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Human Medicines Division

Pharmacovigilance Risk Assessment Committee (PRAC) Minutes for the meeting on 13-16 May 2024

Chair: Sabine Straus – Vice-Chair: Martin Huber

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

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Official address Domenico Scarlattilaan 6 • 1083 HS Amsterdam • The Netherlands

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1. Introduction

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

The Chairperson opened the 13-16 May 2024 meeting by welcoming all participants. The meeting was held remotely.

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, alternates¹ 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. No new or additional competing interests were declared. 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 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 13-16 May 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 08-11 April 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 08-11 April 2024 were published on the EMA website on 12 June 2024 ([EMA/PRAC/262385/2024](#)).

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

2.1. Newly triggered procedures

None

¹ 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

3.3.1. Hydroxyprogesterone (NAP) - EMEA/H/A-31/1528

Applicant(s): various

PRAC Rapporteur: Amelia Cupelli; PRAC Co-rapporteur: Nathalie Gault

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

Background

A referral procedure under Article 31 of Directive 2001/83/EC for hydroxyprogesterone caproate (17-OHPC) is to be concluded. The review was initiated following the results of a pharmaco-epidemiological study by *Murphy et al*² that showed that in utero exposure to 17-OHPC may be associated with a higher risk of cancer in the offspring. In addition, the results from another study by *Blackwell et al*³ (PROLONG study) suggested that 17-OHPC is no more effective than placebo in preventing recurrent premature birth or medical complications due to prematurity in the new-born infant. For further background, see [PRAC minutes May 2023](#), [PRAC minutes October 2023](#) and [PRAC minutes January 2024](#). A final assessment of the data submitted was produced by the Rapporteurs according to the agreed timetable.

Discussion

PRAC discussed the conclusion(s) reached by the Rapporteurs.

PRAC reviewed the totality of the data available for 17-OHPC-containing products in relation to the risk of cancer in offspring exposed to 17-OHPC in utero, as well as available efficacy data, and assessed their impact on the benefit-risk balance of those products. These data included the responses submitted in writing by the MAHs, the results of a pharmaco-

² Murphy C.C., et al., In utero exposure to 17 α -hydroxyprogesterone caproate and risk of cancer in offspring. *Am J Obstet Gynecol.* 2022, 226(1): 132.e1-132.-e14. doi:10.1016/j.ajog.2021.10.035

³ Blackwell, S.C., et al., 17-OHPC to prevent recurrent preterm birth in singleton gestations (PROLONG Study): A multicenter, international, randomized double-blind trial. *Am J Perinatol.* 2020, 37(2): 127-136 doi:10.1055/s-0039-3400227

epidemiological study by *Murphy et al*, data submitted during the review by its authors as well as the outcome of the consultation with an ad-hoc expert group (AHEG).

PRAC considered that the results of this pharmaco-epidemiological study suggest an increased risk of cancer in offspring exposed to 17-OHPC in utero. This potential risk is of relevance in all therapeutic indications where an exposure in utero to 17-OHPC is possible. PRAC concluded that this risk is possible but cannot be confirmed due to study limitations.

PRAC also considered the possibility of implementing risk minimisation measures but no measures that would effectively prevent in utero exposure to 17-OHPC could be identified.

In addition, PRAC considered the results of the PROLONG study and meta-analyses⁴ in the context of available data on efficacy of 17-OHPC-containing products in the prevention of premature parturition, and concluded that they showed no efficacy. Furthermore, PRAC noted that there is limited data of efficacy in other obstetrical and gynaecological indications for which 17-OHPC is authorised.

As a consequence, PRAC concluded that the benefit-risk balance of 17-OHPC-containing products is no longer favourable in all authorised indications and recommended the suspension of the marketing authorisations for 17-OHPC-containing products.

Summary of recommendation(s)/conclusions

- PRAC adopted a recommendation to suspend the marketing authorisations for 17-OHPC-containing products to be considered by CMDh for a position.
- PRAC agreed on the distribution of a direct healthcare professional communication ([DHPC](#)) together with a communication plan.

Post-meeting note 1: the press release 'Hydroxyprogesterone caproate medicines to be suspended from the EU market' ([EMA/225201/2024](#)) was published on the EMA website on 17 May 2024.

Post-meeting note 2: On 28 June 2024, the press release ([EMA/298147/2024](#)) following the adoption of the CMDh position was published on the EMA website.

Post-meeting note 3: On 05 July 2024, the assessment report ([EMA/263875/2024](#)) for the procedure was published on the EMA website.

3.4. Re-examination procedures⁵

None

3.5. Others

None

⁴ Stewart L.A., et al. Evaluating progestogens for preventing preterm birth international collaborative (EPPPIC): meta-analysis of individual participant data from randomised controlled trials. *Lancet* 2021;397:1183–94

Care A., et al. Interventions to prevent spontaneous preterm birth in women with singleton pregnancy who are at high risk: systematic review and network meta-analysis *BMJ* 2022; 376 :e064547 doi:10.1136/bmj-2021-064547

⁵ Re-examination of PRAC recommendation under Article 32 of Directive 2001/83/EC

4. Signals assessment and prioritisation⁶

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. Eptinezumab – VYEPTI (CAP); erenumab – AIMOVIG (CAP); fremanezumab – AJOVY (CAP); galcanezumab – EMGALITY (CAP)

Applicant(s): H. Lundbeck A/S (Vyepti), Novartis Europharm Limited (Aimovig), TEVA GmbH (Ajoyv), Eli Lilly Nederland B.V. (Emgality)

PRAC Rapporteur: to be appointed

Scope: Signal of insomnia

EPITT 20077 – New signal

Lead Member State(s): FI, NL

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 insomnia was identified by the Norwegian Medicines Agency, based on 5 spontaneous cases reported for erenumab, fremanezumab, galcanezumab in the national database, as well as on approximately 500 cases retrieved from EudraVigilance, 1,020 cases from VigiBase and the literature. In addition, 1 case reported for eptinezumab was retrieved in Eudravigilance by the Dutch Medicines Evaluation Board (MEB). 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 literature, PRAC agreed that further evaluation of the signal of insomnia following administration of eptinezumab, erenumab, galcanezumab and fremanezumab is warranted.

PRAC appointed Kirsti Villikka as Rapporteur for the signal.

Summary of recommendation(s)

- The MAHs for Vyepti (eptinezumab), Aimovig (erenumab), Ajoyv (fremanezumab) and Emgality (galcanezumab) should submit to EMA, by 31 July 2024, a cumulative review of the signal, including an analysis of all case reports of MedDRA high-level term (HLT) 'disturbances in initiating and maintaining sleep', as well as a review of the published

⁶ 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

literature, reports from studies and a discussion on possible biological plausibility and mechanism of this association. The MAHs should also discuss the need for any potential amendment to the product information (PI) and/ or the risk management plan (RMP), as warranted.

- A 90-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.1.2. Erenumab – AIMOVIG (CAP)

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Kirsti Villikka

Scope: Signal of hypertension

EPITT 20081– New signal

Lead Member State(s): FI

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 hypertension was identified by EMA, based on two observational studies and 247 cases retrieved from EudraVigilance. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by PRAC.

Discussion

Having considered the available evidence including two recent observational studies (Chhabra et al., de Vries Lentsch et al.), PRAC agreed that further evaluation of the signal of hypertension following administration of erenumab is warranted.

Summary of recommendation(s)

- In the PSUR with data lock point 16 May 2024, the MAH should submit to EMA a cumulative review of cases of hypertension, including but not be limited the studies published by *Chhabra et al.*⁷ and *de Vries Lentsch et al.*⁸, as well as the review of spontaneously reported cases including the initiation of a new hypertensive medications or changes in pre-existing antihypertensive medications after reported onset of hypertension. The MAH should also discuss the need for any potential amendment to the product information (PI) and/ or the risk management plan (RMP) as warranted.
- PRAC will assess the cumulative review within the PSUR procedure PSUSA/00010699/202405.

⁷ Chhabra N, Mead-Harvey C, Dadoo CA, et al. Blood pressure elevation in erenumab-treated patients with migraine: A retrospective real-world experience. *Headache* 2024;64:233–42. <https://doi.org/10.1111/head.14679>

⁸ de Vries Lentsch S, van der Arend BWH, Maassen VanDenBrink A, Terwindt GM. Blood Pressure in Patients With Migraine Treated With Monoclonal Anti-CGRP (Receptor) Antibodies: A Prospective Follow-up Study. *Neurology* 2022;99:e1897–904. <https://doi.org/10.1212/WNL.0000000000201008>

4.2. Signals follow-up and prioritisation

4.2.1. Aflibercept – EYLEA (CAP) - EMEA/H/C/002392/SDA/023, YESAFILI (CAP) - EMEA/H/C/006022/SDA/002

Applicant(s): Bayer AG (Eylea), Biosimilar Collaborations Ireland Limited (Yesafili)

PRAC Rapporteur: Nathalie Gault

Scope: Signal of nephropathy toxic after intravitreal administration

EPITT 20024 – Follow-up to January 2024

Background

For background information, see [PRAC minutes January 2024](#).

The MAHs replied to the request for information on the signal of nephropathy toxic after intravitreal administration and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence from case reports in EudraVigilance and the literature, including the data submitted by the MAHs, PRAC agreed no update to the product information of aflibercept-containing medicinal products Eylea and Yesafili is considered warranted at this stage.

Summary of recommendation(s)

- The MAHs for the aflibercept-containing medicinal products Eylea and Yesafili should submit to EMA, within the next PSUR⁹, a cumulative review of all cases of nephropathy associated with intravitreal aflibercept received since the last review, including also the following standardised MedDRA queries (SMQ) (Broad) search terms of 'acute renal failure', 'proteinuria' and 'haemolytic disorders', the high level terms (HLTs) 'glomerulonephritis and nephrotic syndrome', and the preferred terms (PTs) 'thrombotic microangiopathy', 'microangiopathic haemolytic anaemia', 'haemolytic uraemic syndrome', 'thrombotic thrombocytopenic purpura', 'coombs negative haemolytic anaemia', 'coombs test negative', and 'von Willebrand factor multimers abnormal', as well as a review of the published literature, data from spontaneous reports and reports from studies including all cases in EudraVigilance, as well as a discussion on possible biological plausibility and mechanism of this association. The MAHs should also discuss the need for any potential amendment to the product information (PI) and/or the risk management plan (RMP) as warranted.
- PRAC will assess the cumulative review within the PSUR procedure PSUSA/00010020/202511

4.2.2. Baricitinib – OLUMIANT (CAP) - EMEA/H/C/004085/SDA/018

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Signal of hypoglycaemia in diabetic patients

⁹ Data lock point 30 November 2025

EPITT 20038 – Follow-up to January 2024

Background

For background information, see [PRAC minutes January 2024](#).

The MAH replied to the request for information on the signal of hypoglycaemia in diabetic patients and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence in EudraVigilance, published literature including the study by *Waibel et al.*¹⁰ as well as data submitted by the MAH, PRAC agreed that there is sufficient evidence to establish a causal relationship between Olumiant (baricitinib) and hypoglycaemia in diabetic patients. Therefore, the product information should be amended to add a warning on hypoglycaemia in diabetic patients.

Summary of recommendation(s)

- The MAH for Olumiant (baricitinib) should submit to EMA, within 60 days, a variation to amend¹¹ the product information.

4.2.3. Clobazam (NAP)

Applicant(s): various

PRAC Rapporteur: Kimmo Jaakkola

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

EPITT 20041 – Follow-up to January 2024

Background

For background information, see [PRAC minutes January 2024](#).

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

Discussion

Having considered the available evidence in EudraVigilance, literature and the responses of the MAH, PRAC agreed that the current evidence is insufficient to establish a causal relationship between clobazam and DRESS to further warrant an update to the product information and/or risk management plan at present.

Summary of recommendation(s)

- The MAH(s) for clobazam-containing products should monitor cases of DRESS and provide a cumulative review in the next PSUR.

¹⁰ Waibel M, Wentworth JM, So M, et al. Baricitinib and β -cell function in patients with new-onset Type 1 Diabetes. *N Engl J Med.* 2023;389(23):2140-2150. <https://doi.org/10.1056/nejmoa2306691>

¹¹ Update of SmPC section 4.4. The package leaflet is updated accordingly.

4.2.4. Dabrafenib – TAFINLAR (CAP) - EMEA/H/C/002604/SDA/024, FINLEE (CAP) - EMEA/H/C/005885/SDA/003; Trametinib – MEKINIST (CAP) - EMEA/H/C/002643/SDA/019, SPEXOTRAS (CAP) - EMEA/H/C/005886/SDA/002

Applicant: Novartis Europharm Limited

PRAC Rapporteur: David Olsen

Scope: Signal of acute febrile neutrophilic dermatosis

EPITT 20022 – Follow-up to January 2024

Background

For background information, see [PRAC minutes January 2024](#).

The MAH replied to the request for information on the signal of acute febrile neutrophilic dermatosis and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence in EudraVigilance, the literature and the data submitted by the MAH, PRAC agreed that there is sufficient evidence to establish a causal relationship between acute febrile neutrophilic dermatosis and treatment with dabrafenib used in monotherapy or in combination with trametinib. Therefore, the product information for dabrafenib- and trametinib-containing products should be updated to add acute febrile neutrophilic dermatosis as undesirable effect (frequency 'uncommon') to the relevant sections reflecting the adverse reactions following the administration of the active substances as a combination therapy (dabrafenib and trametinib) or as monotherapy (dabrafenib).

Summary of recommendation(s)

- The MAH for dabrafenib-containing products Tafinlar and Finlee, and for the trametinib-containing products Mekinist and Spexotras should submit to EMA, within 60 days, a variation to amend¹² the product information.
- The MAH for trametinib-containing product Mekinist should monitor cases of acute febrile neutrophilic dermatosis via routine pharmacovigilance and assess whether an update of the product information for the section reflecting the adverse reactions following the administration of trametinib as monotherapy is warranted.

4.2.5. Ivacaftor, tezacaftor, elexacaftor - KAFTRIO (CAP) – EMEA/H/C/005269/SDA/017; Ivacaftor - KALYDECO (CAP) - EMEA/H/C/002494/SDA/034; Lumacaftor, ivacaftor - ORKAMBI (CAP) - EMEA/H/C/003954/SDA/018; Tezacaftor, ivacaftor - SYMKEVI (CAP) - EMEA/H/C/004682/SDA/009

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Martin Huber

Scope: Signal of intracranial pressure increased

EPITT 20000 – Follow-up to December 2023¹³

Background

¹² Update of SmPC section 4.8. The package leaflet is updated accordingly.

¹³ Held 27-30 November 2023

For background information, see [PRAC minutes December 2023](#).

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

Discussion

Having considered the available evidence in EudraVigilance and the responses of the MAH, PRAC agreed that there is insufficient evidence to establish a causal relationship between for Kaftrio (elexacaftor/tezacaftor/ivacaftor), Kalydeco (ivacaftor), Orkambi (lumacaftor/ivacaftor) and Symkevi (tezacaftor/ivacaftor) and increased intracranial pressure to further warrant an update to the product information and/or risk management plan at present.

Summary of recommendation(s)

- In the next PSUR (PSUSA/00010868/202404), the MAH for Kaftrio (elexacaftor/tezacaftor/ivacaftor) should monitor intracranial pressure increased in the and consider cases describing a positive dechallenge with corrective treatment as supportive. In addition, the MAH should provide a cumulative review of all cases of hypervitaminosis A including but not limited to MedDRA preferred terms (PTs) hypervitaminosis A, vitamin A abnormal and vitamin A increased, with a review of the published literature, data from spontaneous reports and reports from studies including all cases in EudraVigilance database, as well as a discussion on possible biological plausibility and mechanism of this association. Furthermore, the MAH should discuss whether hypervitaminosis A could be related to the restoration of functions that were previously impaired by cystic fibrosis; this should be in line with other topics that were under discussion in the PSUR procedure (PSUSA/00010868/202310), such as weight gain or fertility after initiation of treatment with cystic fibrosis transmembrane conductance regulator (CFTR) modulators. The MAH should also discuss the need to inform about the restoration of functions and/or to monitor and adjust concomitant treatments received (e.g. vitamin supplements, pancreatic enzyme replacement therapy). The MAH should also discuss the need for any potential amendment to the product information (PI) and/ or the risk management plan (RMP), as warranted.
- The MAH for Kalydeco (ivacaftor), Orkambi (lumacaftor/ivacaftor) and Symkevi (tezacaftor/ivacaftor) should continue to monitor the events of increased intracranial pressure and hypervitaminosis A as part of routine pharmacovigilance.

4.2.6. Manidipine (NAP)

Applicant(s): various

PRAC Rapporteur: Amelia Cupelli

Scope: Signal of ascites

EPITT 20026 – Follow-up to January 2024

Background

For background information, see [PRAC minutes January 2024](#).

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

Discussion

Having considered the available evidence in EudraVigilance and literature, including the data submitted by the MAH(s), PRAC agreed that there is sufficient evidence to establish a causal relationship between manidipine-containing products and ascites. Therefore, the product information for should be updated to add peritoneal dialysis as a warning and peritoneal cloudy effluent as undesirable effect with frequency 'not known'.

Summary of recommendation(s)

- The MAHs for manidipine-containing products should submit to EMA, within 60 days, a variation to amend¹⁴ the product information taking into account the already existing wording in some nationally authorised products where the text needs to be adapted to individual products.

4.2.7. Propofol (NAP)

Applicant(s): various

PRAC Rapporteur: Karen Pernille Harg

Scope: Signal of hepatic failure

EPITT 20020 – Follow-up to January 2024

Background

For background information, see [PRAC minutes January 2024](#).

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

Discussion

Having considered the available evidence in EudraVigilance and literature, including the data submitted by the MAH(s), PRAC agreed that there is sufficient evidence to establish a causal relationship between propofol-containing products and hepatic failure. Therefore, the product information for should be updated to add hepatitis/acute hepatic failure as an undesirable effect with frequency 'not known'.

Summary of recommendation(s)

- The MAHs for propofol-containing products should submit to EMA, within 60 days, a variation to amend¹⁵ the product information taking into account the already existing wording in some nationally authorised products where the text needs to be adapted to individual products.

4.3. Variation procedure(s) resulting from signal evaluation

None

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

¹⁵ Update of SmPC section 4.8. The package leaflet is updated accordingly.

5. Risk management plans (RMPs)

5.1. Medicines in the pre-authorisation phase

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

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

See also Annex I 15.1.

5.1.1. Avacincaptad pegol (CAP MAA) - EMEA/H/C/006153

Scope (pre D-180 phase): Treatment of adults with geographic atrophy (GA) secondary to age-related macular degeneration (AMD)

5.1.2. Ciclosporin (CAP MAA) - EMEA/H/C/006250

Scope (pre D-180 phase): Treatment of dry eye disease in adult patients

5.1.3. Delgocitinib (CAP MAA) - EMEA/H/C/006109

Scope (pre D-180 phase): Treatment of moderate to severe chronic hand eczema (CHE)

5.1.4. Elafibranor (CAP MAA) - EMEA/H/C/006231, Orphan

Applicant: Ipsen Pharma

Scope (pre D-180 phase): Treatment of primary biliary cholangitis (PBC)

5.1.5. Influenza vaccine (live attenuated, nasal) (CAP MAA) - EMEA/H/C/006514

Scope (pre-opinion phase): Active immunisation to prevent influenza disease

5.1.6. Lutetium (177Lu) chloride (CAP MAA) - EMEA/H/C/005882

Scope (pre D-180 phase): Radiolabelling of carrier molecules, which have been specifically developed for radiolabelling with this radionuclide

5.1.7. Zapomeran (CAP MAA) - EMEA/H/C/006207

Scope (pre D-180 phase): Active immunisation to prevent COVID-19

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

See also Annex I 15.2.

5.2.1. Pegcetacoplan - ASPAVELI (CAP) - EMEA/H/C/005553/II/0018, Orphan

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Kimmo Jaakkola

Scope: Submission of an updated RMP version 2.1 in order to revise the category 3 PASS Sobi.PEGCET-301 and Sobi.PEGCET-302

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 Aspaveli, a centrally authorised medicine containing pegcetacoplan, to update the RMP regarding the category 3 PASS Sobi.PEGCET-301 and Sobi.PEGCET-302. 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 advice

- The RMP for Aspaveli (pegcetacoplan) in the context of the variation procedure under evaluation by PRAC and CHMP could be considered acceptable provided that an update to RMP version 2.1 is submitted.
- PRAC considered that the MAH should submit a synopsis of the study Sobi.PEGCET-304 to clearly describe how this study will be conducted and further clarify whether other significant changes in addition to change of data source will take place in study design of previously approved Sobi.PEGCET-301 PASS protocol, variables collected in the study and data analysis planned to be performed. In addition, the MAH should further address whether comparator data is obtained from COMPLETE-study. Taken into account the significant change in the study plan proposed in this variation, PRAC questioned whether this proposed study is still the same (amended) study Sobi.PEGCET-301 or rather a new PASS to further characterise the safety concerns. Finally, due to the rarity of the disease and the recommendation in the product information to use effective contraception in patients with childbearing potential, PRAC agreed to remove the Sobi.PEGCET-302 study from the RMP and that the pregnancy cases should be continued to be monitored via routine pharmacovigilance activities and discussed in the PSURs.

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

See Annex I 15.3.

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. Asciminib - SCEMBLIX (CAP) - PSUSA/00011008/202310

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

Background

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Scemblix, a centrally authorised medicine containing asciminib 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 Scemblix (asciminib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add pancytopenia as an undesirable effect with a frequency 'uncommon'. Therefore, the current terms of the marketing authorisation(s) should be varied¹⁶.
- In the next PSUR, the MAH should provide a cumulative review of all cases of herpes virus infections (HLT ¹⁷Herpes viral infections') and related terms with asciminib in monotherapy from clinical trials, post-marketing and literature focused but not limited to cases with positive rechallenge with asciminib and data from comparative clinical trials. The discussion should also include a comparison on background incidence of HV infections/reactivations in this patient population gathered from all available data in order to establish a clear causal association of herpes virus infections. The MAH should also discuss the need for update the product information, if warranted.

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

6.1.2. Dapagliflozin - EDISTRIDE (CAP); FORXIGA (CAP) - PSUSA/00010029/202310

Applicant: AstraZeneca AB

PRAC Rapporteur: Mari Thorn

Scope: Evaluation of a PSUSA procedure

Background

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Edistride and Forxiga, centrally authorised medicines containing dapagliflozin 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 Highest Level Term

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Edistride and Forxiga (dapagliflozin) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning regarding 'increased haematocrit'. Therefore, the current terms of the marketing authorisation(s) should be varied¹⁸.
- In the next PSUR, the MAH should continue to provide detailed cumulative data of off-label use for dapagliflozin. In addition, the MAH should provide a review of all cases of DRESS, as well as a review of cases of Fournier's gangrene reported in the context of urological surgery.

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. Eculizumab - BEKEMV (CAP); EPYSQLI (CAP); SOLIRIS (CAP) - PSUSA/00001198/202310

Applicant(s): Alexion Europe SAS (Soliris), Amgen Technology (Ireland) Unlimited Company (Bekemv), Samsung Bioepis NL B.V. (Epysqli)

PRAC Rapporteur: Monica Martinez Redondo

Scope: Evaluation of a PSUSA procedure

Background

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Bekemv, Epysqli and Soliris, a centrally authorised medicine containing eculizumab 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 Bekemv, Epysqli and Soliris (eculizumab) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, all MAHs for eculimzumab-containing products should present the adverse reactions associated either to pregnancy, exposure during breastfeeding, medication errors and/or off label use, if any. In addition, the MAHs should present the outcomes of the pregnancy and the birth defects or congenital malformations, if applicable, in the pregnancy cases. Moreover, all MAHs should provide a discussion on all fatal cases. Finally, the MAHs should monitor cases osteomyelitis or pyelonephritis, including a discussion on newly identified cases.
- The MAH Soliris should submit to EMA, as part as a post-authorisation measure, a cumulative review of cases of hepatotoxicity, from all available sources.
- In addition, the MAH Soliris should submit to EMA, a variation to discuss, based on cumulative data, whether the additional risk minimisation measures in place for the risk

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

of meningitis are still warranted. Moreover, the MAH should re-assess the educational materials in place, to further assess and evaluate safety concerns addressed by the educational materials given that some of these risks are well known by healthcare professionals. The MAH should also include a discussion on whether based on the cumulative data, the controlled distribution system can be reconsidered, and the need for any update of the product information and educational materials or other measures are deemed warranted.

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

6.1.4. Nirsevimab - BEYFORTUS (CAP) - PSUSA/00011026/202310

Applicant: Sanofi Winthrop Industrie

PRAC Rapporteur: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

Background

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Beyfortus, a centrally authorised medicine containing nirsevimab 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 Beyfortus (nirsevimab) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAH should continue monitoring cases of serious skin reactions and thrombocytopenia. In addition, the MAH should provide a review of cases of sudden infant death syndrome (SIDS), including data from post-marketing setting and clinical trials. Also, the MAH should discuss the possible reasons leading to medication errors in the dose administered including cases with infants <5kg who received the 100mg dose or infants >5kg who received the 50mg dose and propose necessary risk minimisation measures, as warranted.
- In addition, in view of the available data regarding hypotonic-hyporesponsive episode (HHE) and apnoea case reports, the MAH should, by 16 June 2024, either submit a variation in accordance with Articles 16 and 17 of Regulation (EC) No 726/2004 or provide a justification for not doing so. The MAH should discuss the need for updating the product information and/or 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.

6.1.5. Toremifene - FARESTON (CAP) - PSUSA/00002999/202309

Applicant: Orion Corporation

PRAC Rapporteur: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

Background

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Fareston, a centrally authorised medicine containing toremifene 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 Fareston (toremifene) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include hypertriglyceridemia as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied¹⁹.
- In the next PSUR, the MAH should provide a comprehensive critical evaluation of all related information on type 2 diabetes in association with the use of toremifene from relevant non-clinical, clinical data, scientific literature and spontaneous reports. In addition, the MAH should provide reviews of cases of bone disorders and muscles disorders, as well as of pancreatitis, including data from literature, clinical trials and post-marketing setting.

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.

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

See also Annex I 16.2.

6.2.1. Buprenorphine²⁰- BUVIDAL (CAP); NAP - PSUSA/00000459/202309

Applicant: Camurus AB (Buvidal), various

PRAC Rapporteur: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

Background

Buprenorphine is an opioid partial agonist at the μ (mu) opioid receptor and an antagonist at the κ (kappa) opioid receptor administered sublingually or for injection (subcutaneous) for the treatment of opioid dependence. Buprenorphine is also utilised sublingually and intravenously/intramuscularly in low doses for the treatment of moderate to severe pain. Buprenorphine is also indicated for the treatment of moderate to severe cancer pain and severe pain which does not respond to non-opioid analgesics as transdermal patch.

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

²⁰ All formulations except implants

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of Bupival, a centrally authorised medicine containing buprenorphine, and nationally authorised medicines containing buprenorphine 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 buprenorphine-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include drug-drug interaction with gabapentinoids as well as with anticholinergics, and to add dental caries as an undesirable effect with a frequency 'not known' for oromucosal products containing buprenorphine. The product information should also be updated to reinforce information about opioid use disorder (OUD). In addition, the package leaflet should be updated to reinforce information on the importance to store products in a safe and secure place to avoid intoxication and on the use of injection only into the subcutaneous tissue. Therefore, the current terms of the marketing authorisations should be varied²¹.
- In the next PSUR, all MAHs for buprenorphine-containing products should provide cumulative reviews of cases of arthralgia and suicidal events, including data from post marketing setting and literature and discuss whether an update of the product information is warranted. In addition, the MAHs should also address the following topics: hyperalgesia, toxic leukoencephalopathy, fatal cases, off label use and sleep-related breathing disorders.

The frequency of PSUR submission should be revised from three-yearly to four-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.

6.2.2. Buprenorphine, naloxone - SUBOXONE (CAP); ZUBSOLV (CAP); NAP - PSUSA/00002113/202309

Applicant(s): Accord Healthcare S.L.U. (Zubsolv), Indivior Europe Limited (Suboxone), various

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Buprenorphine and naloxone are opioids and as a combination buprenorphine/naloxone it is administered sublingually in the treatment of opioid dependence.

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

Summary of recommendation(s) and conclusions

²¹ Update of SmPC sections 4.2, 4.4, 4.5, 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion

- Based on the review of the data on safety and efficacy, the benefit-risk balance of buprenorphine/naloxone-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add the drug-drug interaction between buprenorphine/naloxone and gabapentinoids and to add dental caries as an undesirable effect with a frequency 'not known'. In addition, the package leaflet should be updated to reinforce information on the importance to store products in a safe and secure place to avoid intoxication. Therefore, the current terms of the marketing authorisations should be varied²².
- In the next PSUR, the MAHs should provide a cumulative review on suicidal ideation events in association with buprenorphine/naloxone, including data from post-marketing sources, clinical trials and literature and discuss on possible mechanism of action. The MAHs should include a causality assessment, as well as to discuss whether there is a need to update the product information. In addition, the MAHs should provide a cumulative review of cases of 'interaction with anticholinergics' and discuss on the need to update the product information.

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

6.2.3. Leflunomide - ARAVA (CAP); LEFLUNOMIDE MEDAC (CAP); LEFLUNOMIDE ZENTIVA (CAP); NAP - PSUSA/00001837/202309

Applicant(s): Medac Gesellschaft für klinische Spezialpräparate mbH (Leflunomide medac), Sanofi-Aventis Deutschland GmbH (Arava), Zentiva, k.s. (Leflunomide Zentiva), various

PRAC Rapporteur: Liana Martirosyan

Scope: Evaluation of a PSUSA procedure

Background

Leflunomide is a pyrimidine synthesis inhibitor and it is indicated for the treatment of adult patients with active rheumatoid arthritis (RA) as a 'disease-modifying antirheumatic drug' (DMARD) and for the treatment of active psoriatic arthritis.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of Arava, Leflunomide Medac and Leflunomide Zentiva, centrally authorised medicines containing leflunomide, and nationally authorised medicines containing leflunomide 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 leflunomide-containing product(s) in the approved indication(s) remains unchanged.

²² Update of SmPC sections 4.5 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion

- Nevertheless, the product information should be updated to add a warning about impaired wound healing after surgery. Therefore, the current terms of the marketing authorisations should be varied²³.
- In the next PSUR, the MAH of the innovator product should provide cumulative reviews of cases of hepatitis B virus reactivation, dry mouth, all types of herpes infections, nephrolithiasis and discuss whether product information updates are warranted. In addition, the MAH of the innovator product should discuss the effectiveness and usefulness of the additional risk minimization measures (aRMM) specifically related to the safety concerns hepatic reactions, blood cytopenia, and infections, and to discuss the need for maintaining latter safety concerns in the RMP. Based on this discussion, the MAH may propose removal of part of the key-messages of the aRMM and removal of part of the safety concerns in the RMP to be submitted in a specific variation.

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.

6.2.4. Posaconazole - NOXAFIL (CAP); NAP - PSUSA/00002480/202310

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

PRAC Rapporteur: Nathalie Gault

Background

Posaconazole is a broad-spectrum triazole antifungal compound indicated for the treatment of fungal infections and the prophylaxis of invasive fungal infections.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of Noxafil, a centrally authorised medicine containing posaconazole, and nationally authorised medicines containing posaconazole 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 posaconazole-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add photosensitivity reaction as a warning and as an undesirable effect with a frequency 'not known'. Moreover, the product information should be updated to include a warning on the drug-drug interaction between posaconazole and flucloxacillin. Therefore, the current terms of the marketing authorisations should be varied²⁴.

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.

²³ Update of SmPC section 4.4. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion

²⁴ Update of SmPC sections 4.4, 4.5 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion

6.2.5. Teriflunomide - AUBAGIO (CAP); TERIFLUNOMIDE ACCORD (CAP); TERIFLUNOMIDE MYLAN (CAP); NAP - PSUSA/00010135/202309

Applicant(s): Accord Healthcare S.L.U. (Teriflunomide Accord), Mylan Pharmaceuticals Limited (Teriflunomide Mylan), Sanofi Winthrop Industrie (AUBAGIO), various

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Teriflunomide is an immunosuppressant indicated for the treatment of adult patients and paediatric patients aged 10 years and older with relapsing remitting multiple sclerosis (RRMS).

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of Aubagio, Teriflunomide Accord and Teriflunomide Mylan, centrally authorised medicines containing teriflunomide, and nationally authorised medicines containing teriflunomide 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 teriflunomide-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include herpes virus infections as a warning and as an undesirable effect with a frequency 'common'. Therefore, the current terms of the marketing authorisations should be varied²⁵.
- In the next PSUR, the MAH for the innovator for teriflunomide-containing product should provide cumulative reviews of dental and gingival disorders, acute renal failure, urolithiasis, tuberculosis infections, skin ulcers, venous thrombosis, and tendon rupture and tenosynovitis, including data from clinical trials, post-marketing setting and literature, as well as causality assessments. In addition, the MAH Sanofi should present any new data on paternal exposure and transfer of teriflunomide to female partners via semen, including any new publications as well as a cumulative review of cases of paternal exposure. The originator MAH Sanofi should also provide a cumulative review of cases of (subacute) cutaneous lupus erythematosus in the next PSUR and discuss a possible association with teriflunomide, including a discussion on the need to update of the product information. Finally, the MAH Sanofi should also discuss the need and usefulness of each of the specific adverse reaction follow-up questionnaires currently in place for teriflunomide in the next PSUR. The discussion should include information about distribution, response rate and added value of each questionnaire.

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.

²⁵ 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

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

See also Annex I 16.3.

6.3.1. Acitretin (NAP) - PSUSA/00000051/202310

Applicant(s): various

PRAC Lead: Marie Louise Schougaard Christiansen

Scope: Evaluation of a PSUSA procedure

Background

Acitretin is a synthetic aromatic analogue of retinoic acid. Retinol (a derivative of Vitamin A) is known to be essential for normal epithelial growth and differentiation. Acitretin is indicated for treatment of severe forms of psoriasis including erythrodermic psoriasis and local or generalized pustular psoriasis; severe disorders of keratinization such as congenital ichthyosis, pityriasis rubra pilaris, and Darier's disease; other disorders of keratinization which may be resistant to other therapies and lichen planus.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing acitretin 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 acitretin-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the warning regarding psychiatric disorder and to add altered mood and psychotic disorder as undesirable effects with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied²⁶. In case the product information of nationally approved products already includes a more precise wording regarding these two undesirable effects, this latter wording should remain. In addition, the PSUR safety concern 'psychiatric disorders' (or other related description in the respective MAHs' PSUR safety concerns signifying psychiatric disorders) should be reclassified as an important identified risk for future PSURs.
- In the next PSUR, all MAHs for acitretin-containing products should continue to present data on the estimated use of acitretin in pregnant women and in women who became pregnant within 3 years after discontinuation of acitretin and comment on the publication by Reinold J. et al.²⁷ (2023), as well as discuss the benefit-risk balance in women of child-bearing age considering the new published information, as well as on the need for further risk minimisation measures in view of the long-lasting teratogenic risk after stopping treatment in younger women. In the next PSUR, the MAHs are requested to present a status on the progress of this qualitative study. Furthermore, in the next PSUR, the MAHs are requested to report the final assessment outcome of the

²⁶ Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position

²⁷ Reinold J, Kollhorst B, Temme HL, et al. Use of Acitretin Among Girls and Women of Childbearing Age and Occurrence of Acitretin-Exposed Pregnancies in Germany. *Clin Drug Investig.* 2023;43(11):865-872. doi:10.1007/s40261-023-01314-2

survey EUPAS38096/DE/H/xxxx/WS/1115 and to report in which countries a new DHPC was circulated based on national decision. In the next PSUR, all MAHs should provide cumulative reviews of cases under MedDRA HLT 'Purpura and related conditions' and clearly elaborate on information on diagnosis of the event, other clinical manifestations, laboratory findings, biopsies, comorbidities, concomitant medication and medical history and discuss the need for an update of the product information.

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. Adapalene, benzoyl peroxide (NAP) - PSUSA/0000059/202309

Applicant(s): various

PRAC Lead: Mari Thorn

Scope: Evaluation of a PSUSA procedure

Background

Adapalene/benzoyl peroxide is a combination of a retinoid and an antibacterial agent acting respectively by retinoid-like activity and oxidation of proteins and it is indicated for the topical treatment of acne vulgaris when comedones, papules and pustules are present.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing adapalene/benzoyl peroxid 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 adapalene/benzoyl peroxide-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include erythema and skin exfoliation (scaling) as undesirable effects with a frequency 'common'. Therefore, the current terms of the marketing authorisation(s) should be varied²⁸.
- In the next PSUR, the MAHs should provide a cumulative review of cases of dermatitis bullous, including a causality assessment, and discuss the need for an update of the product information.

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

6.3.3. Baclofen²⁹ (NAP) - PSUSA/00000294/202309

Applicant(s): various

PRAC Lead: Eamon O'Murchu

²⁸ 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

²⁹ Oral use, for muscle spasticity indication only

Scope: Evaluation of a PSUSA procedure

Background

Baclofen is a muscle relaxant indicated, for oral use, for the treatment of spasticity of the skeletal muscles in multiple sclerosis, spastic conditions occurring in spinal-cord diseases of infectious, degenerative, traumatic, neoplastic, or unknown origin: e.g. spastic spinal paralysis, amyotrophic lateral sclerosis, syringomyelia, transverse myelitis, traumatic paraplegia or paraparesis, and compression of the spinal cord; muscle spasm of cerebral origin, as well as following cerebrovascular accidents or in the presence of neoplastic or degenerative brain disease. In children, it is indicated for the symptomatic treatment of spasticity of cerebral origin, especially due to infantile cerebral palsy, as well as following cerebrovascular accidents or in the presence of neoplastic or degenerative brain disease. It is also indicated for the symptomatic treatment of muscle spasms occurring in spinal cord diseases of infectious, degenerative, traumatic, neoplastic, or unknown origin such as multiple sclerosis, spastic spinal paralysis, amyotrophic lateral sclerosis, syringomyelia, transverse myelitis, traumatic paraplegia or paraparesis, and compression of the spinal cord.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of baclofen-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add encephalopathy as a warning and as an undesirable effect with a frequency 'not known', as well as to add encephalopathy and generalised slowing on electroencephalogram (EEG) as symptoms of baclofen overdose. Therefore, the current terms of the marketing authorisation(s) should be varied³⁰.
- In the next PSUR, the MAHs for baclofen-containing products should provide cumulative reviews of cases of psoriasis and psoriasis exacerbation and discuss the need for an update of the product information. The MAHs should also provide an updated review of cases of myoclonus at therapeutic doses in addition to a review of myoclonic status epilepticus at therapeutic doses and in cases of overdose, including a discussion on the need for updating the product information.

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. Diclofenac³¹ (NAP) - PSUSA/00010342/202309

Applicant(s): various

PRAC Lead: Karin Erneholm

³⁰ Update of SmPC sections 4.4, 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

³¹ Topical formulations only

Scope: Evaluation of a PSUSA procedure

Background

Diclofenac is a potent non-steroidal anti-inflammatory drug (NSAID) with effective analgesic, anti-inflammatory, and antipyretic properties. Diclofenac is authorized in different pharmaceutical forms: gel, cream, cutaneous solution, cutaneous foam, topical spray, transdermal patch, oromucosal solution and eye drops. For cutaneous use, it is indicated for relief of pain, inflammation, and swelling in soft-tissue injuries, localised forms of soft tissue rheumatism, non-serious arthritis of the knee or fingers and topical treatment of actinic keratosis. For ophthalmic use, it is indicated in post-operative inflammation in cataract surgery, symptomatic treatment of chronic non-infectious conjunctivitis, pre- and postoperative inhibition of miosis in cataract surgery, maintenance of mydriasis during cataract surgery, treatment of ocular inflammation, ocular pain, and photophobia following refractive surgery, post-operative treatment of the inflammation of the anterior segment of the eye. For oromucosal use, it is indicated for the symptomatic treatment of states of irritation and inflammation including those associated with pain inside the oral cavity (for example, gingivitis, stomatitis, pharyngitis) and following conservative dental treatment or extractions.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing diclofenac (topical formulations only) 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 diclofenac-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information for all topical formulations except ophthalmic solutions should be updated to add the use of diclofenac during the third trimester of pregnancy as a contraindication and to add/amend a warning regarding the use in pregnancy for diclofenac-containing medicinal products for topical use (gel, cream, cutaneous solution, cutaneous foam, topical spray, transdermal patch, oromucosal solution), if similar or stricter information regarding use in pregnancy is not already included. For ophthalmic formulations, the product information should be updated to amend a warning/precaution regarding the use in pregnancy for diclofenac-containing medicinal products for ophthalmic use, if similar or stricter information regarding use in pregnancy is not already included. Therefore, the current terms of the marketing authorisation(s) should be varied³².

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

6.3.5. Levofloxacin³³ (NAP) - PSUSA/00010767/202310

Applicant(s): various

³² Update of SmPC sections 4.3 and 4.6. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position

³³ Intravenous and oral use only

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Levofloxacin is a fluoroquinolone antibacterial agent and it is indicated in adults for the treatment of several especially severe bacterial infections.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing levofloxacin (intravenous and oral use formulations) 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 levofloxacin-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning regarding bone marrow failure and myoclonus. Also, the product information should be updated to add bone marrow failure including aplastic anaemia, myoclonus, mania and skin hyperpigmentation as undesirable effects with a frequency 'not known', as well as to add myoclonus as a symptom of levofloxacin overdose. Therefore, the current terms of the marketing authorisation(s) should be varied³⁴.
- In the next PSUR, the MAHs should closely monitor cases of Kounis syndrome, thrombotic microangiopathy, acquired haemophilia, disorders of arteries other than the aorta, optic neuritis, cerebellar syndrome, chronic pigmented purpura, Guillain-Barre syndrome, Encephalopathy, as well as cases of potential interaction of levofloxacin with ACE inhibitors in the context of acute kidney injury. In addition, the MAHs should provide a cumulative review of cases of AGEP, including data from spontaneous reports, studies and literature, as well as a discussion on possible biological plausibility and mechanism of this association and discuss the need for an update of the product information.

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

6.4. Follow-up to PSUR/PSUSA procedures

See Annex I 16.4.

6.5. Variation procedure(s) resulting from PSUSA evaluation

See also Annex I 16.5.

6.5.1. Ioflupane (¹²³I) - DATSCAN (CAP) - EMEA/H/C/000266/II/0067

Applicant: GE Healthcare B.V.

³⁴ Update of SmPC sections 4.4, 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

PRAC Rapporteur: Tiphaine Vaillant

Scope: To update sections 4.4 and 4.5 of the SmPC and section 2 of the Package Leaflet to implement the recommendation of PRAC following the PSUSA procedure (EMA/H/C/PSUSA/00001767/202207). In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet.

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 provide further clarifications regarding drug-drug interaction with modafinil and armodafinil, hydration recommendation 48 hours after administration of ioflupane in patient counselling information and regarding recommendations about the duration of breastfeeding. The MAH submitted a variation to EMA addressing these topics. 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 to update the product information³⁵ in order to add hydration recommendations before the product administration, and to add drug-drug interaction with codeine, dexamphetamine, dexmethylphenidate, methamphetamine and modafinil, as well as with selective serotonin reuptake inhibitor (SSRI) (sertraline already listed in the product information). No update of the product information is needed regarding breastfeeding following administration of ioflupane.

6.5.2. Mitotane - LYSODREN (CAP) - EMA/H/C/000521/II/0030

Applicant: HRA Pharma Rare Diseases

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Update of section 4.4 of the SmPC in order amend an existing warning on hepatic impairment based on a cumulative review of cases with increase of transaminases >5 ULN and the outcome of these elevations after mitotane discontinuation, following the request by PRAC in the PSUSA/00002075/202304

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 in order to provide a cumulative review of cases with increase of transaminases > 5 ULN and the outcome of these elevations after mitotane discontinuation, as well as a proposal for the update of the

³⁵ Update of SmPC sections 4.4 and 4.5. The package leaflet is updated accordingly

product information. 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 supported the update of the product information³⁶ to amend the warning on hepatic impairment.

6.5.3. [Naltrexone hydrochloride, Bupropion hydrochloride - MYSIMBA \(CAP\) - EMEA/H/C/003687/II/0063](#)

Applicant: Orexigen Therapeutics Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: Submission of an update of sections 4.3, 4.4 and 4.5 of the SmPC to update and streamline the relevant wording on opioids as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00010366/202209) adopted in April 2023. The package leaflet is updated accordingly. The RMP version 12.9 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 as requested in the conclusions of the PSUSA procedure. 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 February 2024](#).

Summary of recommendation(s)

- Based on the review of available safety data from EudraVigilance and the literature, and taking into account the MAH position discussed in the context of the oral explanation held on 14 May 2024, PRAC agreed that the terms of the marketing authorisation for naltrexone/bupropion should be varied to strengthen risk minimisation measures related to the important identified risk of interactions with opioids.
- In view of available data and the established pharmacological mechanism of the drug-drug interaction between naltrexone/bupropion and opioids, PRAC considered that seizure, serotonin syndrome and insufficient effects of opioid analgesia and anaesthesia in patients treated with naltrexone/bupropion is at least a reasonable possibility. Therefore, PRAC agreed that further risk minimisation measures are warranted, including amendments to the product information, a prescriber checklist and RMP update, as well as implementation of a patient card for the event of surgery and emergency care. The MAH should also submit a proposal for a DHPC and a communication plan in order to inform healthcare professionals in a timely manner about the newly introduced safety information (i.e., risk of seizure, serotonin syndrome, anaesthetic complications and inadequate pain management associated with co-

³⁶ Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly

administration of opioids and naltrexone/bupropion) and the recommended clinical actions (i.e. to discontinue naltrexone/bupropion at least 3 days before surgery and to perform a test if opioid use is suspected).

- The MAH should submit, to EMA, within 30 days, responses to the request for supplementary information (RSI).

6.6. Expedited summary safety reviews³⁷

None

7. Post-authorisation safety studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)³⁸

See Annex I 17.1.

7.2. Protocols of PASS non-imposed in the marketing authorisation(s)³⁹

See also Annex I 17.2.

7.2.1. Neratinib - NERLYNX (CAP) - EMEA/H/C/004030/MEA 003.3

Applicant: Pierre Fabre Medicament

PRAC Rapporteur: Bianca Mulder

Scope: Amended Protocol / Study PUMA-NER-7402 (version 4.0); Safety of neratinib among breast cancer patients to characterise the incidence and duration of diarrhoea in a real-world setting, describe patient characteristics, incidence rates and duration of diarrhoea, describe use of loperamide and other concomitant antidiarrheal medication, describe adherence to neratinib therapy, assess the impact of neratinib therapy on patient self-reported, health related quality of life and their ability to perform their activities of daily living and to further assess and characterise adverse events hepatic, cardiac (LVEF decreased), pulmonary (interstitial lung disease), reproductive and developmental toxicity

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 part of the [RMP](#) for Nerlynx (neratinib), the MAH was required to conduct Study PUMA-NER-7402 in order to evaluate the incidence of discontinuations due to diarrhoea. The MAH submitted a revised protocol for the study which was assessed by the Rapporteur. PRAC was requested to provide advice to CHMP on the revised protocol submitted by the MAH.

Summary of advice

³⁷ 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

³⁸ In accordance with Article 107n of Directive 2001/83/EC

³⁹ 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

- PRAC agreed with the MAH's proposal to complement the PUMA-NER-7402 (NERLYFE) study listed as category 3 study in the RMP with data from the ELEANOR study to compensate the reduced sample size. However, PRAC considered that the MAH should provide more data about the patients from the ELEANOR study and for which data from quality of life questionnaire is available at baseline and at least one additional timepoint in follow-up. In addition, the MAH should amend the protocol to reflect that upon completion of each analysis, a study report should be submitted. Finally, the MAH should implement further refinements for future study reports of NERLYFE/ELEANOR in relation to the objectives and data presentation.
- The MAH should submit a revised PASS protocol within 60 days to EMA. A 74-days assessment timetable will be followed.

7.3. Results of PASS imposed in the marketing authorisation(s)⁴⁰

7.3.1. Levofloxacin – QUINSAIR (CAP) - EMEA/H/C/PSR/S/0046

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Final study report for a post-marketing, observational safety study of Quinsair (levofloxacin hemihydrate) in patients with cystic fibrosis to evaluate the long-term safety compared to other inhaled approved antibiotic therapies in cystic fibrosis patients

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 in a registry of patients with cystic fibrosis to investigate the long-term safety profile of Quinsair in normal clinical practice. For further background, see [PRAC minutes December 2023](#).

The final study report was submitted to EMA by the MAH on 08 September 2023. PRAC discussed the final study results.

Summary of recommendation(s) and conclusions

- Based on the review of the final report of the non-interventional PASS entitled 'A Post-marketing, Observational Safety Study of Quinsair (Levofloxacin Hemihydrate) in Patients with Cystic Fibrosis [CLI-LEVFLAA1-01]', as well as the MAH's responses to the RSI, PRAC considered that the benefit-risk balance of Quinsair (levofloxacin hemihydrate) remains unchanged.
- As a consequence, PRAC supported the removal of the PASS from the pharmacovigilance plan and as an obligation from Annex-IID on the 'conditions or restrictions with regard to the safe and effective use of the medicinal product'. In addition, PRAC agreed with the removal of the additional monitoring status and consequently the black triangle and additional monitoring statements from the product information. Regarding the RMP, PRAC supported the removal of the following important potential safety concerns and

⁴⁰ In accordance with Article 107p-q of Directive 2001/83/EC

continue monitoring them in the PSUR: 'haemoptysis', 'off label use in <18 years' and 'hepatotoxicity'. In addition, 'long term safety' should be removed as missing information from the RMP. Finally, the footnote in section 4.8 of the SmPC referencing the statement 'adverse events with uncertain relatedness to Quinsair but which are known to be associated with systemic administration of levofloxacin and/or are plausibly associated with Quinsair and were reported more frequently than with placebo in clinical studies' is no longer considered applicable for haemoptysis and thus, the asterisk next to haemoptysis referring to this statement should be deleted.

7.4. Results of PASS non-imposed in the marketing authorisation(s)⁴¹

See also Annex I 17.4.

7.4.1. Guanfacine - INTUNIV (CAP) - EMEA/H/C/003759/II/0033/G

Applicant: Takeda Pharmaceuticals International AG Ireland Branch

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Submission of the final reports from the Drug Utilisation Study (DUS) of Intuniv (guanfacine extended release) in European countries: a prescriber survey (EUPAS18739) and a retrospective database study (EUPAS18735), listed as category 3 studies in the RMP. The RMP version 4.0 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.

The MAH conducted a non-imposed non-interventional PASS in a form of a drug utilisation study which encompasses two studies: a prescriber survey (EUPAS18739) and a retrospective database study (EUPAS18735), listed as category 3 studies in the RMP. These studies aimed to address the off-label use and to describe prescribing patterns of Intuniv, as well as to assess the effectiveness of risk minimisation measures (educational materials available for healthcare professionals) of Intuniv (guanfacine). The Rapporteur assessed the MAH's final study report in addition to the MAH's answers to the request for supplementary information (RSI). For further background, see [PRAC minutes March 2024](#).

Summary of advice

- Based on the available data, the MAH's responses to the RSI and the Rapporteur's review, PRAC considered that the ongoing variation assessing the final study report could be recommended for approval.
- PRAC agreed to remove the educational material (including prescriber checklist) for the healthcare professionals as additional risk minimisation measure from the RMP and from Annex IID on the 'conditions or restrictions with regard to the safe and effective use of the medicinal product'. Moreover, PRAC considered that the list of safety concerns in the RMP should be updated to remove the following important identified risks: bradycardia, syncope, hypotension, withdrawal blood pressure increase, sedative events, and weight

⁴¹ 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

increase, and to keep monitoring these risks as important identified risks in the PSURs. In addition, due to the finalisation of the DUS, PRAC supported the removal of 'off label use' as important potential risk in the RMP and requested the MAH to submit a cumulative review of this risk in the next PSUR.

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

None

7.7. New Scientific Advice

None

7.8. Ongoing Scientific Advice

None

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

None

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

8.1. Annual reassessments of the marketing authorisation

See Annex I 18.1.

8.2. Conditional renewals of the marketing authorisation

See Annex I 18.2.

8.3. Renewals of the marketing authorisation

See Annex I 18.3.

9. Product related pharmacovigilance inspections

9.1. List of planned pharmacovigilance inspections

None

9.2. Ongoing or concluded pharmacovigilance inspections

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

9.3. Others

None

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

10.1. Safety related variations of the marketing authorisation

None

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

None

10.3. Other requests

None

10.4. Scientific Advice

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

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

None

12.1.2. Vote by proxy

None

12.2. Coordination with EMA Scientific Committees or CMDh-v

None

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

None

12.4. Cooperation within the EU regulatory network

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

The EMA Secretariat provided PRAC with an update on the COVID-19 vaccines and treatments, including data on the effectiveness of the booster vaccines on the new SARS Cov-2 variants. An update on the transmission of H5N1 avian influenza virus and Ebola virus was presented to PRAC, including a list of the key elements to take into consideration of a flexible protocol for filovirus vaccines, according to the World Health Organisation. PRAC noted the information.

12.5. Cooperation with International Regulators

12.5.1. International Council for Harmonisation (ICH) M14 Guideline on 'General principles on plan, design and analysis of pharmacoepidemiological studies that utilize real-world data for safety assessment of medicines'

PRAC lead: Annalisa Capuano

The use of pharmacoepidemiological studies as a source of safety evidence for regulatory decision-making has increased globally, with multiple guidelines and best practice documents developed by health authorities and professional societies. Generation of robust safety evidence relies on the quality of the data and the application of sound pharmacoepidemiological methods. This guideline provides internationally harmonised guidance and outlines recommendations and high-level best practices for the conduct and analysis of non-interventional pharmacoepidemiological studies using fit-for-purpose data for the assessment of the safety of medicines, with the aim to streamline the development and regulatory assessment of study protocols and reports, and to improve their ability to be accepted across health authorities. The PRAC lead presented to PRAC the guideline's objectives, as well as an overview of the content, the steps that were made so far in regarding to drafting the guideline, but also the future timelines. PRAC members, on behalf of their National Competent Authorities, were invited to provide their comments on the draft guideline in writing by 31 August 2024. This PRAC consultation phase is running in parallel to a public consultation. PRAC feedback will be incorporated together with the public feedback in the next phase of the guideline finalisation.

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

None

12.7. PRAC work plan

None

12.8. Planning and reporting

12.8.1. EU Pharmacovigilance system - quarterly workload measures and performance indicators – Q1 2024 and predictions

The EMA Secretariat presented to PRAC an overview of the quarterly figures on the EMA pharmacovigilance system-related workload and performance indicators.

12.8.2. PRAC workload statistics – Q1 2024

PRAC was informed on the quarterly and cumulative figures to estimate the evolution of the PRAC workload for Q1 2024, by reflecting on the number of procedures and agenda items covered at each PRAC plenary meeting.

12.9. Pharmacovigilance audits and inspections

12.9.1. Pharmacovigilance systems and their quality systems

None

12.9.2. Pharmacovigilance inspections

None

12.9.3. Pharmacovigilance audits

None

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

12.10.1. Periodic safety update reports

None

12.10.2. Granularity and Periodicity Advisory Group (GPAG)

None

12.10.3. PSURs repository

None

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

In line with the criteria for plenary presentation of updates to the EURD List adopted by PRAC in December 2021, PRAC endorsed the draft revised EURD list, version May 2024, reflecting the PRAC's comments impacting on the data lock point (DLP) and PSUR submission frequencies of the substances/combinations. PRAC endorsed the newly allocated Rapporteurs for upcoming PSUSAs in accordance with the principles previously endorsed by PRAC (see PRAC minutes April 2013).

Post-meeting note: following the PRAC meeting of May 2024, the updated EURD list was adopted by CHMP and CMDh at their May 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 Hube

EMA, together with the Co-Chair SMART Processes WG presented to PRAC the outcome of the discussions around the harmonisation of queries in the PRAC recommendations of signal procedures, following SMART WG Processes stream meeting held in April 2024. In addition, the EMA Secretariat presented an update of the work of the SMART Methods stream, including an update on the progress of the workplan, on the drug-drug interaction reference sets and algorithm, as well as on the Health Data Lab pilot. PRAC was also informed about the launching of the SMART WG webpage on EMA website: [Signal Management Review Technical \(SMART\) Working Group | European Medicines Agency \(europa.eu\)](#)

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](#)

12.13. 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

None

12.21. Others

12.21.1. Antiepileptic drugs and pregnancy

Following the valproate and topiramate referral procedures, the safety of the use of other antiepileptic drugs during pregnancy warrants further considerations. PRAC received input from the EMA pregnancy and lactation community on possible actions to address this topic further, including a suggestion to expand an already EMA funded utilisation and feasibility study, with a risk assessment part. PRAC noted the details provided and agreed on a step wise approach.

13. Any other business

Next meeting on 10-13 June 2024

14. Annex I – Signals assessment and prioritisation⁴²

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 timetables⁴³.

14.1. New signals detected from EU spontaneous reporting systems

14.1.1. Adagrasib – KRAZATI (CAP)

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Kimmo Jaakkola

Scope: Signal of febrile neutropenia

EPITT 20080 – New Signal

Lead Member State(s): FI

⁴² 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

⁴³ 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

14.2. New signals detected from other sources

None

14.3. Variation procedure(s) resulting from signal evaluation

14.3.1. Brolucizumab - BEOVU (CAP) - EMEA/H/C/004913/II/0028

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Gabriele Maurer

Scope: Update of section 4.8 of the SmPC in order to add 'scleritis' to the list of adverse drug reactions (ADRs) with frequency 'not known', following the recommendation by PRAC in the outcome for the signal assessment of scleritis. The package leaflet is updated accordingly

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. Leriglitazone - NEZGLYAL (CAP MAA) - EMEA/H/C/005757, Orphan

Applicant: Minoryx Therapeutics S.L.

Scope (under re-examination): Treatment of cerebral progression and myelopathy in male patients with adrenoleukodystrophy (ALD)

15.1.2. Trastuzumab (CAP MAA) - EMEA/H/C/006252

Scope (pre D-180 phase): Treatment of adult patients with HER2 positive metastatic breast cancer (MBC) and HER2 positive early breast cancer (EBC)

15.1.3. Ustekinumab (CAP MAA) - EMEA/H/C/005805

Scope (pre D-180 phase): Treatment of moderate to severe plaque psoriasis, active psoriatic arthritis, Crohn's disease and ulcerative colitis

15.1.4. Ustekinumab (CAP MAA) - EMEA/H/C/006544

Scope: Treatment of Crohn's disease and ulcerative colitis, moderate to severe plaque psoriasis, active and psoriatic arthritis

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. [Amlodipine, valsartan - AMLODIPINE-VALSARTAN MYLAN \(CAP\) - EMEA/H/C/004037/II/0021](#)

Applicant: Mylan Pharmaceuticals Limited

PRAC Rapporteur: Karin Ernehlm

Scope: Submission of an updated RMP version 4.0 in order to align the safety concerns with the latest version of RMP for amlodipine/valsartan available in the public domain and to bring the RMP in line with the latest RMP template

15.2.2. [Colesevelam - CHOLESTAGEL \(CAP\) - EMEA/H/C/000512/II/0053](#)

Applicant: CHEPLAPHARM Arzneimittel GmbH

PRAC Rapporteur: Bianca Mulder

Scope: Submission of an updated RMP version 2.0 in order to remove important identified and potential risks, as well as missing information to bring it in line with GVP module V. Additionally, epidemiological data on indication and target population, clinical data and postmarketing exposure data was updated

15.2.3. [Fluticasone furoate - AVAMYS \(CAP\) - EMEA/H/C/000770/II/0051/G](#)

Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Adam Przybylkowski

Scope: Grouped application comprising two type II variations as follows:

C.I.11.b – Submission of an updated RMP version 12 in order to remove headache, nasal events (including: epistaxis, nasal ulceration, nasal septum perforation and other nasal events), hypersensitivity, cataract and glaucoma as important identified risks; to remove taste and smell disorders, pyrexia, systemic corticosteroids effect: adrenal suppression, Systemic corticosteroid effect: growth retardation, psychiatric effects as important potential risks and to remove use in pregnancy and lactation, off-label use (sinusitis and children < 6 years of age) as missing information.

C.I.11.b – Submission of an updated RMP version 12 in order to remove targeted follow up questionnaires.

In addition, the MAH took this opportunity to align the RMP template with GVP Module V Revision 2

15.2.4. [Infliximab - REMICADE \(CAP\) - EMEA/H/C/000240/II/0247](#)

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Mari Thorn

Scope: Submission of an updated RMP version 22.1 in order to remove reference to the

immunogenicity substudy as part of protocol REMICADEPIB4002 in Part III. The MAH proposes to discontinue the Dutch portion of the immunogenicity substudy, which is part of protocol REMICADEPIB4002

15.2.5. [Infliximab - ZESSLY \(CAP\) - EMEA/H/C/004647/II/0033](#)

Applicant: Sandoz GmbH

PRAC Rapporteur: Mari Thorn

Scope: Submission of an updated RMP version 4.0 in order to remove the UKIBD (UK) registry from the additional pharmacovigilance activities

15.2.6. [Prasugrel - EFIENT \(CAP\) - EMEA/H/C/000984/II/0037](#)

Applicant: Substipharm

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Submission of an updated RMP version 13 in order to remove of a region-specific additional risk-minimisation activity following previous PSUSA procedure (EMEA/H/C/PSUSA/00002499/202102), as well as to align content and format with new requirements according to GVP Module V Rev. 2. In addition, the MAH took the opportunity to update Annex II of the product information and to update the list of local representatives in the package leaflet

15.2.7. [Sacituzumab govitecan - TRODELVY \(CAP\) - EMEA/H/C/005182/II/0031](#)

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Bianca Mulder

Scope: Submission of an updated RMP version 3.1 in order to propose the removal of some safety concerns and the extension of remaining study milestones to date for category 3 study IMMU-132-15

15.2.8. [Telmisartan - KINZALMONO \(CAP\) - EMEA/H/C/000211/WS2577/0120; MICARDIS \(CAP\) - EMEA/H/C/000209/WS2577/0129; PRITOR \(CAP\) - EMEA/H/C/000210/WS2577/0133](#)

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Amelia Cupelli

Scope: Submission of an updated RMP version 6.1 in order to implement an overall update regarding safety concerns based on literature and post marketing data; and to adapt the RMP to the current RMP format (Rev 2.0.1), in line with GVP Module V, Revision 2

15.2.9. [Telmisartan, hydrochlorothiazide - KINZALKOMB \(CAP\) - EMEA/H/C/000415/WS2611/0123; MICARDISPLUS \(CAP\) - EMEA/H/C/000413/WS2611/0130; PRITORPLUS \(CAP\) - EMEA/H/C/000414/WS2611/0133](#)

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Amelia Cupelli

Scope: Submission of an updated RMP version 9.1 for MicardisPlus, PritorPlus and Kinzalkomb in order to remove all important identified and potential risks from the list of safety concerns and to adapt the RMP to the current RMP format (Rev 2.0.1), in line with GVP Module V, Revision 2

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. Afamelanotide - SCENESSE (CAP) - EMEA/H/C/002548/II/0052, Orphan

Applicant: Clinuvel Europe Limited

PRAC Rapporteur: Martin Huber

Scope: Update of section 4.2 of the SmPC in order to update the posology recommendations by removing the current recommendation of a maximum of four implants per year, based on a literature review and analysis of safety data. The package leaflet is updated accordingly. The RMP version 9.8 has also been submitted. In addition, the MAH took the opportunity to introduce a minor editorial change to the product information

15.3.2. Aflibercept - EYLEA (CAP) - EMEA/H/C/002392/II/0090

Applicant: Bayer AG

PRAC Rapporteur: Nathalie Gault

Scope: Update of sections 4.8 and 5.1 of the SmPC in order to update safety and clinical information based on results from studies PULSAR (20968) and PHOTON (21091). PULSAR (20968) is an ongoing pivotal Phase 3 study to investigate the efficacy and safety of HD aflibercept at treatment intervals of 12 weeks and longer for indication neovascular age-related macular degeneration (nAMD). PHOTON (21091) is an ongoing pivotal phase 2/3 study to investigate the efficacy and safety of HD aflibercept at treatment intervals of 12 weeks and longer for indication diabetic macular oedema. The package leaflet is updated accordingly. The RMP version 34.1 has also been submitted. In addition, the MAH took the opportunity to implement an editorial update in section 6.6 of the SmPC to align the text with other similar products

15.3.3. Alpelisib - PIQRAY (CAP) - EMEA/H/C/004804/II/0022/G

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Bianca Mulder

Scope: Grouped application comprising two type II variations (C.I.4) as follows:
- Update of sections 4.2, 4.4, 4.8 of the SmPC in order to update information on prophylactic use of metformin for hyperglycaemia based on the results from study CBYL719CES01T (METALLICA). METALLICA is a phase II study aimed to evaluate the effect of prophylactic use of metformin for hyperglycaemia in HR-positive, HER2-negative, PIK3CA-mutated advanced breast cancer patients treated with alpelisib plus endocrine

therapy.

- Update of section 4.8 of the SmPC in order to add 'uveitis' to the list of adverse drug reactions (ADRs) with frequency 'Not known' based on a cumulative review of the MAH safety database and literature.

The package leaflet and Annex II are updated accordingly. The RMP version 7.0 has also been submitted

15.3.4. Amivantamab - RYBREVANT (CAP) - EMEA/H/C/005454/II/0013

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Gabriele Maurer

Scope: Extension of indication to include amivantamab in combination with lazertinib for the first-line treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with EGFR exon 19 deletions or exon 21 L858R substitution mutations (EGFRm NSCLC), based on results from study 73841937NSC3003 (MARIPOSA). This is a randomised, open-label, phase 3 study that compares the efficacy and safety of the combination of amivantamab and lazertinib (Arm A) versus osimertinib monotherapy (Arm B) and lazertinib monotherapy (Arm C) in participants with EGFRm NSCLC. The primary objective of the MARIPOSA study was to assess the efficacy of the combination of amivantamab and lazertinib (Arm A), compared with osimertinib (Arm B), as measured by PFS assessed by BICR in adult participants with EGFRm NSCLC. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 4.9, 5.1, 5.2, 6.6 and 9 of the SmPC are updated. The package leaflet is updated in accordance. Version 3.3 of the EU RMP has also been submitted. As part of the application the MAH is requesting a 1-year extension of the market protection

15.3.5. Apixaban - ELIQUIS (CAP) - EMEA/H/C/002148/X/0089/G

Applicant: Bristol-Myers Squibb / Pfizer EEIG

PRAC Rapporteur: Bianca Mulder

Scope: Extension application to:

- 1) Introduce a new pharmaceutical form (granules in single-dose container) associated with a new strength (0.15 mg).
- 2) Introduce a new pharmaceutical form (coated granules in sachet) associated with 3 new strengths (0.5 mg, 1.5 mg and 2 mg);

The above two line extensions are grouped with a type II - C.I.6.a variation:

Extension of indication to include the treatment of venous thromboembolism (VTE) and prevention of recurrent VTE in paediatric patients from 28 days to less than 18 years of age for Eliquis (all strengths), based on a pre-specified interim analysis from study CV185325; this is an open-label, multi-centre, randomised, active controlled trial to provide pharmacokinetic (PK) data and data on anti-Xa activity to support the extrapolation of efficacy to children, to evaluate safety and efficacy of apixaban in children who require anticoagulation for a venous thromboembolism; as a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 4.9, 5.1 and 5.2 of the SmPCs are updated. The package leaflet and Annex II are updated in accordance. Version 21.0 of the RMP has also been submitted

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 acute lymphoblastic leukemia (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. Brolucizumab - BEOVU (CAP) - EMEA/H/C/004913/II/0029

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Gabriele Maurer

Scope: Update of sections 4.2 and 5.1 of the SmPC in order to include information on maintenance treatment and to update efficacy and safety information based on final results from studies CRTH258A2303 (TALON) and CRTH258A2303E1 (TALON Extension). TALON is a 64-week, two-arm, randomised, double-masked, phase IIIb study assessing the efficacy and safety of brolucizumab 6 mg compared to aflibercept 2 mg in a treat-to-control regimen in patients with neovascular age-related macular degeneration. TALON Extension is a 56-week phase IIIb/IV, open-label, one-arm extension study to assess the efficacy and safety of brolucizumab 6 mg in a treat-to-control regimen with maximum treatment intervals up to 20 weeks for the treatment of subjects with neovascular age-related macular degeneration who have completed the CRTH258A2303 (TALON) study.

The package leaflet is updated accordingly. The RMP version 12.0 has also been submitted

15.3.8. Casirivimab, imdevimab - RONAPREVE (CAP) - EMEA/H/C/005814/II/0017

Applicant: Roche Registration GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension of indication to include treatment of paediatric patients from 2 to less than 12 years old, weighing at least 10kg, who do not require supplemental oxygen and who are at increased risk of progression to severe COVID-19 for Ronapreve, based on final results from study COV-2067; this was a seamless, adaptive, phase 3, randomised, double-blinded, placebo-controlled, multi-centre study to evaluate the efficacy, safety, and tolerability of casirivimab+imdevimab combination therapy in paediatric and adult outpatients with mild to moderate 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 4.0 of the RMP has also been submitted

15.3.9. Defatted powder of Arachis hypogaea L., semen (peanuts) - PALFORZIA (CAP) - EMEA/H/C/004917/II/0014/G

Applicant: Aimmune Therapeutics Ireland Limited

PRAC Rapporteur: Kirsti Villikka

Scope: Grouped variation consisting of:

C.I.6.a: Extension of indication to include treatment of patients 1 to 3 years old for PALFORZIA, based on final results from study ARC005; this is a phase 3 randomised, double-blind, placebo-controlled Peanut Oral Immunotherapy Study of Early Intervention for Desensitization (POSEIDON) to evaluate the safety and efficacy of peanut powder in terms of superiority of placebo in children of 1 year to less than 4 years of age with peanut allergy. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 6.5 and 8 of the SmPC are updated. The package leaflet and labelling were updated accordingly. Version 1.1 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 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.

B.II.e.5.a: Introduction of a new pack-size of 16 capsules of 1 mg (Level 0) in blisters for PALFORZIA, 1 mg, oral powder in capsules for opening.

Due to the lack of a suitable pack-size for the up-dosing phase for patients 1 to 3 years old, a new pack size Level 0 for the up-dosing phase will be introduced. Labelling was updated accordingly. In addition, the MAH took the opportunity to update module 3.2.P.3.1 to take out the EU importation site (editorial change)

15.3.10. Dupilumab - DUPIXENT (CAP) - EMEA/H/C/004390/II/0079

Applicant: Sanofi Winthrop Industrie

PRAC Rapporteur: Kimmo Jaakkola

Scope: Extension of indication for DUPIXENT to include treatment of adults as add-on maintenance treatment for uncontrolled chronic obstructive pulmonary disease (COPD) with type 2 inflammation on triple therapy or double therapy if inhaled corticosteroids (ICS) are contraindicated, based on final results from study EFC15804 (BOREAS); this is a phase 3, randomised, double blind, placebo-controlled, multi-centre, parallel group, 52-week study to assess the efficacy, safety and tolerability of dupilumab in patients with moderate-to-severe COPD with type 2 inflammation. 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 in accordance. Version 10.0 of the RMP has also been submitted

15.3.11. Dupilumab - DUPIXENT (CAP) - EMEA/H/C/004390/II/0083

Applicant: Sanofi Winthrop Industrie

PRAC Rapporteur: Kimmo Jaakkola

Scope: Extension of indication to include treatment of moderate to severe chronic spontaneous urticaria (CSU) in adults and adolescents 12 years and older, who are symptomatic despite treatment with H1 antihistamines and who are intolerant to or inadequately controlled by anti-IgE therapy for Dupixent, based on the results from studies EFC16461 (CUPID) study B (pivotal) and study A (supportive); EFC16461 Study B was a 24-week, double-blind, randomised, placebo-controlled study to evaluate the efficacy and safety of dupilumab in adult and adolescent participants with CSU who remained symptomatic despite the use of H1-antihistamine and who were intolerant or incomplete responders to omalizumab and EFC16461 Study A was a 24-week, double-blind, randomised, placebo-controlled study to evaluate the efficacy and safety of dupilumab in

participants with CSU who remained symptomatic despite the use of H1-antihistamine and who were naïve to omalizumab. 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 11.0 of the RMP has also been submitted

15.3.12. Eliglustat - CERDELGA (CAP) - EMEA/H/C/003724/X/0036/G, Orphan

Applicant: Sanofi B.V.

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Extension application to introduce a new strength (21 mg capsule, hard) grouped with an extension of indication (C.I.6.a) to include treatment of paediatric patients with GD1 who are 6 years and older with a minimum body weight of 15 kg, who have been previously treated with enzyme replacement therapy (ERT), and who are CYP2D6 poor metabolisers (PMs), intermediate metabolisers (IMs) or extensive metabolisers (EMs) for Cerdelga, based on interim results from study EFC13738 (open label, two cohort (with and without imiglucerase), multicentre study to evaluate pharmacokinetics, safety, and efficacy of eliglustat in paediatric patients with Gaucher disease type 1 and type 3). 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. The RMP version 8.0 has also been submitted. In addition, the MAH took this opportunity to introduce editorial changes to the product information

15.3.13. Encorafenib - BRAFTOVI (CAP) - EMEA/H/C/004580/WS2538/0034; Binimetinib - MEKTOVI (CAP) - EMEA/H/C/004579/WS2538/0030

Applicant: Pierre Fabre Medicament

PRAC Rapporteur: Rugile Pilviniene

Scope: Extension of indication to include binimetinib in combination with encorafenib for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with a BRAF V600 mutation for MEKTOVI and BRAFTOVI based on results from study PHAROS (study ARRAY-818-202) at the primary completion date; this is a phase II, open-label, multicentre, non-comparative study (interventional). As a consequence, sections 4.1, 4.4, 4.8, 5.1, 5.2, 9 and 10 of the SmPC are updated. The package leaflet is updated in accordance. Version 2.1 of the RMP has also been submitted. As part of the application, the MAH is requesting a 1-year extension of the market protection for MEKTOVI

15.3.14. Empagliflozin, metformin - SYNJARDY (CAP) - EMEA/H/C/003770/II/0078

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Extension of indication to include the treatment of children aged 10 years and above with type 2 diabetes for Synjardy, based on the final results from study 1218-0091 (DINAMO) - a double-blind, randomised, placebo-controlled, parallel group trial to evaluate the efficacy and safety of empagliflozin and linagliptin over 26 weeks, with a double-blind active treatment safety extension period up to 52 weeks, in children and adolescents with type 2 diabetes mellitus. 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 16.0 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

15.3.15. Epcoritamab - TEPKINLY (CAP) - EMEA/H/C/005985/II/0001, Orphan

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Monica Martinez Redondo

Scope: Extension of indication to include treatment of adult patients with relapsed or refractory (R/R) follicular lymphoma (FL) after two or more lines of systemic therapy for TEPKINLY, based on results from the indolent Non-Hodgkins Lymphoma (iNHL) expansion cohort of Study GCT3013-01, the first In human (FIH) phase 1/2 study in R/R B-NHL, with key supportive data from the Phase 1b/2 Study GCT3013-04 in Japanese subjects. Study GCT3013-01 is an ongoing global, single-arm, phase 1/2 study designed to evaluate epcoritamab as monotherapy in R/R B-NHL. As a consequence, sections 1, 3, 4.1, 4.2, 4.4, 4.8, 5.1, 5.2, 6.3, 6.4, 6.5 and 6.6 of the SmPC are updated. The package leaflet and labelling are updated in accordance. Version 2.0 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor changes to the product information

15.3.16. Ganaxolone - ZTALMY (CAP) - EMEA/H/C/005825/II/0005, Orphan

Applicant: Marinus Pharmaceuticals Emerald Limited

PRAC Rapporteur: Adam Przybylkowski

Scope: Update of section 4.2 of the SmPC in order to update dosing instructions in severe hepatic impairment based on data from phase I study 1042-IHF-1001. The RMP version 1.3 has also been submitted

15.3.17. Glycopyrronium - SIALANAR (CAP) - EMEA/H/C/003883/II/0029

Applicant: Proveca Pharma Limited

PRAC Rapporteur: Zane Neikena

Scope: Extension of indication to include treatment of children aged from 2 years and older for SIALANAR, based on the interim results from study PRO/GLY/005. This is a retrospective analysis of real-world data from children aged under 3 years treated with glycopyrronium for severe drooling. As a consequence, sections 4.1, 4.2, and 4.4 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 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

15.3.18. Imlifidase - IDEFIRIX (CAP) - EMEA/H/C/004849/II/0019, Orphan

Applicant: Hansa Biopharma AB

PRAC Rapporteur: Bianca Mulder

Scope: Update of section 5.1 of the SmPC in order to include the description of the final results from post-authorisation efficacy study (PAES) study 17-HMedIdeS-14 listed as a specific obligation in the Annex II (SOB/002); this is a prospective, observational long-term

follow-up study of patients treated with imlifidase (IdeS) prior to kidney transplantation. The primary objective of this trial was to evaluate graft survival in patients who have undergone kidney transplantation after imlifidase administration in earlier trials and relates to both safety and efficacy. The RMP version 1.2 has also been submitted. In addition, the MAH took the opportunity to update section E of Annex II and to implement editorial changes to sections 4.4, 4.6 and 9 of the SmPC. Furthermore, the MAH took the opportunity to bring the product information in line with the latest QRD template version 10.3

15.3.19. Ivacaftor, tezacaftor, elexacaftor - KAFTRIO (CAP) - EMEA/H/C/005269/WS2551/0043; Ivacaftor - KALYDECO (CAP) - EMEA/H/C/002494/WS2551/0121

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Martin Huber

Scope: Extension of the indication for Kaftrio (ivacaftor/tezacaftor/elexacaftor) and Kalydeco (ivacaftor) in a combination regimen to include the treatment of patients with cystic fibrosis (CF) aged 2 years and older who do not carry any F508del mutations and have at least one ivacaftor/tezacaftor/elexacaftor-responsive mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene based on study VX21-445-124, study VX21-445-125 and study VX22-CFD-016. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the Kaftrio SmPC are updated; sections 4.1 and 5.1 of the Kalydeco SmPC are updated. The package leaflet is updated in accordance. In addition, the MAH took this opportunity to introduce editorial changes to the product information

15.3.20. Linzagolix choline - YSELTLY (CAP) - EMEA/H/C/005442/II/0013

Applicant: Theramex Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: Extension of indication to include treatment of endometriosis-associated pain in adult women of reproductive age for YSELTLY, based on final results from studies Edelweiss 3 (18-OBE2109-003) and Edelweiss 6 (19-OBE2109-006) as well as additional supporting studies. Edelweiss 3 is a pivotal phase 3, randomised, double-blind, placebo-controlled, safety and efficacy study to evaluate linzagolix with add-back therapy as a therapy for pain associated with endometriosis, while Edelweiss 6 is an open-label extension study including patients who completed Edelweiss 3 pivotal study regardless of their previous treatment assignment and met the eligibility criteria. 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. As part of the application, the MAH is requesting a 1-year extension of the market protection

15.3.21. Lisocabtagene maraleucel - BREYANZI (CAP) - EMEA/H/C/004731/II/0036/G

Applicant: Bristol-Myers Squibb Pharma EEIG, ATMP

PRAC Rapporteur: Gabriele Maurer

Scope: Grouped application comprising two variations as follows:

C.I.4 – Update of sections 4.4 and 4.8 of the SmPC in order to add immune effector cell-

associated neurotoxicity syndrome (ICANS) as an adverse drug reaction (ADR) based on the cumulative review of MAH safety database and literature. The package leaflet is updated accordingly. In addition, the MAH took this opportunity to introduce editorial changes. A.6 – To include the ATC Code L01XL08 in section 5.1 of the SmPC. RMP version 4.0 has also been submitted

15.3.22. Lumacaftor, ivacaftor - ORKAMBI (CAP) - EMEA/H/C/003954/II/0088

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Eamon O'Murchu

Scope: Submission of the final report from study VX19-809-124 (Study 124), listed as a category 3 study in the RMP. This is a phase 3, open-label, rollover study to evaluate the long-term safety and tolerability of lumacaftor/ivacaftor in cystic fibrosis subjects homozygous for F508del who were 1 to <2 years of age at treatment initiation and who completed the safety follow-up (SFU) visit in Study 122 (Part B) or were lumacaftor/ivacaftor naïve. The RMP version 11.5 has also been submitted

15.3.23. Niraparib, abiraterone acetate - AKEEGA (CAP) - EMEA/H/C/005932/II/0003

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Jan Neuhauser

Scope: Update of sections 4.8 and 5.1 of the SmPC in order to update the frequency of adverse drug reactions and to update information from MAGNITUDE study based on final results from study 64091742PCR3001 (MAGNITUDE) listed as a post-authorisation efficacy study (PAES) in the Annex II. This is a phase 3 randomised, placebo-controlled, double-blind, multicenter study which assessed the efficacy and safety of niraparib 200 mg in combination with AA 1,000 mg once daily plus prednisone or prednisolone 10 mg daily (AAP), compared with placebo plus AAP in men with mCRPC and HRR gene alterations, approximately half of whom had BRCA gene alterations and comprised the prespecified BRCA subgroup.

The Annex II and package leaflet are updated accordingly. The RMP version 2.1 has also been submitted. In addition, the MAH took this opportunity to update the list of local representatives in the package leaflet and to introduce editorial changes to the product information

15.3.24. Ozanimod - ZEPOSIA (CAP) - EMEA/H/C/004835/II/0023

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Update of sections 4.4 and 5.1 of the SmPC in order to update efficacy and safety information based on the final results from study RPC01-3001, listed as a category 3 study in the RMP. This is a multi-site, open label extension trial of RPC1063 in relapsing multiple sclerosis. The study's main objectives were to characterise the long-term safety and tolerability, and the long-term efficacy of ozanimod in patients with relapsing multiple sclerosis. The RMP version 7.0 has also been submitted

15.3.25. Peginterferon alfa-2a - PEGASYS (CAP) - EMEA/H/C/000395/II/0119/G

Applicant: Pharmaand GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Grouped application consisting of extension of indication to include treatment of polycythaemia vera (PV) and essential thrombocytopenia (ET) for PEGASYS, based on published data of clinical studies conducted in support of the efficacy and safety of Pegasys for the treatment of ET and PV. As a consequence, sections 4.1, 4.2, 4.8 and 5.2 of the SmPC are updated. The package leaflet is updated in accordance. Version 10.1 of the RMP has also been submitted. Furthermore, the product information is brought in line with the latest QRD template version 10.3

15.3.26. 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)

15.3.27. Pretomanid - DOVPRELA (CAP) - EMEA/H/C/005167/II/0019/G, Orphan

Applicant: Mylan IRE Healthcare Limited

PRAC Rapporteur: Liana Martirosyan

Scope: Grouped application comprising two variations as follows:

Type II (C.I.4) – Update of sections 4.1 and 5.1 of the SmPC in order to rephrase the indication wording to align with the current WHO definitions. The package leaflet is updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet.

Type IB (C.I.11.z) - Submission of an updated RMP version 2.0 in order to align the safety concerns following the assessment of procedure EMEA/H/C/005167/11/0013

15.3.28. Rilpivirine - EDURANT (CAP) - EMEA/H/C/002264/X/0042/G

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Liana Martirosyan

Scope: Grouped application consisting of: 1) Extension application to introduce a new pharmaceutical form associated with new strength (2.5 mg dispersible tablets). The new presentation is indicated, in combination with other antiretroviral medicinal products, for the treatment of HIV-1 infection in patients ≥ 2 to < 18 years of age and weighing at least 10 kg to less than 25 kg. The product information and RMP have been updated in accordance. 2) Type II variation (C.I.6.a) to modify the approved therapeutic indication of the already authorised 25 mg film-coated tablets presentation to include, in combination with other antiretroviral medicinal products, treatment of human immunodeficiency virus type 1 (HIV-1) infection in antiretroviral treatment-naïve and virologically suppressed (HIV-1 RNA less than 50 copies per ml) paediatric patients from 2 to less than 12 years weighing at least 25 kg, based on final results from study studies TMC278-TiDP38-C213 Cohort 2. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated.

The package leaflet and labelling are updated in accordance. The updated RMP version 10.1 has also been submitted. In addition, the MAH took the opportunity to implement editorial changes to Annex II and to update the list of local representatives in the package leaflet

15.3.29. [Smallpox vaccine \(live modified vaccinia virus Ankara\) - IMVANEX \(CAP\) - EMEA/H/C/002596/II/0100](#)

Applicant: Bavarian Nordic A/S

PRAC Rapporteur: Gabriele Maurer

Scope: Update of section 5.1 of the SmPC in order to add vaccine effectiveness data, and the removal of the two open specific obligations (POX-MVA-039 (SOB02) and SEMVAc (SOB03)), based on the IMVANEX vaccine effectiveness data in real-world use during the 2022 monkeypox outbreak. Consequently, the MAH proposes a switch from exceptional marketing authorisation to full marketing authorisation. The Annex II and package leaflet are updated accordingly. The RMP version 10.0 has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the product information

15.3.30. [Teclistamab - TECVAYLI \(CAP\) - EMEA/H/C/005865/II/0012](#)

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Jana Lukacisinova

Scope: Update of sections 4.2, 4.8, 5.1 of the SmPC in order to amend the recommendations for dose delays, as well as, to update safety and efficacy information based on final results from study 64007957MMY1001 listed as a specific obligation in the Annex II (SOB/005); this is a phase 1/2, first in human, open label, dose escalation study of teclistamab in subjects with relapsed or refractory multiple myeloma. The package leaflet is updated accordingly. The RMP version 4.2 has also been submitted. In addition, the MAH took the opportunity to update Annex II and Annex IV of the product information

15.3.31. [Tildrakizumab - ILUMETRI \(CAP\) - EMEA/H/C/004514/II/0054](#)

Applicant: Almirall S.A

PRAC Rapporteur: Adam Przybylkowski

Scope: Update of section 5.1 of the SmPC in order to update clinical and safety information based on long-term results from the extension periods of the pivotal clinical studies MK-3222-010 (a 64-week, phase 3, randomised, placebo-controlled, parallel design study to evaluate the efficacy and safety/tolerability of subcutaneous tildrakizumab (SCH 900222/MK-3222), followed by an optional long-term safety extension study, in subjects with moderate-to-severe chronic plaque psoriasis (Protocol No. MK-3222-010)) and MK-3222-011 (A 52-Week, Phase 3, Randomised, Active Comparator and Placebo-Controlled, Parallel Design Study to Evaluate the Efficacy and Safety/Tolerability of Subcutaneous Tildrakizumab (SCH 900222 / MK-3222), Followed by an Optional Long-Term Safety Extension Study, in Subjects With Moderate-to-Severe Chronic Plaque Psoriasis). The RMP version 1.4 has also been submitted

15.3.32. Tislelizumab - TEVIMBRA (CAP) - EMEA/H/C/005919/II/0006

Applicant: Beigene Ireland Limited

PRAC Rapporteur: Bianca Mulder

Scope: Extension of indication to include in combination with platinum and fluoropyrimidine-based chemotherapy the first-line treatment of adult patients with human epidermal growth factor receptor-2 (HER-2)-negative locally advanced unresectable or metastatic gastric or gastroesophageal junction (G/GEJ) adenocarcinoma for TEVIMBRA, based on results from the phase 3 study BGB-A317-305 (study 305); this is a global, randomised, double-blind, placebo-controlled study at the approved registrational dosing regimen for Tevimbra (200 mg administered IV Q3W), in combination with platinum and fluoropyrimidine-based chemotherapy, in adult patients with HER-2 negative locally advanced unresectable or metastatic gastric or gastroesophageal junction (G/GEJ) adenocarcinoma. 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 1.2 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the product information

15.3.33. Tislelizumab - TEVIMBRA (CAP) - EMEA/H/C/005919/II/0008

Applicant: Beigene Ireland Limited

PRAC Rapporteur: Bianca Mulder

Scope: Extension of indication to include treatment of adult patients with non-small cell lung cancer (NSCLC) in combination and as monotherapy for TEVIMBRA, based on results from studies BGB-A317-303, BGB-A317-304, BGB-A317-307 and BGB A317-206. 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 2.0 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the product information

15.3.34. Upadacitinib - RINVOQ (CAP) - EMEA/H/C/004760/II/0052

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Petar Mas

Scope: Update of sections 4.2, 4.8 and 5.1 of the SmPC in order to change posology recommendations in adolescents with atopic dermatitis to include the 30mg dose option based on results from studies M16-045, M16-047 and M18-891 (pivotal phase 3 studies with adolescent substudies). The package leaflet is updated accordingly. The RMP version 14.0 has also been submitted

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/00011029/202310

Applicant: Theramex Ireland Limited

PRAC Rapporteur: Karin Erneholm

Scope: Evaluation of a PSUSA procedure

16.1.2. Acalabrutinib - CALQUENCE (CAP) - PSUSA/00010887/202310 (with RMP)

Applicant: AstraZeneca AB

PRAC Rapporteur: Barbara Kovacic Bytyqi

Scope: Evaluation of a PSUSA procedure

16.1.3. Afatinib - GIOTRIF (CAP) - PSUSA/00010054/202309

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.4. Andexanet alfa - ONDEXXYA (CAP) - PSUSA/00010764/202310

Applicant: AstraZeneca AB

PRAC Rapporteur: Bianca Mulder

Scope: Evaluation of a PSUSA procedure

16.1.5. Arsenic trioxide - TRISENOX (CAP) - PSUSA/00000235/202309

Applicant: Teva B.V.

PRAC Rapporteur: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

16.1.6. Axicabtagene ciloleucel - YESCARTA (CAP) - PSUSA/00010703/202310

Applicant: Kite Pharma EU B.V.

PRAC Rapporteur: Karin Erneholm

Scope: Evaluation of a PSUSA procedure

16.1.7. Aztreonam⁴⁴ - CAYSTON (CAP) - PSUSA/00000283/202309

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Liana Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.8. Bexarotene - TARGRETIN (CAP) - PSUSA/00000404/202309

Applicant: Eisai GmbH

PRAC Rapporteur: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

16.1.9. Brolocizumab - BEOVU (CAP) - PSUSA/00010829/202310

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Gabriele Maurer

Scope: Evaluation of a PSUSA procedure

16.1.10. Bupivacaine⁴⁵ - EXPAREL LIPOSOMAL (CAP) - PSUSA/00010889/202310

Applicant: Pacira Ireland Limited

PRAC Rapporteur: Eamon O'Murchu

Scope: Evaluation of a PSUSA procedure

16.1.11. Cetuximab - ERBITUX (CAP) - PSUSA/00000635/202309

Applicant: Merck Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.12. Chenodeoxycholic acid⁴⁶ - CHENODEOXYCHOLIC ACID LEADIANT (CAP) - PSUSA/00010590/202310

Applicant: Leadiant GmbH

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.13. Conestat alfa - RUCONEST (CAP) - PSUSA/00000873/202310

Applicant: Pharming Group N.V

⁴⁴ For inhalation use only

⁴⁵ Liposomal formulations only

⁴⁶ Inborn error in primary bile acid synthesis, xanthomatosi - centrally authorised products only

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.1.14. Coronavirus (COVID-19) vaccine (recombinant protein receptor binding domain fusion heterodimer) - BIMERVAX (CAP) - PSUSA/00011045/202309

Applicant: Hipra Human Health S.L.

PRAC Rapporteur: Zane Neikena

Scope: Evaluation of a PSUSA procedure

16.1.15. Delamanid - DELTYBA (CAP) - PSUSA/00010213/202310

Applicant: Otsuka Novel Products GmbH

PRAC Rapporteur: Jo Robays

Scope: Evaluation of a PSUSA procedure

16.1.16. Denosumab⁴⁷ - XGEVA (CAP) - PSUSA/00009119/202309

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Mari Thorn

Scope: Evaluation of a PSUSA procedure

16.1.17. Dexamethasone⁴⁸ - NEOFORDEX (CAP) - PSUSA/00010480/202309

Applicant: Theravia

PRAC Rapporteur: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

16.1.18. Dostarlimab - JEMPERLI (CAP) - PSUSA/00010931/202310

Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Carla Torre

Scope: Evaluation of a PSUSA procedure

16.1.19. Edoxaban - LIXIANA (CAP); ROTEAS (CAP) - PSUSA/00010387/202310

Applicant(s): Berlin Chemie AG (Roteas), Daiichi Sankyo Europe GmbH (Lixiana)

PRAC Rapporteur: Nathalie Gault

Scope: Evaluation of a PSUSA procedure

⁴⁷ Indicated for skeletal related events associated with bone metastases and for giant cell tumour of bone only

⁴⁸ Centrally authorised product indicated in symptomatic multiple myeloma

16.1.20. Etravirine - INTELENCE (CAP) - PSUSA/00001335/202309

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Nathalie Gault

Scope: Evaluation of a PSUSA procedure

16.1.21. Futibatinib - LYTGObI (CAP) - PSUSA/00000068/202309

Applicant: Taiho Pharma Netherlands B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.22. Herpes zoster vaccine (recombinant, adjuvanted) - SHINGRIX (CAP) - PSUSA/00010678/202310

Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Sonja Hrabcik

Scope: Evaluation of a PSUSA procedure

16.1.23. Histamine⁴⁹ - CEPLENE (CAP) - PSUSA/00001610/202310

Applicant: Laboratoires Delbert

PRAC Rapporteur: Eamon O'Murchu

Scope: Evaluation of a PSUSA procedure

16.1.24. Indacaterol, glycopyrronium bromide - ULTIBRO BREEZHALER (CAP); ULUNAR BREEZHALER (CAP); XOTERNA BREEZHALER (CAP) - PSUSA/00010105/202309

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Evaluation of a PSUSA procedure

16.1.25. Insulin aspart - FIASP (CAP); INSULIN ASPART SANOFI (CAP); KIRSTY (CAP); NOVOMIX (CAP); NOVORAPID (CAP); TRUVELOG MIX 30 (SRD) (CAP) - PSUSA/00001749/202309

Applicant(s): Biosimilar Collaborations Ireland Limited (Kirsty), Novo Nordisk A/S (Fiasp, NovoMix, NovoRapid), Sanofi Winthrop Industrie (Insulin aspart Sanofi, Truvelog Mix 30 (SRD))

PRAC Rapporteur: Mari Thorn

Scope: Evaluation of a PSUSA procedure

⁴⁹ Indicated for acute myeloid leukemia only

16.1.26. Insulin degludec – TRESIBA; insulin degludec, insulin aspart - RYZODEG (CAP); (CAP) - PSUSA/00010036/202309

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Mari Thorn

Scope: Evaluation of a PSUSA procedure

16.1.27. Insulin human⁵⁰ - INSUMAN (CAP) - PSUSA/00010107/202309

Applicant: Sanofi-Aventis Deutschland GmbH

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

16.1.28. Ivacaftor, tezacaftor, elexacaftor - KAFTRIO (CAP) - PSUSA/00010868/202310

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.29. Lasmiditan - RAYVOW (CAP) - PSUSA/00011011/202310

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Anna Mareková

Scope: Evaluation of a PSUSA procedure

16.1.30. Loncastuximab tesirine - ZYNLONTA (CAP) - PSUSA/00011027/202310

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

16.1.31. Mavacamten - CAMZYOS (CAP) - PSUSA/00000074/202310

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

16.1.32. Nintedanib⁵¹ - OFEV (CAP) - PSUSA/00010319/202310

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Barbara Kovacic Bytyqi

⁵⁰ For intraperitoneal use only

⁵¹ Respiratory indication only

Scope: Evaluation of a PSUSA procedure

16.1.33. Niraparib, abiraterone acetate - AKEEGA (CAP) - PSUSA/00011051/202310

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.1.34. Parathyroid hormone - NATPAR (CAP) - PSUSA/00010591/202310

Applicant: Takeda Pharmaceuticals International AG Ireland Branch

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

16.1.35. Pemigatinib - PEMAZYRE (CAP) - PSUSA/00010923/202310

Applicant: Incyte Biosciences Distribution B.V.

PRAC Rapporteur: Bianca Mulder

Scope: Evaluation of a PSUSA procedure

16.1.36. Pitolisant - OZAWADE (CAP); WAKIX (CAP) - PSUSA/00010490/202309

Applicant: Bioprojet Pharma

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

16.1.37. Potassium citrate, potassium hydrogen carbonate - SIBNAYAL (CAP) - PSUSA/00010932/202310

Applicant: Advicenne

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.38. Regorafenib - STIVARGA (CAP) - PSUSA/00010133/202309

Applicant: Bayer AG

PRAC Rapporteur: Bianca Mulder

Scope: Evaluation of a PSUSA procedure

16.1.39. Recombinant respiratory syncytial virus pre-fusion F protein, adjuvanted with AS01E - AREXVY (CAP) - PSUSA/00000031/202311

Applicant: GlaxoSmithkline Biologicals S.A.

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

16.1.40. Selumetinib - KOSELUGO (CAP) - PSUSA/00010936/202310

Applicant: AstraZeneca AB

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.41. Sirolimus⁵² - RAPAMUNE (CAP) - PSUSA/00002710/202309

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Mari Thorn

Scope: Evaluation of a PSUSA procedure

16.1.42. Somatrogon - NGENLA (CAP) - PSUSA/00010982/202310

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.43. Sulfur hexafluoride - SONOVUE (CAP) - PSUSA/00002822/202309

Applicant: Bracco International B.V.

PRAC Rapporteur: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

16.1.44. Talazoparib - TALZENNA (CAP) - PSUSA/00010781/202310

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Carla Torre

Scope: Evaluation of a PSUSA procedure

16.1.45. Talimogene laherparepvec - IMLYGIC (CAP) - PSUSA/00010459/202310

Applicant: Amgen Europe B.V., ATMP

PRAC Rapporteur: Gabriele Maurer

Scope: Evaluation of a PSUSA procedure

16.1.46. Tremelimumab - IMJUDO (CAP) - PSUSA/00011038/202310

Applicant: AstraZeneca AB

PRAC Rapporteur: David Olsen

⁵² For prophylaxis of organ rejection indication only

Scope: Evaluation of a PSUSA procedure

16.1.47. [Tucatinib - TUKYSA \(CAP\) - PSUSA/00010918/202310](#)

Applicant: Seagen B.V.

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

16.1.48. [Volanesorsen - WAYLIVRA \(CAP\) - PSUSA/00010762/202311](#)

Applicant: Akcea Therapeutics Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.49. [Zoonotic influenza vaccine \(H5N1\)⁵³ - FOCLIVIA \(CAP\); prepandemic influenza vaccine \(H5N1\)⁵³ - AFLUNOV \(CAP\); ZOONOTIC INFLUENZA VACCINE SEQIRUS \(CAP\) - PSUSA/00010008/202310](#)

Applicant: Seqirus S.r.l.

PRAC Rapporteur: Amelia Cupelli

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. [Iloprost⁵⁴ - VENTAVIS \(CAP\); NAP - PSUSA/00001724/202309](#)

Applicant: Bayer AG (Ventavis), various

PRAC Rapporteur: Nathalie Gault

Scope: Evaluation of a PSUSA procedure

16.2.2. [Melatonin - CIRCADIN \(CAP\); MELATONIN NEURIM \(CAP\); SLENYTO \(CAP\); NAP - PSUSA/00001963/202309](#)

Applicant: RAD Neurim Pharmaceuticals EEC SARL (Circadin, Melatonin Neurim, Slenyto), various

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.2.3. [Memantine - AXURA \(CAP\); EBIXA \(CAP\); MEMANTINE MERZ \(CAP\); NAP - PSUSA/00001967/202309](#)

Applicant(s): H. Lundbeck A/S (Ebixa), Merz Pharmaceuticals GmbH (Axura, Memantine)

⁵³ Surface antigen, inactivated, adjuvanted

⁵⁴ Nebuliser solution only

Merz), various

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

16.2.4. Sodium oxybate⁵⁵ - XYREM (CAP); NAP - PSUSA/00010612/202310

Applicant: UCB Pharma S.A. (Xyrem), various

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.2.5. Vigabatrin - KIGABEQ (CAP); NAP - PSUSA/00003112/202309

Applicant: ORPHELIA Pharma SAS (Kigabeq), various

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

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

16.3.1. Acetylcysteine (NAP) - PSUSA/00000034/202309

Applicant(s): various

PRAC Lead: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.3.2. Calcium carbonate, famotidine, magnesium hydroxide (NAP) - PSUSA/00001351/202309

Applicant(s): various

PRAC Lead: Nathalie Gault

Scope: Evaluation of a PSUSA procedure

16.3.3. Desflurane (NAP) - PSUSA/00000958/202309

Applicant(s): various

PRAC Lead: Melinda Palfi

Scope: Evaluation of a PSUSA procedure

16.3.4. Felodipine, ramipril (NAP) - PSUSA/00001358/202309

Applicant(s): various

PRAC Lead: Martin Huber

⁵⁵ Oral use

Scope: Evaluation of a PSUSA procedure

16.3.5. Human von Willebrand factor (NAP) - PSUSA/00001642/202309

Applicant(s): various

PRAC Lead: Gabriele Maurer

Scope: Evaluation of a PSUSA procedure

16.3.6. Levofloxacin⁵⁶ (NAP) - PSUSA/00010768/202310

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.3.7. Prulifloxacin (NAP) - PSUSA/00002569/202309

Applicant(s): various

PRAC Lead: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.3.8. Rubidium (⁸²Rb) chloride (NAP) - PSUSA/00010806/202310

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.4. Follow-up to PSUR/PSUSA procedures

16.4.1. Tenofovir disoproxil - VIREAD (CAP) - EMEA/H/C/000419/LEG 279

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Nathalie Gault

Scope: From PSUSA/00002892/202303: Cumulative safety review on dental disorders, increased parathyroid hormone and congenital anomalies

16.5. Variation procedure(s) resulting from PSUSA evaluation

16.5.1. Dabrafenib - FINLEE (CAP) - EMEA/H/C/005885/WS2671/0005; Trametinib - SPEXOTRAS (CAP) - EMEA/H/C/005886/WS2671/0004; Dabrafenib - TAFINLAR (CAP) - EMEA/H/C/002604/WS2671/0067

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ulla Wändel Liminga

⁵⁶ Ocular use only

Scope: Update of section 4.8 of the SmPC for Tafinlar, Finlee and Spexotras in order to add 'Atrioventricular (AV) block' and 'Bundle branch block' to the list of adverse drug reactions (ADRs), following the PRAC recommendation in the PSUR for Mekinist (PSUSA/00010262/202305). The package leaflet is updated accordingly

16.5.2. Rituximab - MABTHERA (CAP) - EMEA/H/C/000165/II/0201/G

Applicant: Roche Registration GmbH

PRAC Rapporteur: Karin Erneholm

Scope: A grouped application comprising of:

Type II (C.I.3.b): Update of sections 4.1, 4.2, 4.3, 4.8, 5.1, 6.2, 6.4 and 6.5 of the SmPC in order to introduce several structural and editorial changes to align with the current SmPC guideline and to remove the educational materials for healthcare professionals (HCPs) and patients, following the request by PRAC in the assessment report for the PSUSA procedure EMA/PRAC/257005/2023. The Annex II, Labelling and package leaflet are updated accordingly. The RMP version 25.0 has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the product information and to update the list of local representatives in the package leaflet. Type I (A.6): To change the ATC Code of rituximab from L01XC02 to L01FA01

16.6. Expedited summary safety reviews⁵⁷

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)⁵⁸

17.1.1. Axicabtagene ciloleucel (CAP) - YESCARTA – EMEA/H/C/PSA/S/0102.4

Applicant: Kite Pharma EU B.V.

PRAC Rapporteur: Karin Erneholm

Scope: Substantial amendment to a protocol for a long-term, non-interventional study of recipients of Yescarta for treatment of relapsed or refractory diffuse large B-cell lymphoma and primary mediastinal B-cell lymphoma [MAH's response to PSA/S/0102.3]

⁵⁷ 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

⁵⁸ In accordance with Article 107n of Directive 2001/83/EC

17.1.2. Evinacumab - Evkeeza (CAP) – EMEA/H/C/PSA/S/0112

Applicant: Regeneron Ireland DAC

PRAC Rapporteur: Mari Thorn

Scope: Substantial amendment to a protocol for an evaluation of the long-term effects of evinacumab treatment in patients with homozygous familial hypercholesterolemia (HoFH):

- safety outcomes in patients with HoFH who are ≥ 12 years old
- frequency and outcomes of pregnancy in female patients with HoFH
- atherosclerosis process over time in patients with HoFH who undergo cardiovascular imaging (as data allow)
- frequency of cardiovascular imaging of patients with HoFH

17.1.3. Methylphenidate hydrochloride (NAP) – EMEA/H/N/PSA/S/0113

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

PRAC Rapporteur: Martin Huber

Scope: Substantial amendments to the protocol for the post-authorisation safety study (PASS) evaluating the long-term cardiovascular and psychiatric safety profile of methylphenidate in adult patients with attention deficit/hyperactivity disorder (ADHD) in European Countries. A revised protocol version 5.2 dated 2 February 2024 was submitted. The most significant changes introduced by the amended protocol concern the study milestones and the data analyses. The MAH also took the opportunity to introduce additional minor changes to the protocol.

17.1.4. Pegzilarginase - LOARGYS (CAP) – EMEA/H/C/PSP/S/0105

Applicant: Immedica Pharma AB

PRAC Rapporteur: Martin Huber

Scope: A European, non-interventional, multicentre, registry-based PASS to evaluate the long-term safety of Loargys treatment in arginase 1 deficiency patients in standard clinical care

17.1.5. Valproate (CAP) – EMEA/H/N/PSP/J/0074.9

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

PRAC Rapporteur: Jean-Michel Dogné

Scope: Responses to the 2nd request for supplementary information (RSI) of the 2nd interim report: observational study to evaluate and identify the best practices for switching of valproate in clinical practice [MAH's response to PSP/J/0074.8], non-interventional retrospective longitudinal study in the UK and France to investigate the therapeutic strategies after discontinuation of valproate (VPA) and related substances in clinical practice: VALSE study (VALNAC09344)

- Response document to PRAC assessment report (Procedure no.: EMEA/H/N/PSP/J/0074.7)
- Sensitivity analysis performed in the SNDS database, the national healthcare data system in France, to specify the indication for the use of valproate and reduce the

proportion of women with unspecified indication

17.2. Protocols of PASS non-imposed in the marketing authorisation(s)⁵⁹

17.2.1. Abaloparatide - ELADYNOS (CAP) - EMEA/H/C/005928/MEA 001.2

Applicant: Theramex Ireland Limited

PRAC Rapporteur: Karin Erneholm

Scope: From initial marketing authorisation application (MAA): REVISED PASS PROTOCOL (Study number not assigned yet); Non-imposed/non-interventional; European non-interventional post-authorisation safety study (PASS) to assess serious cardiovascular events of myocardial infarction (MI), stroke, all-cause and cardiovascular mortality, and arrhythmias for abaloparatide

17.2.2. Alemtuzumab - LEMTRADA (CAP) - EMEA/H/C/003718/MEA 007.17

Applicant: Sanofi Belgium

PRAC Rapporteur: Karin Erneholm

Scope: MAH's response to MEA 007.14 [Amended Protocol OBS13434 version 4]; request for supplementary information (RSI) as adopted in October 2023. A prospective, multicentre, observational, post-authorisation safety study to evaluate the long-term safety profile of LEMTRADA (alemtuzumab) treatment in patients with relapsing forms of multiple sclerosis

17.2.3. Atogepant - AQUIPTA (CAP) - EMEA/H/C/005871/MEA 003

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Rugile Pilviniene

Scope: Study P22-392; Atogepant pregnancy exposure registry: Study P22-392 aims to prospectively evaluate maternal, foetal, and infant outcomes through 12 months of age among women exposed to atogepant during pregnancy

17.2.4. Atogepant - AQUIPTA (CAP) - EMEA/H/C/005871/MEA 004

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Rugile Pilviniene

Scope: Study P22-419; Pregnancy Study; Study P22-419 aims to describe and compare the incidence of pregnancy outcomes in women with migraine who are exposed to atogepant during pregnancy

17.2.5. Dabigatran etexilate - PRADAXA (CAP) - EMEA/H/C/000829/MEA 051.2

Applicant: Boehringer Ingelheim International GmbH

⁵⁹ 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

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: From X/0122/G: REVISED PROTOCOL (3.0) for PASS 1160.307 (non-imposed); Safety of dabigatran etexilate for treatment of venous thromboembolism (VTE) and prevention of recurrent VTE in paediatric patients from birth to less than 2 years of age: A European non-interventional cohort study based on new data collection

17.2.6. Glofitamab - COLUMVI (CAP) - EMEA/H/C/005751/MEA 004

Applicant: Roche Registration GmbH

PRAC Rapporteur: Jana Lukacisinova

Scope: From initial MAA; PASS No BO43309 (non-imposed/non-interventional); Evaluation of the Effectiveness of the Additional Risk Minimisation Measures for Glofitamab - A Survey Among Healthcare Professionals in 10 Countries in the European Economic Area (EEA)

17.2.7. Niraparib, Abiraterone acetate - AKEEGA (CAP) - EMEA/H/C/005932/MEA 001.2

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Jan Neuhauser

Scope: Revised PASS Protocol / Study no.: PCSONCA0485; Study title: Post authorisation safety study to characterise the risk of second primary malignancies (SPM) including MDS/AML among metastatic prostate cancer patients exposed to AKEEGA

17.2.8. Risankizumab - SKYRIZI (CAP) - EMEA/H/C/004759/MEA 010.3

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Liana Martirosyan

Scope: Revised PASS Protocol (v 2.1) / Study no.: P23-654 (Non-imposed/Non-interventional); Title: Long-Term Comparative Cohort Study in Patients with Crohn's Disease in a Real World Setting. Additional long-term data from the real-world experience of patients with Crohn's disease treated with risankizumab to assess product potential risks. A comparative cohort study will be conducted to estimate rates of malignancy (malignancy excluding NMSC, NMSC), serious infections, serious hypersensitivity reactions, and major adverse cardiovascular events (MACE) in risankizumab treated patients with Crohn's disease, relative to alternative systemic therapies (e.g., biologics). MAH's responses to MEA010.2 as adopted in January 2024: The current protocol insufficiently addresses whether duration of treatment (exposure) will be taken into account in the analysis of MACE and also for the other outcomes of interest. The MAH is requested to clarify whether duration of treatment (exposure) will be considered in the analysis of the outcomes of interest or otherwise include this consideration in the protocol

17.2.9. Romosozumab - EVENITY (CAP) - EMEA/H/C/004465/MEA 002.10

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Tiphaine Vaillant

Scope: MAH's response to MEA 002.9 [Protocol Amendment for study OP0004] request for supplementary information as adopted in January 2024

17.2.10. Romosozumab - EVENITY (CAP) - EMEA/H/C/004465/MEA 003.8

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Tiphaine Vaillant

Scope: MAH's response to MEA 003.7 [Protocol Amendment for study OP0006] request for supplementary information as adopted in January 2024

17.2.11. Ruxolitinib - OPZELURA (CAP) - EMEA/H/C/005843/MEA 001.1

Applicant: Incyte Biosciences Distribution B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: From Initial MAA: Revised protocol for PASS INCB 88888-037 (non-imposed non-interventional, RMP, Cat. 3); Title: To evaluate the safety of long-term ruxolitinib cream use with respect to incidence of non-melanoma skin cancers

17.2.12. Somapacitan - SOGROYA (CAP) - EMEA/H/C/005030/MEA 005.1

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Martin Huber

Scope: From X/0006/G: Revised protocol / Study No. NN8640-4787; Paediatric growth hormone deficiency (GHD) register-based study: A non-interventional, observational, register-based study to investigate long-term safety and clinical parameters of somapacitan treatment in paediatric patients with GHD in the setting of routine clinical practice. As a follow-up of MEA 005.1, a revised protocol for the non-imposed, non-interventional PASS should be submitted in clean and change-track format taking into account the comments adopted by PRAC

17.2.13. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/MEA 025.3

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Martirosyan

Scope: From initial MAA: PASS DUS A3921403 (non-imposed RMP Cat. 3); PASS of the utilisation and prescribing patterns of Xeljanz (tofacitinib) using an administrative healthcare database in France, is a descriptive drug utilisation study using real-world data collected from routine clinical care in France. The overall goal is to determine if there is evidence that prescribers in France are compliant with the recommendations and limitations for use described in the tofacitinib additional risk minimisation measures (aRMM) materials

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

None

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

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

- 17.4.1. Dolutegravir, Lamivudine - DOVATO (CAP) - EMEA/H/C/004909/WS2620/0047;
Dolutegravir, Rilpivirine - JULUCA (CAP) - EMEA/H/C/004427/WS2620/0056;
Dolutegravir - TIVICAY (CAP) - EMEA/H/C/002753/WS2620/0092;
Dolutegravir, Abacavir, Lamivudine - TRIUMEQ (CAP) -
EMEA/H/C/002754/WS2620/0118
-

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Martin Huber

Scope: Update of section 4.6 of the SmPC in order to update information about the use of dolutegravir-containing regimens in pregnancy and at conception based on final results from non-interventional Tsepamo study and the Eswatini Birth Outcomes Surveillance study. In addition, data from other cohort studies and pregnancy registries, including the APR, DOLOMITE-EPPICC (Study 208613) and DOLOMITE-NEAT-ID Network study (Study 208759) both listed as category 3 studies in the RMP; and the US Chart Review (Study 212976) as well as data from literature are included. DOLOMITE-EPPICC (Study 208613) is a non-interventional study to Assess 'real-world' maternal and foetal outcomes following DTG use during pregnancy and to describe patterns of dolutegravir utilisation; DOLOMITE NEAT ID Network Study (208759) is a non-interventional, multi-site observational study to define the safety and effectiveness of dolutegravir use in HIV positive pregnant women. The package leaflet is updated accordingly. The RMP version 19 has also been submitted. In addition, the MAH took the opportunity to implement editorial changes to sections 4.4 and 4.5 of the SmPC

- 17.4.2. Epoetin alfa - ABSEAMED (CAP) - EMEA/H/C/000727/WS2615/0108;
Epoetin alfa - BINOCRIT (CAP) - EMEA/H/C/000725/WS2615/0108;
Epoetin alfa - EPOETIN ALFA HEXAL (CAP) - EMEA/H/C/000726/WS2615/0108
-

Applicant: Sandoz GmbH

PRAC Rapporteur: Tiphaine Vaillant

Scope: Submission of the final report from Non-Interventional Post authorisation Safety Study, NI-PASS HX575-507 listed as a category 3 study in the RMP. The non-interventional study (NIS PASS) study HX575-507 was conducted to address a post-approval requirement (MEA 13.5) to evaluate the safety profile of HX575 administered subcutaneous (s.c.) in patients with CKD-induced anaemia under real-life conditions, in order to increase confidence on the safe use of s.c. HX575. The RMP version 19.0 has also been submitted

- 17.4.3. Human normal immunoglobulin - HYQVIA (CAP) - EMEA/H/C/002491/II/0096
-

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Gabriele Maurer

Scope: Update of sections 4.8 and 5.1 of the SmPC in order to update long-term safety information based on final results from studies 161406 'non-interventional post-marketing safety study on the long-term safety of HYQVIA (Global)' listed as category 3 a study in the

⁶¹ In accordance with Article 61a (6) of Regulation (EC) No 726/2004, in line with the revised variations regulation for any submission as of 4 August 2013

RMP and 161302 'non-interventional post-authorisation safety study on the long-term safety of HyQvia in subjects treated with HyQvia'. Both studies were non-interventional, prospective, uncontrolled, multicentre, open-label, post-authorisation studies. The RMP version 15.0 has also been submitted. In addition, the MAH took the opportunity to bring the product information in line with the latest QRD template version 10.3, to update the list of local representatives in the package leaflet and to introduce minor editorial changes to the product information

17.4.4. Human normal immunoglobulin - HYQVIA (CAP) - EMEA/H/C/002491/II/0096

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Gabriele Maurer

Scope: Update of sections 4.8 and 5.1 of the SmPC in order to update long-term safety information based on final results from studies 161406 'non-interventional post-marketing safety study on the long-term safety of HYQVIA (Global)' listed as category 3 a study in the RMP and 161302 'non-interventional post-authorisation safety study on the long-term safety of HyQvia in subjects treated with HyQvia'. Both studies were non-interventional, prospective, uncontrolled, multicentre, open-label, post-authorisation studies. The RMP version 15.0 has also been submitted. In addition, the MAH took the opportunity to bring the product information in line with the latest QRD template version 10.3, to update the list of local representatives in the package leaflet and to introduce minor editorial changes to the product information

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

Applicant: Gruenthal 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

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

Applicant: Alfasigma S.p.A.

PRAC Rapporteur: Martin Huber

Scope: Grouped variation consisting of: 1) Submission of the final report from the effectiveness evaluation survey for Eurartesim (protocol no. 3366) (listed as a category 3 study in the RMP): an 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; 2) Submission of an updated RMP version 16.1 in order to delete 'severe malaria' as missing information from the list of safety specifications

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

17.5.1. Abatacept - ORENCIA (CAP) - EMEA/H/C/000701/MEA 048.12

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Kimmo Jaakkola

Scope: From II-0024: Study number: IM101240 JIA registry; Yearly Recruitment update in the context of MEA-048; An Observational Registry of Abatacept in Patients with Juvenile Idiopathic Arthritis is ongoing. The primary objective is to describe the long-term safety of abatacept treatment for juvenile idiopathic arthritis (JIA) in routine clinical practice by quantifying the incidence rates of serious infections, autoimmune disorders, and malignancies. The data in these studies do not change the safety profile of abatacept. The MAH will supply interim reports from the above-mentioned studies according to the set schedules. Recruitment updates are provided each February, and interim reports will be submitted in 2014, 2019, and 2024. The planned date for submission of final data is 2029

17.5.2. Alemtuzumab - LEMTRADA (CAP) - EMEA/H/C/003718/ANX 009.6

Applicant: Sanofi Belgium

PRAC Rapporteur: Karin Erneholm

Scope: MAH's response to MEA 009.4 request for supplementary information (RSI) and updated protocol [feasibility analysis report for the Cat. 1 non-interventional PASS to investigate the risk of mortality in multiple sclerosis (MS) patients treated with alemtuzumab (LEMTRADA) relative to comparable MS patients using other disease modifying treatments (DMTs)] as adopted by PRAC in January 2024

17.5.3. Chenodeoxycholic acid - CHENODEOXYCHOLIC ACID LEADIANT (CAP) - EMEA/H/C/004061/SOB 003.2

Applicant: Leadiant GmbH

PRAC Rapporteur: Adam Przybylkowski

Scope: Cerebrotendinous Xanthomatosis Registry: Long term Non-Interventional Follow-up of Safety and Effectiveness of Chenodeoxycholic Acid Leadiant. (Refer also to SOB-001) In order to collect long term safety and efficacy data in patients treated with chenodeoxycholic acid, the MAH will submit the results of a study deriving from a registry of patients with inborn errors of primary bile acid synthesis due to sterol 27 hydroxylase deficiency in infants, children and adolescents aged 1 month to 18 years and adults

17.5.4. Cinacalcet - MIMPARA (CAP) - EMEA/H/C/000570/MEA 035.9

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Mari Thorn

Scope: From X-0055: Observational registry study (Study 20180204): To evaluate the risk of hypocalcaemia (e.g., clinical characteristics, laboratory variables [PTH, Ca, and P], hospitalisation due to hypocalcaemia, co-medication, cinacalcet doses) in paediatric patients

treated with cinacalcet

17.5.5. Damoctocog alfa pegol - JIVI (CAP) - EMEA/H/C/004054/ANX 001.3

Applicant: Bayer AG

PRAC Rapporteur: Bianca Mulder

Scope: MAH's response to questions on ANX 001.2 [Second Interim Report: Study number 20904 (HA-SAFE)] as adopted in January 2024

17.5.6. Erenumab - AIMOVIG (CAP) - EMEA/H/C/004447/MEA 001.3

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Kirsti Villikka

Scope: From Initial MAA: NIS - A Non-Interventional Study to examine patient characteristics and drug utilisation patterns in migraine patients treated with prophylactic drugs in the Nordic registries

17.5.7. Lenvatinib - LENVIMA (CAP) - EMEA/H/C/003727/MEA 014.7

Applicant: Eisai GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: From II-0011-G: Third annual progress report for PASS No. E7080-M000-508; HCC: To assess the severity of hepatotoxicity and factors that contribute to hepatotoxicity of lenvatinib, and the influence on overall survival in the Western population. A multicentre, observational post authorisation safety study (PASS), phase 4 study to evaluate the safety and tolerability of lenvatinib in patients with advanced or unresectable hepatocellular carcinoma (STELLAR)

17.5.8. Tozinameran - COMIRNATY (CAP) - EMEA/H/C/005735/MEA 054.2

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Liana Martirosyan

Scope: Study C4591022; Pfizer-BioNTech COVID-19 Vaccine Exposure during Pregnancy: A Non-Interventional Post-Approval Safety Study of Pregnancy and Infant Outcomes in the Organization of Teratology Information Specialists (OTIS)/MotherToBaby Pregnancy Registry

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. Glucarpidase - VORAXAZE (CAP) - EMEA/H/C/005467/S/0025 (without RMP)

Applicant: SERB S.A.S.

PRAC Rapporteur: Martin Huber

Scope: Annual reassessment of the marketing authorisation

18.1.2. Histamine dihydrochloride - CEPLENE (CAP) - EMEA/H/C/000796/S/0048 (without RMP)

Applicant: Laboratoires Delbert

PRAC Rapporteur: Eamon O'Murchu

Scope: Annual reassessment of the marketing authorisation

18.1.3. Susoctocog alfa - OBIZUR (CAP) - EMEA/H/C/002792/S/0056 (without RMP)

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Gabriele Maurer

Scope: Annual reassessment of the marketing authorisation

18.1.4. Tabelecleucel - EBVALLO (CAP) - EMEA/H/C/004577/S/0008 (without RMP)

Applicant: Pierre Fabre Medicament, ATMP

PRAC Rapporteur: Amelia Cupelli

Scope: Annual reassessment of the marketing authorisation

18.1.5. Tagraxofusp - ELZONRIS (CAP) - EMEA/H/C/005031/S/0025 (without RMP)

Applicant: Stemline Therapeutics B.V.

PRAC Rapporteur: Bianca Mulder

Scope: Annual reassessment of the marketing authorisation

18.1.6. Tecovirimat - TECOVIRIMAT SIGA (CAP) - EMEA/H/C/005248/S/0010 (without RMP)

Applicant: SIGA Technologies Netherlands B.V.

PRAC Rapporteur: Martin Huber

Scope: Annual reassessment of the marketing authorisation

18.2. Conditional renewals of the marketing authorisation

18.2.1. Avapritinib - AYVAKYT (CAP) - EMEA/H/C/005208/R/0034 (without RMP)

Applicant: Blueprint Medicines (Netherlands) B.V.

PRAC Rapporteur: Bianca Mulder

Scope: Conditional renewal of the marketing authorisation

18.2.2. Epcoritamab - TEPKINLY (CAP) - EMEA/H/C/005985/R/0004 (without RMP)

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Monica Martinez Redondo

Scope: Conditional renewal of the marketing authorisation

18.2.3. Imlifidase - IDEFIRIX (CAP) - EMEA/H/C/004849/R/0020 (without RMP)

Applicant: Hansa Biopharma AB

PRAC Rapporteur: Bianca Mulder

Scope: Conditional renewal of the marketing authorisation

18.2.4. Larotrectinib - VITRAKVI (CAP) - EMEA/H/C/004919/R/0035 (without RMP)

Applicant: Bayer AG

PRAC Rapporteur: Rugile Pilviniene

Scope: Conditional renewal of the marketing authorisation

18.2.5. Tafasitamab - MINJUVI (CAP) - EMEA/H/C/005436/R/0015 (without RMP)

Applicant: Incyte Biosciences Distribution B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Conditional renewal of the marketing authorisation

18.2.6. Valoctocogene roxaparvovec - ROCTAVIAN (CAP) - EMEA/H/C/005830/R/0011 (with RMP)

Applicant: BioMarin International Limited, ATMP

PRAC Rapporteur: Bianca Mulder

Scope: Conditional renewal of the marketing authorisation

18.3. Renewals of the marketing authorisation

18.3.1. Arsenic trioxide - ARSENIC TRIOXIDE ACCORD (CAP) - EMEA/H/C/005175/R/0009 (without RMP)

Applicant: Accord Healthcare S.L.U.

PRAC Rapporteur: Tiphaine Vaillant

Scope: 5-year renewal of the marketing authorisation

18.3.2. Bortezomib - BORTEZOMIB FRESENIUS KABI (CAP) - EMEA/H/C/005074/R/0010 (without RMP)

Applicant: Fresenius Kabi Deutschland GmbH

PRAC Rapporteur: Amelia Cupelli

Scope: 5-year renewal of the marketing authorisation

18.3.3. Cannabidiol - EPIDYOLEX (CAP) - EMEA/H/C/004675/R/0031 (with RMP)

Applicant: Jazz Pharmaceuticals Ireland Limited

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: 5-year renewal of the marketing authorisation

18.3.4. Deferasirox - DEFERASIROX MYLAN (CAP) - EMEA/H/C/005014/R/0013 (with RMP)

Applicant: Mylan Pharmaceuticals Limited

PRAC Rapporteur: Tiphaine Vaillant

Scope: 5-year renewal of the marketing authorisation

18.3.5. Upadacitinib - RINVOQ (CAP) - EMEA/H/C/004760/R/0051 (without RMP)

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Petar Mas

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 13-16 May 2024 PRAC meeting, which was held remotely.

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Sabine Straus	Chair	The Netherlands	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	
Petar Mas	Member	Croatia	No interests declared	
Barbara Bytyqi	Member	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	
Kirsti Villikka	Member	Finland	No interests declared	
Kimmo Jaakkola	Alternate	Finland	No interests declared	
Tiphaine Vaillant	Member	France	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Nathalie Gault	Alternate	France	No interests declared	
Martin Huber	Member (Vice-Chair)	Germany	No interests declared	
Gabriele Maurer	Alternate	Germany	No restrictions applicable to this meeting	
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:	<p>14.1.1 Adagrasib – KRAZATI</p> <p>15.3.5. Apixaban - ELIQUIS (CAP) - EMEA/H/C/002148/X/0089/G</p> <p>15.3.21. Lisocabtagene maraleucel - BREYANZI (CAP) - EMEA/H/C/004731/II/0036/G</p> <p>15.3.24. Ozanimod - ZEPOSIA (CAP) - EMEA/H/C/004835/II/0023</p> <p>16.1.31. Mavacamten - CAMZYOS (CAP) - PSUSA/00000074/202310</p> <p>17.5.1. Abatacept - ORENCIA (CAP) - EMEA/H/C/000701/MEA 048.12</p>
Melinda Palfi	Alternate	Hungary	No interests declared	
Guðrún Þengilsdóttir	Alternate	Iceland	No restrictions applicable to this meeting	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Rhea Fitzgerald	Member	Ireland	No interests declared	
Amelia Cupelli	Member	Italy	No interests declared	
Zane Neikena	Member	Latvia	No interests declared	
Rugile Pilviniene	Member	Lithuania	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:	<p>3.3.1. Hydroxyprogesterone (NAP) - EMEA/H/A-31/1528</p> <p>4.2.1. Aflibercept - EYLEA (CAP) - EMEA/H/C/002392/SDA/023, YESAFILI (CAP) - EMEA/H/C/006022/SDA/002</p> <p>15.3.2. Aflibercept - EYLEA (CAP) - EMEA/H/C/002392/II/0090</p> <p>16.1.38. Regorafenib - STIVARGA (CAP) - PSUSA/00010133/202309</p> <p>16.2.1. Iloprost - VENTAVIS (CAP); NAP -</p>

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				PSUSA/00001724/202309 17.5.5. Damoctocog alfa pegol - JIVI (CAP) - EMEA/H/C/004054/ANX 001.3 18.2.4. Larotrectinib - VITRAKVI (CAP) - EMEA/H/C/004919/R/0035 (without RMP)
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	
Marjetka Plementas	Alternate	Slovenia	No interests declared	
Maria del Pilar Rayon	Member	Spain	No interests declared	
Monica Martinez Redondo	Alternate	Spain	No interests declared	
Ulla Wändel Liminga	Member	Sweden	No interests declared	
Mari Thorn	Alternate	Sweden	No restrictions	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			applicable to this meeting	
Annalisa Capuano	Member	Independent scientific expert	No interests declared	
Milou-Daniel Drici	Member	Independent scientific expert	No interests declared	
Teresa Herdeiro	Member	Independent scientific expert	No interests declared	
Tania Schink	Member	Independent scientific expert	No participation in discussion, final deliberations and voting on:	17.2.9. Romosozumab - EVENITY (CAP) - EMEA/H/C/004465/ MEA 002.10 17.2.10. Romosozumab - EVENITY (CAP) - EMEA/H/C/004465/ MEA 003.8
Hedvig Marie Egeland Nordeng	Member	Independent scientific expert	No restrictions applicable to this meeting	
Roberto Frontini	Member	Healthcare Professionals' Representative	No restrictions applicable to this meeting	
Salvatore Antonio Giuseppe Messina	Alternate	Healthcare Professionals' Representative	No interests declared	
Michal Rataj	Alternate	Patients' Organisation Representative	No interests declared	
Els Beghein	Expert	Belgium	No interests declared	
Christelle Bizimungu	Expert	Belgium	No restrictions applicable to this meeting	
Laurence de Fays	Expert	Belgium	No interests declared	
Ivana Ljubičić	Expert	Croatia	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Lucie Skálová	Expert	Czechia	No interests declared	
Kirsten Egebjerg Juul	Expert	Denmark	No interests declared	
Frederikke Hillebrand Laustsen	Expert	Denmark	No restrictions applicable to this meeting	
Mette Hjorslev Knudgaard	Expert	Denmark	No interests declared	
Aviaja Højegaard Ammentorp	Expert	Denmark	No interests declared	
Kira Rosenkilde Underbjerg	Expert	Denmark	No interests declared	
Moritz Sander	Expert	Denmark	No interests declared	
Helene Stenbæk Hansen	Expert	Denmark	No restrictions applicable to this meeting	
Cécile Choquet	Expert	France	No interests declared	
Pauline Dayani	Expert	France	No interests declared	
Camille De-Kervasdoue	Expert	France	No interests declared	
Vincent Gazin	Expert	France	No interests declared	
Laurence Girod-Gerin	Expert	France	No interests declared	
Ludivine Martin	Expert	France	No interests declared	
Carline Terendij	Expert	France	No interests declared	
Jelena Katic	Expert	Germany	No interests declared	
Dennis Lex	Expert	Germany	No interests declared	
Anne-Charlotte Lübrow	Expert	Germany	No interests declared	
Gareth Bowen	Expert	Ireland	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Aine McKenna	Expert	Ireland	No interests declared	
Patrizia Felicetti	Expert	Italy	No interests declared	
Carmela Macchiarulo	Expert	Italy	No interests declared	
Pasquale Marchione	Expert	Italy	No interests declared	
Elena Matarangolo	Expert	Italy	No interests declared	
Fiorella Petronzelli	Expert	Italy	No restrictions applicable to this meeting	
Serena Marchetti	Expert	Netherlands	No interests declared	
Paul ten Berg	Expert	Netherlands	No interests declared	
Susanne Dertz	Expert	Norway	No interests declared	
Gunnar Rimul	Expert	Norway	No interests declared	
Cathrine Wisbech	Expert	Norway	No restrictions applicable to this meeting	
Consuelo Argumánez	Expert	Spain	No restrictions applicable to this meeting	
Natividad Galiana	Expert	Spain	No restrictions applicable to this meeting	

Representatives from the European Commission attended the meeting

Observers from FDA (USA), Health Canada (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:

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>