should submit to EMA a variation to include extensive limb swelling as an undesirable effect. The MAH should propose a frequency category accordingly.
- In the next MSSR, the MAH should provide clarifications on the observed/expected analyses made in the context of the review of cases of 'embolic and thrombotic events' and 'thrombotic events with thrombocytopenia'. The MAH should also discuss the findings of the study by *Krammer et al*⁶¹ on reactogenicity in seropositive individuals. In addition, the MAH should provide a cumulative review of cases of anosmia/ageusia.

6.6.2. Coronavirus (COVID-19) mRNA⁶² vaccine (nucleoside-modified) BNT162b1 - COMIRNATY (CAP) - EMEA/H/C/005735/LEG 022.1

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to LEG 022 [cumulative analysis of all cases reporting anaphylaxis after vaccination with Comirnaty ((COVID-19) mRNA vaccine (nucleoside-modified)) as

⁵⁷ Update of SmPC section 6.6

⁵⁸ 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

⁵⁹ Messenger ribonucleic acid

⁶⁰ Extended to specific COVID-19-related procedure(s) during EMA business continuity plan (BCP)

⁶¹ Robust spike antibody responses and increased reactogenicity in seropositive individuals after a single dose of SARS-CoV-2 mRNA vaccine. February 2021. medRxiv 2021.01.29.21250653; <https://doi.org/10.1101/2021.01.29.21250653>

⁶² Messenger ribonucleic acid

requested in the conclusions of the first monthly summary safety report (MSSR) for Comirnaty (COVID-19 mRNA vaccine (nucleoside-modified)) adopted in January 2021] as per the request for supplementary information (RSI) adopted in February 2021

Background

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

The PRAC assessed a cumulative analysis of all cases reporting anaphylaxis after vaccination with Comirnaty ((COVID-19) mRNA vaccine (nucleoside-modified)) requested in the conclusions of the first monthly summary safety report (MSSR) and the MAH's responses to the request for supplementary information (RSI) adopted in February 2021. For further background, see [PRAC minutes January 2021](#) and [PRAC minutes February 2021](#). At the organisational, regulatory and methodological matters (ORGAM)⁶³ meeting on 25 March 2021, the PRAC adopted further conclusions.

Summary of advice/conclusion(s)

- The MAH should keep any new case reports of anaphylaxis under close monitoring. The MAH should consider amendments to the current observation period following administration as necessary depending of the reported cases.

6.6.3. Coronavirus (COVID-19) mRNA⁶⁴ vaccine (nucleoside-modified) - COVID-19 VACCINE MODERNA (CAP) - EMEA/H/C/005791/MEA 011.1

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Hans Christian Siersted

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

Background

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

The PRAC assessed the second monthly summary safety report (MSSR) for COVID-19 Vaccine Moderna (COVID-19 mRNA vaccine (nucleoside-modified)) as part of the safety monitoring of the vaccine. At the organisational, regulatory and methodological matters (ORGAM)⁶⁵ meeting on 25 March 2021, the PRAC adopted its conclusions.

Summary of advice/conclusion(s)

- In the next MSSR, the MAH should include cumulative reviews of cases of seizures, anosmia/ageusia and hypersomnia/narcolepsy. In addition, the MAH should provide a cumulative review of cases of thrombotic events with thrombocytopenia including an observed/expected analysis. Furthermore, the MAH should perform a thorough evaluation of cases of diarrhoea, provide updated reviews of cases of 'paraesthesia and

⁶³ Extended to specific COVID-19-related procedure(s) during EMA business continuity plan (BCP)

⁶⁴ Messenger ribonucleic acid

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

hypoesthesia' and of 'Guillain Barré syndrome and myelitis transverse' as well as a discussion in the context of cases of anaphylaxis on the need to update the product information regarding observation after vaccination. Finally, a clinical overview of the subset of delayed onset injection site reactions should be provided.

6.6.4. Coronavirus (COVID-19) vaccine (ChAdOx1-S [recombinant]) - COVID-19 VACCINE ASTRAZENECA (CAP) - EMEA/H/C/005675/MEA 027

Applicant: AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: First expedited monthly summary safety report for COVID-19 Vaccine AstraZeneca (COVID-19 vaccine vaccine (ChAdOx1-S [recombinant]))

Background

Coronavirus (COVID-19) (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 COVID-19 Vaccine AstraZeneca a centrally authorised vaccine, for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in individuals 18 years of age and older.

The PRAC assessed the first monthly summary safety report (MSSR) for COVID-19 Vaccine AstraZeneca (COVID-19 vaccine (ChAdOx1-S [recombinant])) as part of the safety monitoring of the vaccine. At the organisational, regulatory and methodological matters (ORGAM)⁶⁶ meeting on 25 March 2021, the PRAC adopted its conclusions.

Summary of advice/conclusion(s)

- In the next MSSR, the MAH should provide a cumulative review of serious cases of facial paralysis, hypoaesthesia, paraesthesia and tremor together a causality assessment. In addition, as vaccine use in frail patients with co-morbidities is an RMP missing information, the MAH should provide an analysis of related fatal cases.

7. Post-authorisation safety studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)⁶⁷

See also Annex I 17.1.

7.1.1. Betibeglogene autotemcel – ZYNTGLO (CAP) - EMEA/H/C/PSP/S/0090

Applicant: Bluebird bio (Netherlands) B.V., ATMP⁶⁸

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Protocol for study REG-504: a non-interventional post-authorisation safety and efficacy study to further characterise and contextualise the long-term safety and efficacy of Zynteglo (betibeglogene autotemcel) in patients aged 12 years and older with transfusion-

⁶⁶ Extended to specific COVID-19-related procedure(s) during EMA business continuity plan (BCP)

⁶⁷ In accordance with Article 107n of Directive 2001/83/EC

⁶⁸ Advanced therapy medicinal product

dependent β -thalassaemia (TDT) who do not have a $\beta 0 / \beta 0$ genotype

Background

Betibeglogene autotemcel is a genetically modified autologous CD⁶⁹34+ cell enriched population that contains haematopoietic stem cells (HSC) transduced with lentiviral vector (LVV) encoding the β^{A-T87Q} -globin gene. Zynteglo (betibeglogene autotemcel) is a centrally authorised advanced therapy medicinal product (ATMP) indicated for the treatment of patients 12 years and older with transfusion-dependent β -thalassaemia (TDT) who do not have a $\beta 0 / \beta 0$ genotype, for whom haematopoietic stem cell transplantation (HSCT) is appropriate but a human leukocyte antigen (HLA)-matched related HSC donor is not available.

In order to fulfil the specific obligation to conduct a PASS ([Annex II-D](#)) imposed in accordance with Article 107n(3) of Directive 2001/83/EC, the MAH Bluebird bio (Netherlands) B.V submitted to EMA a protocol version 1.0 for study REG-504 entitled: 'a non-interventional registry study of patients with β -thalassaemia to characterise and contextualise the safety and effectiveness of betibeglogene autotemcel' for review by the PRAC. The PRAC is responsible for evaluating the PASS protocol.

Endorsement/Refusal of the protocol

- The 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). The PRAC agreed that the PASS is non-interventional, but the study design does not fulfil the study objectives at this stage.
- The PRAC considered that the MAH should further outline the main aspects of the data management plan, provide additional information on details of quality control for the European Society for Blood and Marrow Transplantation (EBMT) cohort and information on alignment of quality processes for both cohorts. Moreover, the MAH should clarify with EBMT how long treatment centres provide information on average of their allo-HSCT patients.
- The MAH should submit a revised PASS protocol within 30 days to EMA. A 60 day-assessment timetable will be followed.

7.2. Protocols of PASS non-imposed in the marketing authorisation(s)⁷⁰

See also Annex I 17.2.

7.2.1. Coronavirus (COVID-19) mRNA⁷¹ vaccine (nucleoside-modified) - COMIRNATY (CAP) - EMA/H/C/005735/MEA 011

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Protocol for study C4591010: assessment of occurrence of safety events in real-world use of COVID-19 mRNA vaccine [final clinical study report (CSR) expected in March

⁶⁹ Cluster of differentiation

⁷⁰ 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

⁷¹ Messenger ribonucleic acid

2024] (from initial opinion/marketing authorisation)

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.

As stated in the [RMP](#) of Comirnaty (COVID-19 mRNA vaccine (nucleoside-modified)), the MAH is requested to conduct an assessment of occurrence of safety events in real-world use of COVID-19 mRNA vaccine. The MAH BioNTech Manufacturing GmbH submitted to EMA a protocol version 1.0 for study C4591010 entitled: 'a non-interventional PASS for active safety surveillance of recipients of the Pfizer-BioNTech COVID-19 mRNA vaccine in the EU' which was assessed by the Rapporteur. The PRAC was requested to provide advice to CHMP on the protocol submitted by the MAH.

Summary of advice

- Based on the review of protocol version 1.0 and the assessment from the Rapporteur, the PRAC considered the protocol for Comirnaty (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 update the proposed list of safety events of interest, provide clarification on vaccine reactogenicity between the first and second doses, amend the inclusion and exclusion criteria of the study and add participants' baseline and follow-up questionnaires and healthcare professionals' questionnaires to validate the occurrence of reported safety events.

7.2.2. [Coronavirus \(COVID-19\) mRNA⁷² vaccine \(nucleoside-modified\) - COVID-19 VACCINE MODERNA \(CAP\) - EMEA/H/C/005791/MEA 003](#)

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Hans Christian Siersted

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

Background

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

As stated in the [RMP](#) of COVID-19 Vaccine Moderna (COVID-19 mRNA vaccine (nucleoside-modified)), the MAH is requested to conduct a 'post-marketing safety of SARS-CoV-2 mRNA-1273 vaccine in the US as an active surveillance, signal refinement and self-controlled risk interval (SCRI) signal evaluation in HealthVerity database' which was assessed by the

⁷² Messenger ribonucleic acid

Rapporteur. The PRAC was requested to provide advice to CHMP on the protocol submitted by the MAH.

Summary of advice

- Based on the review of protocol version 1.2 and the assessment from the Rapporteur, the PRAC considered the protocol for COVID-19 Vaccine Moderna (COVID-19 mRNA vaccine (nucleoside-modified)) could be acceptable provided that the protocol is updated before the study starts.
- In particular, the MAH should elaborate on the rationale for estimating background incidence rates in two separated time periods. The MAH should also describe and justify the adverse event of special interest (AESI)-specific risk and control intervals utilised in the self-controlled risk interval (SCRI) analysis and the observed/expected (O/E) analysis. In addition, it is suggested to include certain subgroups of interest to ensure that the subgroups overlap with prioritised vaccinees. Furthermore, the MAH should provide a more in-depth discussion of biases associated with the closed vs. open claims analysis and provide a discussion of the generalisability of the HealthVerity data to the US population.

7.2.3. Coronavirus (COVID-19) mRNA⁷³ vaccine (nucleoside-modified) - COVID-19 VACCINE MODERNA (CAP) - EMEA/H/C/005791/MEA 005

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Hans Christian Siersted

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

Background

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

As stated in the [RMP](#) of COVID-19 Vaccine Moderna (COVID-19 mRNA vaccine (nucleoside-modified)), the MAH is requested to conduct 'an observational pregnancy outcome study to evaluate outcomes of pregnancies in females exposed to mRNA-1273 vaccine during pregnancy (Moderna COVID-19 vaccine pregnancy registry)' which was assessed by the Rapporteur. The PRAC was requested to provide advice to CHMP on the protocol submitted by the MAH.

Summary of advice

- Based on the review of protocol version 0.1 and the assessment from the Rapporteur, the PRAC considered the protocol for COVID-19 Vaccine Moderna (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 clarify whether external comparators are appropriate, propose means for significantly increasing the study size and elaborate on the

⁷³ Messenger ribonucleic acid

definitions for prospective- and retrospective cases respectively. In addition, the MAH should comment on the feasibility of the planned sensitivity analyses and on the relevance of a sensitivity analysis of major malformation for an exposure during the second and third trimester. Furthermore, the MAH should comment on the advantages and limitations as well as the feasibility of the proposed study approach versus using existing pregnancy data collection frameworks.

7.3. Results of PASS imposed in the marketing authorisation(s)⁷⁴

7.3.1. Iron⁷⁵ ⁷⁶ (NAP) - EMEA/H/N/PSR/J/0026

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

PRAC Rapporteur: Tiphaine Vaillant

Scope: MAH's response to PSR/J/0026 [results for a joint study on intravenous iron: evaluation of the risk of severe hypersensitivity reactions, as imposed in the conclusions of the referral under Article 31 of Directive 2001/83/EC (EMEA/H/A-31/1322) for intravenous (IV) iron-containing medicines in 2013]] as per the request for supplementary information (RSI) adopted in October 2020

Background

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

In line with the conclusions reached in 2013 of the referral procedure under Article 31 of Directive 2001/83/EC ([EMEA/H/A-31/1322](#)) conducted by the PRAC for IV iron-containing medicines, MAHs were required as a condition to the marketing authorisations ([Annex IV](#)) to conduct a PASS to assess the risk of anaphylactic or severe immediate hypersensitivity reactions. For further information see [PRAC minutes February 2013](#), [PRAC minutes March 2017](#) and [PRAC minutes October 2019](#)⁷⁷.

The MAH (on behalf of a consortium) submitted a final study report for assessment by the Rapporteur. The PRAC discussed the final study results in addition to the MAH's response to the second request for supplementary information (RSI). For further information, see [PRAC minutes July 2020](#) and [PRAC minutes October 2020](#)⁷⁸.

Summary of recommendation(s) and conclusions

- Based on the review of the final report of the non-interventional PASS entitled 'intravenous iron post-authorisation safety study (PASS): evaluation of the risk of severe hypersensitivity reactions', the MAH's responses to the second RSI and the assessment from the Rapporteur, the PRAC considered that a further request for supplementary information (RSI) was necessary before a recommendation could be

⁷⁴ In accordance with Article 107p-q of Directive 2001/83/EC

⁷⁵ Intravenous (IV)

⁷⁶ Iron(III)-hydroxide dextran complex, iron sucrose complex/iron(III)-hydroxide sucrose complex, ferric carboxymaltose complex, iron(III) isomaltoside complex, sodium ferric gluconate complex

⁷⁷ Held 30 September – 03 October 2019

⁷⁸ Held 28 September – 01 October 2020

made on the benefit-risk balance of IV iron-containing medicines concerned by the PASS final report.

- The MAH/consortium should further clarify the reasons why the databases previously excluded in 2014 have been reassessed as qualified for the study. The MAH/consortium should also provide the planned protocol of the feasibility study exploring the use of other European databases. In addition, the MAH/consortium should propose a new study protocol using the identified and qualified European databases to address the objectives of the imposed PASS. Moreover, other study designs should be investigated by the MAH/consortium in order to decrease the number of patients to be recruited. In particular, PRAC advised case-only designs could present some advantages such as smaller sample size needed. Finally, the MAH/consortium should provide details on the feasibility study report of the European healthcare data source and registry-based approach as soon as available.
- The MAH should submit responses to the RSI within 60 days to EMA. A 60 day-assessment timetable will be followed.

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

Applicant: Bayer AG

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Final study report comprising the pharmaco-epidemiological study programme of rivaroxaban use and potential adverse outcomes in routine clinical practice in the UK, Germany, the Netherlands and Sweden

Background

Rivaroxaban is a factor Xa inhibitor direct oral anticoagulant (DOAC) indicated, as Xarelto a centrally authorised product, in combination with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers. In combination with ASA, it is also indicated for the prevention of atherothrombotic events in adult patients with coronary artery disease (CAD) or symptomatic peripheral artery disease (PAD) at high risk of ischaemic events. In addition, it is indicated for the prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery, for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults. Moreover, it is indicated in adults for the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack. Finally, in children, it is indicated for the treatment of VTE and prevention of VTE recurrence in children and adolescents aged less than 18 years and weighing from 30 kg to 50 kg after at least 5 days of initial parenteral anticoagulation treatment and for the treatment of VTE and prevention of VTE recurrence in term neonates, infants and toddlers, children, and adolescents aged less than 18 years after at least 5 days of initial parenteral anticoagulation treatment.

Xarelto, a centrally authorised medicine containing rivaroxaban, was authorised in 2008. In 2013, the indication(s) were extended to the prevention of atherothrombotic events after ACS under certain conditions. As an imposed study ([Annex II-D](#)) as a 'condition with regard to the safe and effective use of the medicinal product', the MAH was required to conduct a

PASS to explore whether patient characteristics prescribed rivaroxaban for ACS is different from patients in pivotal study in terms of bleeding risk, monitor drug utilisation in hospital setting. Following PRAC assessment, the ongoing and planned studies of the existing PASS programme were expanded to include the ACS indication, and the PASS programme was consequently re-classified to category 1 studies.

The PRAC discussed the final study report from the PASS programme consisting in this procedure in the evaluation of the pharmacoepidemiological study programme of rivaroxaban use and potential adverse outcomes in routine clinical practice in the UK, Germany, the Netherlands and Sweden. The PRAC is responsible for evaluating the PASS final results.

Summary of recommendation(s) and conclusions

- Based on the review of the final report of the non-interventional pharmacoepidemiological study programme of rivaroxaban use and potential adverse outcomes in routine clinical practice in the UK, Germany, the Netherlands and Sweden, the PRAC considered that a request for supplementary information (RSI) is necessary before a final recommendation can be made based on the PASS final report.
- The MAH should submit to EMA clarifications on the data presented. In particular, the MAH should include a tabular comparison of the risk profile between the current PASS study populations and the study ATLAS ACS2-TIMI 51⁷⁹. With regard to the treatment and secondary prevention of venous thromboembolism (VTE-T) indication, data should be presented to allow a direct comparison to the EINSTEIN DVT⁸⁰ and EINSTEIN PE⁸¹ trials, together with data on mortality rate. For the total knee replacement (TKR) and total hip replacement (THR) indications data should be presented to allow a direct comparison of major safety outcomes to the clinical trials supporting approval of the indication and providing labelled frequencies. In addition, the MAH should provide an in-depth analysis of data relating to the important potential risk of embryo-foetal toxicity. Finally, the MAH should provide further clarifications and analyses and propose to update the product information and/or RMP as warranted.
- The MAH should submit responses to the RSI within 120 days to EMA. A 60 day-assessment timetable will be followed.

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

See also Annex I 17.4.

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

Applicant: Bayer AG

PRAC Rapporteur: Tiphaine Vaillant

Scope: Submission of the final study report for the study (listed as a category 3 study in the RMP) evaluating physician knowledge of safety and safe use information for aflibercept

⁷⁹ A phase 3, multicentre, randomized, double-blind, placebo-controlled clinical trial evaluating an oral, direct factor Xa inhibitor (rivaroxaban) in subjects following an acute coronary syndrome

⁸⁰ A phase 3 study: rivaroxaban versus enoxaparin plus a vitamin K antagonist (VKA) in the treatment of acute DVT without symptomatic PE

⁸¹ A phase 3 study: rivaroxaban versus enoxaparin plus a VKA in the treatment of acute PE with or without symptomatic DVT

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

in Europe: a follow-up physician survey. The RMP (version 27.1) is updated accordingly

Background

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

In 2017, the MAH for Eylea (aflibercept) submitted the results of a non-imposed non-interventional PASS (study 16526 – variation II/0039) to evaluate the physician and patient knowledge of safety and safe use information for aflibercept in Europe as stated in the EU educational material for Eylea (aflibercept) (wave 1 survey). As agreed in 2018 and as stated in the RMP of Eylea (aflibercept), the MAH revised the prescriber guide and conducted a follow-up survey (wave 2 survey) to evaluate the effectiveness of the risk minimisation measures following revision and redistribution of the materials. The Rapporteur assessed the MAH's final study report. The Rapporteur assessed the MAH's final study report together with the MAH's responses to the requests for supplementary information (RSI). For further background, see [PRAC minutes January 2021](#).

Summary of advice

- Based on the available data, the MAH's response to the RSI and the Rapporteur's review, the PRAC considered that the ongoing variation assessing the final study report can be recommended for approval.
- The PRAC agreed on the content of a direct healthcare professional communication ([DHPC](#)) along with a communication plan for its distribution in order to inform healthcare professionals (HCPs) on a reported cluster of intraocular pressure (IOP) increase, to provide them with key messages regarding IOP surveillance and management of IOP increase, to clarify the correct use of the product, the size of the recommended needle and to administer exactly the recommended dose in order to reduce the risk of overdose/medication error.
- The PRAC supported the update of the RMP and simplification of the educational material to HCPs. PRAC also agreed with the submission and review of yearly reports to monitor IOP increase reporting rates.

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

See Annex I 17.5.

7.6. Others

See Annex I 17.6.

7.7. New Scientific Advice

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

7.8. Ongoing Scientific Advice

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

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

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

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

8.1. Annual reassessments of the marketing authorisation

See Annex I 18.1.

8.2. Conditional renewals of the marketing authorisation

See also Annex I 18.2.

8.2.1. Remdesivir - VEKLURY (CAP) - EMEA/H/C/005622/R/0015 (with RMP)

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Eva Jirsová

Scope: Conditional renewal of the marketing authorisation

Background

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

Veklury, a centrally authorised product containing remdesivir, was authorised under a conditional marketing authorisation in 2020. Based on the fulfilment of specific obligation(s) and safety data, the MAH submitted a request for yearly renewal of the marketing authorisation for opinion by the CHMP. The PRAC is responsible for providing advice to the CHMP on this conditional renewal with regard to safety and risk management aspects.

Summary of advice

- Based on the review of the status of the fulfilment of specific obligations (SO), safety data submitted for Veklury (remdesivir) and the joint CHMP-PRAC Rapporteurs' assessment report, PRAC considered that the conditional renewal could be finalised if satisfactory clarification is given on some pending issues. Regarding the RMP, it could be considered acceptable provided that an update to RMP version 1.1 is submitted. PRAC agreed with the update of the list of safety concerns in light of the fulfilment of SO. However, the MAH should consider including the study in pregnant women with COVID-19 as a category 3 study in the RMP to better characterize missing information in this

population (US commitment 3919-11⁸³). In addition, the MAH should consider collaborating with the CONSIGN⁸⁴ consortium and add the study as a category 3 study in the RMP.

8.3. Renewals of the marketing authorisation

See Annex I 18.3.

9. Product related pharmacovigilance inspections

9.1. List of planned pharmacovigilance inspections

None

9.2. Ongoing or concluded pharmacovigilance inspections

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

9.3. Others

None

10. Other safety issues for discussion requested by 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.

⁸³ Study 3919-11 on the use of remdisivir in pregnant women

⁸⁴ COVID-19 infection and medicines in pregnancy

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

11.1. Safety related variations of the marketing authorisation

11.1.1. Gabapentin (NAP) - DE/H/XXXX/WS/691

Applicant: Pfizer Pharma (Gabapentin Pfizer, Neurontin)

PRAC Lead: Martin Huber

Scope: PRAC consultation on a work-sharing variation procedure evaluating an analysis of cases of suicidality and feasibility assessment for an epidemiological study investigating the suicidal risk of gabapentin/gabapentinoids as discussed at PRAC and agreed by CMDh following the conclusion of the PSUSA procedure (PSUSA/00001499/201902) concluded in October 2019, on request of Germany

Background

Gabapentin is an anti-epileptic drug indicated as monotherapy and as adjunctive therapy in the treatment of partial seizures with and without secondary generalisation and for the treatment of peripheral neuropathic pain such as painful diabetic neuropathy and post-herpetic neuralgia, subject to certain conditions.

In the context of the evaluation of worksharing procedure consisting in evaluating an analysis of cases of suicidality and feasibility assessment for an epidemiological study investigating the suicidal risk of gabapentin/gabapentinoids, as requested in the assessment of the last PSUR single assessment (PSUSA) procedure, Germany as the lead Member State (LMS) requested a PRAC advice on its assessment. For further background, see [PRAC minutes October 2019](#)⁸⁵.

Summary of advice

- Based on the review of the available information and the LMS assessment, the PRAC agreed that there is at least a reasonable possibility of a causal association between treatment with gabapentin and suicidal ideation. The PRAC supported the LMS' proposed update of the existing warning of the product information⁸⁶ on suicidal ideation and behavior. In addition, the PRAC advised to add 'suicidal ideation' as an undesirable effect. Finally, PRAC agreed that 'suicide/self-injury' in the context of discontinuation/withdrawal of gabapentin should be closely monitored in future PSURs.

11.2. Other requests

None

⁸⁵ Held 30 September – 03 October 2019

⁸⁶ Update of SmPC sections 4.4 and 4.8. The package leaflet is to be updated accordingly

12. Organisational, regulatory and methodological matters

12.1. Mandate and organisation of the PRAC

None

12.2. Coordination with EMA Scientific Committees or CMDh-v

None

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

12.3.1. Scientific Advisory Groups (SAG) – launch of public call for expression of interests for renewal of mandate of all therapeutic SAGs: preparation

The topic was postponed until April/May 2021.

12.3.2. Scientific Advisory Groups (SAG) - renewal of the mandate of the Inter-Committee SAG Oncology (SAG-O) - request for nominations

The topic was postponed until April/May 2021.

12.4. Cooperation within the EU regulatory network

12.4.1. Coronavirus (COVID-19) pandemic - update

The EMA Secretariat updated the PRAC on the activities of the [COVID-19 EMA pandemic Task Force](#) (ETF), including an overview of ongoing clinical trials and epidemiological studies and initiatives, as well as a summary of medicines in development and medicines authorised for other indications, as potential treatments for COVID-19, and their safety surveillance. In addition, the EMA Secretariat also presented to PRAC an overview dated March 2021 on EMA-funded observational studies of COVID-19 vaccines. PRAC welcomed this initiative of monthly overviews.

12.4.2. Safety communication – relevant aspects for European regulators

PRAC Lead: Sabine Straus

At the organisational, regulatory and methodological matters (ORGAM) meeting on 25 March 2021, in light of a recent study⁸⁷ published in 2020 in the BMJ on differences in the number, timing and transparency of public safety communications by leading medicines regulators, aspects that influence the communication of safety issues were presented to PRAC. In the framework of a study conducted by the Dutch National competent Authority (MEB) and Dutch Universities, PRAC members were invited to answer to a survey in this respect.

⁸⁷ Bhasale, BMJ 2020

12.5. Cooperation with International Regulators

None

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

None

12.7. PRAC work plan

None

12.8. Planning and reporting

None

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

The PRAC endorsed the draft revised EURD list, version March 2021, reflecting the PRAC's comments impacting on the data lock point (DLP) and PSUR submission frequencies of the substances/combinations. The PRAC endorsed the newly allocated Rapporteurs for

upcoming PSUSAs in accordance with the principles previously endorsed by the PRAC (see [PRAC minutes April 2013](#)).

Post-meeting note: following the PRAC meeting of March 2021, the updated EURD list was adopted by the CHMP and CMDh at their March 2021 meetings and published on the EMA website on 31/03/2021, see:

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

12.11. Signal management

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

PRAC Lead: Menno van der Elst

The PRAC was updated on the progress from the signal management review technical (SMART) working group meeting on methods held remotely on 28 January 2021. In the context of vaccine monitoring, the SMART working group (WG) discussed potential other methodologies for signal refinement and analyses of fatality cases in EudraVigilance. The EMA Secretariat presented the observed to expected (O/E) analysis in order to summarise to PRAC the testing methods for vaccine monitoring during a pandemic at EMA and to share experience on O/E analysis and next steps. 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

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

Post-meeting note: The updated additional monitoring list was published on the EMA website on 31/03/2021, see: [Home>Human Regulatory>Post-authorisation>Pharmacovigilance>Medicines under additional monitoring>List of medicines under additional monitoring](#)

12.13. EudraVigilance database

12.13.1. Activities related to the confirmation of full functionality

None

12.13.2. EudraVigilance – annual report 2020

The EMA secretariat presented to the PRAC the 2020 EudraVigilance annual report for the European Parliament, the Council and the Commission in line with Article 24(2), paragraph 2 of Regulation (EC) No. 726/2004. Following the EMA Management Board meeting in March 2021, the report will be submitted to the EU institutions and published on the EMA website.

Post-meeting note: On 11 March 2021, the EudraVigilance annual report 2020 ([EMA/620104/2020](#)) was published on the EMA website.

12.14. Risk management plans and effectiveness of risk minimisations

12.14.1. Risk management systems

None

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

None

12.15. Post-authorisation safety studies (PASS)

12.15.1. Advanced therapy medicinal products (ATMPs) - EU data sources for long-term safety and efficacy follow-up

Following discussion in February 2021 at PRAC (for background, see [PRAC minutes February 2021](#)) and CAT, the EMA Secretariat presented to PRAC a further consolidated document entitled 'EMA Committees Position on using EBMT as a data source for imposed studies for the long-term safety and efficacy follow-up for ATMPs'. PRAC endorsed the document. As a next step, the document will be discussed at CAT in March 2021 for final endorsement.

12.15.2. Post-authorisation Safety Studies – imposed PASS

None

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

None

12.16. Community procedures

12.16.1. Referral procedures for safety reasons

None

12.17. Renewals, conditional renewals, annual reassessments

None

12.18. Risk communication and transparency

12.18.1. Public participation in pharmacovigilance

None

12.18.2. Safety communication

None

12.19. Continuous pharmacovigilance

12.19.1. Incident management

None

12.20. Others

12.20.1. Commission implementing Regulation (EU) No 520/2012 – scoping paper

The EMA Secretariat and European Commission (EC) representative to PRAC presented to PRAC a proposal to revise the existing Commission implementing regulation EU (No) 520/2012 for PRAC to provide its input and comment. Overall, PRAC welcomed the proposed revisions and endorsed the scoping paper with proposed revisions. Further discussion will be scheduled in due course.

12.20.2. EMA-funded studies - new call for framework contractors

The EMA Secretariat informed the PRAC of a new call for framework contractors for EMA-funded-studies to support Committees due for publication on 12 March 2021 in the Official Journal of the European Union (OJEU). The scope of studies was extended to pre-clinical research, veterinary studies, statistical research, qualitative research, pharmaco-epidemiological research and quality of medicine. New contracts are planned to be in place in September 2021 at the latest for a duration of four years. PRAC members were invited to disseminate this information to research groups in their respective Member States.

13. Any other business

None

14. Annex I – Signals assessment and prioritisation⁸⁸

14.1. New signals detected from EU spontaneous reporting systems

As per agreed criteria for new signal(s), the PRAC adopted without further plenary discussion the recommendation of the Rapporteur to request MAH(s) to submit a cumulative review following standard timetables⁸⁹.

14.1.1. Donepezil (NAP)

Applicant(s): various

PRAC Rapporteur: Martin Huber

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

EPITT 19667 – New signal

Lead Member State(s): DE

14.1.2. Octreotide (NAP)

Applicant(s): various

PRAC Rapporteur: Ronan Grimes

Scope: Signal of pancreatic exocrine insufficiency

EPITT 19661 – New signal

Lead Member State(s): IE

14.2. New signals detected from other sources

None

15. Annex I – Risk management plans

15.1. Medicines in the pre-authorisation phase

As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of the RMP for the below-mentioned medicines under evaluation for initial marketing authorisation application. Information on the medicines containing the below-listed active substance(s) will be made available following the CHMP opinion on their marketing authorisation(s).

⁸⁸ 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

⁸⁹ Either MA(s)'s submission within 60 days followed by a 60 day-timetable assessment or MAH's submission cumulative review within an ongoing or upcoming PSUR/PSUSA procedure (if the DLP is within 90 days), and no disagreement has been raised before the meeting

15.1.1. Insulin human (rDNA) – EMEA/H/C/005331

Scope: Treatment of patients with diabetes mellitus who require intravenous insulin

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

Applicant: Rhythm Pharmaceuticals Limited

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

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

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

15.2.1. Alpelisib - PIQRAY (CAP) - EMEA/H/C/004804/II/0001

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Menno van der Elst

Scope: Submission of an updated RMP (version 2.0) in order to replace the following studies (listed as category 3 studies in the RMP): 1) study CBYL719C2402: a retrospective cohort study to evaluate the risk of hyperglycaemia in patients with advanced breast cancer treated with Piqray (alpelisib) in the real world setting; 2) study CBYL719A0IC02: an open-label, multicentre, phase 3b study to evaluate the safety and tolerability of alpelisib in combination with fulvestrant for the treatment of men and postmenopausal women with hormone receptor-positive (HR+), epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer with a PIK3CA⁹⁰ mutation, after disease progression following an endocrine based regimen, by: 3) study CBYL719C2404: A non-interventional PASS of Piqray (alpelisib) in combination with fulvestrant in postmenopausal women, and men, with HR+, HER2 negative, locally advanced or metastatic breast cancer with a PIK3CA mutation in the real-world setting in European countries. Additionally, a separated healthcare professional (HCP) survey (CBYL719A0IC02) is proposed as part of the pharmacovigilance plan

15.2.2. Cerliponase alfa - BRINEURA (CAP) - EMEA/H/C/004065/II/0027, Orphan

Applicant: BioMarin International Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of an updated RMP (version 3.2) in order to change the final date for completion from July 2020 to May 2024 of the post-authorisation efficacy study (PAES) study 190-203: a phase 2, open-label, multicentre study to evaluate safety, tolerability, and efficacy of intra-cerebroventricular cerliponase alfa in paediatric patients < 18 years of age with neuronal ceroid lipofuscinosis type 2 (CLN2) disease

⁹⁰ Phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alfa

15.2.3. Emicizumab - HEMLIBRA (CAP) - EMEA/H/C/004406/II/0021

Applicant: Roche Registration GmbH

PRAC Rapporteur: Amelia Cupelli

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)

15.2.4. Lopinavir, ritonavir - LOPINAVIR/RITONAVIR MYLAN (CAP) - EMEA/H/C/004025/II/0016

Applicant: Mylan S.A.S

PRAC Rapporteur: Adrien Inoubli

Scope: Submission of an updated RMP (version 4.0) in order to bring the RMP in line with revision 2.0.1 of the guidance on the format of RMP in the EU (template) and revision 2 of GVP module V on 'Risk management systems' and to align the safety concerns with those of the reference medicinal product

15.2.5. Rasagiline - AZILECT (CAP) - EMEA/H/C/000574/WS2011/0087; RASAGILINE RATIOPHARM (CAP) - EMEA/H/C/003957/WS2011/0019

Applicant: Teva B.V.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Submission of an updated RMP (version 3.0) following the completion of study TV1030-CNS-50024 (listed as a category 3 study in the RMP): a non-interventional retrospective cohort study which was conducted using the United States Medicare research database to assess the potential risk of melanoma associated with the use of rasagiline mesylate in patients with Parkinson's disease (as assessed and concluded in procedure WS/1749 finalised in September 2020). The MAH took the opportunity to introduce a minor update to the targeted follow-up questionnaire for the important potential risk of malignant melanoma and to revise the list of safety concerns in line with revision 2.0.1 of the guidance on the format of RMP in the EU (template)

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

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of an updated RMP (version 13.0) in order to bring it in line with revision 2 of GVP module V on 'Risk management systems' including consequential

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

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

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

15.3.1. Andexanet alfa - ONDEXXYA (CAP) - EMEA/H/C/004108/II/0009/G

Applicant: Alexion Europe SAS

PRAC Rapporteur: Menno van der Elst

Scope: Grouped variations consisting of an update of section 5.2 of the SmPC in order to update pharmacokinetic (PK) information based on the clinical study results (CSR) from: 1) study 19-514 evaluating the PK comparability of generation 1 process 3 andexanet and generation 2 andexanet (PK comparability); 2) study 16-508: a phase 2 randomised, double-blind, placebo-controlled study to evaluate the efficacy, safety, tolerability and PK/pharmacodynamics (PD) of andexanet alfa administered to healthy Japanese and Caucasian subjects (Japanese ethnicity study). Annex II-D on 'Specific obligation to complete post-authorisation measures for the conditional marketing authorisation' is updated accordingly. The RMP (version 2.1) is updated in accordance

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

Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension of indication to include treatment of lupus nephritis. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 38) are updated in accordance

15.3.3. Ceritinib - ZYKADIA (CAP) - EMEA/H/C/003819/II/0034

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Annika Folin

Scope: Update of sections 4.2, 4.4, 4.8 and 5.1 of the SmPC in order to reflect the results of study CLDK378A2112: a multicentre, randomized open label study to assess the

systemic exposure, efficacy and safety of 450 mg ceritinib taken with a low-fat meal and 600 mg ceritinib taken with a low-fat meal as compared with that of 750 mg ceritinib taken in the fasted state in adult patients with anaplastic lymphoma kinase (ALK) rearranged (ALK-positive) metastatic non-small cell lung cancer (NSCLC). The package leaflet and the RMP (version 16.0) 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 10.1). The MAH also introduced other editorial changes including information on sodium content in line with the Annex to the European Commission (EC) guideline on 'excipients in the labelling and package leaflet of medicinal products for human use' and the removal of the black triangle

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

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Tiphaine Vaillant

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

15.3.5. Dabrafenib - TAFINLAR (CAP) - EMEA/H/C/002604/II/0049

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Annika Folin

Scope: Submission of the final report from study 201710 (listed as a category 3 study in the RMP): a non-interventional study to perform evaluation of secondary malignancies in

patients treated with dabrafenib in randomized controlled trials. The RMP (version 10.0) is updated accordingly

15.3.6. Evolocumab - REPATHA (CAP) - EMEA/H/C/003766/II/0048

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Kimmo Jaakkola

Scope: Submission of the final report from study 20130286 (listed as a category 3 study in the RMP): a double blind, randomised, placebo controlled, multicentre study to evaluate safety, tolerability, and efficacy on low-density lipoprotein cholesterol (LDL-C) of evolocumab in human immunodeficiency virus (HIV) positive patients with hyperlipidemia and mixed dyslipidemia. The RMP (version 6.0) is updated accordingly

15.3.7. Infliximab - REMSIMA (CAP) - EMEA/H/C/002576/II/0095

Applicant: Celltrion Healthcare Hungary Kft.

PRAC Rapporteur: Kimmo Jaakkola

Scope: Update of section 4.2 of the SmPC to add a new posology for the rheumatoid arthritis indication that does not include intravenous (IV) induction doses prior subcutaneous use. The package leaflet and the RMP (version 13.1) are updated accordingly

15.3.8. Ixazomib - NINLARO (CAP) - EMEA/H/C/003844/II/0026, Orphan

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Annika Folin

Scope: Update of Annex II-E on 'Specific obligation to complete post-authorisation measures for the conditional marketing authorisation' of the product information to reflect the completion of study C16014: a phase 3, randomized, double-blind, multicentre study comparing ixazomib plus lenalidomide and dexamethasone versus placebo plus lenalidomide and dexamethasone in adult patients with newly diagnosed multiple myeloma not eligible for stem cell transplantation (SCT) (in fulfilment of SOB 003). The RMP (version 5.1) is updated accordingly. In addition, a minor editorial change is proposed to section 4.2 of the SmPC in order to improve the consistency with other sections of the SmPC. Finally, the MAH took the opportunity to update the list of local representatives in the package leaflet

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

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Anette Kirstine Stark

Scope: Submission of the 5 year data including data on late relapses from the following ongoing studies: 1) study CAMN107I2201 (ENESTfreedom): a phase 2, single-arm, open-label, multicentre nilotinib treatment-free remission (TFR) study in patients with breakpoint cluster region gene/Abelson proto-oncogene 1 (BCR-ABL1) positive chronic myeloid leukaemia in chronic phase (CML-CP), who had achieved durable minimal residual disease (MRD) status on first-line nilotinib treatment; 2) study CAMN107A2408 (ENESTop): a phase

2, single-arm, open-label, multicentre study, evaluating TFR in patients with BCR-ABL1-positive CML-CP who achieved a sustained molecular response of MR4.5 on nilotinib treatment after switching from imatinib to nilotinib. The RMP (version 23.0) is updated accordingly

15.3.10. Ipilimumab - YERVOY (CAP) - EMEA/H/C/002213/WS1881/0085; nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/WS1881/0091

Applicant(s): Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include first-line treatment of adult patients with unresectable malignant pleural mesothelioma (MPM) for Opdivo (nivolumab) in combination with Yervoy (ipilimumab). As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 20.0 for Opdivo, version 30.0 for Yervoy) are updated in accordance

15.3.11. Ivacaftor - KALYDECO (CAP) - EMEA/H/C/002494/II/0089, Orphan

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Extension of indication to extend the indication of Kalydeco (ivacaftor) tablets in combination regimen with Kaftrio (ivacaftor/tezacaftor/elexacaftor) tablets for the treatment of adults and adolescents aged 12 years and older with cystic fibrosis (CF) who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. As a consequence, sections 4.1, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 9.2) are updated in accordance

15.3.12. Ivacaftor, tezacaftor, elexacaftor - KAFTRIO (CAP) - EMEA/H/C/005269/II/0001, Orphan

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Martin Huber

Scope: Extension of indication to patients with cystic fibrosis (CF) aged 12 years and older who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR gene), regardless of the second allele (F/any), based on efficacy data from study 104: a phase 3, randomized, double-blind, controlled study evaluating the efficacy and safety of elexacaftor (VX-445) combination therapy in subjects with CF who are heterozygous for the F508del mutation and a gating or residual function mutation (F/G and F/RF genotypes). 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 1.1) are updated accordingly

15.3.13. Migalastat - GALAFOLD (CAP) - EMEA/H/C/004059/II/0029, Orphan

Applicant: Amicus Therapeutics Europe Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension of indication to include long-term treatment of adolescents 12 to < 16

years with a confirmed diagnosis of Fabry disease (α -galactosidase A deficiency) and who have an amenable mutation. As a consequence, sections 4.1, 4.2, 4.8 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 4.0) are updated accordingly

15.3.14. Migalastat - GALAFOLD (CAP) - EMEA/H/C/004059/II/0030, Orphan

Applicant: Amicus Therapeutics Europe Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of section 5.1 of the SmPC based on final results from study AT1001-042 (listed as a category 3 study in the RMP: an open-label, non-comparative, long-term extension study to evaluate long term safety and efficacy of migalastat in monotherapy in subjects with Fabry disease. The RMP (version 5.0) is updated accordingly

15.3.15. Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/II/0095

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include adjuvant treatment of adult patients with resected oesophageal, or gastro-oesophageal junction cancer who have residual pathologic disease following prior neoadjuvant chemoradiotherapy based on study CA209-577: a randomized, multicenter, double blind, phase 3 study of adjuvant nivolumab or placebo in subjects with resected esophageal, or gastroesophageal junction cancer. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 22.0) are updated in accordance

15.3.16. Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/II/0096

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to use Opdivo (nivolumab) in combination with fluoropyrimidine- and platinum-based combination chemotherapy, in first-line treatment of adult patients with advanced or metastatic gastric, gastro-oesophageal junction (GEJ) or oesophageal adenocarcinoma based on study CA209-649: a randomized, multicentre, open-label, phase 3 study of nivolumab plus ipilimumab or nivolumab in combination with oxaliplatin plus fluoropyrimidine versus oxaliplatin plus fluoropyrimidine in subjects with previously untreated advanced or metastatic gastric or gastroesophageal junction cancer. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 6.6 of the SmPC are updated. The package leaflet and the RMP (version 21.0) are updated in accordance

15.3.17. Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/II/0098

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of section 5.1 of the SmPC in order to update overall survival (OS) information based on the final OS data for study CA209-238 (listed as an obligation in the Annex II and in the RMP): a Phase 3, randomised double-blind study of Opdivo (nivolumab)

versus Yervoy (ipilimumab) in patients who have undergone complete resection of stage IIIb/c or stage IV melanoma. The MAH took also the opportunity to update section 4.8 of the SmPC to pull the safety data sets of nivolumab as monotherapy across advanced metastatic and adjuvant settings. The package leaflet and the RMP (version 17.2) are updated accordingly. Finally, the MAH took the opportunity to introduce minor editorial and formatting revisions throughout the product information

15.3.18. 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

15.3.19. Parathyroid hormone - NATPAR (CAP) - EMEA/H/C/003861/II/0026, Orphan

Applicant: Shire Pharmaceuticals Ireland Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Submission of the final results for study PAR-C10-008: a long-term open-label study investigating the safety and tolerability of a Natpar (parathyroid hormone) for the treatment of adults with hypoparathyroidism – a clinical extension study (RACE). As a consequence, section 5.1 of the SmPC is updated to reflect 72-month data from the study. The RMP (version 3.0) is updated accordingly and in line with revision 2 of GVP module V on 'Risk management systems'

15.3.20. Pembrolizumab - KEYTRUDA (CAP) - EMEA/H/C/003820/II/0099

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication for Keytruda (pembrolizumab) to include in combination with chemotherapy, treatment of locally recurrent unresectable or metastatic triple negative breast cancer in adults whose tumours express programmed death-ligand 1 (PD-L1) with a combined positive score (CPS) ≥ 10 and who have not received prior chemotherapy for metastatic disease. As a consequence, sections 4.1, 4.2 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 31.1) are updated in accordance

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

Applicant: Bioprojet Pharma

PRAC Rapporteur: Kirsti Villikka

Scope: Grouped variations consisting of an update of sections 4.2, 4.4, 4.5, 5.1 and 5.2 of the SmPC based on new clinical data from: 1) study P09-10 (HARMONY III): an open-label naturalistic pragmatic study to assess the long-term safety of pitolisant in the treatment of excessive daytime sleepiness (EDS) (with or without cataplexy) in narcolepsy; 2) study P16-02: a randomised, double-blind, active- and placebo-controlled, single-dummy, 4-way crossover study to determine the abuse potential of pitolisant compared to phentermine and placebo, in healthy, non-dependent recreational stimulant users. The proposed update also includes results of a post approval network meta-analysis which compares efficacy and safety of multiple treatments, multi-arm studies, and multi-criteria treatment decisions. The package leaflet and the RMP (version 6.0) are updated accordingly

15.3.22. 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 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

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

Applicant: AstraZeneca AB

PRAC Rapporteur: Ilaria Baldelli

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

15.3.24. Tedizolid phosphate - SIVEXTRO (CAP) - EMEA/H/C/002846/II/0037

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Update of section 5.1 of the SmPC in order to update the description of the potential risk of emergence of drug resistance with tedizolid phosphate based on final results from study 'surveillance of tedizolid activity and resistance (STAR)' (listed as a category 3 study

in the RMP): a surveillance study established in January 2014 to monitor tedizolid susceptibility activity and emergence of resistance across the US, 11 European Union countries, Russia and Turkey. The RMP (version 6.2) is updated accordingly

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

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

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

15.3.26. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/II/0027

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Update of sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC of Xeljanz (tofacitinib) 11 mg prolonged-release tablets in order to include the treatment of active psoriatic arthritis (PsA) in adult patients who have had an inadequate response or who have been intolerant to a prior disease modifying antirheumatic drug therapy; as an alternative to the immediate release film-coated tablets. Section 4.2 of the SmPC for Xeljanz (tofacitinib) film-coated tablets is also updated to include switching with the prolonged-release tablet in the treatment of PsA. The package leaflet and the RMP (version 13.1) are updated accordingly

15.3.27. Trametinib - MEKINIST (CAP) - EMEA/H/C/002643/II/0043

Applicant: Novartis Europharm Limited

PRAC Rapporteur: David Olsen

Scope: Submission of the final report from study 201711 (listed as a category 3 study in the RMP): a study to identify and characterize the risk of cardiomyopathy and subsequent sequelae, including safety evaluations of patient populations at highest risk for developing these toxicities, based on 7 randomized controlled clinical studies with trametinib monotherapy or in combination with other anti-cancer agents. The RMP (version 17.0) is updated accordingly

15.3.28. Trastuzumab - ZERCEPAC (CAP) - EMEA/H/C/005209/II/0008

Applicant: Accord Healthcare S.L.U.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Addition of a new fill weight for Zercepac (trastuzumab) powder for concentrate for solution for infusion, 420 mg/vial (EU/1/20/1456/003). The strength (concentration after reconstitution) is identical to the previously authorised finished product 150mg/vial

presentation. The RMP (version 1.2) is updated accordingly

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

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Nikica Mirošević Skvrce

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

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

Based on the assessment of the following PSURs, the PRAC concluded that the benefit-risk balance of the below-mentioned medicines remains favourable in the approved indication(s) and adopted a recommendation to maintain the current terms of the marketing authorisation(s) together with the assessment report. As per agreed criteria, the procedures listed below were finalised at the PRAC level without further plenary discussion.

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

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

16.1.1. Afibercept⁹¹ - ZALTRAP (CAP) - PSUSA/00010019/202008

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

16.1.2. Apalutamide - ERLEADA (CAP) - PSUSA/00010745/202008

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

16.1.3. Asenapine - SYCREST (CAP) - PSUSA/00000256/202008

Applicant: N.V. Organon

PRAC Rapporteur: Ana Sofia Diniz Martins

⁹¹ Oncological indication(s) only

Scope: Evaluation of a PSUSA procedure

16.1.4. Ataluren - TRANSLARNA (CAP) - PSUSA/00010274/202007

Applicant: PTC Therapeutics International Limited

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.5. Bempedoic acid - NILEMDO (CAP); bempedoic acid, ezetimibe - NUSTENDI (CAP) - PSUSA/00010841/202008

Applicant(s): Daiichi Sankyo Europe GmbH

PRAC Rapporteur: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

16.1.6. Bictegravir, emtricitabine, tenofovir alafenamide - BIKTARVY (CAP) - PSUSA/00010695/202008

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.7. Botulinum toxin type A - NUCEIVA (CAP) - PSUSA/00010796/202007

Applicant: Evolus Pharma Limited

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.8. Burosumab - CRYSVITA (CAP) - PSUSA/00010669/202008

Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.9. Catridecacog - NOVOTHIRTEEN (CAP) - PSUSA/00010034/202007

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

16.1.10. Chlormethine - LEDAGA (CAP) - PSUSA/00010587/202008

Applicant: Helsinn Birex Pharmaceuticals Limited

PRAC Rapporteur: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

16.1.11. Cobicistat - TYBOST (CAP) - PSUSA/00010081/202008

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.1.12. Cobimetinib - COTELLIC (CAP) - PSUSA/00010450/202008

Applicant: Roche Registration GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.13. Corifollitropin alfa - ELONVA (CAP) - PSUSA/00000875/202007

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.14. Daunorubicin, cytarabine - VYXEOS LIPOSOMAL (CAP) - PSUSA/00010701/202008

Applicant: Jazz Pharmaceuticals Ireland Limited

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Evaluation of a PSUSA procedure

16.1.15. Eliglustat - CERDELGA (CAP) - PSUSA/00010351/202008

Applicant: Genzyme Europe BV

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

16.1.16. Eravacycline - XERAVA (CAP) - PSUSA/00010718/202008

Applicant: Tetrphase Pharmaceuticals Ireland Limited

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.17. Ex vivo expanded autologous human corneal epithelial cells containing stem cells - HOLOCLAR (CAP) - PSUSA/00010352/202008

Applicant: Holostem Therapie Avanzate s.r.l., ATMP⁹²

PRAC Rapporteur: Rhea Fitzgerald

⁹² Advanced therapy medicinal product

Scope: Evaluation of a PSUSA procedure

16.1.18. Ferric maltol - FERACCRU (CAP) - PSUSA/00010476/202008

Applicant: Norgine B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.19. Hydrocortisone⁹³ - ALKINDI (CAP) - PSUSA/00010674/202008

Applicant: Diurnal Europe BV

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

16.1.20. Ibuprofen⁹⁴ - PEDEA (CAP) - PSUSA/00001712/202007

Applicant: Recordati Rare Diseases

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

16.1.21. Lamivudine⁹⁵ - ZEFFIX (CAP) - PSUSA/00001824/202007

Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

16.1.22. Lanadelumab - TAKHZYRO (CAP) - PSUSA/00010743/202008

Applicant: Shire Pharmaceuticals Ireland Limited

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

16.1.23. Lefamulin - XENLETA (CAP) - PSUSA/00010872/202008

Applicant: Nabriva Therapeutics Ireland DAC

PRAC Rapporteur: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

16.1.24. Lomitapide - LOJUXTA (CAP) - PSUSA/00010112/202007

Applicant: Amryt Pharmaceuticals DAC

⁹³ Centrally authorised product(s) for adrenal insufficiency, paediatric use only

⁹⁴ Indicated for the treatment of ductus arteriosus only

⁹⁵ Indicated for the treatment of chronic hepatitis B only

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.25. Methoxy polyethylene glycol-epoetin beta - MIRCERA (CAP) - PSUSA/00002017/202007

Applicant: Roche Registration GmbH

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

16.1.26. Nonacog alfa - BENEFIX (CAP) - PSUSA/00002183/202008

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.27. Panobinostat - FARYDAK (CAP) - PSUSA/00010409/202008

Applicant: Secura Bio Limited

PRAC Rapporteur: Sofia Trantza

Scope: Evaluation of a PSUSA procedure

16.1.28. Patisiran - ONPATTRO (CAP) - PSUSA/00010715/202008

Applicant: Alnylam Netherlands B.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

16.1.29. Pyronaridine, artesunate - PYRAMAX (Art 58⁹⁶) - EMEA/H/W/002319/PSUV/0022

Applicant: Shin Poong Pharmaceutical Co., Ltd.

PRAC Rapporteur: Adrien Inoubli

Scope: Evaluation of a PSUR procedure

16.1.30. Ropeginterferon alfa-2b - BESREMI (CAP) - PSUSA/00010756/202008

Applicant: AOP Orphan Pharmaceuticals AG

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Evaluation of a PSUSA procedure

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

16.1.31. Saxagliptin - ONGLYZA (CAP) - PSUSA/00002685/202007

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.32. Smallpox vaccine (live, modified vaccinia Ankara virus) - IMVANEX (CAP) - PSUSA/00010119/202007

Applicant: Bavarian Nordic A/S

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.33. Telotristat - XERMELO (CAP) - PSUSA/00010639/202008

Applicant: Ipsen Pharma

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.34. Tezacaftor, ivacaftor - SYMKEVI (CAP) - PSUSA/00010730/202008

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

16.1.35. Tisagenlecleucel - KYMRIA (CAP) - PSUSA/00010702/202008 (with RMP)

Applicant: Novartis Europharm Limited, ATMP⁹⁷

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.36. Tocofersolan - VEDROP (CAP) - PSUSA/00002981/202007

Applicant: Recordati Rare Diseases

PRAC Rapporteur: Melinda Palfi

Scope: Evaluation of a PSUSA procedure

16.1.37. Zanamivir⁹⁸ - DECTOVA (CAP) - PSUSA/00010763/202007

Applicant: GlaxoSmithKline Trading Services Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

⁹⁷ Advanced therapy medicinal product

⁹⁸ Centrally authorised product(s) only

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

16.2.1. Duloxetine - CYMBALTA (CAP); DULOXETINE LILLY (CAP); NODETRIP (CAP); YENTREVE (CAP); NAP - PSUSA/00001187/202008

Applicants: Eli Lilly Nederland B.V. (Cymbalta, Duloxetine Lilly, Yentreve), Esteve Pharmaceuticals S.A. (Nodetrip), various

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

16.2.2. Human protein C - CEPROTIN (CAP); NAP - PSUSA/00002563/202007

Applicants: Takeda Manufacturing Austria AG (Ceprotin), various

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

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

16.3.1. Aciclovir, hydrocortisone (NAP) - PSUSA/00009004/202007

Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.3.2. Dimetindene, phenylephrine (NAP) - PSUSA/00001102/202007

Applicant(s): various

PRAC Lead: Marek Juracka

Scope: Evaluation of a PSUSA procedure

16.3.3. Epinephrine (NAP) - PSUSA/00001232/202007

Applicant(s): various

PRAC Lead: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

16.3.4. Escherichia coli lysate (NAP) - PSUSA/00001263/202007

Applicant(s): various

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.3.5. Fenofibrate (NAP) - PSUSA/00001362/202007

Applicant(s): various

PRAC Lead: Laurence de Fays

Scope: Evaluation of a PSUSA procedure

16.3.6. Glyceryl trinitrate (NAP) - PSUSA/00001552/202007

Applicant(s): various

PRAC Lead: Gabriela Jazbec

Scope: Evaluation of a PSUSA procedure

16.3.7. Imipramine (NAP) - PSUSA/00001728/202007

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.3.8. Indium (¹¹¹In) pentetate (NAP) - PSUSA/00009191/202007

Applicant(s): various

PRAC Lead: Laurence de Fays

Scope: Evaluation of a PSUSA procedure

16.3.9. Indium (¹¹¹In) pentetreotide (NAP) - PSUSA/00009192/202007

Applicant(s): various

PRAC Lead: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

16.3.10. Lidocaine hydrochloride, methylprednisolone acetate (NAP) - PSUSA/00001879/202008

Applicant(s): various

PRAC Lead: Zane Neikena

Scope: Evaluation of a PSUSA procedure

16.3.11. Niclosamide (NAP) - PSUSA/00002151/202008

Applicant(s): various

PRAC Lead: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.3.12. Pethidine (NAP) - PSUSA/00002357/202008

Applicant(s): various

PRAC Lead: Melinda Palfi

Scope: Evaluation of a PSUSA procedure

16.3.13. Trimetazidine (NAP) - PSUSA/00003043/202008

Applicant(s): various

PRAC Lead: Ilaria Baldelli

Scope: Evaluation of a PSUSA procedure

16.3.14. Typhoid polysaccharide vaccine (NAP) - PSUSA/00003065/202008

Applicant(s): various

PRAC Lead: Brigitte Keller-Stanislowski

Scope: Evaluation of a PSUSA procedure

16.3.15. Ziprasidone (NAP) - PSUSA/00003146/202007

Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.4. Follow-up to PSUR/PSUSA procedures

16.4.1. Canagliflozin - INVOKANA (CAP) - EMEA/H/C/002649/LEG 015

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Martin Huber

Scope: Detailed review of cases of pancreatitis as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00010077/202003) adopted in November 2020

16.4.2. Canagliflozin, metformin - VOKANAMET (CAP) - EMEA/H/C/002656/LEG 014

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Menno van der Elst

Scope: Detailed review of cases of pancreatitis as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00010077/202003) adopted in November 2020

16.4.3. Choriogonadotropin alfa - OVITRELLE (CAP) - EMEA/H/C/000320/LEG 055.1

Applicant: Merck Europe B.V.

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to LEG 055 [detailed review of criteria for classification of events as 'non-reactions' and methodology for causality assessment as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00000736/201909) adopted in April 2020] as per the request for supplementary information (RSI) adopted in September 2020

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

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

17.1. Protocols of PASS imposed in the marketing authorisation(s)⁹⁹

17.1.1. Eliglustat – CERDELGA (CAP) - EMEA/H/C/PSA/S/0054.2

Applicant: Genzyme Europe BV

PRAC Rapporteur: Eva Segovia

Scope: MAH's response to PSA/S/0054.1 [substantial amendment to a protocol previously agreed in December 2018 (PSA/S/0035) for a prospective multicentre observational post authorisation safety sub-registry to characterise the long-term safety profile of commercial use of Cerdelga (eliglustat) in adult patients with Gaucher disease] as per the request for supplementary information (RSI) adopted in November 2020

17.1.2. Lenalidomide – REVLIMID (CAP) - EMEA/H/C/PSA/S/0067

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Tiphaine Vaillant

Scope: 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)

17.1.3. Voretigene neparvovec – LUXTURN A (CAP) - EMEA/H/C/PSA/S/0066

Applicant: Novartis Europharm Limited; ATMP¹⁰⁰

PRAC Rapporteur: Brigitte Keller-Stanislowski

Scope: Substantial amendment to a protocol previously agreed in July 2019 (PSP/S/0078.1) for a post-authorisation multicentre, multinational, longitudinal, observational safety registry study to collect long-term safety information associated with voretigene neparvovec (vector and/or transgene), its subretinal injection procedure, the concomitant use of corticosteroids, or a combination of these procedures and products

⁹⁹ In accordance with Article 107n of Directive 2001/83/EC

¹⁰⁰ Advanced therapy medicinal product

17.2. Protocols of PASS non-imposed in the marketing authorisation(s)¹⁰¹

17.2.1. Coronavirus (COVID-19) vaccine (ChAdOx1-S [recombinant]) - COVID-19 VACCINE ASTRAZENECA (CAP) - EMEA/H/C/005675/MEA 006.1

Applicant: AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: MAH's response to MEA 006 [protocol for study AZD1222: a pregnancy registry of women exposed to AZD1222 (COVID-19 Vaccine AstraZeneca (COVID-19 vaccine)) immediately before or during pregnancy (C-VIPER) (from initial opinion/marketing authorisation(s) (MA))] as per the request for supplementary information (RSI) adopted in February 2021

17.2.2. Dimethyl fumarate - TECFIDERA (CAP) - EMEA/H/C/002601/MEA 008.5

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Martin Huber

Scope: 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

17.2.3. Esketamine - SPRAVATO (CAP) - EMEA/H/C/004535/MEA 002.1

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Kirsti Villikka

Scope: MAH's response to MEA 002 [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 October 2020

17.2.4. Gilteritinib - XOSPATA (CAP) - EMEA/H/C/004752/MEA 004.1

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Martin Huber

Scope: MAH's response to MEA 004 [protocol for study 2215-PV-0001: a cross-sectional survey study among healthcare professionals (HCPs) to assess awareness and knowledge, an evaluation of the effectiveness of a Xospata (gilteritinib) routine risk minimisation measures (RMM) and an additional risk minimisation measure (aRMM)] as per the request for supplementary information (RSI) adopted in October 2020

¹⁰¹ In accordance with Article 107m of Directive 2001/83/EC, supervised by PRAC in accordance with Article 61a (6) of Regulation (EC) No 726/2004

17.2.5. Isatuximab - SARCLISA (CAP) - EMEA/H/C/004977/MEA 002

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Eva Segovia

Scope: Protocol for study SARSAC09715: a non-interventional PASS survey to evaluate the effectiveness of isatuximab educational materials to minimise the risk of interference for blood typing (minor antigen) (positive indirect Coombs' test)

17.2.6. Ixekizumab - TALTZ (CAP) - EMEA/H/C/003943/MEA 005

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Protocol for study I1F-MC-B015: an observational post-marketing safety study of ixekizumab and other systemic and non-systemic treatments for paediatric psoriasis to further characterise the long-term safety of ixekizumab in paediatric patients with psoriasis with a focus on the important identified risks of inflammatory bowel disease (IBD) and serious infections

17.2.7. Naloxegol - MOVENTIG (CAP) - EMEA/H/C/002810/MEA 002.7

Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Substantial amendment to a protocol previously agreed in July 2020 for study D3820R00006: a post-marketing observational drug utilisation study (DUS) of Moventig (naloxegol) conducted in selected European populations in order to describe demographic, clinical, and treatment characteristics in the baseline of patients treated with naloxegol as well as to describe treatment pattern characteristics of naloxegol utilisation at initiation and follow-up

17.2.8. Naloxegol - MOVENTIG (CAP) - EMEA/H/C/002810/MEA 006.9

Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: 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

17.2.9. Neratinib - NERLYNX (CAP) - EMEA/H/C/004030/MEA 002.3

Applicant: Pierre Fabre Medicament

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to MEA 002.2 [protocol for study PUMA-NER-6202: a randomised study to characterise the incidence and severity of diarrhoea in patients with early stage epidermal growth factor receptor 2 + (HER2+) breast cancer treated with neratinib and intensive loperamide prophylaxis versus neratinib and intensive loperamide prophylaxis plus

a bile acid sequestrant in the first month of treatment [final study results expected in December 2021]] as per the request for supplementary information (RSI) adopted in September 2020

17.2.10. Netarsudil - RHOKIINSA (CAP) - EMEA/H/C/004583/MEA 001.1

Applicant: Aerie Pharmaceuticals Ireland Limited

PRAC Rapporteur: Eva Segovia

Scope: MAH's response to MEA 001 [Protocol for study AR-13324-OBS02: a non-interventional, observational cohort study to investigate the long-term safety of netarsudil beyond 12 months treatment [final clinical study report (CSR) expected in June 2026]] as per the request for supplementary information (RSI) adopted in September 2020

17.2.11. Ozanimod - ZEPOSIA (CAP) - EMEA/H/C/004835/MEA 001

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Protocol for study RPC-1063-MS-004 (listed as a category 3 study in the RMP): a post authorisation multinational long-term non-interventional study (ORION) study on ozanimod real world safety [final clinical study report (CSR) expected in December 2031] (from initial marketing authorisation/opinion)

17.2.12. Semaglutide - OZEMPIC (CAP) - EMEA/H/C/004174/MEA 002.2

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Annika Folin

Scope: MAH's response to MEA 002.1 [substantial amendment to a protocol previously agreed in September 2018 (MEA 002) for study NN9535-4447: an epidemiological database study to estimate the risk of pancreatic cancer in patients with type 2 diabetes mellitus (T2DM) taking semaglutide - a cohort study based on Nordic registry data [final study report expected 5 years after start of study]] as per the request for supplementary information (RSI) adopted in November 2020

17.2.13. Semaglutide - RYBELSUS (CAP) - EMEA/H/C/004953/MEA 001

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Annika Folin

Scope: Protocol for study MTC-22341: a medullary thyroid carcinoma surveillance study, a case-series registry of at least 15 years duration to systematically monitor the annual incidence of medullary thyroid carcinoma in the US and to identify any increase related to the introduction of semaglutide into the marketplace [final study report expected in February 2037] (from initial opinion/marketing authorisation)

17.2.14. Semaglutide - RYBELSUS (CAP) - EMEA/H/C/004953/MEA 002.1

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Annika Folin

Scope: MAH's response to MEA 002 [substantial amendment to a protocol previously agreed in September 2018 (MEA 002) for study NN9535-4447: an epidemiological database study to estimate the risk of pancreatic cancer in patients with type 2 diabetes mellitus (T2DM) taking semaglutide - a cohort study based on Nordic registry data [final study report expected 5 years after start of study]] as per the request for supplementary information (RSI) adopted in November 2020

17.2.15. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/MEA 044.10

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Rhea Fitzgerald

Scope: MAH's response to MEA 044.9 [substantial amendment to a protocol previously agreed in October 2019 for study CNT01275PSO4056: an observational PASS of ustekinumab in the treatment of paediatric patients aged 12 years and older with moderate to severe plaque psoriasis (adolescent registry)] as per the request for supplementary information (RSI) adopted in December 2020

17.3. Results of PASS imposed in the marketing authorisation(s)¹⁰²

None

17.4. Results of PASS non-imposed in the marketing authorisation(s)¹⁰³

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. 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 study to estimate the incidence and to compare the risks of endometrial hyperplasia and endometrial cancer in postmenopausal women initiating either Duavive (estrogens conjugated/bazedoxifene) or estrogen + progestin (E+P) combination hormone replacement therapy (HRT)

¹⁰² In accordance with Article 107p-q of Directive 2001/83/EC

¹⁰³ 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

17.4.3. [Blinatumomab - BLINCYTO \(CAP\) - EMEA/H/C/003731/II/0039, Orphan](#)

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Eva Jirsová

Scope: Submission of the final report from study 20180138 (listed as a category 3 study in the RMP: a long-term follow-up of adult Philadelphia chromosome-negative acute lymphoblastic leukaemia (ALL) relapsed refractory patients enrolled in study 00103311: a phase 3, randomized, open label study investigating the efficacy of the blinatumomab versus standard of care chemotherapy in adult subjects with relapsed/refractory B-precursor ALL (TOWER Study), in order to update the overall survival (OS) Kaplan-Meier probability estimates

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. [Epoetin zeta - RETACRIT \(CAP\) - EMEA/H/C/000872/II/0100](#)

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Martin Huber

Scope: Submission of the final study report for a joint post-authorisation safety cohort study (listed as a category 3 study in the RMP) of Retacrit/Silapo (epoetin zeta) administered subcutaneously for the treatment of renal anemia (PASCO II) in order to estimate the incidence of pure red cell aplasia (PRCA), neutralising antibodies and lack of efficacy and thromboembolic events under treatment with Retacrit/Silapo (epoetin zeta). The RMP (version 16.0) is updated accordingly

17.4.6. [Epoetin zeta - SILAPO \(CAP\) - EMEA/H/C/000760/II/0062](#)

Applicant: Stada Arzneimittel AG

PRAC Rapporteur: Martin Huber

Scope: Submission of the final study report for a joint post-authorisation safety cohort study (listed as a category 3 study in the RMP) of Retacrit/Silapo (epoetin zeta) administered subcutaneously for the treatment of renal anemia (PASCO II) in order to estimate the incidence of pure red cell aplasia (PRCA), neutralising antibodies and lack of efficacy and thromboembolic events under treatment with Retacrit/Silapo (epoetin zeta). The RMP (version 12.0) is updated accordingly

17.4.7. [Ivacaftor - KALYDECO \(CAP\) - EMEA/H/C/002494/II/0094, Orphan](#)

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Submission of the final report from study VX15-770-122 (listed as a category 3 study in the RMP): a study in US cystic fibrosis patients with the R117H-CFTR mutation to confirm the long-term safety and effectiveness of Kalydeco (ivacaftor) including patients <18 years of age, combining data captured in the cystic fibrosis foundation patient registry from an interventional cohort and a non-interventional cohort. In addition, the MAH took the opportunity to propose a change of due date for study 126 (listed as a category 3 in the RMP): a phase 3, 2-arm, open-label study to evaluate the safety and pharmacodynamics of long-term ivacaftor treatment in subjects with cystic fibrosis who are less than 24 months of age at treatment initiation and have an approved ivacaftor-responsive mutation. The RMP (version 10.1) is updated accordingly

17.4.8. Lipegfilgrastim - LONQUEx (CAP) - EMEA/H/C/002556/II/0062

Applicant: Teva B.V.

PRAC Rapporteur: Kirsti Villikka

Scope: Submission of the final report from study XM22-ONC-5002 (listed as a category 3 study in the RMP): a drug utilisation study (DUS) on the prescribing patterns of lipegfilgrastim in the EU. The RMP (version 13.0) is updated accordingly

17.4.9. Lurasidone - LATUDA (CAP) - EMEA/H/C/002713/II/0033

Applicant: Aziende Chimiche Riunite Angelini Francesco A.C.R.A.F. S.p.A.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of the final study report for a non-interventional PASS on the evaluation of the safety profile of lurasidone: a PASS using United States administrative claims databases in order to compare the incidence of important identified risks and important potential risks in patients treated with lurasidone to patients treated with other second-generation oral atypical antipsychotics (OAA's)

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

17.5.1. Alemtuzumab - LEMTRADA (CAP) - EMEA/H/C/003718/MEA 007.10

Applicant: Sanofi Belgium

PRAC Rapporteur: Anette Kirstine Stark

Scope: Five-year interim report for study OBS13434: a prospective, multicentre, observational PASS to evaluate the long-term safety profile of Lemtrada (alemtuzumab) treatment in patients with relapsing forms of multiple sclerosis (MS) and to determine the incidence of adverse events of special interest (AESIs)

17.5.2. Alglucosidase alfa - MYOZYME (CAP) - EMEA/H/C/000636/MEA 024.14

Applicant: Genzyme Europe BV

PRAC Rapporteur: Adrien Inoubli

Scope: Annual report 2020 on adverse events and/or lack of efficacy, immunological data, follow-up growth disturbances in children and data on urinary hexose tetrasaccharide (Hex4) from the Pompe registry: a global, multicentre, observational and voluntary programme designed to collect uniform and meaningful clinical data related to the onset, progression, and treated course of patients with Pompe disease irrespective of treatment status [final clinical study report expected in Q4 2021]

17.5.3. Alglucosidase alfa - MYOZYME (CAP) - EMEA/H/C/000636/MEA 025.14

Applicant: Genzyme Europe BV

PRAC Rapporteur: Adrien Inoubli

Scope: Annual report 2020 on data on patients with renal or hepatic insufficiency from the Pompe registry: a global, multicentre, observational and voluntary programme designed to collect uniform and meaningful clinical data related to the onset, progression, and treated course of patients with Pompe disease irrespective of treatment status [final clinical study report expected in Q4 2021]

17.5.4. Alirocumab - PRALUENT (CAP) - EMEA/H/C/003882/MEA 017.7

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Fourth interim report for study ALIROC07997: a non-interventional safety study using healthcare databases to monitor the safety of Praluent (alirocumab) in patients affected with human immunodeficiency virus (HIV)

17.5.5. Apremilast - OTEZLA (CAP) - EMEA/H/C/003746/MEA 006.5

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Eva Segovia

Scope: Five-year interim results for the UK clinical practice research datalink (CPRD) database data analysis for psoriatic arthritis (PsA) and psoriasis [due date: CPRD data analysis at years 1, 3 and 5 starting from the date of first commercial availability in the UK. Final clinical study report (CSR) expected in June 2021]

17.5.6. Cinacalcet - MIMPARA (CAP) - EMEA/H/C/000570/MEA 035.2

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: First interim report for study 20180204: a registry study to evaluate the incidence and risk of hypocalcaemia in paediatric patients treated with cinacalcet with secondary hyperparathyroidism receiving maintenance dialysis within the International Pediatric Dialysis Network (IPDN) registry

17.5.7. Denosumab - PROLIA (CAP) - EMEA/H/C/001120/LEG 041.1

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Annual interim report year for study 20090522: a PASS on denosumab global safety assessment among women with postmenopausal osteoporosis (PMO) and men with osteoporosis in multiple observational databases [final report expected in 2023]

17.5.8. Eculizumab - SOLIRIS (CAP) - EMEA/H/C/000791/MEA 053.4

Applicant: Alexion Europe SAS

PRAC Rapporteur: Eva Segovia

Scope: Biennial interim report for study M07-001: a prospective registry for an observational, multicentre, multinational study of patients with paroxysmal nocturnal haemoglobinuria (PNH) including MAH's response to MEA 051.1 as per the request for supplementary information (RSI) adopted in March 2019

17.5.9. Empagliflozin - JARDIANCE (CAP) - EMEA/H/C/002677/MEA 005.3

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Eva Segovia

Scope: Fourth interim report for enhanced pharmacovigilance study 1245.146 to evaluate the risk of diabetic ketoacidosis (DKA) in patients treated with empagliflozin-containing product(s) as discussed with the FDA and requested in the conclusions of the referral procedure on sodium-glucose cotransporter-2 (SGLT2) inhibitors under Article 20 of Regulation (EC) No 726/2004 on diabetic ketoacidosis (DKA) (EMA/H/A-20/1419) finalised in 2016 [final clinical study report (CSR) expected in Q4/2021], including MAH's responses to MEA 005.2 as per the request for supplementary information (RSI) adopted in March 2020

17.5.10. Empagliflozin, linagliptin - GLYXAMBI (CAP) - EMEA/H/C/003833/MEA 005.3

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Eva Segovia

Scope: Fourth interim report for enhanced pharmacovigilance study 1245.146 to evaluate the risk of diabetic ketoacidosis (DKA) in patients treated with empagliflozin-containing product(s) as discussed with the FDA and requested in the conclusions of the referral procedure on sodium-glucose cotransporter-2 (SGLT2) inhibitors under Article 20 of Regulation (EC) No 726/2004 on diabetic ketoacidosis (DKA) (EMA/H/A-20/1419) finalised in 2016 [final clinical study report (CSR) expected in Q4/2021], including MAH's responses to MEA 005.2 as per the request for supplementary information (RSI) adopted in March 2020

17.5.11. Empagliflozin, metformin - SYNJARDY (CAP) - EMEA/H/C/003770/MEA 002.3

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Eva Segovia

Scope: Fourth interim report for enhanced pharmacovigilance study 1245.146 to evaluate the risk of diabetic ketoacidosis (DKA) in patients treated with empagliflozin-containing

product(s) as discussed with the FDA and requested in the conclusions of the referral procedure on sodium-glucose cotransporter-2 (SGLT2) inhibitors under Article 20 of Regulation (EC) No 726/2004 on diabetic ketoacidosis (DKA) (EMA/H/A-20/1419) finalised in 2016 [final clinical study report (CSR) expected in Q4/2021], including MAH's responses to MEA 002.2 as per the request for supplementary information (RSI) adopted in March 2020

17.5.12. Imatinib - GLIVEC (CAP) - EMA/H/C/000406/ANX 191.9

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Eva Segovia

Scope: Seventh progress report for study CSTI571I2201: a European observational registry collecting efficacy and safety data in newly diagnosed paediatric Philadelphia positive (Ph+) acute lymphoblastic leukaemia (ALL) patients treated with chemotherapy + imatinib ± haematopoietic stem cell treatment (±HSCT)

17.5.13. Plasmodium falciparum and hepatitis B vaccine (recombinant, adjuvanted) - MOSQUIRIX (Art 58¹⁰⁴) - EMA/H/W/002300/MEA 003.4

Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Jean-Michel Dogné

Scope: Third annual progress report for study EPI-MAL-003 (listed as a category 3 study in the RMP): a phase 4 prospective observational study to evaluate the safety, effectiveness and impact of Mosquirix (plasmodium falciparum and hepatitis B vaccine (recombinant, adjuvanted)) in young children in sub-Saharan Africa in order to estimate the incidence of potential adverse events of special interest (AESI) and other adverse events leading to hospitalisation or death, in children vaccinated with the vaccine

17.5.14. Nonacog beta pegol - REFIXIA (CAP) - EMA/H/C/004178/LEG 006.1

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Yearly progress report for PASS NN7999-4031 (Paradigm 8): a non-interventional study in male haemophilia B patients receiving nonacog beta pegol (N9-GP) prophylaxis treatment to investigate the potential effects of PEG accumulation in the choroid plexus of the brain and other tissues/organs

17.5.15. Romiplostim - NPLATE (CAP) - EMA/H/C/000942/MEA 003.8

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Eva Segovia

Scope: Interim report for surveillance study 20070797: a population based prospective study evaluating the short and long term safety of romiplostim treatment in real-life clinical practice in adult patients with chronic idiopathic (immune) thrombocytopenic purpura (ITP)

¹⁰⁴ Article 58 of Regulation (EC) No 726/2004 allows the Committee for Medicinal Products for Human Use (CHMP) to give opinions, in co-operation with the World Health Organisation (WHO) on medicinal products for human use that are intended exclusively for markets outside of the European Union (EU)

based on national health registry systems in Denmark, Sweden, and Norway (Nordic Country Patient Registry for Romiplostim [NCPRR])

17.5.16. Teduglutide - REVESTIVE (CAP) - EMEA/H/C/002345/ANX 003.6

Applicant: Shire Pharmaceuticals Ireland Limited

PRAC Rapporteur: Anette Kirstine Stark

Scope: 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

17.5.17. Tezacaftor, ivacaftor - SYMKEVI (CAP) - EMEA/H/C/004682/MEA 002.3

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Annual interim report for study VX17-661-117 (study 117) (listed as a category 3 study in the RMP): an observational cohort study on utilisation patterns and real-world effects of tezacaftor and ivacaftor combination therapy (TEZ/IVA) in patients with cystic fibrosis (CF) [final report expected in December 2023]

17.5.18. Tildrakizumab - ILUMETRI (CAP) - EMEA/H/C/004514/MEA 003.3

Applicant: Almirall S.A

PRAC Rapporteur: Adam Przybylowski

Scope: Annual progress report 2020 for study M-14745-40: a European psoriasis registry to collect long-term safety data for tildrakizumab and to further characterise the long-term safety profile of tildrakizumab in the treatment of psoriasis under conditions of routine clinical practice

17.5.19. Venetoclax - VENCLYXTO (CAP) - EMEA/H/C/004106/MEA 002.7

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Eva Jirsová

Scope: Third annual study progress report for study P16-562 (listed as a category 3 study in the RMP): a prospective observational study to assess the long-term safety profile of venetoclax in a Swedish cohort of chronic lymphocytic leukaemia (CLL) patients [final clinical study report expected in December 2025]

17.5.20. Vonicog alfa - VEYVONDI (CAP) - EMEA/H/C/004454/MEA 001.3

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Interim report for study VON (BAX0111) VWF-500 COL (also called ATHN-9 study) (listed as a category 3 study in the RMP): a real world safety and effectiveness study of factor replacement for clinically severe von Willebrand disease (VWD) [final report expected

in 2022]

17.6. Others

17.6.1. Coronavirus (COVID-19) mRNA¹⁰⁵ vaccine (nucleoside-modified) - COVID-19 VACCINE MODERNA (CAP) - EMEA/H/C/005791/MEA 004

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Hans Christian Siersted

Scope: Feasibility assessment 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 mRNA-1273 Vaccine in the EU - an enhanced pharmacovigilance study to provide additional evaluation of adverse events of special interest (AESI) and emerging validated safety signals in European populations; Electronic database assessment of use in pregnant women) [final clinical study report (CSR) expected in December 2023] (from initial opinion/marketing authorisation)

17.6.2. Ertugliflozin - STEGLATRO (CAP) - EMEA/H/C/004315/MEA 002.2

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Feasibility assessment for study 8835-062/000: a PASS to assess the risk of diabetic ketoacidosis (DKA) among patients with type 2 diabetes mellitus (T2DM) treated with ertugliflozin compared to patients treated with other antihyperglycemic agents [final study report due date: December 2023]

17.6.3. Ertugliflozin, metformin hydrochloride - SEGLUROMET (CAP) - EMEA/H/C/004314/MEA 002.2

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Feasibility assessment for study 8835-062/000: a PASS to assess the risk of diabetic ketoacidosis (DKA) among patients with type 2 diabetes mellitus (T2DM) treated with ertugliflozin compared to patients treated with other antihyperglycemic agents [final study report due date: December 2023]

17.6.4. Ertugliflozin, sitagliptin - STEGLUJAN (CAP) - EMEA/H/C/004313/MEA 002.2

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Feasibility assessment for study 8835-062/000: a PASS to assess the risk of diabetic ketoacidosis (DKA) among patients with type 2 diabetes mellitus (T2DM) treated with ertugliflozin compared to patients treated with other antihyperglycemic agents [final study report due date: December 2023]

¹⁰⁵ Messenger ribonucleic acid

17.6.5. Fingolimod - GILENYA (CAP) - EMEA/H/C/002202/MEA 038.2

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Tiphaine Vaillant

Scope: 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

17.7. New Scientific Advice

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

17.8. Ongoing Scientific Advice

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

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

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

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

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

18.1. Annual reassessments of the marketing authorisation

18.1.1. Histamine dihydrochloride – CEPLENE (CAP) - EMEA/H/C/000796/S/0042

Applicant: Noventia Pharma S.r.l.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Annual reassessment of the marketing authorisation

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

Applicant: Santhera Pharmaceuticals (Deutschland) GmbH

PRAC Rapporteur: Amelia Cupelli

Scope: Annual reassessment of the marketing authorisation

18.1.3. Susoctocog alfa - OBIZUR (CAP) - EMEA/H/C/002792/S/0039 (without RMP)

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Annual reassessment of the marketing authorisation

18.1.4. Tafamidis - VYNDAQEL (CAP) - EMEA/H/C/002294/S/0065 (without RMP)

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Tiphaine Vaillant

Scope: Annual reassessment of the marketing authorisation

18.2. Conditional renewals of the marketing authorisation

18.2.1. Entrectinib - ROZLYTREK (CAP) - EMEA/H/C/004936/R/0002 (without RMP)

Applicant: Roche Registration GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Conditional renewal of the marketing authorisation

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

Applicant: Novartis Gene Therapies EU Limited, ATMP¹⁰⁶

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Conditional renewal of the marketing authorisation

18.3. Renewals of the marketing authorisation

18.3.1. Cemiplimab - LIBTAYO (CAP) - EMEA/H/C/004844/R/0017 (without RMP)

Applicant: Regeneron Ireland Designated Activity Company (DAC)

PRAC Rapporteur: Menno van der Elst

Scope: 5-year renewal of the marketing authorisation

18.3.2. Glycopyrronium - SIALANAR (CAP) - EMEA/H/C/003883/R/0018 (without RMP)

Applicant: Proveca Pharma Limited

PRAC Rapporteur: Zane Neikena

Scope: 5-year renewal of the marketing authorisation

¹⁰⁶ Advanced therapy medicinal product

18.3.3. Lenvatinib - KISPLYX (CAP) - EMEA/H/C/004224/R/0043 (without RMP)

Applicant: Eisai GmbH

PRAC Rapporteur: David Olsen

Scope: 5-year renewal of the marketing authorisation

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

Applicant: AstraZeneca AB

PRAC Rapporteur: Ilaria Baldelli

Scope: 5-year renewal of the marketing authorisation

Action: For adoption of advice to CHMP

18.3.5. Tenofovir disoproxil - TENOFOVIR DISOPROXIL ZENTIVA (CAP) - EMEA/H/C/004120/R/0023 (without RMP)

Applicant: Zentiva k.s.

PRAC Rapporteur: Adrien Inoubli

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 08-11 March 2021 meeting (marked as 'a'), additionally for the 18 March 2021 extraordinary meeting (marked as 'b'), and for the 25 March 2021 ORGAM teleconference (marked as 'c').

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Sabine Straus ^{a, b, c}	Chair	Netherlands	No interests declared	Full involvement
Jan Neuhauser ^{a, b, c}	Member	Austria	No interests declared	Full involvement
Sonja Hrabcik ^{a, b}	Alternate	Austria	No interests declared	Full involvement
Jean-Michel Dogné ^{a, b}	Member	Belgium	No interests declared	Full involvement
Laurence de Fays ^{a, b, c}	Alternate	Belgium	No interests declared	Full involvement
Maria Popova-Kiradjieva ^{a, b, c}	Member	Bulgaria	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
Julian Eftimov ^b	Alternate	Bulgaria	No interests declared	Full involvement
Nikica Mirošević Skvrce ^{a, b, c}	Member	Croatia	No interests declared	Full involvement
Panagiotis Psaras ^{a, b}	Member	Cyprus	No interests declared	Full involvement
Christina Sylvia Chrysostomou ^{a, b, c}	Alternate	Cyprus	No interests declared	Full involvement
Eva Jirsová ^{a, b, c}	Member	Czechia	No interests declared	Full involvement
Jana Lukacisinova ^{a, b, c}	Alternate	Czechia	No interests declared	Full involvement
Anette Kirstine Stark ^{a, b, c}	Member	Denmark	No interests declared	Full involvement
Hans Christian Siersted ^{a, b, c}	Alternate	Denmark	No restrictions applicable to this meeting	Full involvement
Maia Uusküla ^{a, b, c}	Member	Estonia	No interests declared	Full involvement
Katrin Kiisk ^b	Alternate	Estonia	No interests declared	Full involvement
Kirsti Villikka ^{a, b, c}	Member	Finland	No interests declared	Full involvement
Kimmo Jaakkola ^{a, b, c}	Alternate	Finland	No interests declared	Full involvement
Adrien Inoubli ^{a, b, c}	Member	France	No interests declared	Full involvement
Tiphaine Vaillant ^{a, b, c}	Alternate	France	No interests declared	Full involvement
Martin Huber ^{a, b, c}	Member (Vice-Chair)	Germany	No interests declared	Full involvement
Brigitte Keller-Stanislawski ^{a, b}	Alternate	Germany	No interests declared	Full involvement
Agni Kapou ^{a, b, c}	Member	Greece	No interests declared	Full involvement
Julia Pallos ^{a, b, c}	Member	Hungary	No restrictions applicable to this meeting	Full involvement
Melinda Palfi ^{a, b}	Alternate	Hungary	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Guðrún Stefánsdóttir a, b, c	Member	Iceland	No participation in discussion, final deliberations and voting on:	6.5.2. Pegfilgrastim - NEULASTA (CAP) - II/0114 15.3.6. Evolocumab - REPATHA (CAP) - II/0048 17.2.4. Gilteritinib - XOSPATA (CAP) - MEA 004.1 17.4.3. Blinatumomab - BLINCYTO (CAP) - II/0039 17.5.5. Apremilast - OTEZLA (CAP) - MEA 006.5 17.5.6. Cinacalcet - MIMPARA (CAP) - MEA 035.2 17.5.7. Denosumab - PROLIA (CAP) - LEG 041.1 17.5.15. Romiplostim - NPLATE (CAP) - MEA 003.8
Rhea Fitzgerald a, b, c	Member	Ireland	No interests declared	Full involvement
Amelia Cupelli a, b, c	Member	Italy	No interests declared	Full involvement
Ilaria Baldelli a, b, c	Alternate	Italy	No interests declared	Full involvement
Zane Neikena a, b, c	Member	Latvia	No interests declared	Full involvement
Rugile Pilviniene a, b, c	Member	Lithuania	No interests declared	Full involvement
Nadine Petitpain b, c	Member	Luxembourg	No restrictions applicable to this meeting	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Anne-Cécile Vuillemin a, b, c	Alternate	Luxembourg	No interests declared	Full involvement
John Joseph Borg a, b, c	Member (CHMP member)	Malta	No interests declared	Full involvement
Benjamin Micallef a, b	Alternate	Malta	No interests declared	Full involvement
Menno van der Elst a, b, c	Member	Netherlands	No interests declared	Full involvement
Liana Gross-Martirosyan a, b, c	Alternate	Netherlands	No interests declared	Full involvement
David Olsen a, b, c	Member	Norway	No participation in final deliberations and voting on:	5.1.4. Vericiguat - EMEA/H/C/005319 6.3.9. Naproxen (NAP) - PSUSA/00002125/202008 6.3.10. Oxymetazoline (NAP) - PSUSA/00002258/202008 7.3.2. Rivaroxaban – XARELTO (CAP) - EMEA/H/C/PSR/S/0027 7.4.1. Aflibercept - EYLEA (CAP) - II/0068 16.3.11. Niclosamide (NAP) - PSUSA/00002151/202008
Karen Pernille Harg a, b, c	Alternate	Norway	No interests declared	Full involvement
Adam Przybylowski a, b, c	Member	Poland	No interests declared	Full involvement
Katarzyna Ziolkowska a, b, c	Alternate	Poland	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
Ana Diniz Martins ^{a, b, c}	Member	Portugal	No interests declared	Full involvement
Marcia Silva ^{a, b, c}	Alternate	Portugal	No interests declared	Full involvement
Roxana Dondera ^{a, b, c}	Member	Romania	No interests declared	Full involvement
Alexandra - Maria Spurni ^{a, b, c}	Alternate	Romania	No interests declared	Full involvement
Michal Radik ^{a, b, c}	Member	Slovakia	No interests declared	Full involvement
Marek Juracka ^{a, b, c}	Alternate	Slovakia	No interests declared	Full involvement
Gabriela Jazbec ^{a, b, c}	Member	Slovenia	No interests declared	Full involvement
Jasmina Klopčič ^b	Alternate	Slovenia	No interests declared	Full involvement
Eva Segovia ^{a, b, c}	Member	Spain	No interests declared	Full involvement
Maria del Pilar Rayon ^{a, b, c}	Alternate	Spain	No interests declared	Full involvement
Ulla Wändel Liminga ^{a, b, c}	Member	Sweden	No interests declared	Full involvement
Annika Folin ^{a, b}	Alternate	Sweden	No interests declared	Full involvement
Birgitta Grundmark ^{a, b}	Member	Independent scientific expert	No interests declared	Full involvement
Daniel Morales ^{a, b}	Member	Independent scientific expert	No interests declared	Full involvement
Hedvig Nordeng ^{a, b}	Member	Independent scientific expert	No interests declared	Full involvement
Antoine Pariente ^{a, b}	Member	Independent scientific expert	No participation in final deliberations and voting on:	5.1.3. Obeticholic acid - MEA/H/C/005249
Milou Daniel Drici ^{a, b, c}	Member	Independent scientific expert	No restrictions applicable to this meeting	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Stefan Weiler ^{a, b}	Member	Independent scientific expert	No restrictions applicable to this meeting	Full involvement
Raymond Anderson ^{a, b}	Member	Healthcare Professionals ' Representative	No interests declared	Full involvement
Roberto Frontini ^{a, b, c}	Alternate	Healthcare Professionals ' Representative	No restrictions applicable to this meeting	Full involvement
Cathalijne van Doorne ^{a, b}	Member	Patients' Organisation Representative	No interests declared	Full involvement
Virginie Hivert ^{a, b, c}	Alternate	Patients' Organisation Representative	No restrictions applicable to this meeting	Full involvement
Ulrike Heissenberger ^b	Expert - via telephone*	Austria	No interests declared	Full involvement
Andrea Laslop ^b	Expert - via telephone*	Austria	No interests declared	Full involvement
Daniela Philadelph ^b	Expert - via telephone*	Austria	No interests declared	Full involvement
Christelle Bizimungu ^{a, b, c}	Expert - via telephone*	Belgium	No restrictions applicable to this meeting	Full involvement
Jamila Hamdani ^b	Expert - via telephone*	Belgium	No interests declared	Full involvement
Cédric Hermans ^b	Expert - via telephone*	Belgium	Expert witness for:	4.1.5. COVID-19 vaccine (ChAdOx1-S [recombinant]) - COVID-19 VACCINE ASTRAZENECA (CAP)

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Flora Musuamba Tshinanu ^b	Expert - via telephone*	Belgium	No restrictions applicable to this meeting	Full involvement
Martine Sabbe ^{a, b, c}	Expert - via telephone*	Belgium	No interests declared	Full involvement
Charlotte Selvais ^c	Expert - via telephone*	Belgium	No interests declared	Full involvement
Françoise Wuillaume ^{a, b}	Expert - via telephone*	Belgium	No interests declared	Full involvement
Ilko Getov ^b	Expert - via telephone*	Bulgaria	No interests declared	Full involvement
Barbara Kovačić ^a	Expert - via telephone*	Croatia	No interests declared	Full involvement
Nina Lalić ^a	Expert - via telephone*	Croatia	No restrictions applicable to this meeting	Full involvement
Ivana Ljubičić ^{a, b}	Expert - via telephone*	Croatia	No restrictions applicable to this meeting	Full involvement
Sanja Prpić ^a	Expert - via telephone*	Croatia	No restrictions applicable to this meeting	Full involvement
Petra Kaftanová ^{b, c}	Expert - via telephone*	Czechia	No interests declared	Full involvement
Annette Cleveland Nielsen ^a	Expert - via telephone*	Denmark	No restrictions applicable to this meeting	Full involvement
Karin Erneholm ^{a, b, c}	Expert - via telephone*	Denmark	No restrictions applicable to this meeting	Full involvement
Peter Horskjær Rose ^a	Expert - via telephone*	Denmark	No interests declared	Full involvement
Marian Hjortlund Allon ^a	Expert - via telephone*	Denmark	No interests declared	Full involvement
Kirstine Moll Harboe ^{a, b}	Expert - via telephone*	Denmark	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Emma Louise Nautrup Ravn Stadsbjerg ^{a, b, c}	Expert - via telephone*	Denmark	No interests declared	Full involvement
Moritz Sander ^a	Expert - via telephone*	Denmark	No interests declared	Full involvement
Per Sindahl ^a	Expert - via telephone*	Denmark	No interests declared	Full involvement
Josiane Uwera ^a	Expert - via telephone*	Denmark	No interests declared	Full involvement
Anita Vibsig Neutzsky-Wulff ^a	Expert - via telephone*	Denmark	No interests declared	Full involvement
Caroline Marie Voss ^a	Expert - via telephone*	Denmark	No interests declared	Full involvement
Päivi Susanna Worsøe ^{a, c}	Expert - via telephone*	Denmark	No interests declared	Full involvement
Martin Zahle Larsen ^a	Expert - via telephone*	Denmark	No interests declared	Full involvement
Kroot Aab ^a	Expert - via telephone*	Estonia	No interests declared	Full involvement
Alar Irs ^b	Expert - via telephone*	Estonia	No restrictions applicable to this meeting	Full involvement
Edward Laane ^b	Expert - via telephone*	Estonia	No restrictions applicable to this meeting	Full involvement
Violaine Closson-Carella ^a	Expert - via telephone*	France	No interests declared	Full involvement
Emmanuel Doyen ^a	Expert - via telephone*	France	No interests declared	Full involvement
Emiliano Gemma ^a	Expert - via telephone*	France	No restrictions applicable to this meeting	Full involvement
Alexis Jacquet ^{a, b}	Expert - via telephone*	France	No restrictions applicable to this meeting	Full involvement
Isabelle Parent du Chatelet ^b	Expert - via telephone*	France	No interests declared	Full involvement
Jean-Michel Race ^b	Expert - via telephone*	France	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
Faustine Vidil ^a	Expert - via telephone*	France	No interests declared	Full involvement
Harald Enzmann ^b	Expert - via telephone*	Germany	No interests declared	Full involvement
Dennis Lex ^{a, c}	Expert - via telephone*	Germany	No restrictions applicable to this meeting	Full involvement
Kerstin Löschcke ^a	Expert - via telephone*	Germany	No interests declared	Full involvement
Jan Mueller-Berghaus ^b	Expert - via telephone*	Germany	No interests declared	Full involvement
Susanne Mueller ^a	Expert - via telephone*	Germany	No restrictions applicable to this meeting	Full involvement
Martina Schussler-Lenz ^a	Expert - via telephone*	Germany	No interests declared	Full involvement
Konstantinos Markopoulos ^b	Expert - via telephone*	Greece	No interests declared	Full involvement
Agnes Gyurasics ^b	Expert - via telephone*	Hungary	No interests declared	Full involvement
Hrefna Gudmundsdottir ^b	Expert - via telephone*	Iceland	No restrictions applicable to this meeting	Full involvement
Jayne Crowe ^b	Expert - via telephone*	Ireland	No interests declared	Full involvement
Grainne Kirwan ^{a, b}	Expert - via telephone*	Ireland	No interests declared	Full involvement
Alessandro Aiuti ^a	Expert - via telephone*	Italy	No restrictions applicable to this meeting	Full involvement
Sara Galluzzo ^b	Expert - via telephone*	Italy	No interests declared	Full involvement
Elita Poplavska ^b	Expert - via telephone*	Latvia	No interests declared	Full involvement
Simona Stankeviciute ^b	Expert - via telephone*	Lithuania	No interests declared	Full involvement
Helen Vella ^b	Expert - via telephone*	Malta	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
Carla Herberts ^a	Expert - via telephone*	The Netherlands	No interests declared	Full involvement
Johann Lodewijk Hillege ^b	Expert - via telephone*	The Netherlands	No interests declared	Full involvement
Marcel Hoefnagel ^b	Expert - via telephone*	The Netherlands	No interests declared	Full involvement
Marianne Klanker ^a	Expert - via telephone*	The Netherlands	No interests declared	Full involvement
Peter Mol ^c	Expert - via telephone*	The Netherlands	No interests declared	Full involvement
Martijn van der Plas ^b	Expert - via telephone*	The Netherlands	No interests declared	Full involvement
Paula van Hennik ^b	Expert - via telephone*	The Netherlands	No interests declared	Full involvement
Inge Zomerdijk ^a	Expert - via telephone*	The Netherlands	No interests declared	Full involvement
Bjorg Bolstad ^b	Expert - via telephone*	Norway	No restrictions applicable to this meeting	Full involvement
Anja Schiel ^b	Expert - via telephone*	Norway	No interests declared	Full involvement
Ingrid Wang ^b	Expert - via telephone*	Norway	No interests declared	Full involvement
Ewa Balkowiec Iskra ^b	Expert - via telephone*	Poland	No interests declared	Full involvement
Bruno Sepodes ^{a, b}	Expert - via telephone*	Portugal	No interests declared	Full involvement
Carla Torre ^b	Expert - via telephone*	Portugal	No interests declared	Full involvement
Fatima Ventura ^b	Expert - via telephone*	Portugal	No participation in final deliberations and voting on:	4.1.5. COVID-19 vaccine (ChAdOx1-S [recombinant]) - COVID-19 VACCINE ASTRAZENECA (CAP)
Simona Badoi ^b	Expert - via telephone*	Romania	No interests declared	Full involvement
Dana Marin ^b	Expert - via telephone*	Romania	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Roxana Stroe ^b	Expert - via telephone*	Romania	No interests declared	Full involvement
Maria Chamorro Somoza ^{a, b}	Expert - via telephone*	Spain	No interests declared	Full involvement
Susana López Hernández ^b	Expert - via telephone*	Spain	No interests declared	Full involvement
María Martínez González ^c	Expert - via telephone*	Spain	No restrictions applicable to this meeting	Full involvement
Luz Medrano de Dios ^a	Expert - via telephone*	Spain	No interests declared	Full involvement
Consuelo Mejias Pavón ^c	Expert - via telephone*	Spain	No interests declared	Full involvement
Fernando Méndez Hermida ^b	Expert - via telephone*	Spain	No interests declared	Full involvement
Milena Peraita Ezcurra ^b	Expert - via telephone*	Spain	No interests declared	Full involvement
Alicia Pérez ^b	Expert - via telephone*	Spain	No interests declared	Full involvement
Sol Ruiz ^b	Expert - via telephone*	Spain	No interests declared	Full involvement
Ana Sagredo ^{a, b}	Expert - via telephone*	Spain	No interests declared	Full involvement
Marcos Timon ^b	Expert - via telephone*	Spain	No interests declared	Full involvement
Helena Back ^a	Expert - via telephone*	Sweden	No interests declared	Full involvement
Charlotte Backman ^{a, b}	Expert - via telephone*	Sweden	No interests declared	Full involvement
Sofia Bosdotter Enroth ^b	Expert - via telephone*	Sweden	No interests declared	Full involvement
Jolanta Gulbinovic ^a	Expert - via telephone*	Sweden	No interests declared	Full involvement
Jessica Mwinyi ^a	Expert - via telephone*	Sweden	No interests declared	Full involvement
A representative from the European Commission attended the meeting				
Meeting run with support from relevant EMA staff				

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

20. Annex III - List of acronyms and abbreviations

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

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

21. Explanatory notes

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

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

(Items 2 and 3 of the PRAC minutes)

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

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

Signals assessment and prioritisation

(Item 4 of the PRAC minutes)

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

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

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

Risk Management Plans (RMPs)

(Item 5 of the PRAC minutes)

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

Assessment of Periodic Safety Update Reports (PSURs)

(Item 6 of the PRAC minutes)

A PSUR is a report providing an evaluation of the benefit-risk balance of a medicine, which is submitted by marketing authorisation holders at defined time points following a medicine's authorisation.

PSURs summarises data on the benefits and risks of a medicine and includes the results of all studies carried out with this medicine (in the authorised and unauthorised indications).

Post-authorisation Safety Studies (PASS)

(Item 7 of the PRAC minutes)

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

Product related pharmacovigilance inspections

(Item 9 of the PRAC minutes)

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

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

<http://www.ema.europa.eu/ema/>