27 March 2025
EMA/PRAC/592992/2024 Corr.1[1]
Human Medicines Division

Pharmacovigilance Risk Assessment Committee (PRAC)

Minutes of PRAC meeting on 25 - 28 November 2024

Chair: Ulla Wändel Liminga – Vice-Chair: Liana Martirosyan

Health and safety information

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

Disclaimers

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

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

Note on access to documents

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

[1] Section 7 numbering corrected due to previously missing section '7.4 Results of PASS non-imposed in the marketing authorisation(s)'

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1. Introduction

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

The Chair opened the meeting by welcoming all participants. The meeting was held in-person.

In accordance with the Agency's policy on handling of declarations of interests of scientific Committees' members and experts, based on the declarations of interest submitted by the Committee members, alternates[2] and experts and on the topics in the agenda of the meeting, the Committee Secretariat announced the restricted involvement of some Committee members, alternates and experts for concerned agenda topics. Participants were asked to declare any changes, omissions or errors to their declared interests concerning the matters for discussion. Restrictions applicable to this meeting are captured in the List of participants included in the minutes.

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 the Rules of Procedure (EMA/PRAC/567515/2012 Rev.3). All decisions taken at this meeting were made in the presence of a quorum of members. All decisions, recommendations and advice were agreed by consensus, unless otherwise specified.

The Chair welcomed the new member(s) and alternate(s) and thanked the departing members/alternates for their contributions to the Committee.

The EMA Secretariat announced the names of the Committee members who delegated their vote via proxy and the Committee members who received such proxy.

1.2. Agenda of the meeting on 25-28 November 2024

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

1.3. Minutes of the previous meeting on 28-31 October 2024

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 28-31 October 2024 were published on the EMA website on 15 January 2025 (EMA/PRAC/583624/2024).

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

2.1. Newly triggered procedures

None

[2] No alternates for COMP

2.2. Ongoing procedures

None

2.3. Procedures for finalisation

None

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

3.1. Newly triggered procedures

None

3.2. Ongoing procedures

None

3.3. Procedures for finalisation

None

3.4. Re-examination procedures[3]

None

3.5. Others

None

4. Signals assessment and prioritisation[4]

For further details, see also the adopted PRAC recommendations on signals under the corresponding month.

4.1. New signals detected from EU spontaneous reporting systems and/or other sources

See also Annex I 14.1.

4.1.1. Adalimumab – AMGEVITA (CAP); AMSPARITY (CAP); HEFIYA (CAP); HUKYNDRA (CAP); HULIO (CAP); HUMIRA (CAP); HYRIMOZ (CAP); IDACIO (CAP); IMRALDI (CAP); LIBMYRIS (CAP); YUFLYMA (CAP)

Applicants: AbbVie Deutschland GmbH & Co. KG (Humira), Amgen Europe B.V. (Amgevita),

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

Biosimilar Collaborations Ireland (Hulio), Celltrion Healthcare Hungary Kft. (Yuflyma), Pfizer Europe MA EEIG (Amsparity), Fresenius Kabi Deutschland GmbH (Idacio), Samsung Bioepis NL B.V. (Imraldi), Sandoz GmbH (Hefiya, Hyrimoz), STADA Arzneimittel AG (Hukyndra, Libmyris)

PRAC Rapporteur: Karin Bolin

Scope: Signal of paradoxical hidradenitis

EPITT 20126 – New signal

Background

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

During routine signal detection activities, a signal of paradoxical hidradenitis was identified by the Spanish Agency of Medicines and Medical Devices (AEMPS), based on 11 cases retrieved from the Spanish spontaneous reporting database (FEDRA) and 2,577 from EudraVigilance as well as the literature. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by PRAC.

Discussion

Having considered the available evidence from case reports in EudraVigilance and the literature, PRAC agreed that further evaluation on the signal of paradoxical hidradenitis is warranted.

Summary of recommendation(s)

- The MAH for the innovator product Humira (adalimumab) should submit to EMA, within 60 days, a cumulative review of the signal, including an analysis of all case reports of MedDRA preferred terms (PTs) hidradenitis, paradoxical skin reaction and paradoxical drug reaction, but only cases of paradoxical hidradenitis should be presented, as well as a discussion on the need for any potential amendment to the product information (PI) and/ or the risk management plan (RMP).
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.2. Signals follow-up and prioritisation

4.2.1. Azathioprine - JAYEMPI (CAP), NAP - EMEA/H/C/005055/SDA/003

Applicant(s): Lipomed GmbH, various

PRAC Rapporteur: Karin Erneholm

Scope: Signal of non-cirrhotic portal hypertension/portosinusoidal vascular disease

EPITT 20091 – Follow-up to July 2024

Background

For background information, see PRAC minutes July 2024.

The MAHs replied to the request for information on the signal of non-cirrhotic portal hypertension/portosinusoidal vascular disease and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence in EudraVigilance, from the literature, and the responses of the MAHs, PRAC concluded that there is sufficient evidence to establish a causal association between azathioprine and non-cirrhotic portal hypertension/portosinusoidal vascular disease. Therefore, the product information should be updated to add non-cirrhotic portal hypertension/portosinusoidal vascular disease as a warning and as an undesirable effect with a frequency 'not known'.

Summary of recommendation(s)

- The MAHs for the azathioprine-containing products should submit to EMA, within 60 days, a variation to amend the product information[5].

4.2.2. Doxycycline (NAP)

Applicant(s): various

PRAC Rapporteur: Liana Martirosyan

Scope: Signal of suicidality; Third party intervention

EPITT 19997 – Follow up to April 2024

Background

For background information, see PRAC minutes April 2024.

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

Discussion

Having considered the available evidence in EudraVigilance, the literature and the DARWIN EU® study results on real-world evidence data[6], the discussion on potential mechanisms and the responses of the MAH, PRAC concluded that the current evidence is insufficient to establish a causal relationship between doxycycline and suicidality to warrant an update to the product information and/or risk management plan at present. No further action is deemed warranted at this stage.

Summary of recommendation(s)

- In the next PSUR, the MAHs of doxycycline-containing products should continue to closely monitor events of suicide/suicide ideation and depression and to include suicide-related events and depression in the list of safety concerns as important potential risk. In addition, the MAHs should perform appropriate follow-up activities for the reports in relation to depression and suicide related events in order to collect more comprehensive data (such as medical and family history, concomitant medication including substance

[5] Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly.
[6] DARWIN EU® - Incidence of suicidality in patients with specific chronic skin conditions | HMA-EMA Catalogues of real-world data sources and studies

and alcohol assumption) that could allow a more complete assessment of each case, as well as to discuss new data and any new relevant publications.

Post meeting note: the study report of the DARWIN EU® - Incidence of suicidality following exposure to doxycycline was published on the EMA website on 29 November 2024.

4.2.3. Nitric oxide - INOMAX (CAP), NAP - EMEA/H/C/000337/SDA/026

Applicant(s): Linde Healthcare AB, various

PRAC Rapporteur: Jo Robays

Scope: Signal of pulmonary oedema in patients with veno-occlusive disease

EPITT 20086 – Follow-up to July 2024

Background

For background information, see PRAC minutes July 2024.

The MAHs replied to the request for information on the signal of pulmonary oedema in patients with veno-occlusive disease and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence in EudraVigilance, from the literature, and the responses of the MAHs, PRAC concluded that there is sufficient evidence to establish a causal association between nitric oxide and pulmonary oedema in patients with veno-occlusive disease. Therefore, the product information should be updated to add a warning on pulmonary veno-occlusive disease.

Summary of recommendation(s)

- The MAHs for nitric oxide-containing products should submit to EMA, within 60 days, a variation to amend the product information[7].

4.2.4. Risperidone[8] (NAP)

Applicant(s): various

PRAC Rapporteur: Martin Huber

Scope: Signal of medication errors associated with accidental overdoses in children and adolescents treated with risperidone 1 mg/mL oral solution

EPITT 20085 – Follow-up to July 2024

Background

For background information, see PRAC minutes July 2024.

The MAH replied to the request for information on the signal of medication errors associated with accidental overdoses in children and adolescents treated with risperidone 1 mg/mL oral solution and the responses were assessed by the Rapporteur.

Discussion

[7] Update of SmPC section 4.4. The package leaflet is updated accordingly.
[8] Oral solution only

Having considered the available evidence from EudraVigilance, the literature and the responses of the MAH, PRAC concluded that there is sufficient evidence to establish a causal association for the risk of medication errors associated with accidental overdoses in children and adolescents treated with risperidone oral solution. Therefore, all MAHs of risperidone oral solution formulations should provide dosing devices with clearly legible, written labels (in 0.25 ml intervals – smaller intervals like 0.05 ml should be marked with lines but are not expected to be labelled with written numbers), including clear instructions along with illustrations in the patient leaflet to educate the patients and caregivers on measuring volumes correctly, as appropriate. Each MAH should introduce appropriate illustrating figures matching the specific dosing device delivered with their risperidone oral solution. The MAHs of risperidone oral solution formulation should also amend the package leaflet accordingly, taking into account the already existing wording in nationally authorised products. Finally, a DHPC for pharmacists to advise the patients on the correct use of the dosing devices might be considered at the discretion of the national competent authorities.

Summary of recommendation(s)

- The MAHs for risperidone oral solution formulations should submit to national competent authorities, within 6 months, a variation to update the package leaflet. For harmonisation purposes, work-sharing variations are to be considered, where applicable.

4.2.5. Rosuvastatin (NAP)

Applicant(s): various

PRAC Rapporteur: Bianca Mulder

Scope: Signal of tubulointerstitial nephritis

EPITT 20084 – Follow-up to July 2024

Background

For background information, see PRAC minutes July 2024.

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

Discussion

Having considered the available evidence in EudraVigilance, literature, studies and the responses of the MAH, PRAC concluded that the current evidence is insufficient to establish a causal relationship between rosuvastatin and tubulointerstitial nephritis (TIN) to further warrant an update to the product information and/or risk management plan at present. No further action is deemed warranted at this stage.

Summary of recommendation(s)

- In the next PSUR, the innovator MAH Grünenthal for Crestor (rosuvastatin) should closely monitor cases containing a biopsy confirming TIN, reporting no concomitant medications for which TIN is listed and in which other causes of TIN are ruled out, as well as provide a cumulative review of increased creatinine levels including pooled data from clinical trials for MedDRA preferred terms (PTs) related to elevated blood/serum creatinine values with a comparison between rosuvastatin and placebo/comparator.

4.3. Variation procedure(s) resulting from signal evaluation

4.3.1. Anakinra - KINERET (CAP) - EMEA/H/C/000363/II/0093

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Karin Erneholm

Scope: Update of section 4.4 of the SmPC in order to add a new warning on 'Amyloidosis (systemic)' based on an updated safety review, following the PRAC recommendation on a signal. In addition, the MAH took the opportunity to correct a numerical error in the SmPC

Background

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

In relation to previous recommendations on signal on amyloidosis, the MAH submitted to EMA a variation to add a new warning on amyloidosis (systemic). PRAC is responsible for adopting an outcome based on the assessment report from the PRAC Rapporteur, to be further considered at the level of CHMP, responsible for adopting an opinion on this variation. For background information, see PRAC minutes April 2024.

Summary of outcome(s)

- Based on the available data and the Rapporteur's assessment, PRAC agreed with the update[9] of the product information to add a warning on amyloidosis (systemic). In addition, PRAC considered that there is currently no need to update the RMP, but in the next PSUR the MAH should closely monitor AIL1RAP-type systemic amyloidosis as an important potential risk.

5. Risk management plans (RMPs)

5.1. Medicines in the pre-authorisation phase

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

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

See also Annex I 15.1.

5.1.1. Atropine - (CAP MAA) - EMEA/H/C/006324

Scope (pre D-180 phase): Treatment of progression of myopia in children aged 3 to 18 years

[9] Update of SmPC section 4.4. The package leaflet is updated accordingly

5.1.2. Belzutifan - (CAP MAA) - EMEA/H/C/005636

Scope (pre D-210 phase): Treatment of adult patients with advanced renal cell carcinoma (RCC) and treatment of adult patients with von Hippel-Lindau (VHL) disease

5.1.3. Govorestat - (CAP MAA) - EMEA/H/C/006270, Orphan

Applicant: Advanz Pharma Limited

Scope (pre D-180 phase): Treatment of adults and children aged 2 years and older with a confirmed diagnosis of classic galactosemia

5.1.4. Human normal immunoglobulin - (CAP MAA) - EMEA/H/C/006423

Scope (pre D-180 phase): Replacement therapy (primary immunodeficiency syndromes and secondary hypogammaglobulinemia), immunomodulation (in primary immune thrombocytopenic purpura, Guillain Barré syndrome, Kawasaki disease and Multifocal Motor Neuropathy)

5.1.5. Lifileucel - (CAP MAA) - EMEA/H/C/004741

Scope (pre D-120 phase): Treatment of unresectable or metastatic melanoma

5.1.6. Nirogacestat - (CAP MAA) - EMEA/H/C/006071, Orphan

Applicant: Springworks Therapeutics Ireland Limited

Scope (pre D-180 phase): Treatment of desmoid tumours

5.1.7. Pneumococcal polysaccharide conjugate vaccine (21-valent) - (CAP MAA) - EMEA/H/C/006267

Scope (pre D-180 phase): For active immunisation for the prevention of invasive disease and pneumonia caused by Streptococcus pneumoniae

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

See also Annex I 15.2.

5.2.1. Eculizumab - SOLIRIS (CAP) - EMEA/H/C/000791/WS2125/0133; Ravulizumab - ULTOMIRIS (CAP) - EMEA/H/C/004954/WS2125/0047

Applicant: Alexion Europe SAS

PRAC Rapporteur: Monica Martinez Redondo

Scope: Submission of an updated RMP version 21.0 for SOLIRIS and RMP version 9.0 for ULTOMIRIS in order to revise the controlled distribution additional risk minimisation measures and to add a new post-authorisation safety study (PASS) intended to evaluate the effectiveness of the revised additional risk minimisation measures for minimising the risk of meningococcal infections in the EU, following the PRAC outcome for PSUSA/00001198/202310 for SOLIRIS. The Annex II is updated accordingly. In addition, the MAH introduced minor updates to the SmPC to align the wording with the updated

Annex II

Background

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

PRAC is evaluating a type II variation procedure for Soliris, a centrally authorised medicine containing eculizumab, and for Ultomiris, a centrally authorised medicine containing ravulizumab to update the RMP to reflect the introduction of a new PASS to evaluate the effectiveness of the revised additional risk minimisation measures for minimising the risk of meningococcal infections in the EU. PRAC is responsible for adopting an outcome based on the assessment report from the PRAC Rapporteur, to be further considered at the level of CHMP, responsible for adopting an opinion on this variation. For further background, see PRAC minutes May 2024.

S**ummary of advice**

- The RMP for Soliris (eculizumab) and for Ultomiris (ravulizumab) in the context of the work sharing variation procedure under evaluation by PRAC and CHMP could be considered acceptable provided that updates to RMP version 21.0 and 9.0 respectively are submitted.
- PRAC agreed with the discontinuation of the controlled distribution system and the amendment of the current educational materials aimed to continue minimising meningitis risk of infections in eculizumab or ravulizumab treated patients. However, PRAC did not support the proposed implementation of a healthcare professional (HCP) tool as a replacement of the controlled distribution system, given the long experience in use of terminal complement inhibitors and the fact that the educational materials in place will remain; thus, pending the response to the request for supplementary information (RSI), PRAC agreed that the MAH should provide an updated patient card to add information on vaccination and re-vaccination dates. In addition, any updates on both the product information and the RMP are pending the RSI response.

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

See also Annex I 15.3.

5.3.1. Cabotegravir - VOCABRIA (CAP) - EMEA/H/C/004976/II/0022

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Martin Huber

Scope: Extension of indication to include in combination with rilpivirine injection, the treatment of adolescents (at least 12 years of age and weighing at least 35 kg) for Vocabria, based on interim results from study 208580 (Phase I/II Study of the Safety, Acceptability, Tolerability, and Pharmacokinetics of Oral and Long-Acting Injectable Cabotegravir and Long-Acting Injectable Rilpivirine in Virologically Suppressed HIV-Infected Children and Adolescents). This is an ongoing Phase 1/Phase 2 multicenter, open-label, non-comparative study evaluating the safety, acceptability, tolerability, and PK of oral and LA injectable CAB and LA injectable RPV in virologically suppressed HIV-infected adolescents 12 to <18 years of age and weighing at least 35 kg who are receiving stable

cART consisting of 2 or more drugs from 2 or more classes of ARV drugs. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 4.1 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to introduce editorial changes. Furthermore, the PI is brought in line with the latest QRD template version 10.4

Background

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

CHMP is evaluating a type II variation for Vocabria, a centrally authorised product containing cabotegravir, to extend the indication to include in combination with rilpivirine injection, the treatment of adolescents, as well as to update relevant sections of the product information. PRAC is responsible for providing advice to CHMP on the necessary updates to the RMP to support this procedure. For further background, see PRAC minutes September 2024.

Summary of advice

- The RMP version 4.2 for Vocabria (cabotegravir) in the context of the variation under evaluation by CHMP is considered acceptable.
- PRAC considered that no new safety concerns are identified for adolescents, therefore no new additional studies need to be conducted in adolescents as part of the pharmacovigilance plan. In addition, as part of the routine pharmacovigilance activities, the MAH should stratify for adolescents the separate cumulative reviews for medication errors/adherence issues in the context of the PSURs as routine pharmacovigilance activities were deemed sufficient to monitor non-adherence to the dosing schedule in this population.

5.3.2. Florbetaben (^{18}F) - NEURACEQ (CAP) - EMA/VR/0000227744

Applicant: Life Molecular Imaging GmbH

PRAC Rapporteur: Martin Huber

Scope: Extension of indication to include monitoring of the biological treatment response to pharmacological and non-pharmacological interventions for NEURACEQ, based on supporting literature. As a consequence, sections 4.1, 4.4 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 6.91 of the RMP has also been submitted. In addition, the MAH took the opportunity to include the proposal to discontinue the inclusion of a paper copy of the SmPC with the product package

Background

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

CHMP is evaluating a type II variation for Neuraceq, a centrally authorised product containing florbetaben, to extend the indication to include monitoring of the biological treatment response, as well as to update relevant sections of the product information. PRAC is responsible for providing advice to CHMP on the necessary updates to the RMP to support this procedure.

Summary of advice

- The RMP for Neuraceq (florbetaben) in the context of the variation procedure under evaluation by CHMP could be considered acceptable provided that an update to RMP version 6.91 is submitted.
- PRAC recommended the removal from the RMP of the important potential risk of PET scan interpretation errors as well as the educational material related to this risk, pending the response to the request for supplementary information (RSI).

5.3.3. Nirmatrelvir, ritonavir - PAXLOVID (CAP) - EMEA/H/C/005973/II/0057/G

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Martin Huber

Scope: Grouped application consisting of:
C.I.4: Update of sections 4.2, 4.4, 4.8 and 5.2 of the SmPC in order to provide a new dosing recommendation in patients with severe renal impairment based on final results from study C4671028; this is a Phase 1, Open-Label, Non-Randomized Study to Investigate the Safety and PK Following Multiple Oral Doses of PF-07321332 (Nirmatrelvir)/Ritonavir in Adult Participants With COVID-19 and Severe Renal Impairment Either on Hemodialysis or Not on Hemodialysis. The Package Leaflet and Labelling are updated accordingly. The updated RMP version 3.1 has also been submitted. In addition, the MAH took the opportunity to implement editorial changes to the SmPC.

Background

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

CHMP is evaluating a type II variation for Paxlovid, a centrally authorised product containing nirmatrelvir/ritonavir, to provide new dosing recommendation to patients with severe renal impairment, update of the RMP and the relevant sections in the product information following the final results from study C4671028. PRAC is responsible for providing advice to CHMP on the necessary updates to the RMP to support this procedure. For further background, see PRAC minutes July 2024.

Summary of advice

- The RMP for Paxlovid (nirmatrelvir/ritonavir) in the context of the variation procedure under evaluation by CHMP could be considered acceptable provided that an update to RMP version 3.1 is submitted.
- PRAC endorsed the removal of 'safety in patients with renal impairment' as missing information from the safety specification based on the submitted data from study C4671028. In addition, PRAC recommended not to include 'medication errors' as an important potential risk. Medication errors should be reviewed in upcoming PSURs. A DHPC was not supported, as PRAC considered sufficient that the new posology for severe renal impairment is being communicated via the product information to alert healthcare professionals appropriately, and thus no further measures beyond the dosing recommendations provided in the product information are considered warranted.

5.3.4. Rilpivirine - REKAMBYS (CAP) - EMEA/H/C/005060/II/0022

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Liana Martirosyan

Scope: Extension of indication to include in combination with cabotegravir injection, the treatment of adolescents (at least 12 years of age and weighing at least 35 kg) for Rekambys, based on interim results from study 208580 (Phase I/II Study of the Safety, Acceptability, Tolerability, and Pharmacokinetics of Oral and Long-Acting Injectable Cabotegravir and Long-Acting Injectable Rilpivirine in Virologically Suppressed HIV-Infected Children and Adolescents). This is an ongoing Phase 1/Phase 2 multicenter, open-label, non-comparative study evaluating the safety, acceptability, tolerability, and PK of oral and LA injectable CAB and LA injectable RPV in virologically suppressed HIV-infected adolescents 12 to <18 years of age and weighing at least 35 kg who are receiving stable cART consisting of 2 or more drugs from 2 or more classes of ARV drugs. Consequently, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 5.1 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to update a local representative in the Package Leaflet. Furthermore, the PI is brought in line with the latest QRD template version 10.4

Background

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

CHMP is evaluating a type II variation for Rekambys, a centrally authorised product containing rilpivirine, to extend the indication to include in combination with cabotegravir injection, the treatment of adolescents. PRAC is responsible for providing advice to CHMP on the necessary updates to the RMP to support this procedure. For further background, see PRAC minutes September 2024.

Summary of advice

- The RMP version 5.2 for Rekambys (rilpivirine) in the context of the variation under evaluation by CHMP is considered acceptable.
- PRAC considered that no new safety concerns are identified for adolescents, therefore no new additional studies are to be conducted in adolescents as part of the pharmacovigilance plan. In addition, as part of the routine pharmacovigilance activities, the MAH should stratify for adolescents the separate cumulative reviews for medication errors/adherence issues in the context of the PSURs. Routine pharmacovigilance activities were deemed sufficient to monitor non-adherence to the dosing schedule in this population.

6. Periodic safety update reports (PSURs)

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

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

See also Annex I 16.1.

6.1.1. Durvalumab - IMFINZI (CAP) - PSUSA/00010723/202404

Applicant: AstraZeneca AB

PRAC Rapporteur: David Olsen

Scope: Evaluation of a PSUSA procedure

Background

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Imfinzi, a centrally authorised medicine containing durvalumab 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 Imfinzi (durvalumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include polymyalgia rheumatica as a warning and as an undesirable effect with a frequency 'rare'. Polymyalgia rheumatica should be included as an undesirable effect with a frequency 'not known' and 'uncommon' following administration of durvalumab in combination with tremelimumab 75 mg and 300 mg, respectively. In addition, the product information should be updated to add transverse myelitis as an undesirable effect with a frequency 'not known' following administration of durvalumab in combination with tremelimumab. Therefore, the current terms of the marketing authorisation(s) should be varied[10].
- In the next PSUR, the MAH should provide a cumulative review of cases of transplant (including corneal graft) rejection reported with durvalumab from all sources. Due to a possible class effect, a literature review should be performed, including literature covering other immune-check inhibitors and transplant (including corneal graft) rejection. The MAH should also provide cumulative reviews of cases of haemophagocytic lymphohistiocytosis (HLH), paraneoplastic neurological syndromes related events, cholangitis and related terms, stress cardiomyopathy and acquired haemophilia. Based on the data, the MAH should discuss whether updates of the product information are warranted.

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

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. Empagliflozin- JARDIANCE (CAP); empagliflozin, metformin - SYNJARDY (CAP) - PSUSA/00010388/202404

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

Background

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Jardiance and Synjardy, centrally authorised medicines containing empagliflozin 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 Jardiance and Synjardy in the approved indication(s) remains unchanged.
- Nevertheless, the product information of both Jardiance and Synjardy should be updated to amend the description of the adverse reactions related to genital infections by adding phimosis/acquired phimosis. In addition, the product information of both medicinal products should be updated to amend the warnings on ketoacidosis and on elevated haematocrit, as well as to indicate that necrotizing fasciitis of the perineum (Fournier´s gangrene) can occur in patients taking empagliflozin regardless of the indication. Therefore, the current terms of the marketing authorisation(s) should be varied[11].
- In the next PSUR, the MAH should continue to provide reviews of cases of the following safety concerns: complicated urinary tract infection, ketoacidosis within on label and off-label use, necrotizing fasciitis of the perineum (Fournier´s gangrene), liver injury, pregnancy/breast-feeding and long-term safety in paediatric population.

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

6.1.3. Fezolinetant - VEOZA (CAP) - PSUSA/00000231/202405

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

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

[11] Update of SmPC sections 4.4 and 4.8. The PRAC AR and PRAC recommendation are transmitted to 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 Veoza (fezolinetant) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the warning regarding ALT and AST elevations and add drug-induced liver injury (DILI) as an undesirable effect with a frequency 'not known', as well as to add a description of selected adverse reactions: ALT increased/AST increased/DILI. Therefore, the current terms of the marketing authorisation(s) should be varied[12]. Moreover, PRAC agreed on the distribution of a DHPC together with a communication plan in order to increase awareness on the new risk of DILI, the need to perform liver function test (LFT) at regular interval and regarding when treatment should not be initiated or stopped based on LFT.
- In the next PSUR, the MAH should continue to provide detailed information on off-label indications and additional adverse events associated with off-label use. In addition, the MAH should continue to monitor cases of DILI and should discuss the effectiveness of the risk minimisation measures (RMMs) in place especially regarding the need to perform LFT before starting and at regular intervals. Based on the data provided, the MAH should propose any additional RMMs to manage this risk as appropriate.
- The MAH should include DILI as an important identified risk in the list of safety concerns in the RMP along with the already included Follow-up Questionnaire for hepatic adverse events as routine pharmacovigilance activity beyond adverse reaction reporting, as well as to include the DHPC as an additional risk minimisation measure. The MAH should submit a revised RMP within 3 months via an appropriate procedure. As part of this procedure, the MAH should propose a study to review the effectiveness of the RMMs i.e. to determine if healthcare professionals (HCPs) follow the new recommendations on performing LFTs prior to and during treatment. As an initial step, a feasibility assessment should be performed and provided. If a study is considered feasible, the MAH should include a synopsis for the study, including possible timelines, study objectives, countries, population and design.

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. Respiratory syncytial virus, glycoprotein f, recombinant, stabilised in the pre-fusion conformation, adjuvanted with AS01E - AREXVY (CAP) - PSUSA/00000031/202405

Applicant: GlaxoSmithkline Biologicals S.A.

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

Background

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Arexvy, a centrally authorised medicine containing respiratory syncytial virus, glycoprotein f,

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

recombinant, stabilised in the pre-fusion conformation, adjuvanted with AS01E 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, and on the data provided by the MAH in writing and during an oral explanation (held on 26 November 2024), the benefit-risk balance of Arexvy (respiratory syncytial virus, glycoprotein f, recombinant, stabilised in the pre-fusion conformation, adjuvanted with AS01E) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add injection site necrosis as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[13].
- In the next PSUR, the MAH should provide cumulative reviews of cases of seizure, thrombocytopenia, and vaccination anxiety-related reactions such as syncope, and discuss whether changes to the product information and/or risk management plan are warranted. Also, the MAH should provide information about any injection site necrosis cases from clinical trials and continue to review new post-marketing cases to identify potential risk factors for injection site necrosis.

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. Tirzepatide - MOUNJARO (CAP) - PSUSA/00011019/202405

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Bianca Mulder

Scope: Evaluation of a PSUSA procedure

Background

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Mounjaro, a centrally authorised medicine containing tirzepatide 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 Mounjaro (tirzepatide) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add delayed gastric emptying and dysaesthesia as undesirable effects with frequency 'uncommon'. In addition, the product information should be updated to amend the warning regarding 'aspiration in association with general anaesthesia or deep sedation' and include a reference to section 4.8. Therefore, the current terms of the marketing authorisation(s) should be varied[14].

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

- In the next PSUR, the MAH should provide a cumulative review of cases of necrotising pancreatitis, including a causality assessment, and discuss whether a need to update the product information is warranted. In addition, the MAH should further monitor and discuss cases of suicidal ideation, malnutrition and intestinal obstruction/ileus in case new information is identified.

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. Tremelimumab - IMJUDO (CAP) - PSUSA/00011038/202404

Applicant: AstraZeneca AB

PRAC Rapporteur: David Olsen

Scope: Evaluation of a PSUSA procedure

Background

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Imjudo, a centrally authorised medicine containing tremelimumab 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 Imjudo (tremelimumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include information on treatment modifications in the event of rhabdomyolysis and myelitis transverse and to add myelitis transverse as an undesirable effect with a frequency 'not known'. Rhabdomyolysis is also to be added as an undesirable effect by including it as an extension of myositis and polymyositis medical concepts. In addition, the product information should be updated to amend the warning/precaution regarding other immune-mediated adverse reactions by adding rhabdomyolysis and myelitis transverse. Therefore, the current terms of the marketing authorisation(s) should be varied[15].
- In the next PSUR, the MAH should update the product information in line with the PRAC recommendation adopted for the PSUSA (PSUSA/00010723/202404), to add polymyalgia rheumatica as an undesirable effect (see 6.1.1 above).

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.

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

6.2.1. Fluticasone furoate - AVAMYS (CAP); NAP - PSUSA/00009154/202404

Applicants: GlaxoSmithKline (Ireland) Limited (Avamys), various

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

Background

Fluticasone furoate is a corticosteroid with potent glucocorticoid activity licensed for the treatment of allergic rhinitis and is available as once daily intranasal spray.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of Avamys a centrally authorised medicine containing fluticasone furoate, and nationally authorised medicines containing fluticasone furoate 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 fluticasone furoate-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include aphonia, dysphonia, dysgeusia, ageusia, anosmia as undesirable effects with a frequency 'not known'. Therefore, the current terms of the marketing authorisations should be varied[16].

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. Tacrolimus[17] - ADVAGRAF (CAP); ENVARSUS (CAP); MODIGRAF (CAP); NAP - PSUSA/00002839/202403

Applicants: Astellas Pharma Europe B.V. (Advagraf, Modigraf), Chiesi Farmaceutici S.p.A. (Envarsus), various

PRAC Rapporteur: Eamon O'Murchu

Scope: Evaluation of a PSUSA procedure

Background

Tarolimus is a macrolide fermentation product of *Streptomyces tsukubaensis* belonging to the pharmacological class of calcineurin inhibitors (CNI) and it is indicated for prophylaxis of transplant rejection in kidney, liver or heart allograft recipients and treatment of allograft rejection resistant to treatment with other immunosuppressive medicinal products.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of Advagraf and Modigraf, centrally authorised medicines containing tacrolimus, and nationally authorised medicines containing tacrolimus (systemic formulations only) and issued a recommendation on their marketing authorisation(s).

[16] Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion
[17] Systemic formulation(s) only

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of tacrolimus-containing product(s) (systemic formulations only) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the existing wording on lymphoproliferative disorders and malignancies by adding 'other malignancies, including skin cancers and Kaposi's sarcoma'. Also, the product information should be updated to include Kaposi's sarcoma as an undesirable effect under 'Neoplasms benign, malignant and unspecified (incl. cysts and polyps)'. Therefore, the current terms of the marketing authorisations should be varied[18].
- In the next PSUR, all MAHs should continue to monitor cases of Kaposi's sarcoma and provide a causality assessment along with updated cumulative reviews. In addition, all MAHs should provide cumulative reviews of cases of syndrome of inappropriate antidiuretic hormone secretion and of angioedema, including data from clinical trials, post-marketing setting and literature, and discuss a potential mechanism of action and whether an update of the product information is warranted.

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

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

See also Annex I 16.3.

6.3.1. Ambrosia artemisiifolia[19] [20] [21] [22] (NAP) - PSUSA/00010693/202404

Applicant(s): various

PRAC Lead: Gabriele Maurer

Scope: Evaluation of a PSUSA procedure

Background

Ambrosia artemisiifolia is formulated as an oral lyophilisate for sublingual administration and contains a standardised allergen extract from short ragweed pollen as active substance. It is indicated for allergy immunotherapy (AIT) in patients diagnosed with ragweed pollen induced allergic rhinitis, with or without conjunctivitis in adults and children (5 years or older).

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

Summary of recommendation(s) and conclusions

[18] Update of SmPC section XX. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion
[19] Allergen for therapy
[20] (302)
[21] Sublingual use only
[22] Medicinal product(s) authorised via decentralised procedure

- Based on the review of the data on safety and efficacy, the benefit-risk balance of ambrosia artemisiifolia-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add oral mucosal discolouration as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[23].

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

6.3.2. Fentanyl[24] (NAP) - PSUSA/00001370/202404

Applicant(s): various

PRAC Lead: Liana Martirosyan

Scope: Evaluation of a PSUSA procedure

Background

Fentanyl is a phenylpiperidine opioid. It is indicated, as transdermal patches, in adults for the management of severe chronic pain that requires continuous long-term opioid administration and for long-term management of severe chronic pain in children from 2 years of age who are receiving opioid therapy. It is also indicated, as solution for injection, in adults and paediatric patients as an opioid analgesic supplement in general or regional anaesthesia, as an anaesthetic premedication, for induction of anaesthesia, as an adjunct in maintenance of general and regional anaesthesia as well as an anaesthetic agent with oxygen in selected high-risk patients undergoing major surgery.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing fentanyl 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 fentanyl-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include in the package leaflet a boxed warning about the nature of the product and the risk of dependence and addiction, directly under the subheading 'Dependence and addiction'. Therefore, the current terms of the marketing authorisation(s) should be varied.
- In the next PSUR, the MAH Janssen should submit a literature review concerning opioid use (as transdermal patches) and fall risk, including a possible mechanism of this risk and discuss the need for a product information update.

[23] Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position.
[24] Transdermal patches, solution for injection

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 EURD list provided for under Article 107c(7) of Directive 2001/83/EC is updated accordingly.

6.3.3. Isotretinoin[25] (NAP) - PSUSA/00010488/202405

Applicant(s): various

PRAC Lead: Maia Uusküla

Scope: Evaluation of a PSUSA procedure

Background

Isotretinoin is a retinoid (vitamin A-derivative) and it is indicated for the oral treatment of severe forms of acne.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing isotretinoin (oral formulation) 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 isotretinoin-containing medicinal products in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, all MAHs should provide cumulative reviews of cases of anal fissure and of Henoch-Schönlein purpura.
- The MAHs should introduce follow-up questionnaires for drug-induces liver injury (DILI) as routine pharmacovigilance activities beyond adverse reaction reporting and signal detection in the RMP.

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. Metformin (NAP) - PSUSA/00002001/202404

Applicant(s): various

PRAC Lead: Amimour Zoubida

Scope: Evaluation of a PSUSA procedure

Background

Metformin is a biguanide with anti-hyperglycaemic effect and it is indicated in the treatment of type 2 diabetes mellitus in adults, particularly in overweight patients, when dietary management and exercise alone does not result in adequate glycaemic control. Metformin may be used as monotherapy or in combination with other oral anti-diabetic agents, or with

[25] Oral formulations only

insulin. It can also be used in children over 10 years old as monotherapy or in combination with insulin.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing metformin 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 metformin-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning on aggravation of mitochondrial encephalopathy with lactic acidosis and stroke-like episodes syndrome (MELAS), and on maternal inherited diabetes and deafness (MIDD) in patients with known mitochondrial diseases. Therefore, the current terms of the marketing authorisation(s) should be varied[26].
- In the next PSUR, all MAHs should provide cumulative reviews of cases of alopecia reported in patients treated with metformin and with co-reported vitamin B12 deficiency and discuss whether an update of the product information is warranted. In addition, all MAHs should continue to closely monitor cases of encephalopathy and pancreatitis, as well as cases where metformin was used in patients with compensated liver cirrhosis.

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

6.3.5. Nebivolol (NAP) - PSUSA/00002129/202403

Applicant(s): various

PRAC Lead: Bianca Mulder

Scope: Evaluation of a PSUSA procedure

Background

Nebivolol is a beta-1 selective beta blocking agent and it is indicated in the treatment of essential hypertension, and in the treatment of stable mild and moderate chronic heart failure in addition to standard treatment in patients ≥70 years of age.

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

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

- Nevertheless, the product information should be updated to include a warning regarding the risk of severe hypoglycaemia following the concomitant use of beta-blockers and sulfonylureas. Therefore, the current terms of the marketing authorisation(s) should be varied[27].
- In the next PSUR, the MAHs should provide cumulative reviews of cases of hallucination in patients treated with nebivolol and discuss whether an update of the product information is warranted. In addition, the MAHs should discuss new publications regarding lichen planus, subcutaneous lupus erythematosus and skin cancer in association with nebivolol, provide a review of post-marketing cases. Also, the MAHs should continue to closely monitor cases of hyperuricaemia, gout and gout arthritis.

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. Oxaliplatin (NAP) - PSUSA/00002229/202404

Applicant(s): various

PRAC Lead: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

Background

Oxaliplatin is an antineoplastic drug belonging to a class of platinum-based compounds and it is indicated, in combination with different medicines, for the treatment of various types of cancer, under certain conditions: colon cancer after complete resection of primary tumour and for treatment of advanced/metastatic colorectal cancer (mCRC). In combination with 5-fluorouracil, folinic acid and bevacizumab, oxaliplatin is indicated in first-line treatment of metastatic colorectal cancer.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing oxaliplatin 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 oxaliplatin-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add 'microangiopathic haemolytic anaemia associated with haemolytic uraemic syndrome (HUS) or Coombs positive haemolytic anaemia' as a footnote of the already listed undesirable effect 'haemolytic anaemia (rare)'. In addition, the product information should be updated to amend the existing warning regarding liver disorders to include splenomegaly. Therefore, the current terms of the marketing authorisation(s) should be varied[28].

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

- In the next PSUR, all MAHs should provide a cumulative review of cases of hepatic failure using the MedDRA HLT 'hepatic failure and associated disorders' from all sources and to continue to closely monitor cases of Guillain-Barre syndrome, oxaliplatin immune-induced syndrome and multiple organ dysfunction syndrome

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

6.3.7. Promethazine (NAP) - PSUSA/00002545/202404

Applicant(s): various

PRAC Lead: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

Background

Promethazine is a potent, long-acting antihistamine with additional anti-emetic, central sedative, and anti-cholinergic properties and it is indicated for the symptomatic treatment for allergic conditions, as an antiemetic, for short-term treatment of insomnia or as a sedative (pre-anaesthesia, paediatric sedative or to enhance analgesic effect).

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing promethazine 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 promethazine-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information of oral formulations and parenteral formulations should be updated to add psychomotor hyperactivity, hallucinations, aggression, neuroleptic malignant syndrome, QT prolongation, Torsade de pointes, thrombocytopenia as undesirable effects with a frequency 'not known' and to amend the recommendations for signs and symptoms of overdose by mentioning that prolonged QT interval and cases of severe arrhythmias with fatal outcome have been described in overdose of phenothiazines. In addition, the product information of oral formulations should be updated to include a warning regarding QT prolongation and on the drug-drug interaction between promethazine and other medicines leading to QT prolongation. Moreover, the product information of parenteral formulations should be updated to include a warning regarding QT prolongation and on severe tissue injury, including gangrene. Therefore, the current terms of the marketing authorisation(s) should be varied[29].
- In the next PSUR, the MAH should monitor the risk of 'drug abuse' that was added as an important potential risk in the list of safety concerns of PSUR(s).

[29] Update of SmPC sections 4.4, 4.5, 4.8 and 4.9. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position

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

6.4. Follow-up to PSUR/PSUSA procedures

See Annex I 16.4. 16.3.1.

6.5. Variation procedure(s) resulting from PSUSA evaluation

See also Annex I 16.5.

6.5.1. Blinatumomab - BLINCYTO (CAP) - EMEA/H/C/003731/II/0054, Orphan

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Jana Lukacisinova

Scope: To update sections 4.2, 4.4, 4.8 of the SmPC to include Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS); and to update section D of Annex II to remove educational materials for physicians, pharmacists and nurses and to include ICANS within neurologic events in educational material for patient/caregivers and patient alert card following the outcome of PSUR procedure EMEA/H/C/PSUSA/00010460/202212. The Package Leaflet is updated accordingly. The RMP version 17.0 has also been submitted

Background

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

Following the evaluation of the most recently submitted PSUR(s) for the above-mentioned medicine(s), PRAC requested the MAH to submit a variation to update the product information to include ICANS as undesirable effect, as well as to update the educational materials. PRAC is responsible for adopting an outcome based on the assessment report from the PRAC Rapporteur, to be further considered at the level of CHMP, responsible for adopting an opinion on this variation.

Summary of recommendation(s)

- Based on the available data and the Rapporteur's assessment, PRAC agreed that the product information should be updated to include information about the risk of ICANS and recommendations on monitoring and treatment of ICANS (sections 4.2, 4.4 and 4.8 and package leaflet). PRAC also considered that the educational materials for physicians and pharmacists can be removed from Annex II-D and that the educational materials for nurses and patients (including patient card) should be updated. However, the MAH should provide additional information regarding dexamethasone dosing as treatment of ICANS, as well as on the use of Cornell Assessment of Paediatric Delirium (CAPD) scores in ICANS identification and management.
- The MAH should submit, to EMA, responses to the request for supplementary information (RSI) which will be assessed following a 60-day timetable.

6.6. Expedited summary safety reviews[30]

None

7. Post-authorisation safety studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)[31]

See Annex I 17.1.

7.2. Protocols of PASS non-imposed in the marketing authorisation(s)[32]

See Annex I 17.2.

7.3. Results of PASS imposed in the marketing authorisation(s)[33]

See also Annex I 17.3.

7.3.1. Aclidinium – BRETARIS GENUAIR (CAP), EKLIRA GENUAIR (CAP); aclidinium, formoterol fumarate dihydrate – BRIMICA GENUAIR (CAP), DUAKLIR GENUAIR - (CAP) - EMEA/H/C/PSR/S/0047

Applicant: Covis Pharma Europe B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Final study report for a post-authorisation safety study to evaluate the potential cardiovascular safety concerns and all-cause mortality described in the risk management plan for aclidinium as monotherapy and fixed-dose combination of aclidinium/formoterol

Background

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

As a condition to the marketing authorisation(s) (Annex II-D), the MAH was required to conduct a non-interventional post-authorisation safety study to evaluate the potential cardiovascular safety concerns and all-cause mortality described in the risk management plan for aclidinium bromide as monotherapy and fixed-dose combination of aclidinium/formoterol.

The final study report was submitted to EMA by the MAH on 5 December 2023. PRAC discussed the final study results in addition to the MAH's responses to the request for supplementary information (RSI). For further background, see PRAC minutes March 2024.

Summary of recommendation(s) and conclusions

[30] 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
[31] In accordance with Article 107n of Directive 2001/83/EC
[32] 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
[33] In accordance with Article 107p-q of Directive 2001/83/EC

- Based on the review of the final report of the non-interventional PASS for aclidinium and aclidinium/formoterol to evaluate the cardiovascular safety endpoint of cardiac arrhythmia among patients with COPD using aclidinium and aclidinium/formoterol, as well as the MAH's responses to the RSI, PRAC considered that the benefit-risk balance of the aclidinium-containing products Bretaris Genuair and Eklira Genuair as well as the aclidinium/formoterol-containing products Brimica Genuair and Duaklir Genuair remains unchanged. As a consequence, PRAC recommended that the terms of the marketing authorisation(s) should be varied to remove the PASS from Annex II-D 'conditions or restrictions with regard to the safe and effective use of the medicinal product' and to remove these products from the list of medicines subject to additional monitoring. In addition, PRAC agreed to update the product information[34] to revise the warning on cardiovascular effects and to add cardiac arrhythmias, including atrial fibrillation and paroxysmal tachycardia, as undesirable effects with a frequency 'uncommon'.

7.4. Results of PASS non-imposed in the marketing authorisation(s)[35]

See Annex I 17.4.

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

See Annex I 17.5.

7.6. Others

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

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 (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.

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

[34] Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly.
[35] In accordance with Article 61a (6) of Regulation (EC) No 726/2004, in line with the revised variations regulation for any submission as of 4 August 2013

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

8.1. Annual reassessments of the marketing authorisation

See Annex I 18.1.

8.2. Conditional renewals of the marketing authorisation

See Annex I 18.2.

8.3. Renewals of the marketing authorisation

See Annex I 18.3. 18.2.1.

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.

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

11.1. Safety related variations of the marketing authorisation

None

11.2. Other requests

None

12. Organisational, regulatory and methodological matters

12.1. Mandate and organisation of PRAC

12.1.1. PRAC membership

The Chair welcomed Zoubida Amimouri as the new alternate for France.

12.1.2. Vote by proxy

Annalisa Capuano gave a proxy to Milou-Daniel Drici to vote on behalf of her for the entire duration of the meeting.

12.2. Coordination with EMA Scientific Committees or CMDh-v

None

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

None

12.4. Cooperation within the EU regulatory network

12.4.1. Health threats and EMA Emergency Task Force (ETF) activities - update

The EMA Secretariat presented to PRAC an update on the evolution of the infection with monkeypox virus in the Democratic Republic of Congo, an update on the spread of human infection with avian influenza A (H5N1) virus in US, as well as data on vaccine effectiveness against these viruses. The EMA Secretariat also highlighted that the activities and composition of ETF will be further broadened in order to be able to address the antimicrobial resistance and to deliver a global response to public health threats. PRAC noted the information.

12.5. Cooperation with International Regulators

None

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

None

12.7. PRAC work plan

12.7.1. PRAC work plan 2025

PRAC lead: Ulla Wändel Liminga, Liana Martirosyan

The EMA Secretariat presented to PRAC the final draft PRAC workplan for 2025. PRAC members were invited to send their final comments or suggestions on the draft work plan by 06 December 2024.

Post-meeting note: The PRAC work plan 2025 was adopted by PRAC via written procedure on 12 December 2024 and published on the EMA website on 16 January 2025 (EMA/PRAC/583868/2024).

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)

PRAC lead: Jana Lukacisinova

The EMA Secretariat and the PRAC Lead presented to PRAC an update on the GPAG activities, as well as the proposed objectives and deliverables included in the GPAG work plan for 2025. PRAC endorsed the GPAG PRAC work plan for 2025.

12.10.3. PSURs repository

None

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

PRAC endorsed the draft revised EURD list, version December 2024, reflecting PRAC's comments impacting on the data lock point (DLP) and PSUR submission frequencies of the substances/combinations. PRAC endorsed the newly allocated Rapporteurs for upcoming PSUSAs in accordance with the principles previously endorsed by PRAC (see PRAC minutes April 2013).

Post-meeting note: following the PRAC meeting of December 2024, the updated EURD list was adopted by CHMP and CMDh at their December 2024 meetings and published on the EMA website, see: Home> Human Regulatory>Post-authorisation>Pharmacovigilance>Periodic safety update reports>> 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: Martin Huber

PRAC was updated on the ongoing activities of the SMART working group – work stream Methods meeting held on 10 October 2024. Among the topics discussed: a summary of the article on 'COVID-19 Vaccines and Heavy Menstrual Bleeding: The Impact of Media Attention on Reporting to EudraVigilance' , a study on masking effect by COVID vaccines and automated de-identification of case narratives (De-identification.isop.final.web). PRAC noted the information.

12.11.2. Signal management – List of substances subject to worksharing

PRAC endorsed the updated list of substances subject to worksharing (Signal management | European Medicines Agency (EMA))

12.12. Adverse drug reactions reporting and additional monitoring

12.12.1. Management and reporting of adverse reactions to medicinal products

None

12.12.2. Additional monitoring

None

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

PRAC was informed on 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, see: Home>Human Regulatory>Post-authorisation>Pharmacovigilance>Medicines under additional monitoring>List of medicines under additional monitoring

12.12.4. Specific adverse drug reaction (ADR) follow-up questionnaire (FUQ) drafting group – update on the activities

PRAC lead: Tiphaine Vaillant

PRAC adopted the Guideline on Specific Adverse Reaction Follow-up questionnaires (Specific AR FUQ) which contains information about the requirements, content, format, dissemination and publication of FUQs. The document will be published on EMA website. The next steps would be to develop and publish the Specific AR FUQ repository as per the requirements outlined in the Guideline. PRAC will be informed about further developments related to this activity.

12.13. EudraVigilance database

12.13.1. Activities related to the confirmation of full functionality

None

12.14. Risk management plans and effectiveness of risk minimisations

12.14.1. Risk management systems

None

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

None

12.15. Post-authorisation safety studies (PASS)

12.15.1. Post-authorisation Safety Studies – imposed PASS

None

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

None

12.16. Community procedures

12.16.1. Referral procedures for safety reasons

None

12.17. Renewals, conditional renewals, annual reassessments

None

12.18. Risk communication and transparency

12.18.1. Public participation in pharmacovigilance

None

12.18.2. Safety communication

None

12.19. Continuous pharmacovigilance

12.19.1. Incident management

None

12.20. Impact of pharmacovigilance activities

12.20.1. Good Pharmacovigilance Practices (GVP) module XVI – Addendum on pregnancy - update

PRAC lead: Ulla Wändel Liminga

The EMA Secretariat provided an overview of the steps and activities taken regarding this document following the public consultation. PRAC discussed the scope and the most important terminology for this guidance, including the pregnancy prevention programme (PPP). The revised draft guidance document is planned to be provided by the author team for PRAC review in February 2025.

12.21. Others

12.21.1. CHMP/Member State Request for PRAC advice – guidance and updated template

PRAC lead: Ulla Wändel Liminga

The EMA Secretariat presented to PRAC a new guidance (along with a revised template) related to the CHMP/MS Request for PRAC advice procedures in order to better describe the background and the steps to be taken as well as responsible functions to draft and manage this type of procedure. PRAC noted the information.

12.21.2. Committees' timetables and deadlines around the end of year holiday period

PRAC agreed with the proposed solutions to update timetables for certain procedures to address the workload and timelines over end-of-year period. For background information, see PRAC minutes October 2024.

13. Any other business

None

14. Annex I – Signals assessment and prioritisation[36]

As per the agreed criteria for new signal(s), PRAC adopted without further plenary discussion the recommendation of the Rapporteur to request MAH(s) to submit a cumulative review following standard timetables[37].

14.1. New signals detected from EU spontaneous reporting systems

14.1.1. Emtricitabine, tenofovir disoproxil – EMTRICITABINE/TENOFOVIR DISOPROXIL KRKA, EMTRICITABINE/TENOFOVIR DISOPROXIL KRKA D.D., EMTRICITABINE/TENOFOVIR DISOPROXIL MYLAN, EMTRICITABINE/TENOFOVIR DISOPROXIL ZENTIVA, TRUVADA (CAP), NAP

Applicant(s): Gilead Sciences Ireland UC (Truvada, Emtricitabine/Tenofovir disoproxil Mylan), KRKA, d.d., Novo mesto (Emtricitabine/Tenofovir disoproxil Krka, Emtricitabine/tenofovir disoproxil Krka d.d.), Zentiva k.s. (Emtricitabine/Tenofovir disoproxil Zentiva), various

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Signal of trigeminal neuralgia

EPITT 20121 – New signal

14.1.2. REGORAFENIB – STIVARGA (CAP)

Applicant: Bayer AG

PRAC Rapporteur: Bianca Mulder

Scope: Signal of nephrotic syndrome

EPITT 20123 – New signal

14.2. New signals detected from other sources

None

[36] 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

[37] Either MAH(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. Annex I – Risk management plans

15.1. Medicines in the pre-authorisation phase

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

15.1.1. ELTROMBOPAG - (CAP MAA) - EMEA/H/C/006459

Scope (pre D-180 phase): Treatment of primary immune thrombocytopenia (ITP), chronic hepatitis C virus (HCV) and acquired severe aplastic anaemia (SAA)

15.1.2. SARGRAMOSTIM - (CAP MAA) - EMEA/H/C/006411

Scope (pre D-180 phase): Treatment for exposure to myelosuppressive doses of radiation

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

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

15.2.1. Clopidogrel - GREPID (CAP) - EMEA/H/C/001059/II/0058

Applicant: Pharmathen S.A.

PRAC Rapporteur: Carla Torre

Scope: Submission of an RMP version 0.1 following procedure EMEA/H/C/001059/IB/0057/G

15.2.2. Obinutuzumab - GAZYVARO (CAP) - EMEA/H/C/002799/II/0059, Orphan

Applicant: Roche Registration GmbH

PRAC Rapporteur: Mari Thorn

Scope: Submission of an updated RMP version 10.0 in order to remove the guided questionnaires (GQ) for secondary malignancies, progressive multifocal leukoencephalopathy and hepatitis B reactivation as well as to update the ATC code and to introduce additional updates

15.2.3. Panobinostat - FARYDAK (CAP) - EMEA/H/C/003725/II/0030, Orphan

Applicant: Pharmaand GmbH

PRAC Rapporteur: Sofia Trantza

Scope: Submission of an updated RMP version 7.0 in order to align the RMP with GVP V and GVP XVII. As a consequence, the MAH proposes to remove severe haemorrhage and severe

infections (including sepsis/pneumonia/reactivation of hepatitis B infection) as important identified risks, and developmental toxicity, carcinogenicity/second primary malignancy (SPM), and medication error as important potential risks. In addition, the MAH proposes to revise the Annex II to reflect the removal of the Patient Card and educational programme as additional risk minimisation measures

15.2.4. Tezepelumab - TEZSPIRE (CAP) - EMEA/H/C/005588/II/0013/G

Applicant: AstraZeneca AB

PRAC Rapporteur: Eva Jirsová

Scope: A grouped application consisting of:
Type II (C.I.11.b): Submission of an updated RMP version V 3, S 1 in order to remove the SUNRISE study (D5180C00024) from the RMP due to discontinuation of the study. This is a Phase 3, randomised, double-blind, parallel-group, placebo-controlled, multicentre study to evaluate the efficacy and safety of tezepelumab 210 mg Q4W administered SC for 28 weeks using an accessorised pre-filled syringe, compared with placebo in reducing OCS use in OCS-dependent adult asthma participants. In addition, the MAH took the opportunity to implement updates to the Targeted Safety Questionnaires (TSQs) and to the Module SI of the RMP to bring it up to date.
Type IB (C.I.11.z): Submission of an updated RMP version V 3, S 1 in order to remove the DESTINATION study (D5180C00018) following procedure EMEA/H/C/005588/11/0004.
Type IB (C.I.11.z): Submission of an updated RMP version V 3, S 1 in order to propose changes to the study design and objectives for the Pregnancy PASS (D5180R00010), following procedure EMEA/H/C/005588/MEA/001.2.
Type IB (C.I.11.z): Submission of an updated RMP version V 3, S 1 in order to propose changes to the study design and objectives for the Cardiac PASS (D5180R00024), following procedure EMEA/H/C/005588/MEA/005

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

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

15.3.1. Acalabrutinib - CALQUENCE (CAP) - EMEA/H/C/005299/II/0025

Applicant: AstraZeneca AB

PRAC Rapporteur: Barbara Kovacic Bytyqi

Scope: Extension of indication to include CALQUENCE in combination with bendamustine and rituximab (BR) as treatment of adult patients with previously untreated Mantle Cell Lymphoma (MCL) based on interim results from study ACE-LY-308 (ECHO, D8220C00004); this is a Phase III, Randomized, Double-blind, Placebo-controlled, Multicenter Study of Bendamustine and Rituximab (BR) Alone Versus in Combination with Acalabrutinib (ACP-196) in Subjects with Previously Untreated Mantle Cell Lymphoma. As a consequence, sections 4.1, 4.2, 4.4, 4.8, and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 6, succession 1 of the RMP has also been submitted. In addition, the MAH took the opportunity to implement editorial changes to the SmPC. As part of the application the MAH is requesting a 1-year extension of the market protection

15.3.2. Acalabrutinib - CALQUENCE (CAP) - EMEA/H/C/005299/II/0026

Applicant: AstraZeneca AB

PRAC Rapporteur: Barbara Kovacic Bytyqi

Scope: Extension of indication to include CALQUENCE as monotherapy for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy based on final results from study ACE-LY-004 (D8225C00002); this is an open-label, phase 2 study of ACP-196 in subjects with Mantle Cell Lymphoma. As a consequence, sections 4.1 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 7 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial and formatting changes to the PI

15.3.3. Adagrasib - KRAZATI (CAP) - EMEA/H/C/006013/II/0010/G

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Kimmo Jaakkola

Scope: A grouped application consisting of:
C.I.4: Update of section 5.1 of the SmPC based on final results from study 849-012 (KRYSTAL-12) listed as a specific obligation in the Annex II. This is a Randomized Phase 3 Study of MRTX849 versus Docetaxel in Patients with Previously Treated Non-Small Cell Lung Cancer with KRAS G12C Mutation. The Package Leaflet is updated accordingly. The RMP version 2.0 has also been submitted. In addition, the MAH took the opportunity to update Annex IIE of the PI.
C.I.4: Update of section 4.8 of the SmPC in order to update safety information based on an integrated analysis of data from interventional studies 849-012 (KRYSTAL-12), 849-007 (KRYSTAL-7) and 849-001 (KRYSTAL-1)

15.3.4. Asciminib - SCEMBLIX (CAP) - EMEA/H/C/005605/II/0017, Orphan

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Eva Jirsová

Scope: Submission of a comprehensive final analysis of the data from study CABL001X2101, listed as a category 3 study in the RMP. This is a phase I, multicenter, open-label study of oral asciminib in patients with chronic myelogenous leukemia or Philadelphia Chromosome-positive acute lymphoblastic leukemia. The RMP version 2.0 has also been submitted

15.3.5. Azacitidine - AZACITIDINE ACCORD (CAP) - EMEA/H/C/005147/X/0021

Applicant: Accord Healthcare S.L.U.

PRAC Rapporteur: Bianca Mulder

Scope: Extension application to introduce a new pharmaceutical form (film-coated tablet) associated with new strengths (200 and 300 mg) and new route of administration (oral use). The RMP (version 2.0) is updated in accordance

15.3.6. Blinatumomab - BLINCYTO (CAP) - EMEA/H/C/003731/II/0056, Orphan

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Jana Lukacisinova

Scope: Extension of indication to include treatment as part of consolidation therapy for the treatment of patients with Philadelphia chromosome negative CD19 positive B-cell precursor ALL for BLINCYTO. The proposed indication is supported by efficacy data from Studies E1910, 20120215, and AALL1331, safety data for Studies E1910, 20120215, AALL1331, MT103-202, and MT103-203, and Pharmacokinetic data for Studies 20120215, AALL1331, MT103-202, MT103-203, and 20190360. As a consequence, sections 4.1, 4.2, 4.8, 5.1, and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 18.0 of the RMP has also been submitted

15.3.7. Bosutinib - BOSULIF (CAP) - EMEA/H/C/002373/X/0058/G

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Martin Huber

Scope: Extension application to introduce a new pharmaceutical form (hard capsules) associated with two new strengths (50 mg and 100 mg) grouped with an extension of indication (C.I.6.a) to include treatment of paediatric patients greater than or equal to 1 year of age with newly-diagnosed (ND) chronic phase (CP) Philadelphia chromosome-positive chronic myelogenous leukaemia (Ph+ CML) for BOSULIF, based on interim results from study ITCC-054/AAML1921 (BCHILD); this is a phase 1/2, multicenter, international, single-arm, open-label study of bosutinib in paediatric patients with newly diagnosed chronic phase or resistant/intolerant Ph+ chronic myeloid leukemia. 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 is updated accordingly. Version 7.0 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the Product Information

15.3.8. Brentuximab vedotin - ADCETRIS (CAP) - EMEA/H/C/002455/II/0111, Orphan

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Bianca Mulder

Scope: Extension of indication for ADCETRIS to include treatment for adult patients with previously untreated CD30+ Stage IIB with risk factors, Stage III or Stage IV HL in combination with etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone (BrECADD), based on final results from phase 3 study HD21 (NCT02661503). This study is titled Treatment Optimization Trial in the First-Line Treatment of Advanced-Stage Hodgkin Lymphoma; Comparison of 4-6 Cycles of Escalated BEACOPP With 4-6 Cycles of BrECADD. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 20.0 of the RMP has also been submitted.
In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet and to implement editorial changes to the SmPC

15.3.9. Cabotegravir - APRETUDE (CAP) - EMEA/H/C/005756/II/0004

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Martin Huber

Scope: Update of sections 4.8, 5.1 and 5.2 of the SmPC to include data from clinical studies in HIV-1 uninfected adolescents (HPTN 083-01 and HPTN 084-01), updated data from the MOCHA study and updated PK data based on a population PK analysis of cabotegravir in adolescents in MOCHA, HPTN 083-01 and HPTN 084-01. In addition, the MAH took the opportunity to update section 4.2 of the SmPC to clarify the wording related to missed doses of oral PrEP and renal impairment, and to implement editorial changes in the SmPC. Furthermore, the MAH took the opportunity to align the PI with the latest QRD template version 10.4. The RMP version 1.1 has also been submitted

15.3.10. Cabozantinib - CABOMETYX (CAP) - EMEA/H/C/004163/II/0040

Applicant: Ipsen Pharma

PRAC Rapporteur: Bianca Mulder

Scope: Extension of indication to include the treatment of adult patients with progressive extra-pancreatic (epNET) and pancreatic (pNET) neuroendocrine tumours after prior systemic therapy for CABOMETYX based on final results from study CABINET (A021602). This is a multicenter, two-arm, randomised, double-blind, placebo-controlled phase 3 study investigating cabozantinib versus placebo in patients with advanced Neuroendocrine Tumors (NET). As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 8.0 of the RMP has also been submitted

15.3.11. Chikungunya virus, strain delta5nsP3, live attenuated - IXCHIQ (CAP) - EMEA/H/C/005797/II/0001

Applicant: Valneva Austria GmbH

PRAC Rapporteur: Gabriele Maurer

Scope: Extension of indication to include active immunisation for the prevention of disease caused by chikungunya virus (CHIKV) in adolescents 12 years and older for IXCHIQ, based on interim 6 months results from study VLA1553-321; this is a randomized, double-blinded, multicentre study to evaluate the immunogenicity and safety of the adult dose of VLA1553 6 months following vaccination in adolescents from 12 years to less than 18 years of age after a single immunization. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 1.1 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the PI

15.3.12. Covid-19 Vaccine (recombinant, adjuvanted) - BIMERVAX (CAP) - EMEA/H/C/006058/II/0017

Applicant: Hipra Human Health S.L.

PRAC Rapporteur: Zane Neikena

Scope: Update of sections 4.4, 4.8 and 5.1 of the SmPC in order to update safety

information and remove the warning for immunocompromised individuals, based on final results from study HIPRA-HH-4 listed as a category 3 study in the RMP; this is a Phase IIb/III, open label, single arm, multi-centre trial to assess the immunogenicity and safety of an additional dose vaccination with a recombinant protein RBD fusion heterodimer candidate (PHH-1V) against SARS-CoV-2, in adults with pre-existing immunosuppressive conditions vaccinated against COVID-19. The Package Leaflet is updated accordingly. The RMP version 1.5 has also been submitted. In addition, the MAH took the opportunity to include information on excipient polysorbate 80, to introduce minor editorial changes to the PI and to bring the PI in line with QRD template version 10.4

15.3.13. Dalbavancin - XYDALBA (CAP) - EMEA/H/C/002840/II/0050

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Rugile Pilviniene

Scope: Extension of indication to include the treatment of acute bacterial skin and skin structure infections (ABSSSI) in paediatric patients from birth, including paediatric patients aged less than 3 months with suspected or confirmed sepsis associated with skin and subcutaneous tissue infections for Xydalba, based on final results from study DUR001-306, together with data from three Phase 1 PK studies (A8841004, DUR001-106, and DUR001-107 (DAL-PK-02)); DUR001-306 was a Phase 3, multicenter, open-label, randomized, comparator controlled trial evaluating the safety and efficacy of a single dose of IV dalbavancin and a 2-dose regimen of once weekly IV dalbavancin (for a total of 14 days of coverage) for the treatment of ABSSSI known or suspected to be due to susceptible Gram-positive organisms in children. As a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 8.0 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to introduce minor editorial changes to the PI and to update the list of local representatives in the Package Leaflet in line with the latest QRD template version 10.4

15.3.14. Dolutegravir - TIVICAY (CAP) - EMEA/H/C/002753/II/0093

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Martin Huber

Scope: Submission of the final study report for Study ING112578 (IMPAACT P1093) (Category 3 PASS); an open-label, Phase 1/2 study designed to select a DTG dose for chronic dosing of infants, children, and adolescents based on PK, safety, and tolerability. As a consequence, a revised RMP version 20 has been provided and the MAH proposes to remove long-term safety data as an area of missing information

15.3.15. Dostarlimab - JEMPERLI (CAP) - EMEA/H/C/005204/II/0032

Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Carla Torre

Scope: Extension of indication for JEMPERLI to include, in combination with carboplatin and paclitaxel, the treatment of adult patients with primary advanced or recurrent endometrial cancer (EC) and who are candidates for systemic therapy based on Interim Analysis 1 and 2 from study RUBY Part 1 (213361). This is a phase 3, randomized, double-blind, controlled

study evaluating the efficacy and safety of dostarlimab plus carboplatin and paclitaxel in primary advanced or recurrent EC versus placebo plus carboplatin and paclitaxel.
As a consequence, sections 4.1, 4.2, 4.4, 4.8, and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 4.0 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to implement editorial changes to the SmPC and to align the PI with the latest QRD template version 10.4

15.3.16. Elranatamab - ELREXFIO (CAP) - EMEA/H/C/005908/II/0005

Applicant: Pfizer Europe Ma EEIG

PRAC Rapporteur: Barbara Kovacic Bytyqi

Scope: Update of section 4.2 of the SmPC to add every four-week dosing schedule after at least 24 weeks of every two-week dosing and to update the recommendations for restarting therapy following dose delay, and update of sections 4.8, 5.1 and 5.2 of the SmPC with long-term efficacy, safety, and clinical pharmacology results (≥2 years of follow-up after the last participant initial dose), based on the final study report of Study C1071003; a Phase 2, open-label, multicentre, non-randomised study of elranatamab monotherapy in participants with MM who are refractory to at least one PI, one IMiD, and one anti-CD38 Ab. The Package Leaflet has been updated in accordance. In addition, the MAH took the opportunity to implement editorial changes in the SmPC and to update the list of local representatives in the Package Leaflet. Further, the provision of the final study report addresses SOB 001, and Annex II has been updated accordingly. A revised RMP version 1.2 was provided as part of the application

15.3.17. Eltrombopag - REVOLADE (CAP) - EMEA/H/C/001110/II/0077

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Monica Martinez Redondo

Scope: Extension of indication to include second-line treatment of paediatric patients aged 2 years and above with acquired severe aplastic anaemia (SAA) for REVOLADE based on the ETB115E2201 (E2201) study primary analysis results; this is a paediatric phase II, open-label, uncontrolled, intra-patient dose escalation study to characterise the pharmacokinetics after oral administration of eltrombopag in paediatric patients with refractory, relapsed severe aplastic anaemia or recurrent aplastic anaemia. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 56.0 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the PI

15.3.18. Etrasimod - VELSIPITY (CAP) - EMEA/H/C/006007/II/0002/G

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Karin Bolin

Scope: A grouped application comprised of two Type II variations, as follows:
C.I.4: Update of sections 4.2, 4.3 and 5.2 of the SmPC in order to amend recommendation regarding administration to patients with severe hepatic impairment and remove contraindication for severe hepatic impairment, based on in vitro studies to further characterise the drug-drug interaction (DDI) potential of metabolites M3 and M6. The Annex

II and Package Leaflet are updated accordingly. The RMP version 1.2 has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the PI.
C.I.13: Submission of the final report from study 24GR036 (hERG Channel Automated Patch-Clamp Test); this is an assessment of the effects of PF-08034694, PF-08034742, PF-08039030, and PF-08039032 on the Kv11.1 (hERG) potassium current

15.3.19. Guselkumab - TREMFYA (CAP) - EMEA/H/C/004271/II/0044

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Gabriele Maurer

Scope: Extension of indication for TREMFYA to include treatment of adult patients with moderately to severely active Crohn's disease (CD) who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic treatment, based on results from GALAXI Phase 2/3 program and the GRAVITI Phase 3 study. GALAXI is a Phase 2/3, randomized, double-blind, placebo- and active-controlled, parallel-group, multicenter protocol to evaluate the efficacy and safety of guselkumab in participants with moderately to severely active CD who have demonstrated an inadequate response or failure to tolerate previous conventional or biologic therapy. GRAVITI is a Phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate the efficacy and safety of guselkumab SC induction therapy in participants with moderately to severely active CD.
As a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1, 5.2, and 5.3 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 10.1 of the RMP has also been submitted. As part of the application the MAH is requesting a 1-year extension of the market protection

15.3.20. Guselkumab - TREMFYA (CAP) - EMEA/H/C/004271/X/0043/G

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Gabriele Maurer

Scope: Extension application to:
- introduce a new pharmaceutical form (concentrate for solution for infusion), a new strength (200 mg) and a new route of administration (intravenous use);
- add a new strength of 200 mg for solution for injection (in pre-filled syringe / pre-filled pen) for subcutaneous use.
This application is grouped with a type II variation (C.I.6.a) 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, a biologic treatment, or a Janus kinase (JAK) inhibitor for Tremfya, based on results of a Phase 2b/3 clinical development programme (CNTO1959UCO3001) consisting of 3 separate studies, an Induction dose finding Study 1 Phase 2b, an Induction Study 2 Phase 3 and a Phase 3 Maintenance Study. These studies were randomized, double-blind, placebo-controlled, parallel-group, multicenter studies that evaluated the efficacy and safety of guselkumab in participants with moderately to severely active UC. As a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1, 5.2 and 5.3 of the SmPC of the already approved form 100 mg solution for injection are updated. The Package Leaflet and Labelling are updated in

accordance. Version 10.1 of the RMP has also been submitted. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet and to introduce editorial changes to the PI

15.3.21. L-lysine hydrochloride, L-arginine hydrochloride - LYSAKARE (CAP) - EMEA/H/C/004541/II/0018

Applicant: Advanced Accelerator Applications

PRAC Rapporteur: Adam Przybylkowski

Scope: Update of sections 4.2, 4.3, 4.4, 4.8 and 5.1 of the SmPC in order to remove the contraindication and update the warning on 'Hyperkalaemia' as well as on 'Metabolic acidosis' and to update safety information based on final results from study CAAA001A12401 listed as a category 3 study in the RMP. This is a multicenter, open-label post authorization safety study to evaluate the effect of LysaKare infusion on serum potassium levels in GEP-NET patients eligible for Lutathera treatment. The RMP version 3.0 has also been submitted

15.3.22. Mavacamten - CAMZYOS (CAP) - EMEA/H/C/005457/II/0011/G

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Kimmo Jaakkola

Scope: Grouped application comprised of 2 Type II Variations as follows:
C.I.4: Update of section 4.2 of the SmPC to change the echocardiography monitoring frequency once a patient is on a stable dose of mavacamten. The proposed update is supported by the clinical data from interim Clinical study report of MAVA-LTE (CV027-003) study: "A Long-term Safety Extension Study of Mavacamten in Adults with Hypertrophic Cardiomyopathy who have completed the MAVERICK-HCM (MYK-461-006) or EXPLORER-HCM (MYK-461-005) trials", modelling & simulation results and safety data from post-approval safety database. The Package Leaflet is updated accordingly.
C.I.4: Update of section 4.2 of the SmPC to introduce the optional use of the Left ventricular outflow track (LVOT) gradient by post-exercise testing to guide dose titration for patient with specific characteristics. The proposed update is supported by the exposure-response modelling and simulation report with LVOT post-exercise gradient, based on the previously developed model with the data from the following studies: MYK-461-004 (PIONEER), MYK-461-005 (EXPLORER), MYK-461-007, MYK-461-008 (MAVA-LTE) and MYK-461-017 (VALOR).
The RMP version 4.0 has also been submitted

15.3.23. Mirikizumab - OMVOH (CAP) - EMEA/H/C/005122/X/0006/G

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Sonja Hrabcik

Scope: Extension application to add a new strength of 200 mg grouped with an extension of indication (C.I.6) to include treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic treatment, for Omvoh, based mainly on final results from study I6T-MC-AMAM; this is a phase 3, multicenter, randomized,

double-blind, placebo- and active-controlled, treat-through study to evaluate the efficacy and safety of mirikizumab in patients with moderately to severely active Crohn's disease. As a consequence, sections 1, 2, 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2, 5.3, 6.1, 6.5, 6.6 and 8 of the SmPC are updated. The Labelling and Package Leaflet are updated in accordance. Version 1.2 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes and to update the list of local representatives in the Package Leaflet. As part of the application, the MAH is requesting a 1-year extension of the market protection.
The following Quality variations are also included as part of this application:

15.3.24. Naloxone - NYXOID (CAP) - EMEA/H/C/004325/II/0019

Applicant: Mundipharma Corporation (Ireland) Limited

PRAC Rapporteur: Liana Martirosyan

Scope: Submission of the interim report from the PAES MR903-9501 listed as an obligation in the Annex II, supported by Real World Evidence from literature and European Take-Home Naloxone programs (THN) demonstrating the effectiveness of Nyxoid in a real-world setting. Study MR903-9501 is a non-interventional multi-national, prospective, mixed methods study of the effectiveness of naloxone (including intranasal Nyxoid) administration by lay people in reversing opioid overdose. The Annex II and the RMP version 3.0 are updated accordingly. In addition, the MAH took the opportunity to introduce minor administrative changes to the Package Leaflet

15.3.25. Niraparib - ZEJULA (CAP) - EMEA/H/C/004249/II/0056, Orphan

Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Jan Neuhauser

Scope: Update of sections 4.8 and 5.1 of the SmPC in order to update efficacy and safety information based on final results from PRIMA study (PR-30-5017-C) listed as a PAES in the Annex II; this is a Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study of Niraparib Maintenance Treatment in Patients with Advanced Ovarian Cancer Following Response on Front-Line Platinum-Based Chemotherapy. The RMP version 9.0 has also been submitted. In addition, the MAH took the opportunity to update section D of Annex II, and to implement editorial changes to the PI

15.3.26. Pemigatinib - PEMAZYRE (CAP) - EMEA/H/C/005266/II/0015, Orphan

Applicant: Incyte Biosciences Distribution B.V.

PRAC Rapporteur: Bianca Mulder

Scope: Extension of indication to include treatment of adults with myeloid/lymphoid neoplasms (MLNs) with Fibroblast Growth Factor Receptor1 (FGFR1) rearrangement for PEMAZYRE, based on final results from study INCB 54828-203 (FIGHT-203); this is a phase 2, open-label, monotherapy, multicenter study to evaluate the efficacy and safety of INCB054828 in subjects with myeloid/lymphoid neoplasms with FGFR1 rearrangement. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8 and 5.1 of the SmPC are updated. The

Package Leaflet is updated in accordance. Version 3.0 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor changes to the PI. As part of the application, the MAH is requesting a 1-year extension of the market protection

15.3.27. Pregabalin - LYRICA (CAP) - EMEA/H/C/000546/X/0127

Applicant: Upjohn EESV

PRAC Rapporteur: Liana Martirosyan

Scope: Extension application to introduce a new pharmaceutical form (orodispersible tablet)

15.3.28. Remdesivir - VEKLURY (CAP) - EMEA/H/C/005622/II/0053/G

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Eva Jirsová

Scope: Grouped application comprising two extensions of indication to include treatment of paediatric patients weighing at least 1.5 kg for VEKLURY, based on final results from study GS-US-540-5823; this is a Phase 2/3 single-arm, open-label study to evaluate the safety, tolerability, pharmacokinetics, and efficacy of remdesivir in participants from birth to < 18 years of age with COVID-19; as a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 8.1 of the RMP has also been submitted

15.3.29. Respiratory syncytial virus vaccine (bivalent, recombinant) - ABRYSVO (CAP) - EMEA/H/C/006027/II/0007

Applicant: Pfizer Europe Ma EEIG

PRAC Rapporteur: Liana Martirosyan

Scope: Extension of indication to include active immunization of individuals 18 through 59 years of age for ABRYSVO, based on final results from C3671023 Substudy A; this is a Phase 3 double-blinded, randomised, placebo-controlled study of safety, tolerability and immunogenicity of Abrysvo in participants ≥18 to <60 years of age at high risk of severe RSV disease due to certain chronic medical conditions. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 1.0 of the RMP has also been submitted. In addition, the MAH took the opportunity to implement editorial changes to the SmPC. Furthermore, as part of the application the MAH is requesting a 1-year extension of the market protection

15.3.30. Sacubitril, valsartan - ENTRESTO (CAP) - EMEA/H/C/004062/WS2738/0065; Sacubitril, valsartan - NEPARVIS (CAP) - EMEA/H/C/004343/WS2738/0062

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Karin Erneholm

Scope: Update of sections 4.8 and 5.3 of the SmPC in order to update information on long-term data in paediatric patients, based on final results from study CLCZ696B2319E1(PANAROMA-HF OLE) listed as a category 3 study in the RMP (MEA/009); this is a phase 3, multicenter, uncontrolled study to evaluate long-term safety and

tolerability of open label sacubitril/valsartan in paediatric patients with heart failure due to systemic left ventricle systolic dysfunction who have completed study CLCZ696B2319 (PANORAMA-HF); the RMP version 8 has also been submitted

15.3.31. Selpercatinib - RETSEVMO (CAP) - EMEA/H/C/005375/X/0031

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Bianca Mulder

Scope: Extension application to introduce a new pharmaceutical form (film-coated tablets) associated with new strengths (40 mg, 80 mg, 120 mg and 160 mg).
The RMP (version 7.1) is updated in accordance

15.3.32. Sugammadex - BRIDION (CAP) - EMEA/H/C/000885/II/0047

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Terhi Lehtinen

Scope: Extension of indication to include treatment of paediatric patients from birth to less than 2 years of age for Bridion based on final results from paediatric study PN169 (MK-8616-P169); this is a Phase 4 double-blinded, randomized, active comparator-controlled clinical trial to study the efficacy, safety, and pharmacokinetics of sugammadex (MK-8616) for reversal of neuromuscular blockade in pediatric participants aged birth to <2 years. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 8.1 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet, to implement minor editorial corrections and to update the information intended for healthcare professionals (HCPs) at the end of the Package Leaflet

15.3.33. Trientine - CUFENCE (CAP) - EMEA/H/C/004111/II/0020

Applicant: Univar Solutions BV

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Submission of the PK/PD sub-study report for study UNV-TR-004 (UNITED) listed as a PAES in the Annex II of the Product Information. This is an open label, prospective study to characterize the pharmacokinetics and pharmacodynamics of Cufence and to investigate the efficacy and safety in Wilson’s disease. The Annex II and the RMP (version 5.0) are updated accordingly

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

Based on the assessment of the following PSURs, PRAC concluded that the benefit-risk balance of the medicine(s) mentioned below 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 the 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. Abaloparatide - ELADYNOS (CAP) - PSUSA/00011029/202404

Applicant: Theramex Ireland Limited

PRAC Rapporteur: Karin Erneholm

Scope: Evaluation of a PSUSA procedure

16.1.2. Andexanet alfa - ONDEXXYA (CAP) - PSUSA/00010764/202404

Applicant: AstraZeneca AB

PRAC Rapporteur: Bianca Mulder

Scope: Evaluation of a PSUSA procedure

16.1.3. Asciminib - SCEMBLIX (CAP) - PSUSA/00011008/202404

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

16.1.4. Capmatinib - TABRECTA (CAP) - PSUSA/00011022/202405

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Carla Torre

Scope: Evaluation of a PSUSA procedure

16.1.5. Cerliponase alfa - BRINEURA (CAP) - PSUSA/00010596/202404

Applicant: BioMarin International Limited

PRAC Rapporteur: Mari Thorn

Scope: Evaluation of a PSUSA procedure

16.1.6. Conestat alfa - RUCONEST (CAP) - PSUSA/00000873/202404

Applicant: Pharming Group N.V

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.1.7. Delamanid - DELTYBA (CAP) - PSUSA/00010213/202404

Applicant: Otsuka Novel Products GmbH

PRAC Rapporteur: Jo Robays

Scope: Evaluation of a PSUSA procedure

16.1.8. Dostarlimab - JEMPERLI (CAP) - PSUSA/00010931/202404

Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Carla Torre

Scope: Evaluation of a PSUSA procedure

16.1.9. Efbemalenograstim alfa - RYZNEUTA (CAP) - PSUSA/00000286/202405

Applicant: Evive Biotechnology Ireland Limited

PRAC Rapporteur: Bianca Mulder

Scope: Evaluation of a PSUSA procedure

16.1.10. Epoetin theta - BIOPOIN (CAP); EPORATIO (CAP) - PSUSA/00001240/202404

Applicant: TEVA GmbH (Biopoin), ratiopharm GmbH (Eporatio)

PRAC Rapporteur: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

16.1.11. Erenumab - AIMOVIG (CAP) - PSUSA/00010699/202405

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Terhi Lehtinen

Scope: Evaluation of a PSUSA procedure

16.1.12. Everolimus[38] - VOTUBIA (CAP) - PSUSA/00001343/202403

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.13. Exagamglogene autotemcel - CASGEVY (CAP) - PSUSA/00000244/202405

Applicant: Vertex Pharmaceuticals (Ireland) Limited, ATMP

PRAC Rapporteur: Bianca Mulder

Scope: Evaluation of a PSUSA procedure

[38] Indicated for astrocytoma (SEGA), renal angiomyolipoma, refractory seizures

16.1.14. Exenatide - BYDUREON (CAP); BYETTA (CAP) - PSUSA/00009147/202403

Applicant: AstraZeneca AB

PRAC Rapporteur: Mari Thorn

Scope: Evaluation of a PSUSA procedure

16.1.15. Febuxostat - ADENURIC (CAP) - PSUSA/00001353/202404

Applicant: Menarini International Operations Luxembourg S.A.

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.1.16. Ivacaftor, tezacaftor, elexacaftor - KAFTRIO (CAP) - PSUSA/00010868/202404

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.17. Ivosidenib - TIBSOVO (CAP) - PSUSA/00011048/202405

Applicant: Les Laboratoires Servier

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Evaluation of a PSUSA procedure

16.1.18. Japanese encephalitis virus (inactivated) - IXIARO (CAP) - PSUSA/00001801/202403

Applicant: Valneva Austria GmbH

PRAC Rapporteur: Gabriele Maurer

Scope: Evaluation of a PSUSA procedure

16.1.19. Latanoprost (eye drop emulsions containing CKC) - CATIOLANZE (CAP) - PSUSA/00000202/202405

Applicant: Santen Oy

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

16.1.20. Lebrikizumab - EBGLYSS (CAP) - PSUSA/00000175/202405

Applicant: Almirall, S.A.

PRAC Rapporteur: Liana Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.21. Linzagolix choline - YSELTY (CAP) - PSUSA/00010998/202405

Applicant: Theramex Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.22. Loncastuximab tesirine - ZYNLONTA (CAP) - PSUSA/00011027/202404

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

16.1.23. Mavacamten - CAMZYOS (CAP) - PSUSA/00000074/202404

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

16.1.24. Niraparib, abiraterone acetate - AKEEGA (CAP) - PSUSA/00011051/202404

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.1.25. Nirsevimab - BEYFORTUS (CAP) - PSUSA/00011026/202404

Applicant: Sanofi Winthrop Industrie

PRAC Rapporteur: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

16.1.26. Palopegteriparatide - YORVIPATH (CAP) - PSUSA/00000173/202405

Applicant: Ascendis Pharma Bone Diseases A/S

PRAC Rapporteur: Lina Seibokiene

Scope: Evaluation of a PSUSA procedure

16.1.27. Parathyroid hormone - NATPAR (CAP) - PSUSA/00010591/202404

Applicant: Takeda Pharmaceuticals International AG Ireland Branch

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

16.1.28. Pegunigalsidase alfa - ELFABRIO (CAP) - PSUSA/00011049/202405

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Liana Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.29. Potassium citrate, potassium hydrogen carbonate - SIBNAYAL (CAP) - PSUSA/00010932/202404

Applicant: Advicenne

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.30. Propranolol[39] - HEMANGIOL (CAP) - PSUSA/00010250/202404

Applicant: Pierre Fabre Medicament

PRAC Rapporteur: Monica Martinez Redondo

Scope: Evaluation of a PSUSA procedure

16.1.31. Recombinant vesicular stomatitis virus - Zaire ebolavirus vaccine (live) - ERVEBO (CAP) - PSUSA/00010834/202405

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Liana Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.32. Regadenoson - RAPISCAN (CAP) - PSUSA/00002616/202404

Applicant: GE Healthcare AS

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

16.1.33. Remdesivir - VEKLURY (CAP) - PSUSA/00010840/202405

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

16.1.34. Ripretinib - QINLOCK (CAP) - PSUSA/00010962/202405

Applicant: Deciphera Pharmaceuticals (Netherlands) B.V.

PRAC Rapporteur: Barbara Kovacic Bytyqi

[39] Centrally authorised product(s) only

Scope: Evaluation of a PSUSA procedure

16.1.35. Sacituzumab govitecan - TRODELVY (CAP) - PSUSA/00010959/202404

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Bianca Mulder

Scope: Evaluation of a PSUSA procedure

16.1.36. Selpercatinib - RETSEVMO (CAP) - PSUSA/00010917/202405

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Bianca Mulder

Scope: Evaluation of a PSUSA procedure

16.1.37. Sirolimus[40] - HYFTOR (CAP) - PSUSA/00000025/202405

Applicant: Plusultra pharma GmbH

PRAC Rapporteur: Mari Thorn

Scope: Evaluation of a PSUSA procedure

16.1.38. Tafamidis - VYNDAQEL (CAP) - PSUSA/00002842/202405

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

16.1.39. Temoporfin - FOSCAN (CAP) - PSUSA/00002885/202404

Applicant: biolitec Pharma Ltd

PRAC Rapporteur: Bianca Mulder

Scope: Evaluation of a PSUSA procedure

16.1.40. Temsirolimus - TORISEL (CAP) - PSUSA/00002887/202403

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.41. Vamorolone - AGAMREE (CAP) - PSUSA/00000223/202404

Applicant: Santhera Pharmaceuticals (Deutschland) GmbH

PRAC Rapporteur: Rhea Fitzgerald

[40] Indicated for treatment of angiofibroma associated with tuberous sclerosis complex only

Scope: Evaluation of a PSUSA procedure

16.1.42. Volanesorsen - WAYLIVRA (CAP) - PSUSA/00010762/202405

Applicant: Akcea Therapeutics Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.43. Zanubrutinib - BRUKINSA (CAP) - PSUSA/00010960/202405

Applicant: BeiGene Ireland Ltd

PRAC Rapporteur: Bianca Mulder

Scope: Evaluation of a PSUSA procedure

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

16.2.1. Enoxaparin sodium - INHIXA (CAP); NAP - PSUSA/00010833/202404

Applicants: Techdow Pharma Netherlands B.V. (Inhixa), various

PRAC Rapporteur: Bianca Mulder

Scope: Evaluation of a PSUSA procedure

16.2.2. Eslicarbazepine acetate - ZEBINIX (CAP); NAP - PSUSA/00001267/202404

Applicants: Bial - Portela & Cª, S.A. (Zebinix), various

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.2.3. Everolimus[41] - AFINITOR (CAP); NAP - PSUSA/00010268/202403

Applicants: Novartis Europharm Limited (Afinitor), various

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.2.4. Thiotepa - TEPADINA (CAP), THIOTEPA RIEMSER (CAP); NAP - PSUSA/00002932/202403

Applicants: ADIENNE S.r.l. S.U. (Tepadina), ESTEVE Pharmaceuticals GmbH (Thiotepa Riemser), various

PRAC Rapporteur: Tiphaine Vaillant

[41] Indicated for advanced renal cell carcinoma, advanced breast cancer, advanced neuroendocrine tumours (gastrointestinal, lung, pancreatic cancers) (NET)

Scope: Evaluation of a PSUSA procedure

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

16.3.1. Amlodipine besilate, ramipril (NAP); amlodipine, hydrochlorothiazide, ramipril (NAP); hydrochlorothiazide, ramipril (NAP) - PSUSA/00010774/202403

Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.3.2. Argipressin (NAP) - PSUSA/00010749/202403

Applicant(s): various

PRAC Lead: Terhi Lehtinen

Scope: Evaluation of a PSUSA procedure

16.3.3. Bupivacaine (NAP); bupivacaine, epinephrine (NAP)- PSUSA/00010335/202404

Applicant(s): various

PRAC Lead: Zane Neikena

Scope: Evaluation of a PSUSA procedure

16.3.4. Carmustine[42] (NAP) - PSUSA/00010349/202404

Applicant(s): various

PRAC Lead: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

16.3.5. Carteolol (NAP) - PSUSA/00000574/202403

Applicant(s): various

PRAC Lead: Anna Mareková

Scope: Evaluation of a PSUSA procedure

16.3.6. Chlorprothixene (NAP) - PSUSA/00000717/202403

Applicant(s): various

PRAC Lead: Zane Neikena

Scope: Evaluation of a PSUSA procedure

[42] Powder and solvent for solution for infusion only

16.3.7. Ciprofloxacin, fluocinolone acetonide (NAP) - PSUSA/00000772/202404

Applicant(s): various

PRAC Lead: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

16.3.8. Dihydroergotamine (NAP) - PSUSA/00001075/202404

Applicant(s): various

PRAC Lead: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.3.9. Ivermectin[43] (NAP) - PSUSA/00010376/202404

Applicant(s): various

PRAC Lead: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

16.3.10. Nitrendipine (NAP) - PSUSA/00002171/202403

Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.3.11. Ofloxacin[44] (NAP) - PSUSA/00002204/202404

Applicant(s): various

PRAC Lead: Petar Mas

Scope: Evaluation of a PSUSA procedure

16.3.12. Promestriene[45] (NAP) - PSUSA/00009271/202403

Applicant(s): various

PRAC Lead: Irina Sandu

Scope: Evaluation of a PSUSA procedure

16.4. Follow-up to PSUR/PSUSA procedures

16.4.1. Dolutegravir - TIVICAY (CAP) - EMEA/H/C/002753/LEG 015.6

Applicant: ViiV Healthcare B.V.

[43] Topical use only
[44] Topical use only
[45] Cream and vaginal capsule(s) only

PRAC Rapporteur: Martin Huber

Scope: MAH's response to LEG 015.4 [2nd Annual Report, RESPOND study] RSI as adopted in April 2024. In relation to the 2nd annual report for the RESPOND study and in view of the new data regarding diabetes mellitus and the use of INSTIs, the MAH should discuss this issue in detail as soon as corresponding publications are available. This should be provided no later than 30 days after the receipt of these data

16.4.2. Dolutegravir, abacavir, lamivudine - TRIUMEQ (CAP) - EMEA/H/C/002754/LEG 010.6

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Martin Huber

Scope: MAH's response to LEG 010.4 [2nd Annual Report, RESPOND study] RSI as adopted in April 2024. In relation to the 2nd annual report for the RESPOND study and in view of the new data regarding diabetes mellitus and the use of INSTIs, the MAH should discuss this issue in detail as soon as corresponding publications are available. This should be provided no later than 30 days after the receipt of these data

16.4.3. Dolutegravir, lamivudine - DOVATO (CAP) - EMEA/H/C/004909/LEG 005.6

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: David Olsen

Scope: MAH's response to LEG 005.4 [2nd Annual Report, RESPOND study] RSI as adopted in April 2024. In relation to the 2nd annual report for the RESPOND study and in view of the new data regarding diabetes mellitus and the use of INSTIs, the MAH should discuss this issue in detail as soon as corresponding publications are available. This should be provided no later than 30 days after the receipt of these data

16.5. Variation procedure(s) resulting from PSUSA evaluation

16.5.1. Human thrombin, human fibrinogen - TACHOSIL (CAP) - EMEA/H/C/000505/II/0131

Applicant: Corza Medical GmbH

PRAC Rapporteur: Gabriele Maurer

Scope: Update of section 4.2 of the SmPC to emphasise correct product handling and section 4.8 of the SmPC to reflect the fact that cases of product non-adhesion issues have been reported, upon request by PRAC following the outcome of the PSUR procedure EMEA/H/C/PSUSA/00010297/202306. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to implement minor editorial changes in the SmPC

16.6. Expedited summary safety reviews[46]

None

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

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

17.1. Protocols of PASS imposed in the marketing authorisation(s)[47]

17.1.1. Alemtuzumab - LEMTRADA (CAP) - EMEA/H/C/PSA/S/0107.2

Applicant: Sanofi Belgium

PRAC Rapporteur: Karin Erneholm

Scope: Substantial amendment to a non-interventional post-authorisation safety study to investigate drug utilisation and safety monitoring patterns for Lemtrada (alemtuzumab) [MAH's response to PSA/S/0107.1]

17.1.2. Tabelecleucel – EBVALLO (CAP) - EMEA/H/C/PSA/S/0115.1

Applicant: Pierre Fabre Medicament, ATMP

PRAC Rapporteur: Amelia Cupelli

Scope: Substantial amendment to an observational, Post-Authorisation Safety Study (PASS) to describe the safety and effectiveness of tabelecleucel in patients with Epstein-Barr Virus positive (EBV+) Post-Transplant Lymphoproliferative Disease (PTLD) in a real-world setting in Europe [MAH's response to PSA/S/0115]

17.2. Protocols of PASS non-imposed in the marketing authorisation(s)[48]

17.2.1. Dexmedetomidine - DEXDOR (CAP) - EMEA/H/C/002268/LEG 016.7

Applicant: Orion Corporation

PRAC Rapporteur: Karin Bolin

Scope: ***REVISED PROTOCOL***
Draft Study Title: Post-hoc analysis of the SPICE III (academic) trial dataset to address the risk of increased mortality among patients ≤65y sedated with dexmedetomidine. (category 3 study)

[46] 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
[47] In accordance with Article 107n of Directive 2001/83/EC
[48] In accordance with Article 107m of Directive 2001/83/EC, supervised by PRAC in accordance with Article 61a (6) of Regulation (EC) No 726/2004

17.2.2. Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/MEA 057.2

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Martin Huber

Scope: MAH Response to MEA 057.1 [***Protocol PASS Study no.: CA184557***] RSI as adopted in June 2024.
Title: Long-term Follow-up of Nivolumab and Ipilimumab (as Monotherapy and as Combination Therapy)-treated Pediatric Patients Enrolled in the Dutch Melanoma Treatment Registry (DMTR).
Further clarification is needed whether the legal requirements are met to include paediatric patients < 12 years of age as a separate off label use cohort, as well as the support from PDCO

17.2.3. Risankizumab - SKYRIZI (CAP) - EMEA/H/C/004759/MEA 002.6

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Liana Martirosyan

Scope: From Initial MAA:
Progress Report /PASS Study P16-751:
Pregnancy Exposures and Outcomes in Psoriasis Patients Treated with Risankizumab: A Cohort Study Utilising Large Healthcare Databases with Mother-Baby Linkage in the United States.

17.2.4. Single-stranded 5' capped mRNA encoding the Respiratory syncytial virus glycoprotein F stabilized in the prefusion conformation - MRESVIA (CAP) - EMEA/H/C/006278/MEA 003

Applicant: Moderna Biotech Spain S.L.

PRAC Rapporteur: Jean-Michel Dogné

Scope: ***PASS Draft Study Protocol / mRNA-1345-P902 and mRNA-1345-P903***(RMP (v. 0.4))
mRNA-1345-P902: Post-Authorization Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of the mRNA-1345 Vaccine for respiratory syncytial virus (RSV) in the United States.
mRNA-1345-P903: Post-Authorization Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of the mRNA-1345 Vaccine for respiratory syncytial virus (RSV) in Europe.

17.2.5. Tozinameran - COMIRNATY (CAP) - EMEA/H/C/005735/MEA 041.7

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Liana Martirosyan

Scope: ***Fourth Protocol Amendment*** / Study C4591036
category 3 study as per RMP based on the Data and Safety Monitoring Board Report (DSMB).
Clinical study to characterize the clinical course, risk factors, long-term sequelae, and

quality of life in children and young adults <21 years with acute post-vaccine myocarditis. (StudyC4591036).
Also includes DSMB review to the 4th Protocol Amendment for study C4591036.

17.2.6. Tozinameran - COMIRNATY (CAP) - EMEA/H/C/005735/MEA 047.5

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Liana Martirosyan

Scope: ***Protocol amendment / Justification for extension of a milestone for study C4591038***
Change request of due date of Final study report from September 2024 to 30 June 2025.
Study C4591038, a category 3 study in the RMP:
Non-interventional study C4591038 - Post Conditional approval active surveillance study among individuals in Europe receiving the Pfizer BioNTech Coronavirus Disease 2019 (COVID-19) vaccine. Sub-study to investigate natural history of postvaccination myocarditis and pericarditis.

17.2.7. Ublituximab - BRIUMVI (CAP) - EMEA/H/C/005914/MEA 001.3

Applicant: Neuraxpharm Pharmaceuticals S.L.

PRAC Rapporteur: Liana Martirosyan

Scope: MAH's responses to MEA 001.2 [***Revised Protocol***/ Study A Long-Term Observational Study of the Safety of Ublituximab Patients with Relapsing Multiple Sclerosis in a Real-World Setting (ENLIGHTEN)] as adopted in June 2024.

17.2.8. Ublituximab - BRIUMVI (CAP) - EMEA/H/C/005914/MEA 002.2

Applicant: Neuraxpharm Pharmaceuticals S.L.

PRAC Rapporteur: Liana Martirosyan

Scope: MAH's responses to MEA 002.1 [***Revised Protocol / Study No TG1101-RMS403***] as adopted in June 2024.
Pregnancy Registry: A Prospective Registry Study of Pregnancy and Infant Outcomes in Patients Treated with BRIUMVI.

17.2.9. Ublituximab - BRIUMVI (CAP) - EMEA/H/C/005914/MEA 003.2

Applicant: Neuraxpharm Pharmaceuticals S.L.

PRAC Rapporteur: Liana Martirosyan

Scope: MAH's responses to MEA 003.1 [***Revised Protocol*** / Study No TG1101-RMS404] as adopted in June 2024.
To Characterize the Safety of Briumvi Use in Pregnant Patients with Multiple Sclerosis Using Data from a US Administrative Healthcare Claims Database.

17.3. Results of PASS imposed in the marketing authorisation(s)[49]

17.3.1. Alemtuzumab - LEMTRADA (CAP) - EMEA/H/C/PSR/S/0050

Applicant: Sanofi Belgium

PRAC Rapporteur: Karin Erneholm

Scope: Final study report for a non-interventional post-authorisation safety study to investigate drug utilisation and safety monitoring patterns for Lemtrada (alemtuzumab)

17.4. Results of PASS non-imposed in the marketing authorisation(s)[50]

17.4.1. Brexucabtagene autoleucel - TECARTUS (CAP) - EMEA/H/C/005102/II/0051, Orphan

Applicant: Kite Pharma EU B.V., ATMP

PRAC Rapporteur: Bianca Mulder

Scope: Submission of the final study report for the non-interventional study KT-EU-472-5966 titled "Quantitative Testing of Health Care Professional Knowledge About Tecartus Risk Minimisation Measures'' listed as a category 3 study in the RMP

17.4.2. COVID-19 mRNA vaccine - SPIKEVAX (CAP) - EMEA/H/C/005791/II/0131

Applicant: Moderna Biotech Spain S.L.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Submission of the final report from study mRNA-1273-919 - An Observational Study to Assess Maternal and Infant Outcomes Following Exposure to Spikevax During Pregnancy, listed as a category 3 study in the RMP

17.4.3. COVID-19 mRNA vaccine - SPIKEVAX (CAP) - EMEA/H/C/005791/II/0142

Applicant: Moderna Biotech Spain S.L.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Submission of the final report from study mRNA-1273-P920 – US PASS (Post Authorization Safety Study in the US) listed as a category 3 study in the RMP; this is a post-marketing safety of elasomeran/davesomeran and andusomeran vaccines in the United States

17.4.4. Deferasirox - EXJADE (CAP) - EMEA/H/C/000670/II/0090

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Tiphaine Vaillant

Scope: Update of section 4.2 of the SmPC in order to update information on posology based on the non-interventional study CICL670A2429 listed as a category 3 study in the RMP. This

[49] In accordance with Article 107p-q of Directive 2001/83/EC
[50] In accordance with Article 61a (6) of Regulation (EC) No 726/2004, in line with the revised variations regulation for any submission as of 4 August 2013

is a survey to assess physicians' knowledge of Exjade posology and biological monitoring recommendations as described in the Educational Materials (EMs)

17.4.5. Dengue tetravalent vaccine (live, attenuated) - DENGVAXIA (CAP) - EMEA/H/C/004171/II/0032

Applicant: Sanofi Pasteur

PRAC Rapporteur: Sonja Hrabcik

Scope: Submission of the final study report for DNG16 (category 3 PASS); a non-interventional Pregnancy Registry for DENGVAXIA, CYD-TDV Dengue Vaccine used to evaluate the safety of CYD-TDV in pregnant women and their offsprings inadvertently exposed during pregnancy or up to 30 days preceding their last menstrual period with regards to maternal, pregnancy, birth, neonatal, and infant outcomes. This submission fulfills MEA/FSR 002

17.4.6. Empagliflozin - JARDIANCE (CAP) - EMEA/H/C/002677/WS2713/0089; Empagliflozin, linagliptin - GLYXAMBI (CAP) - EMEA/H/C/003833/WS2713/0062; Empagliflozin, metformin - SYNJARDY (CAP) - EMEA/H/C/003770/WS2713/0080

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Submission of the final report from study 1245-0097. This is a post-authorisation safety study (PASS) to assess the risk of urinary tract malignancies in relation to empagliflozin exposure in patients with type 2 diabetes: a multi-database European study. The RMP versions 23.0, 17.0 and 11.0 are also submitted for Jardiance, Synjardy and Glyxambi, respectively

17.4.7. Mepolizumab - NUCALA (CAP) - EMEA/H/C/003860/II/0071

Applicant: GlaxoSmithKline Trading Services Limited

PRAC Rapporteur: Gabriele Maurer

Scope: Submission of the final report from the Mepolizumab (Nucala) Pregnancy Exposure Study 200870: a VAMPSS post marketing surveillance study of Mepolizumab safety in pregnancy, listed as a category 3 study in the RMP. This is a non-interventional study to monitor planned and unplanned pregnancies exposed to mepolizumab and to evaluate the possible teratogenic effect of this medication relative to the pregnancy outcomes of major birth defects, preterm delivery, small for gestational age infants and spontaneous abortion or stillbirth. The RMP version 13.0 has also been submitted

17.4.8. Naloxegol - MOVENTIG (CAP) - EMEA/H/C/002810/II/0043

Applicant: Gruenenthal GmbH

PRAC Rapporteur: Eamon O'Murchu

Scope: Submission of the final report from the PASS study D3820R0008 listed as a category 3 study in the RMP. This is a US post-marketing, comparative, observational study to evaluate the cardiovascular safety of Naloxegol in patients with non-cancer pain in

comparison to other treatments for opioid induced constipation. The RMP version 9.0 has also been submitted

17.4.9. Naltrexone hydrochloride, bupropion hydrochloride - MYSIMBA (CAP) - EMEA/H/C/003687/II/0066

Applicant: Orexigen Therapeutics Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: Submission of final report from study NB-453 study, listed as a category 3 study in the RMP. This is a non-interventional qualitative research using online focus groups to assess understanding, attitude and behaviour for usage of the Mysimba Physician Prescribing Checklist (PPC) among physicians in the European Union (EU), following a previous cross-sectional survey that aimed at evaluating the effectiveness of the same PPC (Study NB-452). The RMP version 12.10 has also been submitted

17.4.10. Piperaquine tetraphosphate, artenimol - EURARTESIM (CAP) - EMEA/H/C/001199/II/0040/G

Applicant: Alfasigma S.p.A.

PRAC Rapporteur: Martin Huber

Scope: C.I.13: Submission of the final report from the effectiveness evaluation survey for Eurartesim (protocol no. 3366) listed as a category 3 study in the RMP. This is a European multi-centre online survey to assess physician understanding of the revised edition of the educational material. Consequential changes to RMP version 16.1 have been implemented. C.I.11.b: Submission of an updated RMP version 16.1 in order to delete "Severe Malaria" from the Missing Information

17.4.11. Plasmodium falciparum and hepatitis B vaccine (recombinant, adjuvanted) - MOSQUIRIX (Art 58[51]) - EMEA/H/W/002300/II/0085/G

Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Jean-Michel Dogné

Scope: A grouped application comprised of two type II variations, as follows:

C.I.4: Update of sections 4.4 and 5.1 of the SmPC in order to remove meningitis from the list of important potential risks and add effectiveness data based on EPI-MAL-003 study listed as a category 3 study in the RMP. This is a prospective study to evaluate the safety, effectiveness and impact of the RTS,S/AS01E vaccine in young children in sub-Saharan Africa countries. The Package Leaflet is updated accordingly.
The RMP version 6.0 has also been submitted.
C.I.13: Submission of the final report from study MVPE (Malaria Vaccine Pilot Evaluation) listed as a category 3 study in the RMP. This is a observational study in the context of a cluster-randomized pilot implementation in order to assess the feasibility of delivery, safety, and impact on mortality of the RTS,S/AS01E malaria vaccine delivered through the routine

[51] 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)

immunization services in Kenya, Malawi, and Ghana over 4 years

17.4.12. Vedolizumab - ENTYVIO (CAP) - EMEA/H/C/002782/II/0086

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Adam Przybylkowski

Scope: Submission of amendment 2 (version 3) to the final clinical study report (CSR) for the post authorisation safety study MLN0002-401, listed as a category 3 study in the RMP. This was a prospective, observational, international, multicentre, cohort study comparing vedolizumab with other biologic agents in patients with UC or CD. The final CSR (versions 1 and 2) was submitted and assessed in procedure EMEA/H/C/002782/II/0073. Further review and additional inconsistencies were identified in the analyses and reporting of safety, which are addressed in CSR amendment 2 (version 3)

17.4.13. Zanamivir - DECTOVA (CAP) - EMEA/H/C/004102/II/0020

Applicant: GlaxoSmithKline Trading Services Limited

PRAC Rapporteur: Mari Thorn

Scope: Submission of the final report from study 208140 listed as a category 3 PASS in the RMP. This is an observational study of the safety of zanamivir 10 mg/ml solution for infusion exposure in pregnant women with complicated influenza and their offspring. The RMP version 8.0 has also been submitted

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

17.5.1. Burosumab - CRYSVITA (CAP) - EMEA/H/C/004275/MEA 004.5

Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Gabriele Maurer

Scope: MAH's response to MEA 004.4 [***Second interim study report*** [Study No EUPAS32190]] RSI as adopted in July 2024.
Non-interventional Post-Authorisation Safety Study of Burosumab in the Treatment of Children >1 year of age, Adolescents and Adults with X-linked Hypophosphataemia (protocol number 2019-36-EU-CRY)

17.5.2. Ciltacabtagene autoleucel - CARVYKTI (CAP) - EMEA/H/C/005095/ANX 003.3

Applicant: Janssen-Cilag International NV, ATMP

PRAC Rapporteur: Jo Robays

Scope: From initial MAA
PASS Study 68284528MMY4004
Title: An Observational Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel.
Second Interim Report / Study 68284528MMY4004

17.5.3. Hydroxycarbamide - SIKLOS (CAP) - EMEA/H/C/000689/MEA 035.2

Applicant: Theravia

PRAC Rapporteur: Jo Robays

Scope: ESCORT-HU Extension:
European Sickle Cell Disease Cohort – Hydroxyurea (#2_V1.0)
Fourth Interim Report

17.5.4. Romosozumab - EVENITY (CAP) - EMEA/H/C/004465/MEA 001.10

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Tiphaine Vaillant

Scope: From Initial MAA: PASS Study No. OP0005: European non-interventional post-authorisation safety study (PASS) related to the adherence to the cardiovascular risk minimization measures for romosozumab, by the EU-ADR Alliance.
Six Interim Report / PASS Study No. OP0005

17.5.5. Romosozumab - EVENITY (CAP) - EMEA/H/C/004465/MEA 002.11

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Tiphaine Vaillant

Scope: From Initial MAA: PASS Study No. OP0004: European non-interventional post-authorisation safety study (PASS) related to serious cardiovascular adverse events of myocardial infarction and stroke for romosozumab by the EU-ADR Alliance to evaluate potential differences in terms of serious cardiovascular adverse events between romosozumab and currently available therapies used in comparable patients in real-world conditions.
SIXTH INTERIM REPORT / PASS Study No. OP0004

17.5.6. Romosozumab - EVENITY (CAP) - EMEA/H/C/004465/MEA 003.10

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Tiphaine Vaillant

Scope: From Initial MAA: PASS Study No. OP0006 European non-interventional post-authorisation safety study (PASS) related to serious infections risk for romosozumab by the EU-ADR Alliance to evaluate potential differences in terms of serious infection between romosozumab and currently available therapies used in comparable patients in real-world conditions.
FOURTH INTERIM REPORT (comparative) /PASS Study No. OP0006

17.5.7. Selumetinib - KOSELUGO (CAP) - EMEA/H/C/005244/SOB 004.1

Applicant: AstraZeneca AB

PRAC Rapporteur: Mari Thorn

Scope: Post-Authorisation Safety Study of Paediatric Patients Initiating Selumetinib: A

Multiple-Country Prospective Cohort Study (Report 2)(Version number 1.0)
Second PASS Annual Progress / D1346R00004
The primary objective of this study is:
• To characterise the safety of selumetinib, including up to 6 years of long-term safety, in paediatric patients with NF1-related symptomatic, inoperable PN, 8 to < 18 years old who have not reached Tanner Stage V at the start of selumetinib treatment (Nested Prospective Cohort).
The secondary objective of this study is:
• To describe the paediatric population 3 to < 18 years old with NF1-related symptomatic inoperable PN who start selumetinib in routine clinical practice (Base Cohort).

17.5.8. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/MEA 013.6

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Martirosyan

Scope: Interim study A3921344:
An Active Surveillance, Post-Authorization Study to Characterize the Safety of Tofacitinib in Patients with Moderately to Severely Active Ulcerative Colitis in the Real-World Setting Using Data from the Swedish Quality Register for Inflammatory Bowel Disease. (SWIBREG). (RMP category 3 study)
Second Interim Report

17.5.9. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/MEA 017.4

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Martirosyan

Scope: ***Interim Report***/ Study A3921352
Study A3921352 is an active surveillance, post-authorization study to characterize the safety of tofacitinib in patients with moderately to severely active ulcerative colitis in the real-world setting using data from the United Registries for Clinical Assessment and Research (UR-CARE) in the European Union (EU).

17.5.10. Upadacitinib - RINVOQ (CAP) - EMEA/H/C/004760/MEA 013.5

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Petar Mas

Scope: ***Second Annual Progress Report*** and MAH's responses to MEA 013.4 [Protocol P20-390] RSI as adopted in December 2023. Cohort Study of Long-term Safety of Upadacitinib in the Treatment of Atopic Dermatitis in Denmark and Sweden (PASS Protocol P20-390).

17.6. Others

None

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 medicine(s) listed below and the CHMP Rapporteur's assessment report, PRAC considered that either the renewal of the marketing authorisation procedure could be concluded - and supported the renewal of their marketing authorisations for an unlimited or additional period, as applicable - or no amendments to the specific obligations of the marketing authorisation under exceptional circumstances for the medicines listed below were recommended. As per the 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. Asfotase alfa - STRENSIQ (CAP) - EMEA/H/C/003794/S/0069 (without RMP)

Applicant: Alexion Europe SAS

PRAC Rapporteur: Eamon O'Murchu

Scope: Annual reassessment of the marketing authorisation

18.1.2. Cerliponase alfa - BRINEURA (CAP) - EMEA/H/C/004065/S/0047 (without RMP)

Applicant: BioMarin International Limited

PRAC Rapporteur: Mari Thorn

Scope: Annual reassessment of the marketing authorisation

18.1.3. Eladocagene exuparvovec - UPSTAZA (CAP) - EMEA/H/C/005352/S/0025 (without RMP)

Applicant: PTC Therapeutics International Limited, ATMP

PRAC Rapporteur: Gabriele Maurer

Scope: Annual reassessment of the marketing authorisation

18.1.4. Mecasermin - INCRELEX (CAP) - EMEA/H/C/000704/S/0083 (without RMP)

Applicant: Ipsen Pharma

PRAC Rapporteur: Terhi Lehtinen

Scope: Annual reassessment of the marketing authorisation

18.1.5. Tafamidis - VYNDAQEL (CAP) - EMEA/H/C/002294/S/0095 (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. Exagamglogene autotemcel - CASGEVY (CAP) - EMEA/H/C/005763/R/0006 (without RMP)

Applicant: Vertex Pharmaceuticals (Ireland) Limited, ATMP

PRAC Rapporteur: Bianca Mulder

Scope: Conditional renewal of the marketing authorisation

18.2.2. Parathyroid hormone - NATPAR (CAP) - EMEA/H/C/003861/R/0058 (without RMP)

Applicant: Takeda Pharmaceuticals International AG Ireland Branch

PRAC Rapporteur: Rhea Fitzgerald

Scope: Conditional renewal of the marketing authorisation

18.2.3. Pemigatinib - PEMAZYRE (CAP) - EMEA/H/C/005266/R/0019 (without RMP)

Applicant: Incyte Biosciences Distribution B.V.

PRAC Rapporteur: Bianca Mulder

Scope: Conditional renewal of the marketing authorisation

18.2.4. Sparsentan - FILSPARI (CAP) - EMEA/H/C/005783/R/0004 (without RMP)

Applicant: Vifor France

PRAC Rapporteur: Martin Huber

Scope: Conditional renewal of the marketing authorisation

18.3. Renewals of the marketing authorisation

18.3.1. Alpelisib - PIQRAY (CAP) - EMEA/H/C/004804/R/0028 (without RMP)

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Bianca Mulder

Scope: 5-year renewal of the marketing authorisation

18.3.2. Budesonide, formoterol fumarate dihydrate - GORESP DIGIHALER (CAP) - EMEA/H/C/004882/R/0016 (without RMP)

Applicant: Teva Pharma B.V.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: 5-year renewal of the marketing authorisation

18.3.3. Etanercept - NEPEXTO (CAP) - EMEA/H/C/004711/R/0033 (without RMP)

Applicant: Biosimilar Collaborations Ireland Limited

PRAC Rapporteur: Monica Martinez Redondo

Scope: 5-year renewal of the marketing authorisation

18.3.4. Glasdegib - DAURISMO (CAP) - EMEA/H/C/004878/R/0015 (without RMP)

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Bianca Mulder

Scope: 5-year renewal of the marketing authorisation

18.3.5. Indacaterol, glycopyrronium bromide, mometasone - ENERZAIR BREEZHALER (CAP) - EMEA/H/C/005061/R/0029 (without RMP)

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Jan Neuhauser

Scope: 5-year renewal of the marketing authorisation

18.3.6. Indacaterol, glycopyrronium bromide, mometasone - ZIMBUS BREEZHALER (CAP) - EMEA/H/C/005518/R/0025 (without RMP)

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Jan Neuhauser

Scope: 5-year renewal of the marketing authorisation

18.3.7. Indacaterol, mometasone - ATECTURA BREEZHALER (CAP) - EMEA/H/C/005067/R/0031 (without RMP)

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Jan Neuhauser

Scope: 5-year renewal of the marketing authorisation

18.3.8. Indacaterol, mometasone - BEMRIST BREEZHALER (CAP) - EMEA/H/C/005516/R/0026 (without RMP)

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Jan Neuhauser

Scope: 5-year renewal of the marketing authorisation

18.3.9. Isatuximab - SARCLISA (CAP) - EMEA/H/C/004977/R/0033 (without RMP)

Applicant: Sanofi Winthrop Industrie

PRAC Rapporteur: Monica Martinez Redondo

Scope: 5-year renewal of the marketing authorisation

18.3.10. Luspatercept - REBLOZYL (CAP) - EMEA/H/C/004444/R/0031 (without RMP)

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Jo Robays

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 25-28 November 2024 PRAC meeting, which was held in-person.

An asterisk (*) after the role, in the second column, signals that the member/alternate attended remotely. Additional experts participated in (part of) the meeting, either in person or remotely.

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Ulla Wändel Liminga	Chair	Sweden	No interests declared	
Jan Neuhauser	Member*	Austria	No interests declared	
Sonja Hrabcik	Alternate*	Austria	No interests declared	
Jean-Michel Dogné	Member	Belgium	No interests declared	
Jo Robays	Alternate	Belgium	No interests declared	
Maria Popova-Kiradjieva	Member	Bulgaria	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Petar Mas	Member	Croatia	No interests declared	
Barbara Bytyqi	Alternate	Croatia	No interests declared	
Panagiotis Psaras	Alternate	Cyprus	No interests declared	
Eva Jirsová	Member*	Czechia	No interests declared	
Jana Lukacisinova	Alternate	Czechia	No interests declared	
Marie Louise Schougaard Christiansen	Member	Denmark	No interests declared	
Karin Erneholm	Alternate	Denmark	No interests declared	
Maia Uusküla	Member	Estonia	No interests declared	
Terhi Lehtinen	Member	Finland	No interests declared	
Kimmo Jaakkola	Alternate	Finland	No interests declared	
Tiphaine Vaillant	Member	France	No interests declared	
Zoubida Amimour	Alternate	France	No participation in discussion, final deliberations and voting on:	15.3.3. Adagrasib - KRAZATI (CAP) - EMEA/H/C/006013/II/0010/G 15.3.22. Mavacamten - CAMZYOS (CAP) - EMEA/H/C/005457/II/0011/G 16.1.23. Mavacamten - CAMZYOS (CAP) - PSUSA/00000074/202404 17.2.2. Nivolumab - OPDIVO (CAP) -

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				EMEA/H/C/003985/MEA 057.2 18.3.10. Luspatercept - REBLOZYL (CAP) - EMEA/H/C/004444/R/0031 (without RMP)
Martin Huber	Member*	Germany	No interests declared	
Gabriele Maurer	Alternate	Germany	No participation in discussion, final deliberations and voting on:	17.2.2. Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/MEA 057.2
Sofia Trantza	Member	Greece	No interests declared	
Georgia Gkegka	Alternate*	Greece	No interests declared	
Julia Pallos	Member	Hungary	No participation in discussion, final deliberations and voting on:	15.3.3. Adagrasib - KRAZATI (CAP) - EMEA/H/C/006013/II/0010/G 15.3.22. Mavacamten - CAMZYOS (CAP) - EMEA/H/C/005457/II/0011/G 16.1.23. Mavacamten - CAMZYOS (CAP) - PSUSA/00000074/202404 17.2.2. Nivolumab - OPDIVO (CAP) -

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				EMEA/H/C/003985/MEA 057.2 18.3.10. Luspatercept - REBLOZYL (CAP) - EMEA/H/C/004444/R/0031 (without RMP)
Guðrún Þengilsdóttir	Alternate	Iceland	No interests declared	
Rhea Fitzgerald	Member	Ireland	No interests declared	
Eamon O Murchu	Alternate	Ireland	No interests declared	
Amelia Cupelli	Member	Italy	No interests declared	
Emilio Clementi	Alternate*	Italy	No interests declared	
Zane Neikena	Member	Latvia	No interests declared	
Lina Seibokiene	Alternate	Lithuania	No restrictions applicable to this meeting	
Nadine Petitpain	Member	Luxembourg	No restrictions applicable to this meeting	
John Joseph Borg	Member	Malta	No interests declared	
Liana Martirosyan	Member	Netherlands	No interests declared	
Bianca Mulder	Alternate	Netherlands	No interests declared	
David Olsen	Member	Norway	No participation in discussion, final deliberations and voting on:	14.1.2. Regorafenib – STIVARGA (CAP)

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Pernille Harg	Alternate	Norway	No interests declared	
Adam Przybylkowski	Member*	Poland	No interests declared	
Katarzyna Ziolkowska	Alternate	Poland	No interests declared	
Ana Sofia Diniz Martins	Member	Portugal	No interests declared	
Carla Torre	Alternate	Portugal	No interests declared	
Roxana Dondera	Member	Romania	No interests declared	
Irina Sandu	Alternate*	Romania	No interests declared	
Anna Mareková	Member	Slovakia	No interests declared	
Miroslava Gocova	Alternate*	Slovakia	No interests declared	
Polona Golmajer	Member	Slovenia	No interests declared	
Maria del Pilar Rayon	Member	Spain	No interests declared	
Monica Martinez Redondo	Alternate	Spain	No interests declared	
Mari Thorn	Member	Sweden	No restrictions applicable to this meeting	
Karin Bolin	Alternate	Sweden	No interests declared	
Annalisa Capuano	Member*	Independent scientific expert	No interests declared	
Milou-Daniel Drici	Member	Independent scientific expert	No interests declared	
Maria Teresa Herdeiro	Member	Independent scientific expert	No interests declared	
Patricia McGettigan	Member	Independent scientific expert	No restrictions applicable to this meeting	
Anette Kirstine Stark	Member	Independent scientific expert	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Hedvig Marie Egeland Nordeng	Member	Independent scientific expert	No interests declared	
Roberto Frontini	Member	Healthcare Professionals' Representative	No restrictions applicable to this meeting	
Salvatore Antonio Giuseppe Messana	Alternate	Healthcare Professionals' Representative	No interests declared	
Michal Rataj	Alternate	Patients' Organisation Representative	No interests declared	
Dennis Lex	Expert	Germany	No interests declared	
Charlotte Backman	Expert	Sweden	No interests declared	
Frederikke Hillebrand Laustsen	Expert	Denmark	No restrictions applicable to this meeting	
Evelien de Clercq	Expert	Belgium	No interests declared	
Laurence de Fays	Expert	Belgium	No interests declared	
Veerle Verlinden	Expert	Belgium	No interests declared	
Veronika Deščíková	Expert	Czech Republic	No interests declared	
Jana Kopecka	Expert	Czech Republic	No interests declared	
Jana Šípková	Expert	Czech Republic	No interests declared	
Lucie Skalova	Expert	Czech Republic	No interests declared	
Aviaja Højegaard Ammentorp	Expert	Denmark	No interests declared	
Alexander Braathen	Expert	Denmark	No interests declared	
Helle Gerda Olsen	Expert	Denmark	No interests declared	
Susanne Høpner Rasmussen	Expert	Denmark	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Emma Stadsbjerg	Expert	Denmark	No restrictions applicable to this meeting	
Anissa Benlazar	Expert	France	No interests declared	
Camille De-Kervasdoue	Expert	France	No interests declared	
Roxane Fornacciari	Expert	France	No interests declared	
Stéphane Personne	Expert	France	No interests declared	
Soizic Varet	Expert	France	No interests declared	
Aurélie Vitores	Expert	France	No interests declared	
Anne-Charlotte Lübow	Expert	Germany	No restrictions applicable to this meeting	
Birte Niemann	Expert	Germany	No interests declared	
Magdalena Wielowieyska	Expert	Luxembourg	No restrictions applicable to this meeting	
Negar Babae	Expert	Netherlands	No interests declared	
Esther de Vries	Expert	Netherlands	No interests declared	
Talip Eroglu	Expert	Netherlands	No interests declared	
Helen Gatling	Expert	Netherlands	No interests declared	
Ingrid Schellens	Expert	Netherlands	No interests declared	
Stephany Suoth	Expert	Netherlands	No interests declared	
Lieke van der Velden-van Irsel	Expert	Netherlands	No interests declared	
Elly Vereyken	Expert	Netherlands	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Martin Speth	Expert	Norway	No interests declared	
Natividad Galiana	Expert	Spain	No restrictions applicable to this meeting	
Edurne Lazaro	Expert	Spain	No interests declared	
Maria Martinez Gonzalez	Expert	Spain	No interests declared	
Elin Blom	Expert	Sweden	No interests declared	
A representative from the European Commission attended the meeting				
Observers from Health Canada and WHO attended the meeting.				
Meeting run with support from relevant EMA staff				

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

20. Annex III - List of acronyms and abbreviations

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

List of abbreviations used in EMA human medicines scientific committees and CMDh documents, and in relation to EMA's regulatory activities

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: Referral procedures: human medicines | European Medicines Agency (europa.eu)

Signals assessment and prioritisation

(Item 4 of the PRAC minutes)

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

is a routine part of pharmacovigilance and is essential to ensuring that regulatory authorities have a comprehensive knowledge of a medicine's benefits and risks.
The presence of a safety signal does not mean that a medicine has caused the reported adverse event. The adverse event could be a symptom of another illness or caused by another medicine taken by the patient. The evaluation of safety signals is required to establish whether or not there is a causal relationship between the medicine and the reported adverse event.
The evaluation of safety signals may not necessarily conclude that the medicine caused the adverse event in question. In cases where a causal relationship is confirmed or considered likely, regulatory action may be necessary and this usually takes the form of an update of the summary of product characteristics and the package leaflet.

Risk Management Plans (RMPs)

(Item 5 of the PRAC minutes)

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

Assessment of Periodic Safety Update Reports (PSURs)

(Item 6 of the PRAC minutes)

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

Post-authorisation Safety Studies (PASS)

(Item 7 of the PRAC minutes)

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

Product related pharmacovigilance inspections

(Item 9 of the PRAC minutes)

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

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