10 March 2022
EMA/PRAC/139868/2022
Human Medicines Division

Pharmacovigilance Risk Assessment Committee (PRAC)

Minutes of the meeting on 07-10 June 2021

Chair: Sabine Straus – Vice-Chair: Martin Huber

Disclaimers

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

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

Note on access to documents

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

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1. Introduction

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

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

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

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

The PRAC Chair announced that it was the last PRAC meeting for Birgitta Grundmark, Antoine Pariente and Stefan Weiler as independent experts appointed by the European Commission (EC). The PRAC Chairperson also announced that it was the last PRAC meeting for Amelia Cupelli as the member for Italy, leaving the position of member vacant until further notice. PRAC thanked them for their contribution to the work of PRAC.

1.2. Agenda of the meeting on 07-10 June 2021

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

1.3. Minutes of the previous meeting on 03-06 May 2021

The minutes were adopted with some amendments received during the consultation phase and will be published on the EMA website.

Post-meeting note: the PRAC minutes of the meeting held on 03-06 May 2021 were published on the EMA website on 24 March 2022 (EMA/PRAC/121854/2022).

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

2.1. Newly triggered procedures

None

2.2. Ongoing procedures

None

2.3. Procedures for finalisation

None

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

3.1. Newly triggered procedures

None

3.2. Ongoing procedures

3.2.1. Betibeglogene autotemcel – ZYNTEGLO (CAP) – EMEA/H/A-20/1504

Applicant: Bluebird bio (Netherlands) B.V.; ATMP[1]

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

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

Background

A referral procedure under Article 20 of Regulation (EC) No 726/2004 is ongoing for Zynteglo (betibeglogene autotemcel) as part of the review initiated following the report of a case of acute myeloid leukaemia (AML) in a patient treated for sickle cell disease with a related investigational drug, bb1111. For further background, see PRAC minutes March 2021.

Summary of recommendation(s)/conclusions

- The PRAC adopted a list of outstanding issues (LoOI) to be addressed by the MAH in accordance with a revised timetable (EMA/PRAC/104559/2021 Rev. 1).

3.3. Procedures for finalisation

None

3.4. Re-examination procedures[2]

None

3.5. Others

None

[1] Advanced therapy medicinal product
[2] Re-examination of PRAC recommendation under Article 32 of Directive 2001/83/EC

4. Signals assessment and prioritisation[3]

4.1. New signals detected from EU spontaneous reporting systems

See also Annex I 14.1.

4.1.1. Coronavirus (COVID-19) mRNA[4] vaccine (nucleoside-modified) - COMIRNATY (CAP)

Applicant(s): BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Signal of myocarditis and pericarditis

Action: For adoption of PRAC recommendation

EPITT 19712 – New signal

Lead Member State(s): NL

Background

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

In the context of the fifth monthly summary safety report (MSSR) for Comirnaty (COVID-19 mRNA vaccine (nucleoside-modified)), the MAH performed a review of cases of myocarditis and pericarditis. For further background, see 6.6.1.

Discussion

Based on the review of cases myocarditis and pericarditis within the fifth MSSR and from case reports in EudraVigilance, PRAC considered that a further in-depth evaluation is warranted due to the suggestive time-to-onset, age and gender distribution. Therefore, PRAC agreed that further evaluation of the signal of myocarditis and pericarditis is warranted.

Summary of recommendation(s)

- The MAH for Comirnaty (COVID-19 mRNA vaccine (nucleoside-modified)) should submit to EMA, within 10 days, a review of all cases of myocarditis together with a causality assessment and exploration of possible risk factors taking into account the gender, age and dose distribution of reported cases. The MAH should also discuss possible mechanisms by which the vaccine may cause myocarditis. The MAH should propose to update the product information/RMP as warranted.
- The MAH for Comirnaty (COVID-19 mRNA vaccine (nucleoside-modified)) should submit to EMA, within 10 days, a review of all cases of pericarditis together with a causality assessment and exploration of possible risk factors taking into account the gender, age and dose distribution of reported cases. The MAH should also discuss possible

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

mechanisms by which the vaccine may cause pericarditis. The MAH should propose to update the product information/RMP as warranted.

- A 15-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.1.2. Coronavirus (COVID-19) mRNA[5] vaccine (nucleoside-modified) - COVID-19 VACCINE MODERNA (CAP)

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

PRAC Rapporteur: Hans Christian Siersted

Scope: Signal of myocarditis and pericarditis

Action: For adoption of PRAC recommendation

EPITT 19713 – New signal

Lead Member State(s): DK

Background

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

In the context of the fourth monthly summary safety report (MSSR) for COVID-19 Vaccine Moderna (COVID-19 mRNA vaccine (nucleoside-modified)), the MAH performed a review of cases of myocarditis and pericarditis. For further background, see 6.6.2. 6.6.1.

Discussion

Based on the review of cases myocarditis and pericarditis within the fourth MSSR and from case reports in EudraVigilance, PRAC considered that a further in-depth evaluation is warranted due to the suggestive time-to-onset, age and gender distribution. Therefore, PRAC agreed that further evaluation of the signal of myocarditis and pericarditis is warranted.

Summary of recommendation(s)

- The MAH for COVID-19 Vaccine Moderna (COVID-19 mRNA vaccine (nucleoside-modified)) should submit to EMA, within 10 days, a review of all cases of myocarditis together with a causality assessment and exploration of possible risk factors taking into account the gender, age and dose distribution of reported cases. The MAH should also discuss possible mechanisms by which the vaccine may cause myocarditis. The MAH should propose to update the product information/RMP as warranted.
- The MAH for COVID-19 Vaccine Moderna (COVID-19 mRNA vaccine (nucleoside-modified)) should submit to EMA, within 10 days, a review of all cases of pericarditis together with a causality assessment and exploration of possible risk factors taking into account the gender, age and dose distribution of reported cases. The MAH should also discuss possible mechanisms by which the vaccine may cause pericarditis. The MAH should propose to update the product information/RMP as warranted.

[5] Messenger ribonucleic acid

- A 15-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.2. New signals detected from other sources

None

4.3. Signals follow-up and prioritisation

4.3.1. Cannabidiol – EPIDYOLEX (CAP); calcineurin inhibitors[6]: ciclosporin (NAP); tacrolimus - ADVAGRAF (CAP), ENVARSUS (CAP), MODIGRAF (CAP), TACFORIUS (CAP), NAP mammalian target of rapamycin (mTOR) inhibitors[7]: everolimus – AFINITOR (CAP), VOTUBIA (CAP), NAP; sirolimus – RAPAMUNE (CAP); temsirolimus – TORISEL (CAP), NAP

Applicant(s): Astellas Pharma Europe B.V. (Advagraf, Modigraf), Chiesi Farmaceutici S.p.A. (Envarsus), GW Pharma (International) B.V. (Epidyolex), Novartis Europharm Limited (Afinitor, Votubia), Pfizer Europe MA EEIG (Rapamune, Torisel), Teva B.V. (Tacforius), various

PRAC Rapporteur: Ronan Grimes

Scope: Signal of drug interaction with cannabidiol leading to calcineurin inhibitors and mTOR inhibitors serum levels increased and toxicity

EPITT 19614 – Follow-up to November 2020

Background

For background information, see PRAC minutes of PRAC minutes November 2020[8].

The MAH for the originator products containing temsirolimus and sirolimus respectively submitted a review on the signal of drug interaction with cannabidiol leading to calcineurin inhibitors (ciclosporin, tacrolimus) and mammalian target of rapamycin (mTOR) inhibitors (everolimus, sirolimus, temsirolimus) serum levels increased and toxicity. The review was assessed by the Rapporteur.

Discussion

PRAC considered the regulatory review from the MAH of the originator products containing temsirolimus and sirolimus, additional evidence identified for tacrolimus and everolimus together with the Rapporteur's assessment. PRAC agreed that the evidence remains sufficient to recommend the inclusion of information regarding the risk of interaction with cannabidiol in the product information of medicinal products for systemic use containing calcineurin inhibitors or mTOR inhibitors. Therefore, PRAC agreed to request the MAHs for originator medicinal products containing systemic calcineurin inhibitors and mTOR inhibitors to submit further evidence before reaching a final recommendation.

Summary of recommendation(s)

- The MAHs for originator medicinal products containing systemic calcineurin inhibitors (ciclosporin, tacrolimus) and mTOR inhibitors (everolimus, sirolimus, temsirolimus)

[6] For systemic use
[7] For systemic use
[8] Held 26-29 October 2020

should submit to EMA, within 60 days, a discussion on any new relevant data concerning the interaction with cannabidiol which may have emerged since the last PRAC recommendation and comments on a proposed wording for implementation in the respective product information.

4.3.2. Ceftriaxone (NAP)

Applicant(s): various

PRAC Rapporteur: Zane Neikena

Scope: Signal of hepatitis

EPITT 19603 – Follow-up to February 2021

Background

For background information, see PRAC minutes February 2021.

The MAH of the originator ceftriaxone-containing product(s) replied to the request for information on the signal of hepatitis and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence from EudraVigilance and literature, additional data submitted by the MAH of the originator ceftriaxone-containing product(s), together with the Rapporteur's assessment and taking into account the plausible biological mechanism, PRAC agreed that there is sufficient evidence to establish a causal association between treatment with ceftriaxone and hepatotoxicity. Therefore, PRAC agreed that an update of the product information is warranted to add hepatitis and hepatitis cholestatic as undesirable effects with a frequency not known.

Summary of recommendation(s)

- The MAHs for ceftriaxone-containing product(s) should submit to the National Competent Authorities (NCAs) of the Member States, within 60 days, a variation to amend[9] the product information.

For the full PRAC recommendation, see EMA/PRAC/319259/2021 published on 05 July 2021 on the EMA website.

4.3.3. Coronavirus (COVID-19) vaccine (ChAdOx1-S [recombinant]) - VAXZEVRIA (CAP) - EMEA/H/C/005675/SDA/047

Applicant(s): AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: Signal of capillary leak syndrome

EPITT 19672 – Follow-up to April 2021

Background

For background information, see PRAC minutes April 2021.

[9] Update of SmPC section 4.8. The package leaflet is to be updated accordingly

The MAH replied to the request for information on the signal of capillary leak syndrome (CLS) and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence from case reports in EudraVigilance, the responses from the MAH together with the Rapporteur's assessment, PRAC agreed that there is at least a reasonable possibility that vaccination with Vaxzevria (COVID-19 vaccine (ChAdOx1-S [recombinant]) may be associated with very rare cases of CLS. Therefore, PRAC agreed that an update of the product information is warranted to add CLS as a contraindication to vaccination with Vaxzevria (COVID-19 vaccine (ChAdOx1-S [recombinant]) in individuals who previously experienced episodes of CLS, as a warning and as an undesirable effect with a frequency not known. PRAC also agreed that further evaluation on the mechanism leading to CLS is warranted.

Summary of recommendation(s)

- The MAH for Vaxzevria (COVID-19 vaccine (ChAdOx1-S [recombinant]) should submit to EMA, within 15 days, a variation to amend[10] the product information.
- PRAC agreed on the content of a further direct healthcare professional communication (DHPC) along with a communication plan for its distribution.
- The MAH for Vaxzevria (COVID-19 vaccine (ChAdOx1-S [recombinant]) should submit to EMA, within 30 days, a discussion on hypotheses for a mechanism leading to CLS following vaccination. In addition, the MAH should discuss whether additional data are needed to document the inflammatory response following immunisation with Vaxzevria (COVID-19 vaccine (ChAdOx1-S [recombinant]).
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

For the full PRAC recommendation, see EMA/PRAC/319259/2021 published on 05 July 2021 on the EMA website.

4.3.4. Olanzapine - OLANZAPINE APOTEX (CAP); OLANZAPINE GLENMARK (CAP); OLANZAPINE GLENMARK EUROPE (CAP); OLANZAPINE MYLAN (CAP); OLANZAPINE TEVA (CAP); OLAZAX (CAP); OLAZAX DISPERZI (CAP); ZALASTA (CAP); ZYPADHERA (CAP) - EMEA/H/C/000890/SDA/030; ZYPREXA (CAP) - EMEA/H/C/000115/SDA/051; ZYPREXA VELOTAB (CAP) - EMEA/H/C/000287/SDA/044; NAP

Applicant(s): Apotex Europe BV (Olanzapine Apotex), Eli Lilly Nederland B.V. (Zypadhera, Zyprexa, Zyprexa Velotab), Glenmark Arzneimittel GmbH (Olanzapine Glenmark, Olanzapine Glenmark Europe), Glenmark Pharmaceuticals (Olazax, Olazax Disperzi), Krka, d.d., Novo mesto (Zalasta), Mylan S.A.S (Olanzapine Mylan); Teva B.V. (Olanzapine Teva), various

PRAC Rapporteur: Kimmo Jaakkola

Scope: Signal of cardiomyopathy

EPITT 19663 – Follow-up to February 2021

[10] Update of SmPC sections 4.3, 4.4 and 4.8. The package leaflet is to be updated accordingly

Background

For background information, see PRAC minutes February 2021.

The MAH for the originator medicinal product containing olanzapine replied to the request for information on the signal of cardiomyopathy and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence in databases including EudraVigilance, the literature, data submitted by the MAH for the originator medicinal product containing olanzapine regarding the risk of cardiomyopathy associated with olanzapine together with the Rapporteur's assessment, PRAC considered that at this stage, there is insufficient evidence to establish a causal association between olanzapine use and cardiomyopathy in light of the current knowledge.

Summary of recommendation(s)

- The MAHs of olanzapine-containing products should continue to monitor cases of cardiomyopathy as part of routine safety surveillance.

4.3.5. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/SDA/016

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Signal of major adverse cardiovascular events (MACE) and malignancies excluding non-melanoma skin cancer (NMSC) from a clinical trial[11]

EPITT 19382 – Follow-up to March 2021

Background

For background information, see PRAC minutes March 2021.

The MAH replied to the request for information on the signal of major adverse cardiovascular events (MACE) and malignancies excluding non-melanoma skin cancer (NMSC) and the responses were assessed by the Rapporteur.

Discussion

Having considered the data from completed study A3921133 and the responses submitted by the MAH together with the Rapporteur's assessment, PRAC agreed on an increased risk of non-fatal myocardial infarction (MI) and malignancies excluding NMSC with tofacitinib compared to tumour necrosis fibrosis (TNF) inhibitors. In order to minimise the risk of MI and malignancies in relation to tofacitinib, PRAC recommended that use of tofacitinib in patients with risk factors for MI and malignancies should be only considered if no alternative treatment options are available. Overall, PRAC also considered that the relevance of these findings is not considered limited to patients with moderate to severe rheumatoid arthritis, but they also apply to other approved indications of tofacitinib. Therefore, PRAC agreed that an update of the product information is warranted in order to include relevant risk minimisation measures to minimise the risks of MI and malignancies in clinical practice.

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

Summary of recommendation(s)

- The MAH for Xeljanz (tofacitinib) should submit to EMA, within 60 days, a variation to amend[12] the product information.
- The PRAC agreed on the content of a further direct healthcare professional communication (DHPC) along with a communication plan for its distribution.
- The MAH for Xeljanz (tofacitinib) should submit to EMA, within 60 days, an updated RMP to include lung cancer, lymphoma and MI as important identified risks. These risks should be evaluated as study outcomes in relevant ongoing PASS studies. The protocol of the drug utilisation study, study A3921321[13], should be updated to evaluate the effectiveness of new risk minimisation measures (RMM). Furthermore, the key elements of the existing additional RMM (i.e. healthcare professional (HCP) brochure, prescriber checklist, patient alert card) should be updated accordingly.

For the full PRAC recommendation, see EMA/PRAC/319259/2021 published on 05 July 2021 on the EMA website.

4.4. Variation procedure(s) resulting from signal evaluation

None

5. Risk management plans (RMPs)

5.1. Medicines in the pre-authorisation phase

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

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

5.1.1. Abrocitinib – EMEA/H/C/005452

Scope: Treatment of moderate-to-severe atopic dermatitis in adults and adolescents 12 years and older who are candidates for systemic therapy

5.1.2. Artesunate - EMEA/H/C/005550, Orphan

Applicant: Amivas Ireland Ltd

Scope: Treatment of malaria

5.1.3. Dengue tetravalent vaccine (live, attenuated) - EMEA/H/W/005362

Scope (accelerated assessment): Prevention of dengue disease

[12] Update of SmPC sections 4.2, 4.4, 4.8 and 5.1. The package leaflet is to be updated accordingly
[13] A drug utilisation study (DUS) on the utilisation and prescribing patterns of Xeljanz (tofacitinib) in two European countries using administrative claims databases and national registries for assessment

5.1.4. Dengue tetravalent vaccine (live, attenuated) - EMEA/H/C/005155

Scope (accelerated assessment): Prevention of dengue disease

5.1.5. Enfortumab vedotin - EMEA/H/C/005392

Scope (accelerated assessment): Treatment of locally advanced (LA) or metastatic urothelial cancer (mUC)

5.1.6. Fingolimod - EMEA/H/C/005661

Scope: Treatment of multiple sclerosis

5.1.7. Glucarpidase - EMEA/H/C/005467, Orphan

Applicant: Protherics Medicines Development Europe B.V.

Scope: Treatment of patients at risk of methotrexate toxicity

5.1.8. Lonapegsomatropin - EMEA/H/C/005367, Orphan

Applicant: Ascendis Pharma Endocrinology Division A/S

Scope: Treatment of growth hormone deficiency

5.1.9. Pegcetacoplan - EMEA/H/C/005553, Orphan

Applicant: Apellis Ireland Limited

Scope: Treatment of paroxysmal nocturnal haemoglobinuria (PNH)

5.1.10. Regdanvimab - EMEA/H/C/005854

Applicant: Celltrion Healthcare Hungary Kft.

Scope: Treatment of coronavirus disease-2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

5.1.11. Ripretinib - EMEA/H/C/005614, Orphan

Applicant: Deciphera Pharmaceuticals (Netherlands) B.V.

Scope: Treatment of patients with advanced gastrointestinal stromal tumour (GIST)

5.1.12. Sacituzumab govitecan - EMEA/H/C/005182

Scope (accelerated assessment): Treatment of unresectable locally advanced or metastatic triple-negative breast cancer (mTNBC)

5.1.13. Sodium thiosulfate - EMEA/H/C/005130, PUMA[14]

Scope: Prevention of ototoxicity induced by cisplatin (CIS) chemotherapy in patients of 1 month to < 18 years of age with localized, non-metastatic, solid tumours

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

See also Annex I 15.2.

5.2.1. Pregabalin - LYRICA (CAP) - EMEA/H/C/000546/WS1919/0109; PREGABALIN PFIZER (CAP) - EMEA/H/C/003880/WS1919/0038

Applicant: Upjohn EESV

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Submission of an updated RMP (version 13.0) to include results from recently completed PASS studies, namely: 1) study A0081359: a population-based cohort study of pregabalin to characterize pregnancy outcomes; 2) study A0081106: a 12-month open-label study to evaluate the safety and tolerability of pregabalin as adjunctive therapy in paediatric subjects 1 month to 16 years of age with partial onset seizures and paediatric and adult subjects 5 to 65 years of age with primary generalized tonic-clonic seizures; 3) study A0081042: a double-blind, placebo-controlled, parallel-group, multicentre study of the efficacy and safety of pregabalin as adjunctive therapy in children 1 month through <4 years of age with partial onset seizures; 4) study A0081105: a randomized, double-blind, placebo-controlled, parallel group, multicentre trial of pregabalin as adjunctive therapy in paediatric and adult subjects with primary generalized tonic-clonic seizures. In addition, information on study A0081096: a prospective randomized 12-week controlled study of visual field change in subjects with partial seizures receiving pregabalin or placebo has been updated as well as study A0081365: a phase 4, randomised, double-blind, double-dummy, placebo- and active-controlled, single-dose, six-way crossover study to evaluate the potential for abuse with pregabalin (added as a new FDA[15]-imposed PASS). The clinical study report (CSR) for study A0081359 is included in the submission

Background

Pregabalin is a gamma-aminobutyric acid analogue indicated for the treatment of peripheral and central neuropathic pain in adults, as an adjunctive therapy in adults with partial seizures with or without secondary generalisation, and for the treatment of generalised anxiety disorder (GAD) in adults.

PRAC is evaluating a worksharing type II variation procedure for Lyrica and Pregabalin Pfizer, centrally authorised medicines containing pregabalin, to update the RMP to reflect the introduction of results from recently completed PASS studies and evaluate results from non-interventional studies, such as the population-based cohort study of pregabalin to characterize pregnancy outcomes part of the current procedure ('pregabalin pregnancy outcomes study'). 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

[14] Paediatric-use marketing authorisation(s)
[15] United States Food and Drug Administration

for adopting an opinion on this variation. For further background, see PRAC minutes October 2020[16].

Summary of advice

- The RMP for Lyrica and Pregabalin Pfizer (pregabalin) in the context of the variation procedure under evaluation by PRAC could be considered acceptable provided that an update to RMP version 13.1 and satisfactory responses to the request for supplementary information (RSI) are submitted.
- PRAC supported including in the product information detailed results of the 'pregabalin pregnancy outcomes study', including the observed major congenital malformations (MCM) prevalence rates and prevalence ratios. In addition, the MAH should provide a discussion on the high prevalence of MCM in unexposed group and further information on the propensity-score model. Moreover, the RMP should be updated to remove 'pregnancy and lactation' from the RMP as missing information. As a consequence, the MAH should provide responses to a second request for supplementary information.

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

See also Annex I 15.3.

5.3.1. Cladribine - MAVENCLAD (CAP) - EMEA/H/C/004230/II/0020

Applicant: Merck Europe B.V.

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Update of sections 4.2 and 4.4 of the SmPC in order to change posology recommendations by adding an advice on preventive measures to avoid liver injury and to add a new warning on liver function and liver injury based on a review of post-approval data in MAH's safety database, non-clinical, clinical trial data and scientific literature. The package leaflet and the RMP (version 1.6) are updated accordingly

Background

Cladribine is an immunosuppressant indicated, as Mavenclad, for the treatment of adult patients with highly active relapsing multiple sclerosis (MS) as defined by clinical or imaging features.

CHMP is evaluating a type II variation for Mavenclad, a centrally authorised product containing cladribine, to change posology recommendations by adding an advice on preventive measures to avoid liver injury and to add a new warning on liver function and liver injury based on a review of post-approval data. PRAC is responsible for providing advice to CHMP on the necessary updates to the RMP to support this variation.

Summary of advice

- The RMP for Mavenclad (cladribine) in the context of the variation procedure under evaluation by PRAC and CHMP could be considered acceptable provided that an update to RMP version 1.6 and satisfactory responses to the request for supplementary information (RSI) are submitted.

[16] Held 28 September - 01 October 2020

- PRAC considered that 'liver injury' should be added to the summary of safety concerns as an important identified risk and that there is a need to update the existing educational materials. PRAC also considered the MAH's proposal for a PASS to further explore the safety concern of liver injury. Since spontaneous case reports might not always include information on elements that are important for causality assessment, the MAH should consider instead the development of specific adverse reaction follow-up questionnaires (FUQ) in order to further characterise this risk. In addition, PRAC supported to update the existing prescriber guide and patient guide as educational materials. Finally, the MAH should propose a direct healthcare professional communication (DHPC) and communication plan to communicate to healthcare providers on the risk of liver injury.

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

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Tiphaine Vaillant

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

Background

Deferiprone is an iron chelating agent indicated, as Ferriprox, for the treatment of iron overload in patients with thalassaemia major when current chelation therapy is contraindicated or inadequate. It is also indicated in combination in patients with thalassaemia major when monotherapy with any iron chelator is ineffective, or when prevention or treatment of life-threatening consequences of iron overload (mainly cardiac overload) justifies rapid or intensive correction.

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

Summary of advice

- The RMP for Ferriprox (deferiprone) in the context of the variation procedure under evaluation by PRAC could be considered acceptable provided that an update to RMP version 14.1 and satisfactory responses to the request for supplementary information (RSI) are submitted.
- PRAC supported the inclusion of medication error to the RMP as an important potential risk. The MAH should further explore the possibility to differentiate the colour of the immediate release (IR) and MR tablets to mitigate the risk of confusion between both formulations. In addition, the MAH should discuss the possibility to add the maximum dose in the labelling, patient card and package leaflet of both formulations and should improve the visibility of the patient card attached to the outer packaging. Finally, the MAH should include a proposal for a one-time direct healthcare professional communication (DHPC) together with a communication plan.

6. Periodic safety update reports (PSURs)

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

See also Annex I 16.1.

6.1.1. Arsenic trioxide - TRISENOX (CAP) - PSUSA/00000235/202009

Applicant: Teva B.V.

PRAC Rapporteur: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

Background

Arsenic trioxide causes morphological changes and deoxyribonucleic acid (DNA) fragmentation characteristic of apoptosis in NB4 human promyelocytic leukaemia (PML) cells in vitro and also causes damage or degradation of the fusion protein pro-myelocytic leukaemia/retinoic acid receptor-alpha (PML/RAR alpha). It is indicated, as Trisenox, for induction of remission, and consolidation in adult patients with newly diagnosed low to intermediate risk acute promyelocytic leukaemia (APL) in combination with all-trans-retinoic acid (ATRA) or relapsed/refractory APL, characterised by the presence of the t(15;17) translocation and/or the presence of the PML/RAR alpha gene.

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Trisenox, a centrally authorised medicine containing arsenic trioxide, 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 Trisenox (arsenic trioxide) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- The MAH should submit to EMA, within 90 days, detailed reviews of cases of paresis, bone marrow necrosis, deafness, melanoma, pancreatic cancer, squamous cell carcinoma and toxic epidermal necrolysis. The MAH should also include a discussion on whether additional risk minimisation measures are warranted.
- The MAH should also submit to EMA, within 90 days, a variation to add a time period for contraception following the last dose of arsenic trioxide to the product information, taking into account the Safety Working Party (SWP) response document dated February 2020 on questions from CMDh on 'recommendations on the duration of contraception following the end of treatment with a genotoxic drug'. The MAH should propose an update of the product information as warranted. The variation should also include reviews on the need for pregnancy tests and on the time period for breastfeeding after the last dose of arsenic trioxide. The MAH should propose updates to the product information as warranted.

- In the next PSUR, the MAH should closely monitor the use of arsenic trioxide in the paediatric population and cases of medication errors related to confusion between formulations of arsenic trioxide.

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

6.1.2. Crizanlizumab - ADAKVEO (CAP) - PSUSA/00010888/202011 (with RMP)

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Laurence de Fays

Scope: Evaluation of a PSUSA procedure

Background

Crizanlizumab is selective immunoglobulin (Ig) G2 kappa humanised monoclonal antibody (mAb) indicated, as Adakveo, for the prevention of recurrent vaso-occlusive crises (VOCs) in sickle cell disease patients aged 16 years and older. It can be also used as an add-on therapy to hydroxyurea/hydroxycarbamide (HU/HC) or as monotherapy in patients for whom HU/HC is inappropriate or inadequate.

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Adakveo, a centrally authorised medicine containing crizanlizumab 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 Adakveo (crizanlizumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include recommendations on the management of infusion-related reactions (IRRs), to add severe pain in various locations occurring during infusion or within 24 hours of the infusion as an undesirable effect with a frequency 'not known' and to amend the existing warning on IRRs. Therefore, the current terms of the marketing authorisation(s) should be varied[17].
- In the next PSUR, the MAH should provide in the context of cases of IRRs a detailed review with causality assessment of co-reported serious undesirable effects and cases reporting unlisted undesirable effects. The MAH should also closely monitor effects on haemostasis.
- With regard to study SEG101A2405[18], the MAH should submit, within 120 days, an updated feasibility analysis together with the protocol.

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.

[17] Update of SmPC sections 4.2, 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion
[18] Sickle cell disease (SCD) registry study (listed as a category 3 study in the RMP) to evaluate long-term safety, maternal complications and pregnancy outcomes by using SCD registries

6.1.3. Delamanid - DELTYBA (CAP) - PSUSA/00010213/202010

Applicant: Otsuka Novel Products GmbH

PRAC Rapporteur: Laurence de Fays

Scope: Evaluation of a PSUSA procedure

Background

Delamanid is a nitroimidazo-oxazole derivative indicated, as Deltyba, for use as part of an appropriate combination regimen for pulmonary multi-drug resistant tuberculosis (MDR-TB) in adults, adolescents and children with a body weight of at least 30 kg when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability.

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Deltyba, a centrally authorised medicine containing delamanid, 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 Deltyba (delamanid) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAH should provide a detailed analysis of cases of hallucinations in children. In addition, the MAH should report on the status of implementation of educational material (EM) in Member States to ensure effectiveness of the additional risk minimisation measures.

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. Fostamatinib - TAVLESSE (CAP) - PSUSA/00010819/202010

Applicant: Instituto Grifols, S.A.

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

Background

Fostamatinib is a spleen tyrosine kinase inhibitor indicated, as Tavlesse, for the treatment of chronic immune thrombocytopenia (ITP) in adult patients who are refractory to other treatments.

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

- Nevertheless, the product information should be updated to include headache as an undesirable effect with a frequency 'common'. Therefore, the current terms of the marketing authorisation(s) should be varied[19].
- In the next PSUR, the MAH should provide information on undesirable effects reported following cases of medication error and off-label use.

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

6.1.5. Givosiran - GIVLAARI (CAP) - PSUSA/00010839/202011

Applicant: Alnylam Netherlands B.V.

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Givosiran is a double-stranded small interfering ribonucleic acid (siRNA) indicated, as Givlaari, for the treatment of acute hepatic porphyria (AHP) in adults and adolescents aged 12 years and older.

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Givlaari, a centrally authorised medicine containing givosiran, 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 Givlaari (givosiran) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include pancreatitis as an undesirable effect with a frequency 'common'. Therefore, the current terms of the marketing authorisation(s) should be varied[20].
- In the next PSUR, the MAH should provide a detailed review of cases of blood homocysteine increased, including a literature search, and discuss a possible mechanism of action, as well as the need for risk minimisation measures. In addition, the MAH should include a discussion on thrombotic/embolic events and whether these follow the same mechanism as pulmonary embolism. Finally, the MAH should provide an analysis of the safety profile following long-term treatment compared to short-term treatment.

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

6.1.6. Ibrutinib - IMBRUVICA (CAP) - PSUSA/00010301/202011

Applicant: Janssen-Cilag International NV

[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] 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

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

Background

Ibrutinib is a Bruton's tyrosine kinase inhibitor indicated, as Imbruvica, for the treatment of adult patients with relapsed or refractory mantle cell lymphoma, adult patients with previously untreated chronic lymphocytic leukaemia (CLL) and adult patients with Waldenström's macroglobulinaemia under certain conditions. It is also indicated, alone or in combination with bendamustine and rituximab (BR), for the treatment of adult patients with CLL who have received at least one prior therapy.

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Imbruvica, a centrally authorised medicine containing ibrutinib 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 Imbruvica (ibrutinib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add a warning on hepatic events to advise on patient's assessment prior to treatment and monitoring of the liver function and viral hepatitis status. In addition, it should be updated to include eye haemorrhage as an undesirable effect with a frequency 'uncommon'. Therefore, the current terms of the marketing authorisation(s) should be varied[21].
- In the next PSUR, the MAH should provide cumulative reviews of cases of vasculitis and of cases of hand and foot syndrome. The MAH should discuss whether an update of the product information is warranted. Also, the MAH should provide a discussion on cases of Pseudo-Richter transformation following ibrutinib interruption with a proposal to update the product information as warranted. Finally, the MAH should provide an analysis of cases of uveitis together with a discussion on the need for further risk minimisation measures as warranted.

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

6.1.7. Midostaurin - RYDAPT (CAP) - PSUSA/00010638/202010

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Evaluation of a PSUSA procedure

Background

Midostaurin is a receptor tyrosine kinase inhibitor indicated, as Rydapt, for adult patients with newly diagnosed acute myeloid leukaemia (AML) who are FLT3 mutation-positive under certain conditions. It is also indicated, for the treatment of adult patients with aggressive

[21] 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

systemic mastocytosis (ASM), systemic mastocytosis with associated haematological neoplasm (SM-AHN) or mast cell leukaemia (MCL).

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Rydapt, a centrally authorised medicine containing midostaurin 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 Rydapt (midostaurin) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include in the existing warning of pulmonary toxicity clarifications on the non-infectious aetiology of pneumonitis. It should be also updated to add interstitial lung disease/pneumonitis and electrocardiogram QT prolonged as undesirable effects with a frequency 'very common'. Therefore, the current terms of the marketing authorisation(s) should be varied[22].
- In the next PSUR, the MAH should provide a cumulative review of cases of renal colic and nephrolithiasis and discuss whether an update of the product information is warranted.

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

6.1.8. Nintedanib[23] - OFEV (CAP) - PSUSA/00010319/202010

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

Background

Nindetanib is a triple angiokinase inhibitor blocking vascular endothelial growth factor receptors (VEGFR 1-3), platelet-derived growth factor receptors (PDGFR α and ß) and fibroblast growth factor receptors (FGFR 1-3) kinase activity. It is indicated, as Ofev, for the treatment of idiopathic pulmonary fibrosis (IPF), other chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype and of systemic sclerosis associated interstitial lung disease (SSc-ILD) in adults.

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

[22] 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
[23] Respiratory indication(s) only

- Nevertheless, the product information should be updated to add thrombotic microangiopathy (TMA) as a warning. Therefore, the current terms of the marketing authorisation(s) should be varied[24].
- In the next PSUR, the MAH should provide a discussion of any adverse events reported following medication errors.

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.

6.1.9. Pegvaliase - PALYNZIQ (CAP) - PSUSA/00010761/202011

Applicant: BioMarin International Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

Background

Pegvaliase is a PEGylated recombinant phenylalanine ammonia lyase enzyme indicated, as Palynziq, for the treatment of patients with phenylketonuria (PKU) aged 16 years and older who have inadequate blood phenylalanine control despite prior management with available treatment options.

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Palynziq, a centrally authorised medicine containing pegvaliase 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 Palynziq in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include dyspnoea as an undesirable effect with a frequency 'common'. Therefore, the current terms of the marketing authorisation(s) should be varied[25].
- In the next PSUR, the MAH should provide a discussion of the publication by *Rohr et al.*[26] and any other available evidence on the use of Palynziq (pegvaliase) in breastfeeding women. The MAH should propose to update the product information as warranted. The MAH should also provide a comprehensive review of cases of dizziness and discuss the need for an update of the product information as warranted.

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

[24] Update of SmPC section 4.4 of the SmPC. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion
[25] Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion
[26] Rohr F, Kritzer A, Harding CO, Viau K, Levy HL. Discontinuation of pegvaliase therapy during maternal PKU pregnancy and postnatal breastfeeding: Aacase report. Mol Genet Metab Rep. 2020 Jan 10;22

6.1.10. Regorafenib - STIVARGA (CAP) - PSUSA/00010133/202009

Applicant: Bayer AG

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

Background

Regorafenib is an oral multi-kinase inhibitor indicated, as Stivarga, as monotherapy for the treatment of adult patients with metastatic colorectal cancer (CRC) who have been previously treated with, or are not considered candidates for available therapies and for the treatment of unresectable or metastatic gastrointestinal stromal tumours (GIST) who progressed on or are intolerant to prior treatment with imatinib and sunitinib. It is also indicated for the treatment of hepatocellular carcinoma (HCC) who have been previously treated with sorafenib.

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Stivarga, a centrally authorised medicine containing regorafenib 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 Stivarga (regorafenib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add constipation as an undesirable effect with a frequency 'very common' and to include hepatic failure as a warning and as an undesirable effect. Also, the product information should be updated to add abdominal pain and back pain as the most frequently reported types of pain. Therefore, the current terms of the marketing authorisation(s) should be varied[27].

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.

6.1.11. Remdesivir - VEKLURY (CAP) - PSUSA/00010840/202011

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

Background

Remdesivir is an antiviral medicine recommended, as Veklury, for the treatment of coronavirus disease 2019 (COVID-19) in adults and adolescents from 12 years of age and weighing at least 40 kilograms with pneumonia requiring supplemental oxygen.

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

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Veklury (remdesivir) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add sinus bradycardia as undesirable effect with a frequency of 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[28].
- In the next PSUR, the MAH should provide cumulative reviews of cases of elevated bilirubin and of delirium and seizure along with a causality assessment. The MAH should also provide details of all cases reporting possible drug-drug interactions with remdesivir, including a literature review. In addition, the MAH should provide further details on cases of acute pancreatitis. Finally, the MAH should closely monitor cases of hypersensitivity including infusion related reactions, of hepatotoxicity and of nephrotoxicity.

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.

6.1.12. Rituximab - BLITZIMA (CAP); MABTHERA (CAP); RITEMVIA (CAP); RIXATHON (CAP); RIXIMYO (CAP); RUXIENCE (CAP); TRUXIMA (CAP) - PSUSA/00002652/202011

Applicant(s): Celltrion Healthcare Hungary Kft. (Blitzima, Ritemvia, Truxima), Pfizer Europe MA EEIG (Ruxience), Roche Registration GmbH (MabThera), Sandoz GmbH (Rixathon, Riximyo)

PRAC Rapporteur: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

Background

Rituximab is a monoclonal antibody indicated, as Blitzima, Mabthera, Ritemvia, Rixathon, Riximyo, Ruxience, Truxima, in adults for the treatment of non-Hodgkin's lymphoma (NHL), relapsed/refractory chronic lymphocytic leukaemia (CLL), rheumatoid arthritis, granulomatosis with polyangiitis and microscopic polyangiitis as well as pemphigus vulgaris under certain conditions. Blitzima, Ritemvia, Ruxience, Truxima in combination with chemotherapy are indicated for the treatment of paediatric patients (aged ≥ 6 months to < 18 years old) with previously untreated advanced stage CD[29]20 positive diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma (BL)/Burkitt leukaemia (mature B-cell acute leukaemia) (BAL) and Burkitt-like lymphoma (BLL).

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of Blitzima, Mabthera, Ritemvia, Rixathon, Riximyo, Ruxience and Truxima, centrally authorised medicines containing rituximab and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

[28] 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
[29] Cluster of differentiation

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Blitzima, Mabthera, Ritemvia, Rixathon, Riximyo, Ruxience and Truxima containing rituximab in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the existing warning on malignancy to state that data do not show any increased risk of malignancy in autoimmune indications. In addition, the product information should be updated to include updated information on breast-feeding. Therefore, the current terms of the marketing authorisation(s) should be varied[30].
- In the next PSUR, the MAHs should provide cumulative reviews of cases of acute polyneuropathy/Guillain-Barré syndrome, enteroviral meningoencephalitis, thromboembolic events and psoriatic conditions, including data from clinical trials, post-marketing setting and literature. The MAHs should discuss the need to update the product information and/or RMP as warranted. In addition, the MAHs should provide a detailed review and discussion on the rationale for the recommendation on breastfeeding after treatment with rituximab, including bioavailability data in breast milk, breast fed infant and elimination data. Moreover, the MAHs should provide an updated cumulative review on breastfeeding and any new information regarding rituximab excretion into breastmilk, including data from post-marketing setting, clinical trials and literature and discuss the need for an update of the product information as warranted.

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

6.1.13. Sulfur hexafluoride - SONOVUE (CAP) - PSUSA/00002822/202009

Applicant: Bracco International B.V.

PRAC Rapporteur: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

Background

Sulfur hexafluoride is an ultrasound contrast agent used, as SonoVue, with ultrasound imaging to enhance the echogenicity of the blood, or of fluids in the urinary tract which results in an improved signal to noise ratio.

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of SonoVue, a centrally authorised medicine containing sulfur hexafluoride 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 SonoVue (sulfur hexafluoride) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the existing warning on hypersensitivity reactions in order to highlight the role of polyethylene glycol (PEG) in the occurrence of these reactions and to strengthen the existing wording on

[30] Update of SmPC sections 4.4 and 4.6. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion

hypersensitivity reactions. Therefore, the current terms of the marketing authorisation(s) should be varied[31].

- In the next PSUR, the MAH should closely monitor all cases with fatal outcome, regardless of the cause of death. Also, the MAH should provide an analysis of the reporting rates of the most serious allergic and anaphylactic reactions, including life-threatening reactions with fatal outcomes.

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.

6.1.14. Susoctocog alfa - OBIZUR (CAP) - PSUSA/00010458/202011 (with RMP)

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

Background

Susoctocog alfa is a recombinant, B-domain deleted, porcine sequence factor VIII indicated, as Obizur, for the treatment of bleeding episodes in adult patients with acquired haemophilia caused by antibodies to factor VIII.

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Obizur, a centrally authorised medicine containing susoctocog alfa 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 Obizur (susoctocog alfa) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include information on dosing and immunogenicity as warnings relating to anamnestic reaction and lack of efficacy. Therefore, the current terms of the marketing authorisation(s) should be varied[32].
- In the next PSUR, the MAH should include a detailed review of case follow-up on lack of drug effect (LODE).

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.

[31] 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
[32] Update of SmPC sections 4.4, 4.8 and 5.1. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion

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. Posaconazole - NOXAFIL (CAP); NAP - PSUSA/00002480/202010

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

PRAC Rapporteur: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

Background

Posaconazole is a broad-spectrum triazole antifungal agent indicated for the treatment of fungal infections and the prophylaxis of invasive fungal infections under certain conditions.

Based on the assessment of the PSURs, PRAC reviewed the benefit-risk balance of Noxafil, a centrally authorised medicine containing posaconazole, and nationally authorised medicine(s) containing posaconazole and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of posaconazole-containing products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include information on drug-drug interaction between posaconazole and all-trans retinoic acid (ATRA) also called tretinoin. Therefore, the current terms of the marketing authorisations should be varied[33].
- In the next PSUR, the MAH Merck should provide a discussion on reported cases of off-label use.

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

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

See also Annex I 16.3.

6.3.1. Baclofen[34] (NAP) - PSUSA/00000294/202009

Applicant(s): various

PRAC Lead: Ronan Grimes

Scope: Evaluation of a PSUSA procedure

[33] Update of SmPC section 4.5. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion
[34] Oral use only

Background

Baclofen is an antispastic agent acting at the spinal level indicated, for oral use, for the treatment of spasticity of voluntary muscle resulting from disorders such as multiple sclerosis, spinal lesions, cerebral palsy, cerebrovascular accidents, traumatic head injury and meningitis under certain conditions. It is also indicated for the treatment of alcohol use disorder (AUD) in one Member State.

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 products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add tinnitus as a symptom of overdose with baclofen and to amend the existing warning on renal impairment to reflect the risk of baclofen toxicity at a dose of 5 mg/day in patients with end stage renal failure undergoing chronic haemodialysis. Therefore, the current terms of the marketing authorisation(s) should be varied[35].
- In the next PSUR, the MAHs should include cumulative analyses of the risk of encephalopathy, of signs and symptoms of baclofen overdose and of severe cutaneous adverse reactions (SCARs) with baclofen. Bases on the analyses, the MAHs should propose to update the product information as warranted. Finally, the MAHs should include 'suicidality/suicidal ideation' as an important potential risk in the PSUR summary of safety concerns.

Due to different safety profile of baclofen indicated in muscle spasticity from that of baclofen indicated for the treatment of AUD, the EURD list entry on 'baclofen (oral)' should be revised to 'baclofen (oral) for muscle spasticity indication' only. As baclofen indicated for the treatment of AUD is only authorised in one Member State, future PSUR will be assessed at the national level. The frequency of PSUR submission of 'baclofen (oral) for muscle spasticity indication' should be revised from two-yearly to three-yearly and the next PSUR should be submitted to EMA within 90 days of the data lock point. The list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC is updated accordingly.

6.3.2. Desogestrel, ethinylestradiol (NAP) - PSUSA/00000967/202009

Applicant(s): various

PRAC Lead: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

Background

Desogestrel and ethinylestradiol are steroid hormones used as combined oral contraceptives and indicated for the prevention of pregnancy under certain conditions.

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

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing desogestrel/ethinylestradiol 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 desogestrel/ethinylestradiol-containing products in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAHs should provide a review of cases of glioma.

PRAC noted that there is inconsistent information regarding angioedema in the product information of ethinylestradiol-containing medicinal products as a single agent and fixed dose combinations and considered that the product information of these medicinal products should be updated to add hereditary and acquired angioedema as a warning and as an undesirable effect with a frequency 'not known'. Further consideration should be given at the level of CMDh.

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

6.3.3. Hydroxyzine (NAP); hydroxyzine chloride (NAP), hydroxyzine pamoate (NAP)[36] - PSUSA/00001696/202011

Applicant(s): various

PRAC Lead: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

Background

Hydroxyzine is a piperazine derivative indicated in the symptomatic treatment of anxiety in adults, the symptomatic treatment of pruritus in adult and paediatric population from 12 months of age, sleep disorders and anxiety in the paediatric population. It is also indicated in one Member State as a gel for the treatment of pruritus and other symptoms of localised pruritic skin disorders, for insect bites, and for skin irritation due to excessive sun exposure.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing hydroxyzine, hydroxyzine chloride and hydroxyzine pamoate respectively and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of hydroxyzine-, hydroxyzine chloride- and hydroxyzine pamoate-containing medicinal products in the approved indication(s) remains unchanged.

[36] Including all fixed combinations

- Nevertheless, the product information should be updated to add weight increased with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[37].
- In the next PSUR, the MAHs should closely monitor cases of drug reaction with eosinophilia and systemic symptoms (DRESS). The MAHs should also provide a review of cases of increased appetite and include a proposal to update the product information as warranted.

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

6.3.4. Perindopril (NAP) - PSUSA/00002354/202010

Applicant(s): various

PRAC Lead: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

Background

Perindopril is an angiotensin converting enzyme (ACE) inhibitor indicated for the treatment of hypertension, stable coronary artery disease by reduction of risk of cardiac events in patients with a history of myocardial infarction and/or revascularisation and for the treatment of symptomatic heart failure.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing perindopril 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 perindopril-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add the following undesirable effects: syndrome of inappropriate antidiuretic hormone secretion (SIADH), flushing, anuria and oliguria with a frequency 'rare' and depression with a frequency 'uncommon'. The product information should be also updated to amend the frequency of acute renal failure in patients with hypertension, stable coronary artery disease or symptomatic heart failure from 'very rare' to 'rare'. Therefore, the current terms of the marketing authorisation(s) should be varied[38].

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.

PRAC considered that the risk of SIADH, depression, flushing, anuria and oliguria as well as a change in frequency for acute renal failure in patients with hypertension, stable coronary

[37] 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
[38] 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

artery disease or symptomatic heart failure, is also relevant to be included in fixed dose combinations containing perindopril. Further consideration should be given at the level of CMDh.

6.3.5. Polystyrene sulfonate (NAP) - PSUSA/00002472/202010

Applicant(s): various

PRAC Lead: Jana Lukacisinova

Scope: Evaluation of a PSUSA procedure

Background

Polystyrene sulfonate is a polymer cation exchange resin indicated for the treatment of hyperkalaemia under certain conditions.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing polystyrene sulfonate 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 polystyrene sulfonate-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the existing warning on gastrointestinal stenosis and ischaemia in patients treated with polystyrene sulfonate alone or in combination with sorbitol. Therefore, the current terms of the marketing authorisation(s) should be varied[39].
- In the next PSUR, the MAH(s) should consider the inclusion of information about correct administration via feeding tube in the product information to avoid delay in hyperkalaemia treatment due to possible obstruction of feeding tube. The MAH(s) should also include a thorough review of serious gastrointestinal risks associated with the use of polystyrene sulfonate together with an evaluation of the effectiveness of current routine risk minimisation measures in place. The MAH(s) should propose to include an update of the product information as warranted.

The frequency of PSUR submission should be revised from eight-yearly to yearly and the next PSUR should be submitted to EMA within 90 days of the data lock point. The list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC is updated accordingly. MAHs of medicinal products referred to in Articles 10(1), 10a, 14, 16a of Directive 2001/83/EC as amended should submit PSUR(s).

6.4. Follow-up to PSUR/PSUSA procedures

See also Annex I 16.4.

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

6.4.1. Hydroxycarbamide - SIKLOS (CAP) - EMEA/H/C/000689/LEG 034

Applicant: Addmedica S.A.S.

PRAC Rapporteur: Laurence de Fays

Scope: Review of available data on paediatric patients < 2 years of age and on pregnancy as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00001692/202006) adopted by PRAC in January 2021

Background

Hydroxycarbamide is an orally active antineoplastic agent indicated, as Siklos, a centrally authorised product, for the prevention of vaso-occlusive crises including acute chest syndrome in adults, adolescents and children older than 2 years suffering from symptomatic sickle cell syndrome.

Following the evaluation of the most recently submitted PSUR(s) for the above-mentioned medicine(s), PRAC requested the MAH to submit a review of available data on paediatric patients < 2 years of age and on pregnancy. For further background, see PRAC minutes January 2021. The responses were assessed by the Rapporteur for further PRAC advice.

Summary of advice/conclusion(s)

- Based on the available data and the Rapporteur's assessment, PRAC agreed that the product information should be updated to implement further paediatric and pregnancy data.
- The MAH of Siklos (hydroxycarbamide) should submit to EMA, within 60 days, a variation to amend[40] the product information. The MAH should propose relevant text to update the pharmacodynamic properties to summarize the paediatric data in children < 2-year-old from the two randomised placebo-controlled clinical trials (BABY HUG[41] and NOHARM[42]) and subsequent cohort studies providing supporting efficacy and safety data where relevant. The MAH should also propose relevant text for the pregnancy section to reflect that current data do not allow to draw conclusion relevant for healthcare professionals (HCP) regarding the risk in pregnancy.

6.4.2. Hydroxycarbamide - XROMI (CAP) - EMEA/H/C/004837/LEG 005

Applicant: Nova Laboratories Ireland Limited

PRAC Rapporteur: Laurence de Fays

Scope: Review of available data on paediatric patients < 2 years of age and on pregnancy as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00001692/202006) adopted by PRAC in January 2021

Background

Hydroxycarbamide is an orally active antineoplastic agent indicated, as Xromi, a centrally authorised product, for the prevention of vaso-occlusive complications of sickle cell disease (SCD) in patients over 2 years of age.

[40] Update of SmPC sections 4.2, 4.6 and 5.1. The package leaflet is updated accordingly
[41] A multicentre, randomised, controlled trial to explore the use of hydroxycarbamide in very young children with sickle-cell anaemia
[42] A randomised, placebo-controlled, monocentric prospective parallel group study

Following the evaluation of the most recently submitted PSUR(s) for the above-mentioned medicine(s), PRAC requested the MAH to submit a review of available data on paediatric patients < 2 years of age and on pregnancy. For further background, see PRAC minutes January 2021. The responses were assessed by the Rapporteur for further PRAC advice.

Summary of advice/conclusion(s)

- Based on the available data and the Rapporteur's assessment, PRAC agreed that the product information should be updated to implement further paediatric and pregnancy data.
- The MAH of Xromi (hydroxycarbamide) should submit to EMA, within 60 days, a variation to amend[43] the product information. The MAH should propose relevant text for the pregnancy section to reflect that current data do not allow to draw conclusion relevant for healthcare professionals (HCP) regarding the risk in pregnancy.
- In the next PSUR, the MAH should discuss the need for an update of the product information regarding lactation taking into account the available data.

6.4.3. Methotrexate - JYLAMVO (CAP) - EMEA/H/C/003756/LEG 002.1

Applicant: Therakind (Europe) Limited

PRAC Rapporteur: Martin Huber

Scope: MAH's response to LEG 002 [comprehensive review of the value of performing liver biopsies as a diagnostic tool to monitor hepatotoxicity of methotrexate in non-oncologic indications as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00002014/201910) adopted in May 2020] as per the request for supplementary information (RSI) adopted in January 2021

Background

Methotrexate is a folic acid antagonist indicated, as Jylamvo a centrally authorised product, for the treatment of active rheumatoid arthritis, juvenile idiopathic arthritis (JIA), psoriasis and severe psoriatic arthritis, under certain conditions. It is also indicated in oncology, as maintenance treatment of acute lymphoblastic leukaemia (ALL) in adults, adolescents and children aged 3 years and over.

Following the evaluation of the most recently submitted PSUR(s) for the above-mentioned medicine(s), PRAC requested the MAH to submit a review of the value of performing liver biopsies as a diagnostic tool to monitor hepatotoxicity of methotrexate in non-oncologic indications. For further background, see PRAC minutes May 2020 and PRAC minutes January 2021. The initial responses together with the responses to the request for supplementary information (RSI) were assessed by the Rapporteur for further PRAC advice.

Summary of advice/conclusion(s)

- Based on the review of the available information and evidence, PRAC supported the LMS assessment, namely on non-initiation and treatment discontinuation if there are persistent or significant abnormalities in liver function tests, other non-invasive investigations of hepatic fibrosis or liver biopsies, applicability of the wording to patients

[43] Update of SmPC sections 4.2, 4.6 and 5.1. The package leaflet is updated accordingly

with Crohn's disease and agreement that it is not necessary to state the prevalence of hepatotoxicity in patients with psoriasis.

- The MAH should comment on the proposed updates[44] to the warning section of the product information. The MAH should discuss the need for an update of the package leaflet and submit a proposed wording as warranted.

6.4.4. Methotrexate - NORDIMET (CAP) - EMEA/H/C/003983/LEG 003.1

Applicant: Nordic Group B.V.

PRAC Rapporteur: Martin Huber

Scope: MAH's response to LEG 003 [comprehensive review of the value of performing liver biopsies as a diagnostic tool to monitor hepatotoxicity of methotrexate in non-oncologic indications as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00002014/201910) adopted in May 2020] as per the request for supplementary information (RSI) adopted in January 2021

Background

Methotrexate is a folic acid antagonist indicated, as Nordimet, a centrally authorised product, for the treatment of active rheumatoid arthritis, juvenile idiopathic arthritis (JIA), psoriasis and severe psoriatic arthritis, under certain conditions.

Following the evaluation of the most recently submitted PSUR(s) for the above-mentioned medicine(s), PRAC requested the MAH to submit a review of the value of performing liver biopsies as a diagnostic tool to monitor hepatotoxicity of methotrexate in non-oncologic indications. For further background, see PRAC minutes May 2020 and PRAC minutes January 2021. The initial responses together with the responses to the request for supplementary information (RSI) were assessed by the Rapporteur for further PRAC advice.

Summary of advice/conclusion(s)

- Based on the review of the available information and evidence, PRAC supported the LMS assessment, namely on non-initiation and treatment discontinuation if there are persistent or significant abnormalities in liver function tests, other non-invasive investigations of hepatic fibrosis or liver biopsies, applicability of the wording to patients with Crohn's disease and agreement that it is not necessary to state the prevalence of hepatotoxicity in patients with psoriasis.
- The MAH should comment on the proposed updates[45] to the warning section of the product information. The MAH should discuss the need for an update of the package leaflet and submit a proposed wording as warranted.

6.4.5. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/LEG 049.1

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Rhea Fitzgerald

Scope: MAH's response to LEG 049 [cumulative review of cases of major adverse cardiovascular events (MACE), including fatal cases, as requested in the conclusions of the

[44] SmPC section 4.4
[45] SmPC section 4.4

PSUR single assessment (PSUSA) procedure (PSUSA/00003085/201912) adopted in July 2020] as per the request for supplementary information (RSI) adopted in January 2021

Background

Ustekinumab is a fully human immunoglobulin (Ig)G1κ monoclonal antibody interleukin inhibitor indicated, as Stelara a centrally authorised product, for the treatment of adult patients with moderately to severely active Crohn's disease, of adult patients with moderately to severely active ulcerative colitis, of adult patients with moderately to severely active ulcerative colitis, of moderate to severe plaque psoriasis in adults, of moderate to severe plaque psoriasis in children and adolescent patients from the age of 6 years and older as well as for the treatment of active psoriatic arthritis (PsA) under certain conditions.

Following the evaluation of the most recently submitted PSUR(s) for the above-mentioned medicine(s), PRAC requested the MAH to submit further data on cases of major adverse cardiovascular events (MACE). For background, see PRAC minutes July 2020 and PRAC minutes January 2021. The initial responses together with the responses to the request for supplementary information (RSI) were assessed by the Rapporteur for further PRAC advice.

Summary of advice/conclusion(s)

- Based on the available data and the Rapporteur's assessment, PRAC agreed that the product information should be updated to add cardiovascular events as a warning.
- The MAH of Stelara (ustekinumab) should submit to EMA, within 60 days, a variation to amend[46] the product information.
- In the final report of study PSOLAR[47], the MAH should provide new user analyses of MACE and of all-cause mortality retaining non-biologics as comparator and stratified by the presence or absence of PsA.
- The MAH should continue to monitor cardiovascular events other than MACE in PSURs.

6.5. Variation procedure(s) resulting from PSUSA evaluation

6.5.1. Decitabine - DACOGEN (CAP) - EMEA/H/C/002221/II/0044, Orphan

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Tiphaine Vaillant

Scope: Update of section 4.6 of the SmPC in order to update information on fertility, pregnancy and lactation as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00009118/202005) adopted in January 2021. The package leaflet is updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives for Italy in the package leaflet and to include some editorial changes in the product information to align with standard English spelling

Background

Decitabine is a cytidine deoxynucleoside analogue indicated, as Dacogen, for the treatment of adult patients with newly diagnosed de novo or secondary acute myeloid leukaemia (AML),

[46] Update of SmPC section 4.4. The package leaflet is updated accordingly
[47] A multicentre, open registry of patients with plaque psoriasis who are candidates for systemic therapy including biologics

according to the World Health Organisation (WHO) classification, who are not candidates for standard induction chemotherapy.

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 in line with the conclusions of the PSUR single assessment (PSUSA) procedure. For background information, see PRAC minutes January 2021. PRAC is responsible for adopting an outcome based on the assessment report from the PRAC Rapporteur, to be further considered at the level of CHMP, responsible for adopting an opinion on this variation.

Summary of advice/conclusion(s)

- Based on the available data and the Rapporteur's assessment, PRAC agreed that in light of the potential teratogen risk of decitabine the inclusion of a request for a pregnancy test before the start of treatment with Dacogen (decitabine) is appropriate. PRAC also agreed with adding a six-month duration of contraception following completion of treatment with Dacogen (decitabine) in line with the recommendation of the last PSUR single assessment (PSUSA) procedure adopted in January 2021 and taking into account the Safety Working Party (SWP) response document dated February 2020 on questions from CMDh on 'recommendations on the duration of contraception following the end of treatment with a genotoxic drug'.
- PRAC agreed with the proposed amendments[48] of the product information.

6.6. Expedited summary safety reviews[49]

6.6.1. Coronavirus (COVID-19) mRNA[50] vaccine (nucleoside-modified) - COMIRNATY (CAP) - EMEA/H/C/005735/MEA 002.4

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

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

Background

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

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

Summary of advice/conclusion(s)

- In the next MSSR[51], the MAH should provide cumulative reviews and data. These include a cumulative review of cases of acute disseminated encephalomyelitis (ADEM) together

[48] Update of SmPC section 4.6. The package leaflet is updated accordingly
[49] 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
[50] Messenger ribonucleic acid
[51] Submission date on 15 June 2021

with a proposal to update the product information as warranted, the results of the observed/expected (O/E) analyses for stress cardiomyopathy as well as a detailed review of cases of trigeminal neuralgia.

- In the next PSUR, the MAH should include detailed reviews of cases of serious arrythmia, of serious acute pancreatitis, of acquired haemophilia, of menstrual disorders/haemorrhages and of hear loss. The MAH should propose to update the product information as warranted.

Regarding myocarditis and pericarditis, see under 4.1.1.

6.6.2. Coronavirus (COVID-19) mRNA[52] vaccine (nucleoside-modified) - COVID-19 VACCINE MODERNA (CAP) - EMEA/H/C/005791/MEA 011.3

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Hans Christian Siersted

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

Background

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

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

Summary of advice/conclusion(s)

- In the next MSSR[53], the MAH should provide cumulative reviews and data. These include reviews of cases of asthenic conditions, of appendicitis and of hearing loss.
- In the next PSUR, the MAH should present a discussion of cumulative cases of thrombosis in unusual locations, including cerebral venous sinus thrombosis (CVST) and splanchnic thrombosis. In addition, the MAH should include a review on exacerbation of disease in patients with autoimmune or inflammatory disorders and should comment on whether the current wording regarding the reactogenicity safety profile is still adequate in the product information. Moreover, the MAH should perform a cumulative review of cases of extensive swelling of the limb as well as an overview of cases of paraesthesia/hypoesthesia which are not considered part of anxiety-related/stress-related reactions. The MAH should propose to update the product information as warranted.

Regarding myocarditis and pericarditis, see under 4.1.2.

[52] Messenger ribonucleic acid
[53] Submission date on 15 June 2021

6.6.3. Coronavirus (COVID-19) vaccine (Ad26.COV2-S, recombinant) - COVID-19 VACCINE JANSSEN (CAP) – EMEA/H/C/005737/MEA 014.1

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Ulla Wändel Liminga

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

Background

COVID-19 vaccine (Ad26.COV2-S [recombinant]) is a monovalent vaccine composed of a recombinant, replication-incompetent human adenovirus type 26 vector that encodes a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) full-length spike (S) glycoprotein indicated as COVID-19 vaccine Janssen, a centrally authorised vaccine for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older.

PRAC assessed the second monthly summary safety report (MSSR) for COVID-19 vaccine Janssen (COVID-19 vaccine (Ad26.COV2-S [recombinant])) as part of the safety monitoring of the vaccine. At the plenary meeting, PRAC adopted its conclusions.

Summary of advice/conclusion(s)

- In the next MSSR[54], the MAH should provide cumulative reviews and data. These include reviews of diarrhoea, dizziness, lymphadenopathy, tinnitus, transient sensory changes, vomiting and Guillain-Barré syndrome (GBS). The MAH should also closely follow-up case(s) of capillary leak syndrome (CLS). For thrombotic events associated with thrombocytopenia (TTS), the MAH should refine its analyses.

6.6.4. Coronavirus (COVID-19) vaccine (ChAdOx1-S [recombinant]) - VAXZEVRIA (CAP) - EMEA/H/C/005675/MEA 027.2

Applicant: AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: Third expedited monthly summary safety report for Vaxzevria (COVID-19 vaccine (ChAdOx1-S [recombinant])) during the coronavirus disease (COVID-19) pandemic

Background

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

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

[54] Submission date on 15 June 2021

Summary of advice/conclusion(s)

- In the next MSSR[55], the MAH should provide cumulative reviews and data. These include an in-depth review of cases of Guillain-Barré syndrome (GBS) with a refined observed/expected analysis, a discussion on the biological plausibility and possible mechanism(s) for a causal association between GBS and vaccination with Vaxzevria (COVID-19 vaccine (ChAdOx1-S [recombinant]) and a proposal to update the product information as warranted. The MAH should also provide reviews of all serious cases of serious facial paralysis, hypoesthesia, paraesthesia and tremor. Regarding thrombotic events associated with thrombocytopenia (TTS), the MAH should apply the same search strategy to retrieve all cases of TTS and cases of TTS after the second dose. Moreover, the MAH should include a review of cases of acute disseminated encephalomyelitis (ADEM) and encephalitis. Furthermore, the MAH should perform reviews of cases of myocarditis and pericarditis with a discussion on risk factors and immunologic mechanism. The MAH should propose to update the product information as warranted.
- In the following MSSR[56], the MAH should provide cumulative reviews of cases of extensive limb swelling (ELS), of cases of menstrual disorders and of cases of severe cutaneous adverse reactions (SCARs).
- In the next PSUR, the MAH should provide cumulative reviews of cases of hearing loss and of trigeminal neuralgia. For the latter, the MAH should include an in-depth causality assessment and a disproportionality analysis.

7. Post-authorisation safety studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)[57]

See also Annex I 17.1.

7.1.1. Valproate (NAP) - EMEA/H/N/PSP/J/0094

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

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Protocol for a joint retrospective study of multiple European data sources characterising neurodevelopmental disorders in children exposed in utero to valproate and/or other antiepileptic drugs with long-term follow-up

Background

Sodium valproate is indicated for the treatment of epilepsy and for the treatment of manic episodes when lithium is contraindicated or not tolerated. Valproate is also indicated in some EU Member States in prophylaxis of migraine attacks.

In line with the conclusions reached in 2018 of the referral procedure under Article 31 of Directive 2001/83/EC (EMEA/H/A-31/1454) conducted by PRAC for valproate-containing medicines, MAHs were required as a condition to the marketing authorisation(s) (Annex IV) to conduct a PASS preferably based on existing registries to further characterise the foetal

[55] Submission date on 15 June 2021
[56] Submission date on 15 July 2021
[57] In accordance with Article 107n of Directive 2001/83/EC

anticonvulsant syndrome (FASC) in children with valproate in utero exposure as compared to other anti-epileptic drugs.

The MAH Sanofi-Aventis Recherche & Développement on behalf of a consortium submitted to EMA protocol version 1.0 of a PASS entitled: 'characterisation of neurodevelopmental disorders in children exposed in utero to valproate and/or other antiepileptic drugs with long-term follow-up: a retrospective study of multiple European data sources' for review by PRAC.

Endorsement/Refusal of the protocol

- PRAC, having considered the protocol version 1.0 in accordance with Article 107n of Directive 2001/83/EC, objected to the draft protocol for the above listed medicinal product(s). PRAC agreed that the PASS is non-interventional but the study design does not fulfil the study objectives at this stage.
- PRAC agreed that clarifications and complementary information are needed before drawing final conclusions on the protocol. In particular, the MAH/consortium should provide clarifications on the study sample to allow analysis at the neurodevelopmental disorders (NDD) subtype level and study time periods and duration of follow up of children. In addition, the MAH/consortium should further discuss the choice of antiepileptic drug (AED) comparators in the analyses. The MAH/consortium should also align the proposed data analysis with the defined objectives. Moreover, the possible dose-dependent risk for NDD should be investigated as valproate daily dose is an important driver for the estimated risk for major congenital malformation risk.
- The MAH/consortium should submit a revised PASS protocol within 60 days to EMA. A 60 days-assessment timetable will be followed.

7.2. Protocols of PASS non-imposed in the marketing authorisation(s)[58]

See Annex I 17.2.

7.3. Results of PASS imposed in the marketing authorisation(s)[59]

None

7.4. Results of PASS non-imposed in the marketing authorisation(s)[60]

See Annex I 17.4.

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

See Annex I 17.5.

7.6. Others

See Annex I 17.6.

[58] 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
[59] In accordance with Article 107p-q of Directive 2001/83/EC
[60] In accordance with Article 61a (6) of Regulation (EC) No 726/2004, in line with the revised variations regulation for any submission as of 04 August 2013

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

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

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

11.1.1. Levothyroxine (NAP) - DE/H/XXXX/WS/674

Applicant: Berlin Chemie AG (Menarini Group) (Berlthyrox)

PRAC Lead: Martin Huber

Scope: PRAC consultation on the need for a communication strategy in the context of a worksharing quality variation for Berlthyrox (levothyroxine) on request of Germany

Background

Levothyroxine (or L-thyroxine) is a synthetic isomeric form of the thyroid hormone, thyroxine (T4). It is used to treat thyroid hormone deficiency including the severe form known as myxedema coma.

A worksharing variation (DE/H/XXXX/WS/674) on quality aspects is currently being assessed by Germany.

In the context of the evaluation of this national worksharing variation procedure, Germany requested PRAC advice on its ongoing assessment regarding the handling of the transition period and a communication strategy to support a secure transition period to a new formulation and a communication strategy needed to ensure a secure transition.

Summary of advice

- Based on the review of the available information and the assessment from Germany, PRAC supported the need for communication measures for healthcare professionals and patients during the transition period to a new formulation of the medicinal product

containing levothyroxine to minimise the risk of thyroid imbalance and associated adverse reactions, and to ensure that patients are sufficiently informed.

- With reference to the PRAC advice dated January 2018, PRAC advised that a direct healthcare professional communication (DHPC) and a patient information sheet are useful for implementation in the framework of the ongoing procedure. PRAC agreed on the content of a DHPC and a communication plan. Additional communication information may be considered at Member States' level by National Competent Authorities (NCAs) as needed. For further background, see PRAC minutes January 2018.
- PRAC acknowledged that due to specificities of the healthcare system in each Member State, the decision on risk communication/minimisation tools of the communication package should be decided at the level of relevant NCAs.

11.2. Other requests

11.2.1. Methotrexate[61] (NAP) - DE/H/PSUFU/00002014/201910

Applicant(s): Addenda Pharma, Especialidades Farmacéuticas Centrum S.A., Gebro Pharma, medac, Morningside Healthcare Limited, Mylan, Nordic Group, Orion Pharma, Pfizer, Remedica, Rompharm, Sandoz, Teva

PRAC Lead: Martin Huber

Scope: PRAC further consultation on a PSUR follow-up (PSU FU) procedure evaluating comprehensive reviews of the value of performing liver biopsies as a diagnostic tool to monitor hepatotoxicity of methotrexate in non-oncologic indications, as discussed at PRAC and agreed by CMDh following the conclusion of the PSUSA procedure (PSUSA/00002014/201910) concluded in May 2020, on request of Germany

Background

Methotrexate is a folic acid antagonist indicated for the treatment of autoimmune disease such as active rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), psoriasis and severe psoriatic arthritis, as well as in the treatment of cancer such as lymphoblastic leukaemia (ALL), subject to certain conditions.

Based on the assessment of the recent PSUR single assessment (PSUSA) procedure for methotrexate (PSUSA/00002014/201910) concluded in May 2020, PRAC considered that reviews of the value of performing liver biopsies as a diagnostic tool to monitor hepatotoxicity of methotrexate in non-oncologic indication(s) should be further assessed.

On request of CMDh, MAH(s) for nationally approved methotrexate-containing product(s) submitted the requested safety reviews for evaluation within a worksharing periodic safety update follow-up (PSU FU) procedure. In the context of the ongoing evaluation of the PSU FU procedure (DE/H/PSUFU/00002014/201910), Germany, as lead Member State (LMS), requested PRAC to further advice on its assessment. For further background, see to PRAC minutes May 2020 and PRAC minutes January 2021.

Summary of advice

- Based on the review of the available information and evidence, PRAC supported the LMS assessment, namely on non-initiation and treatment discontinuation if there are

[61] In non-oncology indication(s)

persistent or significant abnormalities in liver function tests, other non-invasive investigations of hepatic fibrosis or liver biopsies, applicability of the wording to patients with Crohn's disease and agreement that it is not necessary to state the prevalence of hepatotoxicity in patients with psoriasis.

- PRAC supported the proposed updates[62] to the product information subject to some amendments.

12. Organisational, regulatory and methodological matters

12.1. Mandate and organisation of PRAC

12.1.1. Mandate of PRAC Chairperson and vice-Chairperson

In line with the PRAC rules of procedure (EMA/PRAC/567515/2012 Rev.2), the EMA Secretariat presented to PRAC the modalities for the prolongation of the Chair's and vice-Chair's mandates and alternatively for the election of a new Chairperson/vice-Chairperson as applicable. Should the current Chair and vice-Chair express their wish to prolong their mandates for a second three year-term, a vote for the Chair would take place in July 2021 with a mandate start in September 2021, and a vote for the vice-Chair in September 2021 with a mandate start in October 2021. Further discussion is planned in July 2021.

12.2. Coordination with EMA Scientific Committees or CMDh-v

12.2.1. Committee for Medicinal Products for Human Use (CHMP)-PRAC collaboration group – safety specification assessment responsibilities for generic medicinal products in initial marketing authorisation applications

Following a proposal by the CHMP-PRAC collaboration group, and support from CHMP and PRAC, the EMA Secretariat presented to PRAC the final agreement to transfer the assessment of RMP safety specifications for generic medicinal products (under Article 10(1) of Directive 2001/83/EC) from CHMP to PRAC for initial marketing authorisation applications (iMA) in the centralised procedure route to streamline the review process of safety specifications. The first RMP assessment reports for generics performed in full by PRAC are expected in January 2022. Relevant assessment report template will be update in due course. PRAC welcomed this change in the review process.

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

None

12.4. Cooperation within the EU regulatory network

12.4.1. Coronavirus (COVID-19) pandemic - update

The EMA Secretariat updated PRAC on the activities of the COVID-19 EMA pandemic Task Force (ETF), including an overview of ongoing clinical trials and epidemiological studies and

[62] SmPC section 4.4

initiatives, as well as a summary of medicines in development and medicines authorised for other indications, as potential treatments for COVID-19, and their safety surveillance. The EMA Secretariat also presented to PRAC an overview of COVID vaccines safety issues (Gantt chart).

12.5. Cooperation with International Regulators

None

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

None

12.7. PRAC work plan

None

12.8. Planning and reporting

None

12.9. Pharmacovigilance audits and inspections

12.9.1. Pharmacovigilance systems and their quality systems

None

12.9.2. Pharmacovigilance inspections

None

12.9.3. Pharmacovigilance audits

None

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

12.10.1. Periodic safety update reports

None

12.10.2. Granularity and Periodicity Advisory Group (GPAG)

PRAC Lead: Menno van der Elst, Maia Uusküla

On behalf of the GPAG, the EMA Secretariat presented to PRAC an update on the EURD tool and the responses to the recent Member States (MS) survey. As a reminder the EURD tool is a statistical tool to support decision making for determining PSUR frequencies of EURD list entries centred on risk-based criteria as per GVP module VII on 'Periodic safety update

report'. The EMA Secretariat presented the outcome of the MS survey. PRAC agreed with the proposed GPAG recommendation to implement the EURD list tool to generate frequencies for further EURD list entries.

12.10.3. PSURs repository

None

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

PRAC endorsed the draft revised EURD list, version June 2021, reflecting the PRAC's comments impacting on the data lock point (DLP) and PSUR submission frequencies of the substances/combinations. PRAC endorsed the newly allocated Rapporteurs for upcoming PSUSAs in accordance with the principles previously endorsed by PRAC (see PRAC minutes April 2013).

Post-meeting note: following the PRAC meeting of June 2021, the updated EURD list was adopted by CHMP and CMDh at their June 2021 meetings and published on the EMA website on 30 June 2021, see:

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

12.11. Signal management

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

None

12.12. Adverse drug reactions reporting and additional monitoring

12.12.1. Management and reporting of adverse reactions to medicinal products

None

12.12.2. Additional monitoring

None

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

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

Post-meeting note: The updated additional monitoring list was published on the EMA website on 30 June 2021, see: Home>Human Regulatory>Post-authorisation>Pharmacovigilance>Medicines under additional monitoring>List of medicines under additional monitoring

12.13. EudraVigilance database

12.13.1. Activities related to the confirmation of full functionality

None

12.13.2. Coronavirus (COVID-19) pandemic - National competent authorities (NCA) prioritisation of individual case safety report (ICSRs) submissions to EudraVigilance - Note for guidance

The EMA Secretariat presented to PRAC a draft note for guidance on National Competent Authorities (NCAs) prioritisation of individual case safety report (ICSR) submission to EudraVigilance in the context of COVID-19 pandemic. This includes a set of prioritisation criteria to mitigate impact on signal detection activities and on ability to identify rapidly new potential safety concerns related to COVID-19 vaccines or other products. The EMA Secretariat presented to PRAC a proposal for a non-urgent information (NUI) to be distributed to the Member States in this context. PRAC members were invited to provide comments until 14 June 2021. Further updates will be scheduled in due course.

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

12.14.3. Coronavirus (COVID-19) pandemic - coreRMP19: variants guidance for RMP requirements, traceability and others

As a follow-up to the discussion in May 2021 (for background, see PRAC minutes May 2021), the EMA Secretariat presented, on behalf of the EMA-PRAC drafting group, a draft revised document on 'Consideration on core requirements for RMPs of COVID-19 vaccines'. The revised document was brought in line with the current knowledge and experience with RMP and monthly summary safety reviews (MSSR) assessment for COVID-19 vaccines, requirements for variants and new strains variations. PRAC adopted the revised document.

Post-meeting note: On 16 June 2021, the coreRMP19 guidance version 3.0 (EMA/PRAC/234052/2021) was published on the EMA website.

12.14.4. Good pharmacovigilance practice (GVP) module XVI on 'Risk minimisation measures: selection of tools and effectiveness indicators' – revision 3 and addendum II on principles and methods to evaluate the effectiveness of risk minimisation measures (RMM)

PRAC Lead: Sabine Straus

Following the public consultation for draft revised GVP module XVI on 'Risk minimisation measures: selection of tools and effectiveness indicators' and addendum II on 'Methods for effectiveness evaluation' held in Q1 2021, the EMA Secretariat presented to PRAC an

overview of the comments received. PRAC discussed the comments. Follow-up discussion will be planned in due course.

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. Others

12.20.1. Good Pharmacovigilance Practice (GVP) – mid-year update

PRAC Lead: Sabine Straus

PRAC was provided with an overview of the GVP module status, including an update on the ongoing or planned work on new or revised GVP modules together with their scope, proposed timelines for PRAC discussion and adoption. This also included an outline of the planned GVP updates for inclusion in the work plan 2022.

12.20.2. Research and innovation workstream

The EMA secretariat presented to PRAC for information a summary of recent and future activities in the EMA workstream's areas of Innovation Task Force (ITF), horizon scanning and business pipeline/forecasting.

12.20.3. Titanium dioxide (E171) – European Commission (EC) letter

On request of the European Commission (EC), the EMA secretariat presented to PRAC a request to provide a scientific analysis to evaluate the impact of the European Food Safety Authority (EFSA) opinion dated May 2021 with regards to titanium dioxide (E171) on medicinal products. PRAC was informed about the timelines given to EMA for providing the final report to the EC. A drafting group of the Quality Working Party (QWP) was set up accordingly. A final report to EC is due in September 2021. PRAC noted the EC request to EMA.

13. Any other business

None

14. Annex I – Signals assessment and prioritisation[63]

14.1. New signals detected from EU spontaneous reporting systems

As per agreed criteria for new signal(s), PRAC adopted without further plenary discussion the recommendation of the Rapporteur to request MAH(s) to submit a cumulative review following standard timetables[64].

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

Applicant(s): AbbVie Deutschland GmbH & Co. KG (Humira), Amgen Europe B.V. (Amgevita), Celltrion Healthcare Hungary Kft. (Yuflyma), Fresenius Kabi Deutschland GmbH (Idacio), Mylan S.A.S (Hulio), Pfizer Europe MA EEIG (Amsparity), Samsung Bioepis NL B.V. (Imraldi), Sandoz GmbH (Hefiya, Hyrimoz)

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of acquired haemophilia

EPITT 19688 – New signal

Lead Member State(s): SE

[63] Each signal refers to a substance or therapeutic class. The route of marketing authorisation (MA) 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

[64] Cumulative review(s) requested as part of a 60 days followed by a 60 day-timetable assessment or within an ongoing or upcoming PSUR/PSUSA procedure (if the data lock point (DLP) is within 90 days), and no disagreement has been raised before the meeting

14.1.2. Bupropion (NAP)

Applicant(s): various

PRAC Rapporteur: Liana Gross Martirosyan

Scope: Signal of acute generalised exanthematous pustulosis (AGEP)

EPITT 19704 – New signal

Lead Member State(s): NL

14.1.3. Lenvatinib – KISPLYX (CAP); LENVIMA (CAP)

Applicant(s): Eisai GmbH

PRAC Rapporteur: Annika Folin

Scope: Signal of colitis

EPITT 19691 – New signal

Lead Member State(s): SE

14.1.4. Lumacaftor, ivacaftor – ORKAMBI (CAP)

Applicant(s): Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Rhea Fitzgerald

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

EPITT 19702 – New signal

Lead Member State(s): IE

14.2. New signals detected from other sources

None

15. Annex I – Risk management plans

15.1. Medicines in the pre-authorisation phase

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

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

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

15.2.1. Cholic acid - ORPHACOL (CAP) - EMEA/H/C/001250/II/0040, Orphan

Applicant: Laboratoires CTRS

PRAC Rapporteur: Sofia Trantza

Scope: Submission of an updated RMP (version 4.0) in order to reflect the current status of the additional risk minimisation measures. Furthermore, the RMP is brought in line with revision 2.0.1 of the guidance on the format of RMP in the EU (template) and the agreed protocol (PSA/S/0051) for a patient surveillance database to monitor accumulating data on efficacy and safety in the treatment of inborn errors in primary bile acid synthesis due to 3β-hydroxy-Δ5-C27-steroid oxidoreductase deficiency or Δ4-3-oxosteroid-5β-reductase deficiency with Orphacol (cholic acid) in infants, children, adolescents and adults as agreed in May 2020

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

Applicant: Merck Europe B.V.

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Submission of an updated RMP (version 1.5) in order to bring it in line with revision 2.0.1 of the guidance on the format of RMP in the EU (template). In addition, the MAH took the opportunity to include long-term safety data from the completed PREMIERE registry: a prospective observational long-term safety registry of multiple sclerosis patients who have participated in cladribine clinical studies; and to remove it from the pharmacovigilance plan. Furthermore, the status of the post-approval safety study MS 700568-0002: a long term, prospective, observational cohort study evaluating the safety profile in patients with highly active relapsing multiple sclerosis (RMS) newly started on oral cladribine (CLARION); and study MS 700568-0004: pregnancy outcomes in women exposed to oral cladribine: a multi-country cohort database study (CLEAR) are updated. Finally, the RMP is updated in line with the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00010634/201907) adopted in January 2020

15.2.3. Desloratadine - AERIUS (CAP) - EMEA/H/C/000313/WS2057/0098; AZOMYR (CAP) - EMEA/H/C/000310/WS2057/0102; NEOCLARITYN (CAP) - EMEA/H/C/000314/WS2057/0096

Applicant: Organon N.V.

PRAC Rapporteur: Laurence de Fays

Scope: Submission of an updated RMP (version 2.1) in order to bring it in line with revision 2.0.1 of the guidance on the format of RMP in the EU (template), which includes updates to the list of safety concerns. It also reflects the completion of study EUPAS15038 (listed as a category 3 study in the RMP): a Nordic register-based study which studied the association between the use of desloratadine and risk of seizures, supraventricular tachycardia, and atrial fibrillation or flutter as per the conclusions of procedure WS1655 finalised in January 2020

15.2.4. Fulvestrant - FASLODEX (CAP) - EMEA/H/C/000540/II/0073

Applicant: AstraZeneca AB

PRAC Rapporteur: Annika Folin

Scope: Update of the RMP (version 13) in line with revision 2 of GVP module V on 'Risk management systems' resulting in the removal of additional risk minimisation measures for important identified risks and reclassification of safety concerns as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00001489/202004) adopted in January 2021

15.2.5. Ibritumomab tiuxetan - ZEVALIN (CAP) - EMEA/H/C/000547/II/0053

Applicant: Ceft Biopharma s.r.o.

PRAC Rapporteur: Anette Kirstine Stark

Scope: Submission of an updated RMP (version 5.0) in line with revision 2 of GVP module V on 'Risk management systems'

15.2.6. Ipilimumab - YERVOY (CAP) - EMEA/H/C/002213/WS2043/0087; nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/WS2043/0102

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Submission of an updated RMP (version 19.3 for Opdivo, version 31 for Yervoy) to change the final due date for the post-authorisation efficacy study (PAES) study CA2098Y8: a phase 3b, randomized, double-blind study of nivolumab combined with ipilimumab versus nivolumab monotherapy for patients with previously untreated advanced renal cell carcinoma and intermediate- or poor-risk factors, from '30 September 2021' to '30 June 2022'. In addition, the MAH took the opportunity to include a minor editorial revision in the French translation of the product information

15.2.7. Ritonavir - NORVIR (CAP) - EMEA/H/C/000127/II/0161

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Submission of an updated RMP (version 7.1) in order to bring it in line with revision 2.0.1 of the guidance on the format of RMP in the EU (template). In addition, the MAH reviewed the information contained in the RMP and removed the important identified risk of toxicity of Norvir (ritonavir) oral solution in preterm neonates, removed missing information regarding use of ritonavir in elderly patients. Finally, the MAH proposed to provide an analysis of the antiretroviral pregnancy registry (APR) data with the submission of PSUR

15.2.8. Sildenafil - REVATIO (CAP) - EMEA/H/C/000638/II/0091

Applicant: Upjohn EESV

PRAC Rapporteur: Menno van der Elst

Scope: Submission of an updated RMP (version 7.0) in line with revision 2 of GVP module V on 'Risk management systems'. Consequently, the educational programme for the risk of hypotension is proposed to be terminated

15.2.9. Simoctocog alfa - NUWIQ (CAP) - EMEA/H/C/002813/WS2064/0043; VIHUMA (CAP) - EMEA/H/C/004459/WS2064/0024

Applicant: Octapharma AB

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of an updated RMP (version 11) to remove the following completed studies: 1) study GENA-05: immunogenicity, efficacy and safety of treatment with simoctocog alfa in previously untreated patients with severe haemophilia A; 2) study GENA-15: extension study for patients who completed GENA-05 (NuProtect)- to investigate immunogenicity, efficacy and safety of treatment with simoctocog alfa. As a consequence, 'safety in previously untreated patients', 'children < 2 years' and 'immune tolerance induction' are removed as missing information in the list of safety concerns. Finally, the RMP is brought in line with revision 2 of GVP module V on 'Risk management systems'

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

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

15.3.1. Abemaciclib - VERZENIOS (CAP) - EMEA/H/C/004302/II/0013

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Extension of indication to include Verzenios (abemaciclib) in combination with endocrine therapy for adjuvant treatment of patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, node-positive early breast cancer at high risk of recurrence. As a consequence, sections 4.1, 4.2, 4.4, 4.6, 4.8, 5.1 and 5.3 of the SmPC are updated. The package leaflet and the RMP (version 1.1) are updated in accordance

15.3.2. Avapritinib - AYVAKYT (CAP) - EMEA/H/C/005208/X/0004/G, Orphan

Applicant: Blueprint Medicines (Netherlands) B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Grouped applications consisting of: 1) line extension to add two new strengths of film-coated tablets (25 mg and 50 mg); 2) introduction of a new therapeutic indication to include treatment of adult patients with advanced systemic mastocytosis (AdvSM), including aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated haematological neoplasm (SM-AHN) and mast cell leukaemia (MCL), after at least one systemic therapy for Ayvakyt (avapritinib) based on the results of study BLU-285-2101: a phase 1 study of avapritinib in patients with AdvSM and relapsed or refractory myeloid malignancies and study BLU-285-2202: An open-label, single arm, phase 2 study to evaluate efficacy and safety of avapritinib in patients with AdvSM. The new indication is applicable to the new and existing presentations (25 mg, 50 mg, 100 mg and 200 mg film-coated tablets). As a consequence, sections 1, 2, 3, 4.1, 4.2, 4.4, 4.5, 4.6, 4.8, 5.1, 5.2, 5.3, 6.1 and 8 of the SmPC are updated. The labelling, package leaflet and the RMP

(version 1.1) are updated in accordance

15.3.3. Brivaracetam – BRIVIACT (CAP) – EMEA/H/C/003898/II/0032/G

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Adam Przybylkowski

Scope: Grouped variations consisting of: 1) extension of indication to include patients from 1 month to 4 years of age for treatment with Briviact (brivaracetam). As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The RMP (version 8.0) is updated accordingly. Furthermore, the product information is brought in line with the latest quality review of documents (QRD) template (version 10.2). The MAH took the opportunity to implement minor editorial updates; 2) extension of the shelf life after the first opening of Briviact (brivaracetam) oral solution (supported by real time data); 3) addition of a 1 mL oral syringe and its adaptor for the paediatric population. The package leaflet and labelling are updated in accordance

15.3.4. Cabozantinib - COMETRIQ (CAP) - EMEA/H/C/002640/II/0044, Orphan

Applicant: Ipsen Pharma

PRAC Rapporteur: Menno van der Elst

Scope: Update of Annex II-E on 'Specific obligation to complete post-authorisation measures for the conditional marketing authorisation' and section 5.1 of the SmPC to remove the specific obligation (SOB 001) and the reference to the conditional approval based on the final results from study XL184-401 (EXAMINER): a randomised, double-blind study to evaluate the efficacy and safety of cabozantinib (XL184) at 60 mg/day compared to a 140 mg/day in progressive, metastatic medullary thyroid cancer patients. The package leaflet and the RMP (version 5.4) are updated accordingly. As a consequence, the MAH proposed to revert from a conditional marketing authorisation to a full marketing authorisation. Additionally, the MAH took the opportunity to bring the product information in line with the latest quality review of documents (QRD) template (version 10.2 Rev 1) and to add information relating to sodium content in the product information in line with the guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use'. Finally, the MAH updated some details of local representatives

15.3.5. Coronavirus (COVID-19) vaccine (ChAdOx1-S [recombinant]) - VAXZEVRIA (CAP) - EMEA/H/C/005675/II/0002

Applicant: AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: Update of sections 4.8, 5.1, 6.3 and 6.6 of the SmPC in order to update the safety profile and to add the adverse drug reactions: abdominal pain and urticaria with frequency uncommon and pain in extremity and influenza-line illness with frequency common based on the primary analysis from the pooled pivotal studies (listed as a specific obligation in the Annex II) namely: 1) study COV001: a phase 1/2 study to determine efficacy, safety and immunogenicity of the candidate coronavirus disease (COVID-19) vaccine ChAdOx1 nCoV-19 in UK healthy adult volunteers; 2) study COV002: a single-blind, randomised, controlled, phase 2/3 trial assessing the safety and immunogenicity of ChAdOx1 nCoV-19 vaccine

administered in a prime-boost regimen in young and old adults conducted in the UK; 3) study COV003: a single-blinded, multicentre, randomised, controlled phase 3 trial assessing the safety, efficacy, and immunogenicity of AZD1222 in participants in Brazil; 4) study COV005: a blinded, multicentre, randomised, controlled phase 1/2 trial assessing the safety, efficacy, and immunogenicity of AZD1222 in participants in South Africa. The MAH took the opportunity to introduce some editorial changes throughout the product information. The package leaflet, labelling and the RMP (version 2.1) are updated accordingly

15.3.6. Dapagliflozin - EDISTRIDE (CAP) - EMEA/H/C/004161/WS2069/0048/G; FORXIGA (CAP) - EMEA/H/C/002322/WS2069/0067/G

Applicant: AstraZeneca AB

PRAC Rapporteur: Annika Folin

Scope: Grouped variations consisting of the submission of the final study reports of the DETERMINE studies (listed as category 3 studies in the RMP): 1) study D169EC00001: an international, multicentre, parallel-group, randomised, double-blind, placebo-controlled, phase 3 study evaluating the effect of dapagliflozin on exercise capacity in patients with heart failure with preserved ejection fraction (HFpEF); 2) study D169EC00002: an international, multicentre, parallel-group, randomised, double-blind, placebo-controlled, phase 3 study evaluating the effect of dapagliflozin on exercise in patients with heart failure with reduced ejection fraction (HFrEF). The RMP (version 25) is updated accordingly

15.3.7. Dengue tetravalent vaccine (live, attenuated) - DENGVAXIA (CAP) - EMEA/H/C/004171/II/0016/G

Applicant: Sanofi Pasteur

PRAC Rapporteur: Sonja Hrabcik

Scope: Grouped variations consisting of an update of section 4.5 of the SmPC to include co-administration data on Gardasil/Cervarix (human papillomavirus vaccine) and Adacel (tetanus toxoid/reduced diphtheria toxoid and acellular/pertussis vaccine (adsorbed)) based on the final results of studies (listed as category 3 studies in the RMP) dedicated to immunogenicity and safety of the concomitant administration, namely: 1) study CYD66: a phase 3b, randomised, multicentre, open-label study in 688 subjects aged from 9 to 60 years in the Philippines; 2) study CYD67: a phase 3b, randomised, open-label, multicentre study in 528 subjects aged 9 to 13 years in Malaysia; 3) study CD71: a phase 3b, randomised, open-label, multicentre study in 480 female subjects aged 9 to 14 years in Mexico. The package leaflet and the RMP (version 6.1) are updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet

15.3.8. Elbasvir, grazoprevir - ZEPATIER (CAP) - EMEA/H/C/004126/II/0029

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Extension of indication to include treatment of chronic hepatitis C (CHC) in paediatric patients 12 years of age and older who weigh at least 30 kg. As a consequence,

sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 4.1) are updated in accordance. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet

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

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Kimmo Jaakkola

Scope: Grouped variations consisting of: 1) extension of indication to include a new paediatric indication in paediatric patients aged 10 years and over with heterozygous familial hypercholesterolaemia as an adjunct to diet, alone or in combination with other lipid-lowering therapy, to reduce low-density lipoprotein cholesterol (LDL-C) based on results of study 20120123 (HAUSER-RCT): a randomized, multicentre, placebo-controlled, double blind, parallel group, 24-week trial in 158 paediatric patients aged 10 to > 18 years with heterozygous familial hypercholesterolaemia. As a consequence, sections 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 7.0) are updated in accordance; 2) extension of indications to modify the existing indication for treatment of adults and paediatric patients aged 10 years and over with homozygous familial hypercholesterolaemia in combination with other lipid-lowering therapies based on interim results from study 20120124 (HAUSER-OLE): an open label, single arm, multicentre, 80-week trial to evaluate the safety, tolerability and efficacy of Repatha (evolocumab) for LDL-C reduction in paediatric patients from aged ≥ 10 to < 18 years of age with homozygous familial hypercholesterolaemia. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet is updated accordingly

15.3.10. Exenatide - BYETTA (CAP) - EMEA/H/C/000698/II/0075

Applicant: AstraZeneca AB

PRAC Rapporteur: Annika Folin

Scope: Update of sections 4.2 and 5.1 of the SmPC based on the results of study H8O-MC-GWBQ (assessed by CHMP as part of PAM P46 048): a 28-week, randomised, double-blind, placebo-controlled study to evaluate the safety and efficacy of exenatide twice daily in 120 patients aged 10 to 17 years; and study 2993-124: a randomised, single-blind, placebo-controlled, dose-rising study to evaluate the pharmacokinetic (PK), pharmacodynamic (PD) and tolerability of exenatide in adolescent patients. The RMP (version 35.1) is updated accordingly

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

Applicant: Menarini International Operations Luxembourg S.A.

PRAC Rapporteur: Jan Neuhauser

Scope: Update of sections 4.4, 4.8 and 5.1 of the SmPC based on the final results from study FAST (Febuxostat versus Allopurinol Streamlined Trial) (listed as a category 3 study in the RMP): an interventional study investigating the cardiovascular safety of febuxostat in comparison with allopurinol in patients with chronic symptomatic hyperuricaemia. The package leaflet and the RMP (version 8.0) are updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet and to

update the warning relevant to the content of sodium according to the Annex to the European Commission guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use'

15.3.12. Filgrastim - ACCOFIL (CAP) - EMEA/H/C/003956/II/0046/G

Applicant: Accord Healthcare S.L.U.

PRAC Rapporteur: Kirsti Villikka

Scope: Grouped variations consisting of: 1) introduction of a new presentation Accofil 12 MU/0.2 mL solution for injection or infusion in pre-filled syringe; 2) introduction of a new presentation, Accofil 70 MU/0.73 mL solution for injection or infusion in pre-filled syringe. The product information and the RMP (version 5) are updated accordingly

15.3.13. Guselkumab - TREMFYA (CAP) - EMEA/H/C/004271/II/0028

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of sections 4.8 and 5.1 of the SmPC to reflect 5 years data from the final study reports of pivotal psoriasis studies (listed as category 3 studies in the RMP), namely: 1) study PSO3001: a phase 3, multicentre, randomized, double-blind, placebo and active comparator-controlled study evaluating the efficacy and safety of guselkumab in the treatment of subjects with moderate to severe plaque-type psoriasis; 2) study PSO3002: a phase 3, multicentre, randomized, double-blind, placebo and active comparator-controlled study evaluating the efficacy and safety of guselkumab for the treatment of subjects with moderate to severe plaque-type psoriasis with randomized withdrawal and retreatment. In the long-term extension part of these studies subjects received open-label guselkumab every 8 weeks (q8w) starting at week 52 in PSO3001 and at week 76 in PSO3002, with the last dose at week 252 and the last safety follow-up visit at week 264. The RMP (version 8.1) is updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet

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

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Rhea Fitzgerald

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

15.3.15. Ivacaftor - KALYDECO (CAP) - EMEA/H/C/002494/WS2085/0099; ivacaftor, tezacaftor, elexacaftor - KAFTRIO (CAP) - EMEA/H/C/005269/WS2085/0014

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Martin Huber

Scope: Update of sections 4.4 and 4.8 of the SmPC following cases of liver failure reported in the post marketing setting. The package leaflet and the RMP (version 3.1 for Kaftrio) are updated accordingly

15.3.16. Lacosamide - LACOSAMIDE UCB (CAP) - EMEA/H/C/005243/WS2049/0009/G; VIMPAT (CAP) - EMEA/H/C/000863/WS2049/0091/G

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Grouped applications consisting of: 1) extension of indication to include patients from 1 month to 4 years of age for treatment of partial-onset seizures with or without secondary generalisation as monotherapy and adjunctive therapy. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The RMP (version 16.0) is updated accordingly; 2) change of a measuring or administration device; 3) change in the shelf-life or storage conditions of the finished product. The package leaflet and labelling are updated in accordance

15.3.17. Lenvatinib - KISPLYX (CAP) - EMEA/H/C/004224/II/0045

Applicant: Eisai GmbH

PRAC Rapporteur: David Olsen

Scope: Extension of indication to include lenvatinib in combination with pembrolizumab first line treatment of adults with advanced renal cell carcinoma (RCC). As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 13.0) are updated in accordance. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet

15.3.18. Lenvatinib - LENVIMA (CAP) - EMEA/H/C/003727/II/0042

Applicant: Eisai GmbH

PRAC Rapporteur: Annika Folin

Scope: Extension of indication to include lenvatinib in combination with pembrolizumab for the treatment of adult patients with advanced endometrial carcinoma (EC) who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation. As a consequence, sections 4.1, 4.2, 4.8, and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 14.0) are updated in accordance. In addition, the MAH took the opportunity to make minor editorial changes to the SmPC and update the list of local representatives in the package leaflet in line with the latest quality review of documents (QRD) template (version 10.2)

15.3.19. Lorlatinib - LORVIQUA (CAP) - EMEA/H/C/004646/II/0013

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Update of sections 4.2, 4.4 and 4.8 of the SmPC in order to include hypertension and hyperglycaemia as new adverse drug reactions (ADRs) with frequency common and very common respectively together with recommended dose modifications and warnings, based on data from study B7461006: a phase 3, randomized, open-label study of lorlatinib monotherapy versus crizotinib monotherapy in the first-line treatment of patients with advanced anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC). In addition, the pooled safety dataset has been updated to include data from study B7461001: a phase 1/2 open-label, multiple-dose, dose-escalation, safety, pharmacokinetic, pharmacodynamic and anti-tumour efficacy exploration study; and study B7461006. As a consequence, the frequencies of ADRs have been updated in section 4.8 of the SmPC and existing warnings on hyperlipidaemia and lipase and amylase increase have been amended. The package leaflet and the RMP (version 2.0) is updated accordingly

15.3.20. Mepolizumab - NUCALA (CAP) - EMEA/H/C/003860/II/0036/G

Applicant: GlaxoSmithKline Trading Services Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Grouped variations consisting of: 1) extension of indication to include eosinophilic granulomatosis with polyangiitis (EGPA). As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 7) are updated in accordance. In addition, the MAH took the opportunity to update the local representative for Italy in the package leaflet; 2) addition of a new pack size of 9x100mg/mL multipack for pre-filled pens 100 mg/mL solution for injection and another pack size of 9x100mg/mL multipack for pre-filled syringes 100 mg/mL solution for injection. As a consequence, sections 6.5 and 8 of the SmPC and the package leaflet are updated accordingly. Annex III-A on 'labelling' is also updated to include information relating to the new pack sizes

15.3.21. Midostaurin - RYDAPT (CAP) - EMEA/H/C/004095/II/0018/G, Orphan

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Grouped variations consisting of: 1) update of sections 4.5 and 5.2 of the SmPC in order to add drug-drug interaction information with P-glycoprotein (P-gp), breast cancer resistance protein (BCRP) and cytochrome P450 2D6 (CYP2D6) substrates (digoxin, rosuvastatin, and dextromethorphan) based on final results from study CPKC412A2121 (listed as a category 3 study in the RMP): a phase 1, open-label, drug-drug interaction study. The package leaflet is updated accordingly (MEA 005.3); 2) update of sections 4.5 and 5.2 of the SmPC in order to add drug-drug interaction information with CYP2B6, CYP2C8, CYP3A4 substrates based on the final results from study CPKC412A2122 (listed as a category 3 study in the RMP): a phase 1, open-label, drug-drug interaction study. The package leaflet is updated accordingly (MEA 007.2); 3) update of sections 4.5 and 4.6 of the SmPC in order to add drug-drug interaction information with oral contraceptives and information on pregnancy and contraception based on final results from study

CPKC412A2123 (listed as a category 3 study in the RMP): a phase 1, open-label, drug-drug interaction study. The package leaflet is updated accordingly (MEA 008.2); 4) update of section 5.2 of the SmPC in order to update pharmacokinetic information on organic anion transporting polypeptide 1B1 (OATP1B1) transporters based on final results from physiological based pharmacokinetic (PBPK) modelling study DMPK R2000528 (listed as category 3 study in the RMP) (MEA 009); 5) update of sections 4.2, 4.4 and 5.2 of the SmPC in order to amend posology instructions, an existing warning and pharmacokinetic information for patients with severe hepatic impairment based on final results from study CPKC412A2116 (listed as category 3 study in the RMP): an open label, multiple dose study to evaluate the pharmacokinetic (PK) of midostaurin in subjects with mild, moderate and severe hepatic impairment compared to matched healthy subjects (MEA010). The RMP (version 6.0) is updated accordingly. In addition, the MAH took the opportunity to introduce minor changes to edit the wording related to the ethanol excipient in the package leaflet in line with the Annex to the European Commission guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use' (SANTE-2017-11668)

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

Applicant: Amicus Therapeutics Europe Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension of indication to include long-term treatment of adolescents 12 to < 16 years with a confirmed diagnosis of Fabry disease (α-galactosidase A deficiency) and who have an amenable mutation. As a consequence, sections 4.1, 4.2, 4.8 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 4.0) are updated accordingly

15.3.23. Netupitant, palonosetron - AKYNZEO (CAP) - EMEA/H/C/003728/X/0031

Applicant: Helsinn Birex Pharmaceuticals Limited

PRAC Rapporteur: Ilaria Baldelli

Scope: Extension application to introduce a new pharmaceutical form (concentrate for solution for infusion). The RMP (version 2.8) is updated accordingly

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

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

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

15.3.25. Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/II/0100

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include adjuvant treatment of adults with muscle invasive urothelial carcinoma (MIUC) who are at high risk of recurrence after undergoing radical resection of MIUC. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 23.0) are updated in accordance

15.3.26. Obinutuzumab - GAZYVARO (CAP) - EMEA/H/C/002799/II/0044/G, Orphan

Applicant: Roche Registration GmbH

PRAC Rapporteur: Annika Folin

Scope: Grouped variations consisting of: 1) update of sections 4.2, 4.8 and 5.1 of the SmPC in order to include the administration of obinutuzumab as a short duration infusion (SDI) of approximately 90 minutes in patients with follicular lymphoma (FL) based on the end of induction safety and efficacy data from the ongoing phase 4 study MO40597 (GAZELLE): a multicentric, open-label, single arm study of obinutuzumab short duration infusion (SDI) in patients with previously untreated advanced FL. The package leaflet and the RMP (version 8.0) are updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet; 2) submission of an updated RMP (version 8.0) to change the due date for the submission of the final clinical safety report (CSR) for study BO21223 (GALLIUM) (listed as a category 3 study in the RMP): a multicentre, phase 3, open-label, randomized study in previously untreated patients with advanced indolent non-Hodgkin's lymphoma evaluating the benefit of obinutuzumab plus chemotherapy compared with rituximab plus chemotherapy followed by obinutuzumab or rituximab maintenance therapy in responders, from Q4 2021 to Q1 2022; to remove important identified risks as per conclusions of the PSUR single assessment (PSUSA) (PSUSA/00010279/201910) concluded in May 2020; to correct the clinical cut-off dates and trial exposure data from previously conducted studies

15.3.27. Parathyroid hormone - NATPAR (CAP) - EMEA/H/C/003861/II/0029, Orphan

Applicant: Shire Pharmaceuticals Ireland Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Submission of the final results of study SHP634-101: an open-label, randomised, crossover study to assess the pharmacokinetic and pharmacodynamic profiles of once-daily and twice-daily dose regimens of recombinant human parathyroid hormone (rhPTH[1-84]) administered subcutaneously to subjects with hypoparathyroidism. Further clinical evaluation of an alternative dosing regimen is no longer warranted, as outlined in the current specific obligation (study SHP634-403). The conditional marketing authorisation can therefore be converted into a standard marketing authorisation (no longer subject to a specific obligation) valid for 5 years. The RMP (version 3.2) is updated accordingly

15.3.28. Pembrolizumab - KEYTRUDA (CAP) - EMEA/H/C/003820/II/0104

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to include pembrolizumab in combination with lenvatinib first

line treatment of adults with advanced renal cell carcinoma (RCC). As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 32.1) are updated in accordance

15.3.29. Pembrolizumab - KEYTRUDA (CAP) - EMEA/H/C/003820/II/0105

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to include pembrolizumab in combination with lenvatinib for the treatment of advanced endometrial carcinoma in adults who have disease progression following prior systemic therapy in any setting and who are not candidates for curative surgery or radiation. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 33.1) are updated in accordance

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

Applicant: Bioprojet Pharma

PRAC Rapporteur: Kirsti Villikka

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

15.3.31. Ruxolitinib - JAKAVI (CAP) - EMEA/H/C/002464/II/0050

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Annika Folin

Scope: Update of sections 4.2 and 5.1 of the SmPC to include the final results of study CINC424A2201 (EXPAND) (listed as a category 3 study in the RMP): a phase 1b open-label, dose-finding study intended to establish the maximum safe starting dose (MSSD) of ruxolitinib tablets administered orally to patients with myelofibrosis (MF) in previous unstudied population of patients who had baseline platelet counts ≥50×109/L and <100×109/L. The package leaflet and the RMP (version 12.0) are updated accordingly. The RMP is also brought in line with revision 2 of GVP module V on 'Risk management systems' and in line with the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00010015/202002) adopted in October 2020

15.3.32. Ruxolitinib - JAKAVI (CAP) - EMEA/H/C/002464/II/0053

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Annika Folin

Scope: Extension of indication to include treatment of patients with graft versus host disease (GvHD) aged 12 years and older who have inadequate response to corticosteroids or other systemic therapies. 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 and the RMP (version 13.0) are updated in accordance. In addition, the MAH took the opportunity to update the list of local representatives for the Netherlands in the package leaflet

15.3.33. Secukinumab - COSENTYX (CAP) - EMEA/H/C/003729/II/0076

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Eva Segovia

Scope: Update of sections 4.2 and 5.1 of the SmPC in order to introduce a new posology regimen for adult plaque psoriasis patients and psoriatic arthritis patients with concomitant moderate to severe plaque psoriasis based on the final results of study CAIN457A2324 (and exposure-response modelling): a randomised, double-blind, multicentre study assessing short (16 weeks) and long-term efficacy (up to 1 year), safety, and tolerability of sub-cutaneous secukinumab in subjects of body weight 90 kg or higher with moderate to severe chronic plaque-type psoriasis. The package leaflet and the RMP (version 9.0) are updated accordingly

15.3.34. Ticagrelor - BRILIQUE (CAP) - EMEA/H/C/001241/II/0049

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to include, in co-administration with acetylsalicylic acid (ASA), the prevention of stroke in adult patients with acute ischaemic stroke or transient ischaemic attack (TIA), based on the final results of study D5134C00003 (THALES): a phase 3, international, multicentre, randomised, double-blind, placebo-controlled study to investigate the efficacy and safety of ticagrelor and ASA compared with ASA in the prevention of stroke and death in patients with acute ischaemic stroke or transient ischaemic attack. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 13.0) are updated in accordance

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

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

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

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

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

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

15.3.37. Trastuzumab - HERCEPTIN (CAP) - EMEA/H/C/000278/II/0168

Applicant: Roche Registration GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of sections 4.2 and 4.4 of the SmPC in order to modify the administration instructions by removing the observation time currently stipulated after administration and to amend the existing warning respectively based on final results from study MO28048 (SafeHER) (listed as a category 3 study in the RMP): a phase 3 prospective, two cohort non-randomized, multicentre, multinational, open label study to assess the safety of assisted- and self-administered subcutaneous Herceptin (trastuzumab) as adjuvant therapy in patients with operable human epidermal growth factor receptor 2 (HER2)-positive early breast cancer. The package leaflet and the RMP (version 22) are updated accordingly

15.3.38. Trastuzumab emtansine - KADCYLA (CAP) - EMEA/H/C/002389/II/0055

Applicant: Roche Registration GmbH

PRAC Rapporteur: Anette Kirstine Stark

Scope: Submission of the final clinical study report (CSR) of study MO28231 (KAMILLA): a two-cohort, open-label, multicentre study of trastuzumab emtansine (T-DM1) in human epidermal growth factor receptor 2 (HER2)-positive locally advanced or metastatic breast cancer patients who have received prior anti-HER2 and chemotherapy-based treatment in order to address the safety concerns of: ventricular dysfunction, safety in elderly patients and the use of a non-validated HER2 test. The RMP (version 13) is updated accordingly

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

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Nikica Mirošević Skvrce

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

patients. The RMP (version 5.0) is updated accordingly

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

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

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

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

16.1.1. Aclidinium bromide, formoterol fumarate dihydrate - BRIMICA GENUAIR (CAP); DUAKLIR GENUAIR (CAP) - PSUSA/00010307/202011

Applicant(s): AstraZeneca AB

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.2. Afatinib - GIOTRIF (CAP) - PSUSA/00010054/202009

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

16.1.3. Alpelisib - PIQRAY (CAP) - PSUSA/00010871/202011

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

16.1.4. Andexanet alfa - ONDEXXYA (CAP) - PSUSA/00010764/202010

Applicant: Alexion Europe SAS

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.5. Autologous $CD34^+$ enriched cell fraction that contains $CD34^+$ cells transduced with retroviral vector that encodes for the human adenosine deaminase (ADA)

complementary deoxyribonucleic acid (cDNA) sequence - STRIMVELIS (CAP) - PSUSA/00010505/202011

Applicant: Orchard Therapeutics (Netherlands) BV, ATMP[65]

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.6. Avatrombopag - DOPTELET (CAP) - PSUSA/00010779/202011

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

16.1.7. Axicabtagene ciloleucel - YESCARTA (CAP) - PSUSA/00010703/202010

Applicant: Kite Pharma EU B.V., ATMP[66]

PRAC Rapporteur: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

16.1.8. Bezlotoxumab - ZINPLAVA (CAP) - PSUSA/00010576/202010

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.9. Buprenorphine[67] - SIXMO (CAP) - PSUSA/00010778/202011

Applicant: L. Molteni & C. dei Fratelli Alitti Societa di Esercizio S.p.A.

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.10. Cefiderocol - FETCROJA (CAP) - PSUSA/00010849/202011

Applicant: Shionogi B.V.

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.11. Ceftaroline fosamil - ZINFORO (CAP) - PSUSA/00010013/202010

Applicant: Pfizer Ireland Pharmaceuticals

PRAC Rapporteur: Maia Uusküla

[65] Advanced therapy medicinal product
[66] Advanced therapy medicinal product
[67] Implant(s) only

Scope: Evaluation of a PSUSA procedure

16.1.12. Cetuximab - ERBITUX (CAP) - PSUSA/00000635/202009

Applicant: Merck Europe B.V.

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

16.1.13. Cobicistat, elvitegravir, emtricitabine, tenofovir alafenamide - GENVOYA (CAP) - PSUSA/00010449/202011

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ilaria Baldelli

Scope: Evaluation of a PSUSA procedure

16.1.14. Conestat alfa - RUCONEST (CAP) - PSUSA/00000873/202010

Applicant: Pharming Group N.V

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.1.15. Dalbavancin - XYDALBA (CAP) - PSUSA/00010350/202011

Applicant: Allergan Pharmaceuticals International Limited

PRAC Rapporteur: Rugile Pilviniene

Scope: Evaluation of a PSUSA procedure

16.1.16. Daratumumab - DARZALEX (CAP) - PSUSA/00010498/202011

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Evaluation of a PSUSA procedure

16.1.17. Darbepoetin alfa - ARANESP (CAP) - PSUSA/00000932/202010

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.18. Defibrotide - DEFITELIO (CAP) - PSUSA/00010086/202010

Applicant: Gentium S.r.l.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.19. Denosumab[68] - XGEVA (CAP) - PSUSA/00009119/202009

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.20. Dinutuximab beta - QARZIBA (CAP) - PSUSA/00010597/202011

Applicant: EUSA Pharma (Netherlands) B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.21. Diphtheria, tetanus, pertussis antigens (pertussis toxoid, filamentous haemagglutinin, pertactin) (acellular, component), hepatitis B (rDNA), poliomyelitis (inactivated), haemophilus type b conjugate vaccines (adsorbed) - INFANRIX HEXA (CAP) - PSUSA/00001122/202010

Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

16.1.22. Dolutegravir, rilpivirine - JULUCA (CAP) - PSUSA/00010689/202011

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

16.1.23. Durvalumab - IMFINZI (CAP) - PSUSA/00010723/202010

Applicant: AstraZeneca AB

PRAC Rapporteur: David Olsen

Scope: Evaluation of a PSUSA procedure

16.1.24. Ebola Zaire vaccine (live, attenuated) - ERVEBO (CAP) - PSUSA/00010834/202011

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.25. Edoxaban - LIXIANA (CAP); ROTEAS (CAP) - PSUSA/00010387/202010

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

PRAC Rapporteur: Adrien Inoubli

[68] Indicated for skeletal related events associated with bone metastases and for giant cell tumour of bone

Scope: Evaluation of a PSUSA procedure

16.1.26. Emicizumab - HEMLIBRA (CAP) - PSUSA/00010668/202011

Applicant: Roche Registration GmbH

PRAC Rapporteur: Ilaria Baldelli

Scope: Evaluation of a PSUSA procedure

16.1.27. Empagliflozin, linagliptin - GLYXAMBI (CAP) - PSUSA/00010539/202011

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

16.1.28. Erenumab - AIMOVIG (CAP) - PSUSA/00010699/202011

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

16.1.29. Etelcalcetide - PARSABIV (CAP) - PSUSA/00010533/202011

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ilaria Baldelli

Scope: Evaluation of a PSUSA procedure

16.1.30. Fexinidazole - FEXINIDAZOLE WINTHROP (Art 58[69]) - EMEA/H/W/002320/PSUV/0005

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUR procedure

16.1.31. Fosamprenavir - TELZIR (CAP) - PSUSA/00001470/202010

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

16.1.32. Glasdegib - DAURISMO (CAP) - PSUSA/00010859/202011

Applicant: Pfizer Europe MA EEIG

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

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.33. Glycopyrronium bromide, formoterol - BEVESPI AEROSPHERE (CAP) - PSUSA/00010739/202010

Applicant: AstraZeneca AB

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.1.34. Granisetron[70] - SANCUSO (CAP) - PSUSA/00010101/202010

Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Rugile Pilviniene

Scope: Evaluation of a PSUSA procedure

16.1.35. Idarucizumab - PRAXBIND (CAP) - PSUSA/00010435/202010

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.36. Indacaterol, glycopyrronium bromide - ULTIBRO BREEZHALER (CAP); ULUNAR BREEZHALER (CAP); XOTERNA BREEZHALER (CAP) - PSUSA/00010105/202009

Applicant(s): Novartis Europharm Limited

PRAC Rapporteur: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

16.1.37. Insulin degludec - TRESIBA (CAP); insulin degludec, insulin aspart - RYZODEG (CAP) - PSUSA/00010036/202009

Applicant(s): Novo Nordisk A/S

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

16.1.38. Insulin glargine, lixisenatide - SULIQUA (CAP) - PSUSA/00010577/202011

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

[70] Transdermal patch only

16.1.39. Irinotecan[71] - ONIVYDE PEGYLATED LIPOSOMAL (CAP) - PSUSA/00010534/202010

Applicant: Les Laboratoires Servier

PRAC Rapporteur: David Olsen

Scope: Evaluation of a PSUSA procedure

16.1.40. Ixazomib - NINLARO (CAP) - PSUSA/00010535/202011

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

16.1.41. Ketoconazole[72] - KETOCONAZOLE HRA (CAP) - PSUSA/00010316/202011

Applicant: HRA Pharma Rare Diseases

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

16.1.42. Larotrectinib - VITRAKVI (CAP) - PSUSA/00010799/202011

Applicant: Bayer AG

PRAC Rapporteur: Rugile Pilviniene

Scope: Evaluation of a PSUSA procedure

16.1.43. Letermovir - PREVYMIS (CAP) - PSUSA/00010660/202011

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

16.1.44. Lurasidone - LATUDA (CAP) - PSUSA/00010114/202010

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

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.45. Macitentan - OPSUMIT (CAP) - PSUSA/00010115/202010 (with RMP)

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

[71] Liposomal formulation(s) only
[72] Centrally authorised product(s) only

16.1.46. Melatonin - CIRCADIN (CAP); SLENYTO (CAP) - PSUSA/00001963/202009

Applicant(s): RAD Neurim Pharmaceuticals EEC SARL

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.1.47. Meningococcal group B vaccine (recombinant, adsorbed) - TRUMENBA (CAP) - PSUSA/00010607/202010

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

16.1.48. Mercaptamine[73] - CYSTAGON (CAP); PROCYSBI (CAP) - PSUSA/00010573/202010

Applicant(s): Chiesi Farmaceutici S.p.A. (Procysbi), Recordati Rare Diseases (Cystagon)

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

16.1.49. Necitumumab - PORTRAZZA[74] - PSUSA/00010471/202011

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Rugile Pilviniene

Scope: Evaluation of a PSUSA procedure

16.1.50. Nelarabine - ATRIANCE (CAP) - PSUSA/00002132/202010

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

16.1.51. Obinutuzumab - GAZYVARO (CAP) - PSUSA/00010279/202010

Applicant: Roche Registration GmbH

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

16.1.52. Onasemnogene abeparvovec - ZOLGENSMA (CAP) - PSUSA/00010848/202011

Applicant: Novartis Gene Therapies EU Limited, ATMP[75]

PRAC Rapporteur: Ulla Wändel Liminga

[73] Treatment of nephropathic cystinosis only
[74] European Commission (EC) decision on the marketing authorisation (MA) cessation of Portrazza dated 18 February 2021
[75] Advanced therapy medicinal product

Scope: Evaluation of a PSUSA procedure

16.1.53. Ozanimod - ZEPOSIA (CAP) - PSUSA/00010852/202011

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

16.1.54. Padeliporfin - TOOKAD (CAP) - PSUSA/00010654/202011

Applicant: Steba Biotech S.A

PRAC Rapporteur: Maia Uusküla

Scope: Evaluation of a PSUSA procedure

16.1.55. Pandemic influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) - FOCLIVIA (CAP); prepandemic influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) - AFLUNOV (CAP) - PSUSA/00010008/202010

Applicant(s): Seqirus S.r.l

PRAC Rapporteur: Ilaria Baldelli

Scope: Evaluation of a PSUSA procedure

16.1.56. Parathyroid hormone - NATPAR (CAP) - PSUSA/00010591/202010

Applicant: Shire Pharmaceuticals Ireland Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

16.1.57. Pasireotide - SIGNIFOR (CAP) - PSUSA/00009253/202010

Applicant: Recordati Rare Diseases

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

16.1.58. Patiromer - VELTASSA (CAP) - PSUSA/00010618/202010

Applicant: Vifor Fresenius Medical Care Renal Pharma France

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

16.1.59. Pazopanib - VOTRIENT (CAP) - PSUSA/00002321/202010

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

16.1.60. Prasterone[76] - INTRAROSA (CAP) - PSUSA/00010672/202011

Applicant: Endoceutics S.A.

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.61. Rurioctocog alfa pegol - ADYNOVI (CAP) - PSUSA/00010663/202011

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.62. Sotagliflozin - ZYNQUISTA (CAP) - PSUSA/00010766/202010

Applicant: Guidehouse Germany GmbH

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.63. Stiripentol - DIACOMIT (CAP) - PSUSA/00002789/202011

Applicant: BIOCODEX

PRAC Rapporteur: Maia Uusküla

Scope: Evaluation of a PSUSA procedure

16.1.64. Talazoparib - TALZENNA (CAP) - PSUSA/00010781/202010

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Evaluation of a PSUSA procedure

16.1.65. Talimogene laherparepvec - IMLYGIC (CAP) - PSUSA/00010459/202010

Applicant: Amgen Europe B.V., ATMP[77]

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.66. Tenofovir alafenamide - VEMLIDY (CAP) - PSUSA/00010575/202011

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ilaria Baldelli

[76] Pessary, vaginal use only
[77] Advanced therapy medicinal product

Scope: Evaluation of a PSUSA procedure

16.1.67. Tofacitinib - XELJANZ (CAP) - PSUSA/00010588/202011

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.68. Toremifene - FARESTON (CAP) - PSUSA/00002999/202009

Applicant: Orion Corporation

PRAC Rapporteur: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

16.1.69. Turoctocog alfa - NOVOEIGHT (CAP) - PSUSA/00010138/202010

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.70. Vestronidase alfa - MEPSEVII (CAP) - PSUSA/00010709/202011

Applicant: Ultragenyx Germany GmbH

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

16.1.71. Volanesorsen - WAYLIVRA (CAP) - PSUSA/00010762/202011

Applicant: Akcea Therapeutics Ireland Limited

PRAC Rapporteur: Martin Huber

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. Bosentan - STAYVEER (CAP); TRACLEER (CAP); NAP - PSUSA/00000425/202011

Applicants: Janssen-Cilag International NV (Stayveer, Tracleer), various

PRAC Rapporteur: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

16.2.2. Insulin human - ACTRAPID (CAP), INSUMAN (CAP); insulin human, insulin isophane[78] - ACTRAPHANE (CAP), INSULATARD (CAP), MIXTARD (CAP), PROTAPHANE (CAP); NAP - PSUSA/00001753/202010

Applicants: Novo Nordisk A/S (Actraphane, Actrapid, Insulatard, Mixtard, Protaphane), Sanofi-Aventis Deutschland GmbH (Insuman), various

PRAC Rapporteur: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

16.2.3. Micafungin - MYCAMINE (CAP); NAP - PSUSA/00002051/202010

Applicants: Astellas Pharma Europe B.V. (Mycamine), various

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

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

16.3.1. ^{13C}-methacetin (NAP) - PSUSA/00010846/202010

Applicant(s): various

PRAC Lead: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.3.2. Acitretin (NAP) - PSUSA/00000051/202010

Applicant(s): various

PRAC Lead: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

16.3.3. Adapalene, benzoyl peroxide (NAP) - PSUSA/00000059/202009

Applicant(s): various

PRAC Lead: Annika Folin

Scope: Evaluation of a PSUSA procedure

16.3.4. Amlodipine, atorvastatin, perindopril (NAP) - PSUSA/00010431/202010

Applicant(s): various

PRAC Lead: Jana Lukacisinova

Scope: Evaluation of a PSUSA procedure

[78] Subcutaneous and intravenous uses only

16.3.5. Atorvastatin, perindopril (NAP) - PSUSA/00010679/202010

Applicant(s): various

PRAC Lead: Ilaria Baldelli

Scope: Evaluation of a PSUSA procedure

16.3.6. Beractant (NAP) - PSUSA/00000384/202010

Applicant(s): various

PRAC Lead: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

16.3.7. Bisoprolol (NAP) - PSUSA/00000419/202009

Applicant(s): various

PRAC Lead: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

16.3.8. Bisoprolol, perindopril (NAP) - PSUSA/00010462/202010

Applicant(s): various

PRAC Lead: Michal Radik

Scope: Evaluation of a PSUSA procedure

16.3.9. Calcium carbonate, famotidine, magnesium hydroxide (NAP) - PSUSA/00001351/202009

Applicant(s): various

PRAC Lead: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

16.3.10. Clevidipine (NAP) - PSUSA/00010288/202011

Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.3.11. Desflurane (NAP) - PSUSA/00000958/202009

Applicant(s): various

PRAC Lead: Melinda Palfi

Scope: Evaluation of a PSUSA procedure

16.3.12. Epinephrine, lidocaine (NAP) - PSUSA/00001233/202009

Applicant(s): various

PRAC Lead: Ronan Grimes

Scope: Evaluation of a PSUSA procedure

16.3.13. Etifoxine (NAP) - PSUSA/00001321/202010

Applicant(s): various

PRAC Lead: Maria Popova-Kiradjieva

Scope: Evaluation of a PSUSA procedure

16.3.14. Human von Willebrand factor (NAP) - PSUSA/00001642/202009

Applicant(s): various

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.3.15. Idebenone[79] (NAP) - PSUSA/00001721/202009

Applicant(s): various

PRAC Lead: John Joseph Borg

Scope: Evaluation of a PSUSA procedure

16.3.16. Ketotifen[80] (NAP) - PSUSA/00001813/202010

Applicant(s): various

PRAC Lead: Ilaria Baldelli

Scope: Evaluation of a PSUSA procedure

16.3.17. Lidocaine (NAP) - PSUSA/00001861/202009

Applicant(s): various

PRAC Lead: Ronan Grimes

Scope: Evaluation of a PSUSA procedure

16.3.18. Minoxidil[81] (NAP) - PSUSA/00002066/202010

Applicant(s): various

PRAC Lead: Ronan Grimes

Scope: Evaluation of a PSUSA procedure

[79] Non-centrally authorised product(s) only
[80] Oral formulation(s) only
[81] All except topical formulation(s)

16.3.19. Minoxidil[82] (NAP) - PSUSA/00002067/202010

Applicant(s): various

PRAC Lead: Ronan Grimes

Scope: Evaluation of a PSUSA procedure

16.3.20. Prulifloxacin (NAP) - PSUSA/00002569/202010

Applicant(s): various

PRAC Lead: Ilaria Baldelli

Scope: Evaluation of a PSUSA procedure

16.3.21. Rubidium (^{82}Rb) chloride (NAP) - PSUSA/00010806/202010

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.3.22. Salmeterol (NAP) - PSUSA/00002681/202010

Applicant(s): various

PRAC Lead: Annika Folin

Scope: Evaluation of a PSUSA procedure

16.3.23. Tetrabenazine (NAP) - PSUSA/00002911/202010

Applicant(s): various

PRAC Lead: Ronan Grimes

Scope: Evaluation of a PSUSA procedure

16.3.24. Triamcinolone[83] (NAP) - PSUSA/00010137/202009

Applicant(s): various

PRAC Lead: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Evaluation of a PSUSA procedure

16.4. Follow-up to PSUR/PSUSA procedures

16.4.1. Tolvaptan - JINARC (CAP) - EMEA/H/C/002788/LEG 008

Applicant: Otsuka Pharmaceutical Netherlands B.V.

PRAC Rapporteur: Ilaria Baldelli

[82] Topical formulation(s) only
[83] Tablets and injectables only

Scope: Review of cases of rapid correction of hyponatremia and neurological sequelae as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00010395/202005) adopted in January 2021

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)[84]

17.1.1. Blinatumomab – BLINCYTO (CAP) - EMEA/H/C/PSA/S/0065.1

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Eva Jirsová

Scope: MAH's response to PSA/S/0065 [substantial amendment to a protocol previously agreed in November 2017 (PSA/S/0024) for study 20150136 (EUPAS17848): an observational study of blinatumomab safety and effectiveness, utilisation and treatment practices in order to characterise the safety of blinatumomab in routine clinical practice, its effectiveness, medication errors and utilisation] as per the request for supplementary information (RSI) adopted in February 2021

17.1.2. Avapritinib - AYVAKYT (CAP) - EMEA/H/C/PSP/S/0089.1

Applicant: Blueprint Medicines (Netherlands) B.V.

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to PSP/S/0089 [protocol for study BLU-285-1406: an observational study evaluating safety and efficacy of avapritinib in the first line treatment of patients with platelet derived growth factor alpha D842V mutated gastrointestinal stromal tumour (GIST)] as per the request for supplementary information (RSI) adopted in February 2021

17.1.3. Betibeglogene autotemcel – ZYNTEGLO (CAP) - EMEA/H/C/PSP/S/0090.1

Applicant: Bluebird bio (Netherlands) B.V., ATMP[85]

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: MAH's response to PSP/S/0090 [protocol for study REG-504: a non-interventional post-authorisation safety and efficacy study to further characterise and contextualise the long-term safety and efficacy of Zynteglo (betibeglogene autotemcel) in patients aged 12 years and older with transfusion-dependent β-thalassaemia (TDT) who do not have a β0 /β0 genotype] as per the request for supplementary information (RSI) adopted in March 2021

[84] In accordance with Article 107n of Directive 2001/83/EC
[85] Advanced therapy medicinal product

17.1.4. Elosulfase alfa – VIMIZIM (CAP) - EMEA/H/C/PSA/S/0062.1

Applicant: BioMarin International Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: MAH's response to PSA/S/0062 [substantial amendment to a protocol previously agreed in the framework of the initial marketing authorisation(s) for a multicentre, multinational, observational Morquio A Registry Study (MARS) to characterise and describe the mucopolysaccharidosis IV type A (MPS IVA) population as a whole, including the heterogeneity, progression, and natural history of MPS IVA and to track the safety and clinical outcomes of patients with MPS IVA patients treated with Vimizim (elosulfase alfa)] as per the request for supplementary information (RSI) adopted in January 2021

17.1.5. Vestronidase alfa – MEPSEVII (CAP) - EMEA/H/C/PSA/S/0069

Applicant: Ultragenyx Germany GmbH

PRAC Rapporteur: Eva Segovia

Scope: Substantial amendment to a protocol previously agreed in September 2019 (PSP/S/0082) for a PASS to obtain long-term data on effectiveness and safety of treatment with Mepsevii (vestronidase alfa) and to characterise the entire mucopolysaccharidosis VII, including variability of clinical manifestation, progression and natural history

17.2. Protocols of PASS non-imposed in the marketing authorisation(s)[86]

17.2.1. Alpelisib - PIQRAY (CAP) - EMEA/H/C/004804/MEA 002

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Menno van der Elst

Scope: Protocol for study CBYL719C2404: a non-interventional study of Piqray (alpelisib) in combination with fulvestrant in postmenopausal women and men with hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative, locally advanced or metastatic breast cancer with a PIK3CA mutation in the real-world setting in European countries, as per the outcome of variation II/001 finalised in March 2021. The safety concerns addressed are hyperglycaemia and osteonecrosis of the jaw

17.2.2. Coronavirus (COVID-19) mRNA[87] vaccine (nucleoside-modified) - COMIRNATY (CAP) - EMEA/H/C/005735/MEA 017.1

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to MEA 017 [protocol for study vACcine Covid-19 monitoring readinESS (ACCESS)/Vaccine monitoring Collaboration for Europe (VAC4EU): an assessment of occurrence of safety events of interest, including severe or atypical COVID-19 in real-world use of COVID-19 mRNA vaccine [final clinical study report (CSR): expected

[86] 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
[87] Messenger ribonucleic acid

in January 2024] (from initial opinion/marketing authorisation)] as per the request for supplementary information (RSI) adopted in April 2021

17.2.3. Filgotinib - JYSELECA (CAP) - EMEA/H/C/005113/MEA 002

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Protocol for study GS-EU-417-9046: a non-interventional PASS of filgotinib in the treatment of patients with moderate to severe active rheumatoid within the German registry Rheumatoide Arthritis: Beobachtung der Biologika-Therapie (RABBIT) [final report expected in Q4 2029]

17.2.4. Filgotinib - JYSELECA (CAP) - EMEA/H/C/005113/MEA 003

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Protocol for study GS-EU-417-9047: a non-interventional PASS of filgotinib in the treatment of patients with moderate to severe active rheumatoid arthritis within the Anti-Rheumatic Treatment in Sweden (ARTIS) register [final report expected in Q2 2030]

17.2.5. Filgotinib - JYSELECA (CAP) - EMEA/H/C/005113/MEA 004

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Protocol for study GS-EU-417-9048: a non-interventional PASS of filgotinib in the treatment of patients with moderate to severe active rheumatoid arthritis within the British Society for Rheumatology Biologics Register-Rheumatoid Arthritis (BSRBR-RA) [final report expected in Q3 2030]

17.2.6. Filgotinib - JYSELECA (CAP) - EMEA/H/C/005113/MEA 005

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Protocol for study GS-EU-417-5882: a non-interventional PASS of filgotinib in the treatment of patients with moderate to severe active rheumatoid arthritis within the Spanish Registry of Adverse Events of Biological Therapies in Rheumatoid Diseases (BIOBADASER) [final report expected in Q3 2030]

17.2.7. Filgotinib - JYSELECA (CAP) - EMEA/H/C/005113/MEA 006

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Protocol for study GS-EU-417-5883: a non-interventional PASS of filgotinib in the treatment of patients with moderate to severe active rheumatoid arthritis within the Danish Nationwide Clinical Register for Patients with Rheumatoid Arthritis (DANBIO) [final report

expected in Q2 2030]

17.2.8. Inclisiran - LEQVIO (CAP) - EMEA/H/C/005333/MEA 004

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Kimmo Jaakkola

Scope: Protocol for study CKJX839A12011: a non-interventional PASS to estimate the proportion of major congenital malformations among pregnancies exposed to inclisiran during pregnancy reported to Novartis amongst (i) live births and (ii) live births plus still births plus termination of pregnancy for foetal anomaly (TOPFA) - Inclisiran pregnancy outcomes intensive monitoring (PRIM) (from initial opinion/marketing authorisation)

17.2.9. Infliximab - REMSIMA (CAP) - EMEA/H/C/002576/MEA 020.3

Applicant: Celltrion Healthcare Hungary Kft.

PRAC Rapporteur: Kimmo Jaakkola

Scope: MAH's response to MEA 020.2 [protocol for study CT-P13 4.8: an observational, prospective cohort study to evaluate the safety of Remsima (infliximab) subcutaneous in patients with rheumatoid arthritis (RA)] as per the request for supplementary information (RSI) adopted in January 2021

17.2.10. Infliximab - REMSIMA (CAP) - EMEA/H/C/002576/MEA 021.1

Applicant: Celltrion Healthcare Hungary Kft.

PRAC Rapporteur: Kimmo Jaakkola

Scope: MAH's response to MEA 021 [protocol for study CT-P13 4.9: an observational, prospective cohort study to evaluate safety of Remsima (infliximab) subcutaneous in patients with ankylosing spondylitis, psoriatic arthritis, and psoriasis] as per the request for supplementary information (RSI) adopted in October 2020

17.2.11. Ivacaftor, tezacaftor, elexacaftor - KAFTRIO (CAP) - EMEA/H/C/005269/MEA 002.1

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Martin Huber

Scope: MAH's response to MEA 002 [protocol for study VX20-445-120: a five year-registry based study to assess real-world effects and utilisation patterns of elexacaftor/tezacaftor/ivacaftor combination therapy (ELX/TEZ/IVA) in patients with cystic fibrosis (CF)] as per the request for supplementary information (RSI) adopted in January 2021

17.2.12. Lumasiran - OXLUMO (CAP) - EMEA/H/C/005040/MEA 002

Applicant: Alnylam Netherlands B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Protocol for study ALN-GO1-007 an observational PASS to characterise the long-

term real-world safety of lumasiran in patients with primary hyperoxaluria type 1 (PH1) (from initial opinion/marketing authorisation (MA))

17.2.13. Lusutrombopag - MULPLEO (CAP) - EMEA/H/C/004720/MEA 002.2

Applicant: Shionogi B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: MAH's response to MEA 002.1 [protocol for study VV-REG-090246: a PASS exploring the hepatic safety of lusutrombopag Shionogi in patients with Child-Pugh class C liver disease (from initial opinion/marketing authorisation (MA)) [final study report expected in December 2025]] as per the request for supplementary information (RSI) adopted in January 2021

17.2.14. Niraparib - ZEJULA (CAP) - EMEA/H/C/004249/MEA 002.3

Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Jan Neuhauser

Scope: Amendment to a protocol previously agreed in March 2019 for study 3000-04-001: a non-interventional PASS to evaluate the risks of myelodysplastic syndrome (MDS)/ acute myeloid leukaemia (AML) and secondary primary malignancies (SPM) in adult patients with platinum-sensitive, relapsed, high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer receiving maintenance treatment with Zejula (niraparib)]

17.2.15. Sacubitril, valsartan - ENTRESTO (CAP) - EMEA/H/C/004062/MEA 004.9

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Anette Kirstine Stark

Scope: Amendment to a protocol previously agreed in September 2019 together with a feasibility assessment for study CLCZ696B2015 (PASS 3) (listed as a category 3 study in the RMP): a non-interventional post-authorisation European multi-database safety study to assess the risk of myotoxicity, hepatotoxicity and acute pancreatitis in statin-exposed heart failure patients with or without concomitant use of Entresto/Neparvis (sacubitril/valsartan) [final study report expected in December 2022]

17.2.16. Sacubitril, valsartan - NEPARVIS (CAP) - EMEA/H/C/004343/MEA 003.6

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Anette Kirstine Stark

Scope: Amendment to a protocol previously agreed in September 2019 together with a feasibility assessment for study CLCZ696B2015 (PASS 3) (listed as a category 3 study in the RMP): a non-interventional post-authorisation European multi-database safety study to assess the risk of myotoxicity, hepatotoxicity and acute pancreatitis in statin-exposed heart failure patients with or without concomitant use of Entresto/Neparvis (sacubitril/valsartan) [final study report expected in December 2022]

17.2.17. Selexipag - UPTRAVI (CAP) - EMEA/H/C/003774/MEA 003.3

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Adrien Inoubli

Scope: Amendment to a protocol previously agreed in May 2017 for study AC-065A403: a PASS to evaluate risk minimisation measures for mEDication errors with Uptravi (selexipag) during the titration phase in patients with pulmonary arterial hypertension (PAH) in Clinical prAcTicE (EDUCATE)

17.3. Results of PASS imposed in the marketing authorisation(s)[88]

None

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

17.4.1. Anakinra - KINERET (CAP) - EMEA/H/C/000363/II/0078

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Anette Kirstine Stark

Scope: Submission of the final report from study Sobi-ANAKIN-201 (listed as a category 3 study in the RMP): a non-interventional PASS to evaluate the safety of Kineret (anakinra) in the treatment of cryopyrin associated periodic syndromes (CAPS) in routine clinical care with regard to serious infections, malignancies, injection site reactions, allergic reactions and medication errors, including reuse of syringe. The RMP (version 5.4) is updated accordingly. In addition, the RMP is updated to include information about a completed paediatric study (Sobi.ANAKIN-301) assessed as per Article 46 of Regulation No 1901/2006 (P46/031): a randomised, double-blind, placebo-controlled, multicentre, phase 3 study which evaluated the efficacy, safety, pharmacokinetics and immunogenicity of anakinra as compared to placebo in newly diagnosed Still's disease patients (including systemic juvenile idiopathic arthritis [SJIA] and adult-onset Still's disease [AOSD])

17.4.2. Blinatumomab - BLINCYTO (CAP) - EMEA/H/C/003731/II/0039, Orphan

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Eva Jirsová

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

[88] In accordance with Article 107p-q of Directive 2001/83/EC
[89] In accordance with Article 61a (6) of Regulation (EC) No 726/2004, in line with the revised variations regulation for any submission as of 04 August 2013

17.4.3. Certolizumab pegol - CIMZIA (CAP) - EMEA/H/C/001037/II/0099

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of the final report from study RA0020 (listed as a category 3 study in the RMP): a nationwide prospective observational cohort study in Germany on the long-term safety and effectiveness of biologic disease-modifying antirheumatic drugs (bDMARDs) in rheumatoid arthritis (RA). In addition, this submission includes a safety analysis across the 4 completed RA registries (Antirheumatic Therapies in Sweden (ARTIS), National Data Bank (NDB), British Society for Rheumatology Biologics Register (BSRBR) and Rheumatoide Arthritis: Beobachtung der Biologika-Therapie (RABBIT)) as per the conclusions of variations II/0072, II/0081, and II/0087 finalised in January 2019, September 2019 and June 2020 respectively. The RMP (version 19.0) is updated accordingly and in line with revision 2 of GVP module V on 'Risk management systems'

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

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

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

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

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Anette Kirstine Stark

Scope: Grouped variation consisting of: 1) submission of the final report from drug utilisation study 1160.129 (GLORIA AF): a three-phase, international, multicentre, prospective, observational registry programme in patients with newly diagnosed non-valvular atrial fibrillation (NV AF) at risk for stroke in order to investigate patient characteristics influencing the choice of antithrombotic treatment for the prevention of stroke in NV AF patients globally and to collect data from clinical practice settings on important outcome events of antithrombotic treatments for the prevention of stroke; 2) submission of the final report from drug utilisation study 1160.136 (EU GLORIA AF) (listed as a category 3 study in the RMP): a three-phase, international, multicentre, prospective, observational registry programme in patients with newly diagnosed non-valvular atrial fibrillation (NV AF) at risk for stroke in order to investigate patient characteristics influencing the choice of antithrombotic treatment for the prevention of stroke in NV AF patients from participating countries in EU/EEA Member States and to collect data from clinical practice settings on important outcome events of antithrombotic treatments for the prevention of stroke. The RMP (version 39) is updated accordingly

17.4.6. Dibotermin alfa - INDUCTOS (CAP) - EMEA/H/C/000408/II/0100

Applicant: Medtronic BioPharma B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Submission of the final study report from study EUPAS32916 (listed as category 3 study in the RMP): an observational study to evaluate the effectiveness of additional risk minimisation measures for InductOs (dibotermin alfa). The product information and the RMP (version 2.1) are updated accordingly. In addition, the MAH took the opportunity to submit study protocol for study EUPAS32916 as suggested by PRAC

17.4.7. Herpes zoster vaccine (recombinant, adjuvanted) - SHINGRIX (CAP) - EMEA/H/C/004336/II/0045

Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Sonja Hrabcik

Scope: Update of section 4.4 of the SmPC in order to add a new warning on an increased risk of Guillain-Barré Syndrome (GBS) after vaccination with Shingrix (herpes zoster vaccine) observed in a post-marketing observational study in individuals aged 65 years or older. The RMP (version 5.1) is updated accordingly. In addition, the MAH took the opportunity to make some editorial changes to the SmPC and to update the list of local representatives in the package leaflet

17.4.8. Human normal immunoglobulin - HYQVIA (CAP) - EMEA/H/C/002491/II/0070/G

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Grouped variations consisting of: 1) update of section 4.6 of the SmPC in order to update information on pregnancy and breast-feeding based on the final results from study 161301 (listed as a category 3 study in the RMP): an observational pregnancy registry study to collect long-term safety data from women treated with HyQvia (human normal immunoglobulin). The package leaflet and the RMP (version 12,0) are updated accordingly. In addition, the MAH took the opportunity to implement minor corrections and editorial changes to the SmPC; 2) submission of an updated RMP (version 12.0) to update the educational material (additional risk minimisation measures) as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00001633/202005)

17.4.9. Lomitapide - LOJUXTA (CAP) - EMEA/H/C/002578/II/0047

Applicant: Amryt Pharmaceuticals DAC

PRAC Rapporteur: Menno van der Elst

Scope: Introduction of an enhanced pharmacovigilance system to evaluate the occurrence and outcomes of pregnancy in females of reproductive potential treated with lomitapide who decide to continue the pregnancy following advice from a teratologist/clinician, replacing the currently-agreed pregnancy exposure register (PER) (listed as part of Annex II-E on 'specific obligation to complete post-authorisation measures for the marketing authorisation under exceptional circumstances'). The RMP (version 6.5) is updated

accordingly. In addition, the MAH took the opportunity to introduce minor administrative changes

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 048.9

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Kimmo Jaakkola

Scope: Annual update report on recruitment for study IM101240 (listed as a category 3 study in the RMP): an observational registry of abatacept in patients with juvenile idiopathic arthritis (JIA registry) to explore the long-term safety of abatacept treatment for JIA in routine clinical practice by quantifying the incidence rates of serious infections, autoimmune disorders and malignancies [final registry report expected by 2029]

17.5.2. Adalimumab - HUMIRA (CAP) - EMEA/H/C/000481/MEA 065.11

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Twelfth interim annual report for study P10-023, a psoriasis patient registry: a 10-year, post-marketing observational study to assess the long term safety of Humira (adalimumab) in adult patients with chronic plaque psoriasis (PS) [final registry report expected in February 2023]

17.5.3. Arsenic trioxide - TRISENOX (CAP) - EMEA/H/C/000388/MEA 050.2

Applicant: Teva B.V.

PRAC Rapporteur: Tiphaine Vaillant

Scope: First interim report for study C18477-ONC-50025: a post-authorisation long term safety cohort study in acute promyelocytic leukaemia (APL) patients treated with Trisenox (arsenic trioxide) to assess the long-term safety of all-trans retinoic acid (ATRA) + arsenic trioxide (ATO) in newly-diagnosed low to intermediate risk APL patients in a real-world clinical practice setting [final report expected in 2Q 2023]

17.5.4. Autologous CD34$^+$ enriched cell fraction that contains CD34$^+$ cells transduced with retroviral vector that encodes for the human adenosine deaminase (ADA) cDNA sequence - STRIMVELIS (CAP) - EMEA/H/C/003854/ANX 004.3

Applicant: Orchard Therapeutics (Netherlands) BV, ATMP[90]

PRAC Rapporteur: Menno van der Elst

Scope: Second interim report for study GSK2696273 – an adenosine deaminase severe combined immunodeficiency (ADA-SCID) registry for patients treated with Strimvelis gene therapy: a long-term prospective, non-interventional follow-up of safety and effectiveness

[90] Advanced therapy medicinal product

17.5.5. Coronavirus (COVID-19) mRNA[91] vaccine (nucleoside-modified) - COVID-19 VACCINE MODERNA (CAP) - EMEA/H/C/005791/MEA 003.1

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Hans Christian Siersted

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

17.5.6. Filgrastim - FILGRASTIM HEXAL (CAP) - EMEA/H/C/000918/MEA 007.10

Applicant: Hexal AG

PRAC Rapporteur: Menno van der Elst

Scope: Tenth annual report for study EP06-501 (SMART): a non-interventional, prospective, long-term safety data collection of Zarzio/Filgrastim Hexal (filgrastim) in healthy unrelated stem cell donors undergoing peripheral blood progenitor cell (PBPC) mobilisation [final clinical study report (CSR) expected in December 2024] together with MAH's response to MEA 007.8 as per the request for supplementary information (RSI) adopted in December 2020

17.5.7. Filgrastim - ZARZIO (CAP) - EMEA/H/C/000917/MEA 007.10

Applicant: Sandoz GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Tenth annual report for study EP06-501 (SMART): a non-interventional, prospective, long-term safety data collection of Zarzio/Filgrastim Hexal (filgrastim) in healthy unrelated stem cell donors undergoing peripheral blood progenitor cell (PBPC) mobilisation [final clinical study report (CSR) expected in December 2024] together with MAH's response to MEA 007.8 as per the request for supplementary information (RSI) adopted in December 2020

17.5.8. Insulin human - INSUMAN (CAP) - EMEA/H/C/000201/MEA 041.4

Applicant: Sanofi-Aventis Deutschland GmbH

PRAC Rapporteur: Jean-Michel Dogné

Scope: Fifth interim report for Insuman (insulin human) implantable registry HUBIN-C-06380: a European observational cohort of patients with type 1 diabetes treated via intraperitoneal route with Insuman implantable 400 IU/mL (insulin human) in Medtronic MiniMed implantable pump

[91] Messenger ribonucleic acid

17.5.9. Lumacaftor, ivacaftor - ORKAMBI (CAP) - EMEA/H/C/003954/ANX 003.6

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: MAH's response to ANX 003.5 [fourth annual report for study VX14 809 108 (listed as a category 1 study in Annex II and the RMP): an observational study to evaluate the utilisation patterns and long-term effects of lumacaftor/ivacaftor therapy in patients with cystic fibrosis (CF) [final report expected in December 2021] as per the request for supplementary information (RSI) adopted in February 2021

17.5.10. Mercaptamine - CYSTADROPS (CAP) - EMEA/H/C/003769/MEA 001.3

Applicant: Recordati Rare Diseases

PRAC Rapporteur: Eva Segovia

Scope: First annual report for study CYT-DS-001 (listed as a category 3 study in the RMP): an open-label longitudinal PASS to assess the safety of Cystadrops (mercaptamine) in paediatric and adult cystinosis patients in long term use

17.5.11. Sacubitril, valsartan - ENTRESTO (CAP) - EMEA/H/C/004062/MEA 002.6

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Anette Kirstine Stark

Scope: Fourth interim results for study CLCZ696B2014 (PASS 1) (listed as a category 3 study in the RMP): a non-interventional post-authorisation European multi-database safety study to characterise the risk of angioedema and other specific safety events of interest in association with the use of Entresto/Neparvis (sacubitril/valsartan) in adult patients with heart failure [final report expected in Q4/2022]

17.5.12. Sacubitril, valsartan - NEPARVIS (CAP) - EMEA/H/C/004343/MEA 002.3

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Anette Kirstine Stark

Scope: Fourth interim results for study CLCZ696B2014 (PASS 1) (listed as a category 3 study in the RMP): a non-interventional post-authorisation European multi-database safety study to characterise the risk of angioedema and other specific safety events of interest in association with the use of Entresto/Neparvis (sacubitril/valsartan) in adult patients with heart failure [final report expected in Q4/2022]

17.5.13. Sarilumab - KEVZARA (CAP) - EMEA/H/C/004254/MEA 002.5

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Eva Segovia

Scope: Second interim report for safety surveillance programme using existing EU rheumatoid arthritis (RA) registries conducted in four countries: Germany (German Register for Rheumatoid Arthritis Observation of Biologic Therapy (RABBIT) (OBS15180)), Spain

(Spanish Registry for Adverse Events for Biological Therapy in Rheumatic Diseases (BIOBASASER) (6R88-RA-1720)), Sweden (Register for Antirheumatic Therapies in Sweden (ARTIS) (OBS15220)) and UK (British Society for Rheumatology Biologicals Register (BSRBR) (6R88-RA-1634)

17.5.14. Selexipag - UPTRAVI (CAP) - EMEA/H/C/003774/MEA 001.6

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Adrien Inoubli

Scope: Fourth annual interim report for PASS AC-065A401 (EXPOSURE): an observational cohort study of pulmonary arterial hypertension (PAH) patients newly-treated with either Uptravi (selexipag) or any other PAH-specific therapy in routine clinical practice [final study report expected in 2023]

17.5.15. Tisagenlecleucel - KYMRIAH (CAP) - EMEA/H/C/004090/ANX 003.5

Applicant: Novartis Europharm Limited, ATMP[92]

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Third semi-annual report for a study based on disease registry CCTL019B2401 (listed as a category 1 study in Annex II and the RMP): a non-interventional PASS in acute lymphoblastic leukaemia (ALL) and diffuse large B-cell lymphoma (DLBCL) patients in order to further characterise the safety, including long-term safety, of Kymriah (tisagenlecleucel) [final study report expected in December 2038] (European Society for Blood and Marrow Transplant (EBMT) data only)

17.5.16. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/MEA 008.3

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: First interim study report for study A3921312 (listed as a category 3 study in the RMP): a prospective non-interventional comparative active surveillance PASS of serious infection, malignancy, cardiovascular and other adverse event rates among patients treated with Xeljanz (tofacitinib) for moderately to severely active rheumatoid arthritis (RA) within the British Society for Rheumatology Biologics Register-Rheumatoid Arthritis (BSRBR-RA)

17.5.17. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/MEA 009.3

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: First interim study report for study A3921314 (listed as a category 3 study in the RMP): a prospective non-interventional comparative active surveillance PASS of serious infection, malignancy, cardiovascular and other adverse event rates among patients treated with Xeljanz (tofacitinib) for moderately to severely active rheumatoid arthritis (RA) within the Swedish (ARTIS) register

[92] Advanced therapy medicinal product

17.5.18. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/MEA 010.3

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: First interim study report for study A3921316 (listed as a category 3 study in the RMP): a prospective non-interventional comparative active surveillance PASS of serious infection, malignancy, cardiovascular and other adverse event rates among patients treated with Xeljanz (tofacitinib) for moderately to severely active rheumatoid arthritis (RA) within the Spanish registry of adverse events of biological therapies and biosimilars in rheumatoid diseases (BIOBADASER)

17.5.19. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/MEA 011.3

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: First interim study report for study A3921317 (listed as a category 3 study in the RMP): a prospective non-interventional comparative active surveillance PASS of serious infection, malignancy, cardiovascular and other adverse event rates among patients treated with Xeljanz (tofacitinib) for moderately to severely active rheumatoid arthritis (RA) within the German registry Rheumatoide Arthritis: Beobachtung der Biologika-Therapie (RABBIT)

17.5.20. Ulipristal acetate - ESMYA (CAP) - EMEA/H/C/002041/MEA 018.5

Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Annika Folin

Scope: Fifth yearly progress report for study PGL14-001: a prospective, multinational, multicentre, non-interventional study to evaluate the long-term safety of Esmya (ulipristal acetate) in particular the endometrial safety and the current prescription and management patterns of Esmya (ulipristal acetate) in a long-term treatment setting [final clinical study report (CSR) expected in 2023]

17.5.21. Umeclidinium - ROLUFTA ELLIPTA (CAP) - EMEA/H/C/004654/ANX 003

Applicant: GlaxoSmithKline Trading Services Limited

PRAC Rapporteur: Ilaria Baldelli

Scope: Interim report for study 201038 (EU PASS 10316): non-interventional post-authorisation safety (PAS) observational cohort study to quantify the incidence and comparative safety of selected cardiovascular and cerebrovascular events in chronic obstructive pulmonary disease (COPD) patients with umeclidinium/vilanterol (UMEC/VI) combination, or inhaled UMEC versus tiotropium

17.5.22. Umeclidinium, vilanterol - ANORO ELLIPTA (CAP) - EMEA/H/C/002751/ANX 001.2

Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Ilaria Baldelli

Scope: Interim report for study 201038 (EU PASS 10316): non-interventional post-authorisation safety (PAS) observational cohort study to quantify the incidence and comparative safety of selected cardiovascular and cerebrovascular events in chronic obstructive pulmonary disease (COPD) patients with umeclidinium/vilanterol (UMEC/VI) combination, or inhaled UMEC versus tiotropium

17.5.23. Umeclidinium, vilanterol - LAVENTAIR ELLIPTA (CAP) - EMEA/H/C/003754/ANX 001.2

Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Ilaria Baldelli

Scope: Interim report for study 201038 (EU PASS 10316): non-interventional post-authorisation safety (PAS) observational cohort study to quantify the incidence and comparative safety of selected cardiovascular and cerebrovascular events in chronic obstructive pulmonary disease (COPD) patients with umeclidinium/vilanterol (UMEC/VI) combination, or inhaled UMEC versus tiotropium

17.5.24. Umeclidinium bromide - INCRUSE ELLIPTA (CAP) - EMEA/H/C/002809/ANX 001.2

Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Ilaria Baldelli

Scope: Interim report for study 201038 (EU PASS 10316): non-interventional post-authorisation safety (PAS) observational cohort study to quantify the incidence and comparative safety of selected cardiovascular and cerebrovascular events in chronic obstructive pulmonary disease (COPD) patients with umeclidinium/vilanterol (UMEC/VI) combination, or inhaled UMEC versus tiotropium

17.5.25. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/MEA 044.11

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Rhea Fitzgerald

Scope: Third interval safety registry for study CNTO1275PSO4056: an observational PASS of ustekinumab in the treatment of paediatric patients aged 12 years and older with moderate to severe plaque psoriasis (adolescent registry)

17.6. Others

17.6.1. Avatrombopag - DOPTELET (CAP) - EMEA/H/C/004722/MEA 002.3

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Eva Segovia

Scope: MAH's response to MEA 002.2 [feasibility assessment for study AVA-CLD-402: evaluation of the feasibility of conducting a PASS of Doptelet (avatrombopag) in patients with severe chronic liver disease (CLD) and of the use of potential European electronic health care databases] as per the request for supplementary information (RSI) adopted in January 2021

17.6.2. Ciclosporin - VERKAZIA (CAP) - EMEA/H/C/004411/MEA 001.3

Applicant: Santen Oy

PRAC Rapporteur: Jan Neuhauser

Scope: Feasibility assessment report for study Oxon 114-59 (version 3.0): a feasibility study for a case-control study linked to existing cancer registries to understand the data sources and analytic methods available to quantify the risk of periocular skin cancer, conjunctival or corneal neoplasia in children treated with Verkazia (ciclosporin)

17.6.3. Fentanyl - INSTANYL (CAP) - EMEA/H/C/000959/LEG 028.3

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Tiphaine Vaillant

Scope: Fourth six-monthly update on the development of the child-resistant multi-dose nasal spray DoseGuard as requested in the conclusions of procedure R/0049 finalised in April 2019

17.7. New Scientific Advice

None

17.8. Ongoing Scientific Advice

None

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

None

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

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

18.1. Annual reassessments of the marketing authorisation

18.1.1. Clofarabine - EVOLTRA (CAP) - EMEA/H/C/000613/S/0072 (without RMP)

Applicant: Genzyme Europe BV

PRAC Rapporteur: Tiphaine Vaillant

Scope: Annual reassessment of the marketing authorisation

18.1.2. Velmanase alfa - LAMZEDE (CAP) - EMEA/H/C/003922/S/0019 (without RMP)

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Jan Neuhauser

Scope: Annual reassessment of the marketing authorisation

18.2. Conditional renewals of the marketing authorisation

18.2.1. Bulevirtide - HEPCLUDEX (CAP) - EMEA/H/C/004854/R/0003 (without RMP)

Applicant: MYR GmbH

PRAC Rapporteur: Adam Przybylkowski

Scope: Conditional renewal of the marketing authorisation

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

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Laurence de Fays

Scope: Conditional renewal of the marketing authorisation

18.2.3. Larotrectinib - VITRAKVI (CAP) - EMEA/H/C/004919/R/0014 (without RMP)

Applicant: Bayer AG

PRAC Rapporteur: Rugile Pilviniene

Scope: Conditional renewal of the marketing authorisation

18.3. Renewals of the marketing authorisation

18.3.1. Baricitinib - OLUMIANT (CAP) - EMEA/H/C/004085/R/0025 (without RMP)

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: 5-year renewal of the marketing authorisation

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

Applicant: Mylan S.A.S

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: 5-year renewal of the marketing authorisation

18.3.3. Edotreotide - SOMAKIT TOC (CAP) - EMEA/H/C/004140/R/0019 (with RMP)

Applicant: Advanced Accelerator Applications

PRAC Rapporteur: Ronan Grimes

Scope: 5-year renewal of the marketing authorisation

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

Applicant: KRKA, d.d., Novo mesto

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: 5-year renewal of the marketing authorisation

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

Applicant: Mylan S.A.S

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: 5-year renewal of the marketing authorisation

18.3.6. Enoxaparin sodium - INHIXA (CAP) - EMEA/H/C/004264/R/0076 (with RMP)

Applicant: Techdow Pharma Netherlands B.V.

PRAC Rapporteur: Menno van der Elst

Scope: 5-year renewal of the marketing authorisation

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

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ilaria Baldelli

Scope: 5-year renewal of the marketing authorisation

18.3.8. Insulin aspart - FIASP (CAP) - EMEA/H/C/004046/R/0028 (with RMP)

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Annika Folin

Scope: 5-year renewal of the marketing authorisation

18.3.9. Lonoctocog alfa - AFSTYLA (CAP) - EMEA/H/C/004075/R/0037 (with RMP)

Applicant: CSL Behring GmbH

PRAC Rapporteur: Sonja Hrabcik

Scope: 5-year renewal of the marketing authorisation

18.3.10. Sildenafil - GRANPIDAM (CAP) - EMEA/H/C/004289/R/0009 (without RMP)

Applicant: Accord Healthcare S.L.U.

PRAC Rapporteur: Menno van der Elst

Scope: 5-year renewal of the marketing authorisation

18.3.11. Tenofovir disoproxil - TENOFOVIR DISOPROXIL MYLAN (CAP) - EMEA/H/C/004049/R/0022 (without RMP)

Applicant: Mylan S.A.S

PRAC Rapporteur: Adrien Inoubli

Scope: 5-year renewal of the marketing authorisation

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

Applicant: STADA Arzneimittel AG

PRAC Rapporteur: Ronan Grimes

Scope: 5-year renewal of the marketing authorisation

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

Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Ronan Grimes

Scope: 5-year renewal of the marketing authorisation

19. Annex II – List of participants

including any restrictions with respect to involvement of members / alternates / experts following evaluation of declared interests for the 07-10 June 2021 meeting (marked as "[a]"), and for the 24 June 2021 ORGAM teleconference (marked as "[b]").

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Sabine Straus [a, b]	Chair	The Netherlands	No interests declared	Full involvement
Jan Neuhauser [a, b]	Member	Austria	No interests declared	Full involvement
Sonja Hrabcik [a]	Alternate	Austria	No interests declared	Full involvement
Jean-Michel Dogné [a, b]	Member	Belgium	No interests declared	Full involvement
Laurence de Fays [a, b]	Alternate	Belgium	No interests declared	Full involvement
Maria Popova-Kiradjieva [a]	Member	Bulgaria	No interests declared	Full involvement
Nikica Mirošević Skvrce [a, b]	Member	Croatia	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Panagiotis Psaras [a]	Member	Cyprus	No interests declared	Full involvement
Christina Sylvia Chrysostomou [a, b]	Alternate	Cyprus	No interests declared	Full involvement
Eva Jirsová [a, b]	Member	Czechia	No interests declared	Full involvement
Jana Lukacisinova [a, b]	Alternate	Czechia	No interests declared	Full involvement
Anette Kirstine Stark [a, b]	Member	Denmark	No interests declared	Full involvement
Hans Christian Siersted [a]	Alternate	Denmark	No participation in discussion, final deliberations and voting on:	15.3.20. Mepolizumab - NUCALA (CAP) - EMEA/H/C/003860/II/0036/G
Maia Uusküla [a]	Member	Estonia	No interests declared	Full involvement
Kirsti Villikka [a, b]	Member	Finland	No interests declared	Full involvement
Kimmo Jaakkola [a]	Alternate	Finland	No interests declared	Full involvement
Adrien Inoubli [a, b]	Member	France	No interests declared	Full involvement
Tiphaine Vaillant [a, b]	Alternate	France	No interests declared	Full involvement
Martin Huber [a, b]	Member (Vice-Chair)	Germany	No interests declared	Full involvement
Brigitte Keller-Stanislawski [a]	Alternate	Germany	No interests declared	Full involvement
Agni Kapou [a]	Member	Greece	No interests declared	Full involvement
Julia Pallos [a, b]	Member	Hungary	No participation in final deliberations and voting on:	11.2.1. Levothyroxine (NAP) - DE/H/XXXX/WS/674, 16.1.25. Edoxaban - LIXIANA (CAP); ROTEAS (CAP) -

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				PSUSA/00010387/202010, 16.2.2. Insulin human - ACTRAPID (CAP), INSUMAN (CAP); insulin human, insulin isophane - ACTRAPHANE (CAP), INSULATARD (CAP), MIXTARD (CAP), PROTAPHANE (CAP); NAP - PSUSA/00001753/202010
Melinda Palfi [a]	Alternate	Hungary	No interests declared	Full involvement
Guðrún Stefánsdóttir [a, b]	Member	Iceland	No participation in discussion, final deliberations and voting on:	14.1.1. Adalimumab – AMGEVITA (CAP); AMSPARITY (CAP); HEFIYA (CAP); HULIO (CAP); HUMIRA (CAP); HYRIMOZ (CAP); IDACIO (CAP); IMRALDI (CAP); YUFLYMA (CAP), 15.3.9. Evolocumab - REPATHA (CAP) - EMEA/H/C/003766/II/0049/G,

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				16.1.17. Darbepoetin alfa - ARANESP (CAP) - PSUSA/00000932/202010, 16.1.19. Denosumab - XGEVA (CAP) - PSUSA/00009119/202009, 16.1.29. Etelcalcetide - PARSABIV (CAP) - PSUSA/00010533/202011, 16.1.65. Talimogene laherparepvec - IMLYGIC (CAP) - PSUSA/00010459/202010, 17.1.1. Blinatumomab – BLINCYTO (CAP) - EMEA/H/C/PSA/S/0065.1, 17.4.2. Blinatumomab - BLINCYTO (CAP) - EMEA/H/C/003731/II/0039, 18.3.7. Etelcalcetide - PARSABIV (CAP) - EMEA/H/C/003995/R/0017
Rhea Fitzgerald [a, b]	Member	Ireland	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Ilaria Baldelli [a, b]	Alternate	Italy	No interests declared	Full involvement
Zane Neikena [a, b]	Member	Latvia	No interests declared	Full involvement
Rugile Pilviniene [a, b]	Member	Lithuania	No interests declared	Full involvement
Nadine Petitpain [a, b]	Member	Luxembourg	No restrictions applicable to this meeting	Full involvement
Anne-Cécile Vuillemin [b]	Alternate	Luxembourg	No interests declared	Full involvement
John Joseph Borg [a]	Member (CHMP member)	Malta	No interests declared	Full involvement
Menno van der Elst [a, b]	Member	The Netherlands	No interests declared	Full involvement
Liana Gross-Martirosyan [a]	Alternate	The Netherlands	No interests declared	Full involvement
David Olsen [a, b]	Member	Norway	No participation in final deliberations and voting on:	6.1.10. Regorafenib - STIVARGA (CAP) - PSUSA/00010133/202009, 16.1.42. Larotrectinib - VITRAKVI (CAP) - PSUSA/00010799/202011, 18.2.3. Larotrectinib - VITRAKVI (CAP) - EMEA/H/C/004919/R/0014
Karen Pernille Harg [a, b]	Alternate	Norway	No interests declared	Full involvement
Adam Przybylkowski [a]	Member	Poland	No interests declared	Full involvement
Katarzyna Ziolkowska [b]	Alternate	Poland	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Ana Diniz Martins [a, b]	Member	Portugal	No interests declared	Full involvement
Marcia Silva [a, b]	Alternate	Portugal	No interests declared	Full involvement
Roxana Dondera [a]	Member	Romania	No interests declared	Full involvement
Alexandra - Maria Spurni [a, b]	Alternate	Romania	No interests declared	Full involvement
Marek Juracka [a, b]	Alternate	Slovakia	No interests declared	Full involvement
Jasmina Klopcic [a, b]	Alternate	Slovenia	No interests declared	Full involvement
Eva Segovia [a]	Member	Spain	No interests declared	Full involvement
Maria del Pilar Rayon [a, b]	Alternate	Spain	No interests declared	Full involvement
Ulla Wändel Liminga [a, b]	Member	Sweden	No interests declared	Full involvement
Annika Folin [a, b]	Alternate	Sweden	No interests declared	Full involvement
Birgitta Grundmark [b]	Member	Independent scientific expert	No interests declared	Full involvement
Daniel Morales [a]	Member	Independent scientific expert	No interests declared	Full involvement
Hedvig Nordeng [a]	Member	Independent scientific expert	No interests declared	Full involvement
Antoine Pariente [a]	Member	Independent scientific expert	No restrictions applicable to this meeting	Full involvement
Milou Daniel Drici [a, b]	Member	Independent scientific expert	No restrictions applicable to this meeting	Full involvement
Stefan Weiler [a]	Member	Independent scientific expert	No interests declared	Full involvement
Raymond Anderson [a]	Member	Healthcare Professionals' Representative	No interests declared	Full involvement
Roberto Frontini [a, b]	Alternate	Healthcare Professionals' Representative	No participation in final	15.2.9. Simoctocog alfa - NUWIQ (CAP) -

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			deliberations and voting on:	EMEA/H/C/002813/WS2064/0043; VIHUMA (CAP) - EMEA/H/C/004459/WS2064/0024
Cathalijne van Doorne [a, b]	Member	Patients' Organisation Representative	No interests declared	Full involvement
Virginie Hivert [a]	Alternate	Patients' Organisation Representative	No restrictions applicable to this meeting	Full involvement
Els Beghein [a]	Expert - via Webex*	Belgium	No interests declared	Full involvement
Christelle Bizimungu [a]	Expert - via Webex*	Belgium	No restrictions applicable to this meeting	Full involvement
Inne Crevecoeur [a]	Expert - via Webex*	Belgium	No restrictions applicable to this meeting	Full involvement
Sophie Goethals [a]	Expert - via Webex*	Belgium	No restrictions applicable to this meeting	Full involvement
Jamila Hamdani [a]	Expert - via Webex*	Belgium	No interests declared	Full involvement
Tom Lams [a]	Expert - via Webex*	Belgium	No interests declared	Full involvement
Martine Sabbe [a, b]	Expert - via Webex*	Belgium	No interests declared	Full involvement
Flora Musuamba Tshinanu [a]	Expert - via Webex*	Belgium	No restrictions applicable to this meeting	Full involvement
Françoise Wuillaume [a]	Expert - via Webex*	Belgium	No interests declared	Full involvement
Barbara Kovačić [a]	Expert - via Webex*	Croatia	No interests declared	Full involvement
Ivana Ljubičić [a]	Expert - via Webex*	Croatia	No restrictions	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			applicable to this meeting	
Michaela Dlouhá [a]	Expert - via Webex*	Czechia	No interests declared	Full involvement
Petra Kaftanová [a, b]	Expert - via Webex*	Czechia	No interests declared	Full involvement
Kristýna Schneiderová [a]	Expert - via Webex*	Czechia	No interests declared	Full involvement
Petra Vacková [a]	Expert - via Webex*	Czechia	No interests declared	Full involvement
Marian Hjortlund Allon [a]	Expert - via Webex*	Denmark	No interests declared	Full involvement
Karin Erneholm [a]	Expert - via Webex*	Denmark	No restrictions applicable to this meeting	Full involvement
Moritz Sander [a]	Expert - via Webex*	Denmark	No interests declared	Full involvement
Ane Blicher Schelde [a]	Expert - via Webex*	Denmark	No restrictions applicable to this meeting	Full involvement
Emma Louise Nautrup Ravn Stadsbjerg [a]	Expert - via Webex*	Denmark	No interests declared	Full involvement
Josiane Uwera [a]	Expert - via Webex*	Denmark	No restrictions applicable to this meeting	Full involvement
Päivi Susanna Worsøe [a]	Expert - via Webex*	Denmark	No interests declared	Full involvement
Sarah Bendahou [a]	Expert - via Webex*	France	No restrictions applicable to this meeting	Full involvement
Violaine Closson-Carella [a]	Expert - via Webex*	France	No interests declared	Full involvement
Stéphanie Hueber [a]	Expert - via Webex*	France	No restrictions applicable to this meeting	Full involvement
Faustine Vidil [a]	Expert - via Webex*	France	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Maxim Frizler [a]	Expert - via Webex*	Germany	No interests declared	Full involvement
Dennis Lex [a]	Expert - via Webex*	Germany	No restrictions applicable to this meeting	Full involvement
Susanne Müller [a]	Expert - via Webex*	Germany	No interests declared	Full involvement
Martina Schussler-Lenz [a]	Expert - via Webex*	Germany	No interests declared	Full involvement
Konstantinos Markopoulos [a]	Expert - via Webex*	Greece	No interests declared	Full involvement
Niamh Buckley [a]	Expert - via Webex*	Ireland	No interests declared	Full involvement
Grainne Kirwan [a]	Expert - via Webex*	Ireland	No interests declared	Full involvement
Alessandro Aiuti [a]	Expert - via Webex*	Italy	No restrictions applicable to this meeting	Full involvement
Amelia Cupelli [a, b]	Expert - via Webex*	Italy	No interests declared	Full involvement
Ineke Crijns [a]	Expert - via Webex*	The Netherlands	No restrictions applicable to this meeting	Full involvement
Astrid de Gooijer-van Ee [a]	Expert - via Webex*	The Netherlands	No interests declared	Full involvement
Carla Herberts [a]	Expert - via Webex*	The Netherlands	No restrictions applicable to this meeting	Full involvement
Marianne Klanker [a]	Expert - via Webex*	The Netherlands	No interests declared	Full involvement
Marcel Kwa [a]	Expert - via Webex*	The Netherlands	No interests declared	Full involvement
Petrus Luijsterburg [a]	Expert - via Webex*	The Netherlands	No interests declared	Full involvement
Viktoriia Starokozhko [a]	Expert - via Webex*	The Netherlands	No restrictions applicable to this meeting	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Sophia Venzke [a]	Expert - via Webex*	The Netherlands	No interests declared	Full involvement
Ita Walsh [a]	Expert - via Webex*	The Netherlands	No interests declared	Full involvement
Inge Zomerdijk [a]	Expert - via Webex*	The Netherlands	No interests declared	Full involvement
Polona Golmajer [a]	Expert - via Webex*	Slovenia	No interests declared	Full involvement
Petra Brina Kovačič [a]	Expert - via Webex*	Slovenia	No interests declared	Full involvement
Consuelo Mejías Pavón [a]	Expert - via Webex*	Spain	No interests declared	Full involvement
Helena Back [a]	Expert - via Webex*	Sweden	No interests declared	Full involvement
Charlotte Backman [a]	Expert - via Webex*	Sweden	No interests declared	Full involvement
Karin Hellgren [a]	Expert - via Webex*	Sweden	No restrictions applicable to this meeting	Full involvement
Jessica Mwinyi [a]	Expert - via Webex*	Sweden	No interests declared	Full involvement
A representative from the European Commission attended the meeting				
Meeting run with support from relevant EMA staff				

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

20. Annex III - List of acronyms and abbreviations

For a list of acronyms and abbreviations used in the PRAC minutes, see:
Home>Committees>PRAC>Agendas, minutes and highlights

21. Explanatory notes

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

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

(Items 2 and 3 of the PRAC minutes)

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

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

Signals assessment and prioritisation

(Item 4 of the PRAC minutes)

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

Risk Management Plans (RMPs)

(Item 5 of the PRAC minutes)

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

Assessment of Periodic Safety Update Reports (PSURs)

(Item 6 of the PRAC minutes)

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

Post-authorisation Safety Studies (PASS)

(Item 7 of the PRAC minutes)

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

Product related pharmacovigilance inspections

(Item 9 of the PRAC minutes)

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

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