16 January 2020
EMA/PRAC/287927/2020
Inspections, Human Medicines Pharmacovigilance and Committees Division

Pharmacovigilance Risk Assessment Committee (PRAC)

Minutes of PRAC meeting on 25-28 November 2019

Chair: Sabine Straus – Vice-Chair: Martin Huber

Health and safety information

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

Disclaimers

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

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

Note on access to documents

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

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1. Introduction

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

The Chairperson opened the 25-28 November 2019 meeting by welcoming all participants.

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 the Rules of Procedure. All decisions taken at this meeting were made in the presence of a quorum of members (i.e. 24 or more members were present in the room). All decisions, recommendations and advice were agreed unanimously, unless otherwise specified.

1.2. Agenda of the meeting on 25-28 November 2019

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 28-31 October 2019

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

Post-meeting note: the PRAC minutes of the meeting held on 28-31 October 2019 were published on the EMA website on 28 February 2020 (EMA/PRAC/107813/2020).

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

2.4. Planned public hearings

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. Fluorouracil and related substances: capecitabine - CAPECITABINE ACCORD (CAP); CAPECITABINE MEDAC (CAP); CAPECITABINE TEVA (CAP); ECANSYA (CAP); XELODA (CAP); NAP flucytosine (NAP); 5-fluorouracil (5-FU) (NAP); tegafur (NAP); tegafur, gimeracil, oteracil – TEYSUNO (CAP) - EMEA/H/A-31/1481

Applicants: Accord Healthcare S.L.U. (Capecitabine Accord), Krka, d.d., Novo mesto (Ecansya), Medac Gesellschaft fur klinische Spezialpraparate mbH (Capecitabine medac), Nordic Group B.V. (Teysuno), Roche Registration GmbH (Xeloda), Teva B.V. (Capecitabine Teva), various

PRAC Rapporteur: Jean-Michel Dogné; PRAC Co-rapporteur: Martin Huber

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

Background

A referral procedure under Article 31 of Directive 2001/83/EC is ongoing for fluorouracil-, capecitabine- and tegafur-containing medicines for systemic use in order to review the genotyping and phenotyping methods as well as their availability across the EU for the detection of dihydropyrimidine dehydrogenase (DPD) deficiency responsible for severe and fatal toxicity. The ongoing procedure also reviews the value of the existing screening methods in identifying patients at increased risk of severe side effects as well as the need for updating existing recommendations for pre-treatment evaluation of DPD activity in patients to receive treatment with 5-fluorouracil (5-FU) or related substances. For further background, see PRAC minutes March 2019, PRAC minutes July 2019 and PRAC minutes October 2019[1].

Summary of recommendation(s)/conclusions

- The PRAC discussed the joint assessment reports produced by the Rapporteurs.
- The PRAC received feedback on the responses from the ad-hoc inter-Committee Scientific Advisory Group on Oncology (SAG-O) meeting held on 11 October 2019.
- The PRAC adopted a second list of outstanding issues (LoOI) to be addressed by the MAHs in accordance with a revised timetable (EMA/PRAC/165647/2019 Rev.3).

[1] Held 30 September – 03 October 2019

Post-meeting note: Following requests from MAH(s) to extend the timelines for submission of the responses to the second LoOI, the PRAC adopted on 10/12/2019 a revised timetable (EMA/PRAC/165647/2019 Rev. 4) by written procedure.

3.3. Procedures for finalisation

None

3.4. Re-examination procedures[2]

None

3.5. Others

None

4. Signals assessment and prioritisation[3]

4.1. New signals detected from EU spontaneous reporting systems

See also Annex 14.1.

4.1.1. Insulin: insulin aspart – FIASP (CAP), NOVOMIX (CAP), NOVORAPID (CAP); insulin aspart, insulin degludec – RYZODEG (CAP), TRESIBA (CAP); insulin bovine (NAP); insulin degludec, liraglutide – XULTOPHY (CAP); insulin determir – LEVEMIR (CAP); insulin glulisine – APIDRA (CAP); insulin human – ACTRAPID (CAP), ACTRAPHANE (CAP), INSULATARD (CAP), INSUMAN (CAP), MIXTARD (CAP), PROTAPHANE (CAP), NAP; insulin lispro – HUMALOG (CAP), INSULIN LISPRO SANOFI (CAP), LIPROLOG (CAP); insulin porcine (NAP)

Applicant(s): Eli Lilly Nederland B.V. (Humalog, Liprolog, Liprolog Junior Kwikpen), Novo Nordisk A/S (Actraphane, Actrapid, Fiasp, Insulatard, Levemir, Mixtard, NovoMix, NovoRapid, Protaphane, Ryzodeg, Tresiba, Xultophy), Sanofi-Aventis Deutschland GmbH (Apidra, Insuman), Sanofi-aventis groupe (Insulin Lispro Sanofi), various

PRAC Rapporteur: Hans Christian Siersted

Scope: Signal of cutaneous amyloidosis

EPITT 19499 – New signal

Lead Member State(s): BE, DK, SE, NL, UK

Background

Insulin is a peptide hormone produced by beta cells of the pancreatic islets. As medicinal products, insulin (of human and animal origin) and insulin analogues are indicated for the treatment of diabetes under various conditions.

[2] Re-examination of PRAC recommendation under Article 32 of Directive 2001/83/EC
[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

The exposure for insulin human and insulin analogues[4] is estimated to be more than 483 million patients-years worldwide since their marketing authorisations.

During routine signal detection activities, a signal of cutaneous amyloidosis was identified by Denmark, based on 68 cases of cutaneous amyloidosis and amyloidosis retrieved from EudraVigilance. Denmark as the lead Member State (LMS)/Rapporteur for Levemir (insulin detemir), Apidra (insulin glulisine) and Actrapid, Actraphane, Insulatard, Insuman, Mixtard, Protaphane (insulin human) confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

Based on the available evidence, the PRAC considered that there is a sufficient likelihood of a causal association between insulins and cutaneous amyloidosis. The PRAC agreed that the product information should be updated accordingly and recommended that the MAHs of insulin-containing medicinal products (Novo Nordisk A/S, Lilly Nederland B.V, Sanofi-Aventis Deutschland GmbH and Wockhardt UK Ltd) provide their comments on a proposal to amend the product information.

The PRAC appointed Hans Christian Siersted as Rapporteur for the signal.

Summary of recommendation(s)

- The MAHs Novo Nordisk A/S, Lilly Nederland B.V, Sanofi-Aventis Deutschland GmbH and Wockhardt UK Ltd for insulin-containing medicinal products should submit to the EMA, within 60 days, comments on the proposal for amending the product information agreed by the PRAC.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.2. New signals detected from other sources

4.2.1. Andexanet alfa – ONDEXXYA (CAP)

Applicant(s): Portola Netherlands B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Signal of erroneous assay results for levels of anti-factor Xa activity with use of andexanet alfa

EPITT 19493 – New signal

Lead Member State(s): NL

Background

Andexanet alfa is a recombinant form of human factor Xa (FXa) protein that has been modified to lack FXa enzymatic activity. Ondexxya (andexanet alfa) is a centrally authorised product indicated for the reversal of anticoagulation due to life-threatening or uncontrolled bleeding in adult patients treated with a direct FXa inhibitor (apixaban or rivaroxaban).

[4] Insulin aspart, insulin degludec, insulin determir, insulin glargine, insulin glulisine, insulin lispro

During routine signal detection activities, a signal of erroneous assay results for levels of anti-factor Xa activity with use of andexanet alfa was identified by Sweden. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information on the cases of erroneous assay results for levels of anti-factor Xa activity with use of andexanet alfa. As a result, the PRAC requested a cumulative review of cases and available data on the use of anti-FXa levels for clinical decision making with andexanet.

Summary of recommendation(s)

- The MAH for Ondexxya (andexanet alfa) should submit to the EMA, within 60 days, a cumulative review of cases on this signal, including an analysis of all case reports of erroneous assay results for levels of anti-FXa activity and related terms, together with a review of the scientific literature.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.2.2. Ifosfamide (NAP)

Applicant(s): various

PRAC Rapporteur: Annika Folin

Scope: Signal of increased risk of encephalopathy

EPITT 19433 – New signal

Lead Member State(s): SE

Background

Ifosfamide is an alkylating agent. Ifosfamide-containing medicinal products are indicated for the treatment of various malignancies in oncology and haematology for children and adults.

During routine signal detection activities, a signal of increased risk of encephalopathy with ifosfamide solution for infusion was identified by France, based on a national pharmacovigilance survey following the observation of clusters of encephalopathy cases reported from oncological hospital settings. Sweden as the lead Member State (LMS) confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the available evidence and agreed that further evaluation of the signal on the potentially increased risk of encephalopathy with ifosfamide solution for infusion compared with ifosfamide powder is warranted. The PRAC recommended that the results of all available studies are further assessed. The review should also be supported by an analysis of EudraVigilance data.

The PRAC appointed Annika Folin as Rapporteur for the signal.

Summary of recommendation(s)

- The Rapporteur should assess the results of the available studies and the overview of EudraVigilance data which is to be provided by the EMA within 60 days.

- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.3. Signals follow-up and prioritisation

4.3.1. Thiazide, thiazide-like diuretics and combinations: bendroflumethiazide (NAP); chlortalidone (NAP); cicletanine (NAP); clopamide (NAP); cyclopenthiazide (NAP); hydrochlorothiazide (NAP); hydrochlorothiazide, aliskiren – RASILEZ HCT (CAP); hydrochlorothiazide, amlodipine, valsartan - EXFORGE HCT (CAP); hydrochlorothiazide, irbesartan – COAPROVEL (CAP), IFIRMACOMBI (CAP), IRBESARTAN HYDROCHLOROTHIAZIDE ZENTIVA (CAP), IRBESARTAN/HYDROCHLOROTHIAZIDE TEVA (CAP), KARVEZIDE (CAP); hydrochlorothiazide, telmisartan – ACTELSAR HCT (CAP), KINZALKOMB (CAP), MICARDISPLUS (CAP), PRITORPLUS (CAP), TOLUCOMBI (CAP); hydrochlorothiazide, valsartan, amlodipine - COPALIA HCT (CAP), DAFIRO HCT (CAP); hydroflumethiazide (NAP); indapamide (NAP); metipamide (NAP); metolazone (NAP); xipamide (NAP)

Applicant(s): Actavis group PTC ehf (Actelsar HCT), Bayer AG (Kinzalkomb, PritorPlus), Boehringer Ingelheim International GmbH (MicardisPlus), Krka, d.d., Novo mesto (Ifirmacombi, Tolucombi), Noden Pharma DAC (Rasilez HCT), Novartis Europharm Limited (Copalia HCT, Dafiro HCT, Exforge HCT), Sanofi-Aventis groupe (CoAprovel, Karvezide), Teva B.V. (Irbesartan/Hydrochlorothiazide Teva), Zentiva k.s. (Irbesartan Hydrochlorothiazide Zentiva), various

PRAC Rapporteur: Martin Huber

Scope: Signal of choroidal effusion

EPITT 19468 – Follow-up to October 2019

Background

For background information, see PRAC minutes October 2019[5].

The Rapporteur provided an assessment of case reports of choroidal effusion reported with thiazide and thiazide-like diuretics in EudraVigilance and in the literature.

Discussion

Having considered the available evidence from EudraVigilance and the literature, the PRAC agreed that there is a sufficient likelihood of a causal relationship between choroid effusion and thiazide and thiazide-like diuretics. The PRAC recommended that the MAHs of thiazide and originator thiazide-like diuretic-containing products should comment on a proposal to amend the product information.

Summary of recommendation(s)

- The MAHs for thiazide and thiazide-like diuretic-containing products should submit to EMA, within 30 days, comments on the proposal to amend the product information.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

[5] Held 30 September-03 October 2019

5. Risk management plans (RMPs)

5.1. Medicines in the pre-authorisation phase

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

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

See also Annex 15.1.

5.1.1. Influenza vaccine (surface antigen, inactivated) - EMEA/H/C/004993

Scope: Active immunisation against influenza in the elderly (65 years of age and older) and in children 6 months to less than 6 years of age

5.1.2. Isatuximab - EMEA/H/C/004977, Orphan

Applicant: Sanofi-aventis groupe

Scope: Treatment in combination with pomalidomide and dexamethasone, of adult patients with relapsed and refractory multiple myeloma (RRMM) who have received at least two prior therapies including lenalidomide and a proteasome inhibitor (PI) and who have demonstrated disease progression on the last therapy

5.1.3. Lifitegrast - EMEA/H/C/004653

Scope: Treatment of moderate to severe dry eye disease in adults for whom prior artificial tears has not been sufficient

5.1.4. Onasemnogene abeparvovec - EMEA/H/C/004750, Orphan

Applicant: AveXis Netherlands B.V., ATMP[6]

Scope (accelerated assessment): Treatment of spinal muscular atrophy (SMA)

5.1.5. Ozanimod - EMEA/H/C/004835

Scope: Treatment of multiple sclerosis

5.1.6. Pexidartinib - EMEA/H/C/004832, Orphan

Applicant: Daiichi Sankyo Europe GmbH

Scope: Treatment of adult patients with symptomatic tenosynovial giant cell tumour (TGCT), also referred to as giant cell tumour of the tendon sheath (GCT-TS) or pigmented villonodular synovitis (PVNS)

[6] Advanced therapy medicinal product

5.1.7. Satralizumab - EMEA/H/C/004788, Orphan

Applicant: Roche Registration GmbH

Scope (accelerated assessment): Treatment of adult and adolescent patients from 12 years of age with neuromyelitis optica spectrum disorders (NMOSD)

5.1.8. Semaglutide - EMEA/H/C/004953

Scope: Treatment of type 2 diabetes mellitus (T2DM)

5.1.9. Treprostinil sodium - EMEA/H/C/005207, Orphan

Applicant: SciPharm Sarl, Hybrid

Scope: Treatment of thromboembolic pulmonary hypertension (CTEPH)

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

See Annex 15.2.

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

See also Annex 15.3.

5.3.1. Granisetron - SANCUSO (CAP) - EMEA/H/C/002296/II/0056/G

Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Rugile Pilviniene

Scope: Grouped variations consisting of: 1) update of section 5.2 of the SmPC to add pharmacokinetic (PK) information following the completion of paediatric PK study 392MD/44/C: an open-label, cross-over, pharmacokinetic study to assess the safety and pharmacokinetics of transdermal granisetron (Sancuso patch) and intravenous (IV) granisetron in a paediatric oncology population (aged 13 to 17 years). The RMP (version 4.0) is updated accordingly; 2) update of the RMP in line with revision 2 of the guidance on the format of RMP in the EU (template). The MAH took the opportunity to update the pregnancy information in section 4.6 to align with the quality review document (QRD) template

Background

Granisetron is a serotonin ($5HT_3$) antagonists indicated, as Sancuso, for the in adults for the prevention of nausea and vomiting associated with moderately or highly emetogenic chemotherapy, for a planned duration of 3 to 5 consecutive days, where oral anti-emetic administration is complicated by factors making swallowing difficult.

The CHMP is evaluating a type II variation procedure for Sancuso, a centrally authorised product containing granisetron, to add pharmacokinetic (PK) information following the completion of paediatric PK study 392MD/44/C. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this type II variation.

Summary of advice

- The RMP for Sancuso (granisetron) in the context of the procedure under evaluation by the CHMP could be considered acceptable provided that an update to RMP version 4.0 and satisfactory responses to the request for supplementary information (RSI) are submitted.
- The PRAC agreed to keep pregnancy as missing information in the summary of safety concerns. In view of the recent final recommendation of the signal on 'birth defects following in-utero exposure during the first trimester of pregnancy arising from recent publications (EPITT 19353)' for ondansetron and other serotonin $5HT_3$ receptor antagonist (for further background, see PRAC minutes July 2019), the PRAC agreed that that the MAH should provide further data before agreeing on the implementation of a follow-up questionnaire (FUQ) in line with the 'guideline on the exposure to medicinal products during pregnancy: need for post-authorisation data' (EMEA/CHMP/313666/2005).

5.3.2. Roflumilast - DAXAS (CAP) - EMEA/H/C/001179/II/0038

Applicant: AstraZeneca AB

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Submission of an updated RMP (version 19) to amend the list of safety concerns and remove additional risk minimisation measures (aRMM) as advised by PRAC in November 2018. In addition, the RMP is brought in line with revision 2 of GVP module V on 'Risk management systems' and revision 2 of the guidance on the format of RMP in the EU (template) leading to a reclassification of safety concerns. As a consequence, Annex II-D on 'conditions or restrictions with regard to the safe and effective use of the medicinal product' is updated. The MAH took the opportunity to introduce minor changes in section 4.4 of the SmPC and in the package leaflet in line with the latest quality review of documents (QRD) template (version 10.1)

Background

Roflumilast is a phosphodiesterase type 4 (PDE4) inhibitor indicated, as Daxas, for maintenance treatment of severe chronic obstructive pulmonary disease (COPD) (forced expiratory volume (FEV1) post-bronchodilator less than 50% predicted) associated with chronic bronchitis in adult patients with a history of frequent exacerbations as add on to bronchodilator treatment.

The CHMP is evaluating a type II variation procedure for Daxas, a centrally authorised product containing roflumilast, to amend the list of safety concerns and review the need to maintain the existing additional risk minimisation measures (aRMM) as requested in the advice adopted by PRAC at its November 2018[7] meeting. For further background, see PRAC minutes November 2018.

The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this type II variation.

Summary of advice

- The RMP for Daxas (roflumilast) in the context of the procedure under evaluation by the CHMP could be considered acceptable provided that an update to RMP version 19.1 and

[7] Held 29-31 October 2018

satisfactory responses to the request for supplementary information (RSI) are submitted.

- The PRAC agreed with the proposal to remove the existing educational material and the patient alert card (PAC) as the risks are adequately managed by the current product information. Therefore, the existing aRMM are no longer warranted and Annex II-D on 'conditions or restrictions with regard to the safe and effective use of the medicinal product' is updated accordingly. The PRAC agreed with routine risk minimisation.

6. Periodic safety update reports (PSURs)

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

See also Annex 16.1.

6.1.1. Apixaban - ELIQUIS (CAP) - PSUSA/00000226/201905

Applicant: Bristol-Myers Squibb / Pfizer EEIG

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

Background

Apixaban is a factor Xa inhibitor, direct oral anticoagulant (DOAC) indicated, as Eliquis, for the prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective hip or knee replacement surgery, for the prevention of stroke and systemic embolism (SE) in adult patients with non-valvular atrial fibrillation (NVAF), with one or more risk factors, such as prior stroke or transient ischaemic attack (TIA); age ≥ 75 years; hypertension; diabetes mellitus; symptomatic heart failure (NYHA[8] class ≥ II). It is also indicated for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Eliquis, a centrally authorised medicine containing apixaban, 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 Eliquis (apixaban) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include in the section on interaction with other medicinal products, fluconazole among inhibitors which are not considered strong inhibitors of both CYP3A4[9] and P-glycoprotein (P-gp). Therefore, the current terms of the marketing authorisation(s) should be varied[10].

[8] New York Heart Association
[9] Cytochrome P450 3A4
[10] Update of SmPC section 4.5. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

- In the next PSUR, the MAH should closely monitor cases of arthralgia and arthropathy and provide a cumulative safety review.
- The MAH should submit to the EMA, within 60 days, a cumulative review of cases of angioedema.

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

6.1.2. Cerliponase alfa - BRINEURA (CAP) - PSUSA/00010596/201904

Applicant: BioMarin International Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Background

Cerliponase alfa is a recombinant form of human tripeptidyl peptidase 1 (rhTPP1) indicated, as Brineura, for the treatment of neuronal ceroid lipofuscinosis type 2 (CLN2) disease, also known as tripeptidyl peptidase 1 (TPP1) deficiency.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Brineura, a centrally authorised medicine containing cerliponase 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 Brineura (cerliponase alfa) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to refine the existing warning on anaphylactic reaction and to add it as an undesirable effect with a frequency 'common'. Therefore, the current terms of the marketing authorisation(s) should be varied[11].

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

6.1.3. Durvalumab - IMFINZI (CAP) - PSUSA/00010723/201904

Applicant: AstraZeneca AB

PRAC Rapporteur: David Olsen

Scope: Evaluation of a PSUSA procedure

Background

Durvalumab is a fully human, immunoglobulin G1 kappa (IgG1κ) monoclonal antibody that selectively blocks the interaction of programmed death-ligand 1 (PD-L1) with programmed

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

cell death protein 1 (PD-1) and CD[12]80 indicated, as Imfinzi for the monotherapy treatment of locally advanced, unresectable non-small cell lung cancer (NSCLC) in adults whose tumours express PD-L1 on ≥ 1% of tumour cells and whose disease has not progressed following platinum-based chemoradiation therapy.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Imfinzi (durvalumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to refine the 'recommended treatment modifications' and amend the existing warning on immune-mediated rash to reflect pemphigoid. In addition, pemphigoid is added as an undesirable effect with a frequency 'uncommon'. Therefore, the current terms of the marketing authorisation(s) should be varied[13].

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. Erenumab - AIMOVIG (CAP) - PSUSA/00010699/201905

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

Background

Erenumab is a human monoclonal antibody that binds to the calcitonin gene-related peptide (CGRP) receptor. It is indicated, as Aimovig, for prophylaxis of migraine in adults who have at least 4 migraine days per month.

Based on the assessment of the periodic safety update report (PSUR), the PRAC reviewed the benefit-risk balance of Aimovig, a centrally authorised medicine containing erenumab 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 Aimovig (erenumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add a warning on hypersensitivity reactions and to include anaphylaxis and angioedema as undesirable effects with a frequency 'common'. Therefore, the current terms of the marketing authorisation(s) should be varied[14].

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

- In the next PSUR, the MAH should provide a further detailed review of cases related to anaphylactic reactions including temporal relationship and other medications to further substantiate the warning and to add possible further risk minimisation measures to the product information. Frequencies of the hypersensitivity reactions should be presented with a justification. The MAH should also present information on cases of infants receiving breast milk from mothers being treated with erenumab.

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. Insulin glargine, lixisenatide - SULIQUA (CAP) - PSUSA/00010577/201905

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

Background

Insulin glargine is a basal insulin analog and lixisenatide a glucagon-like peptide 1 (GLP-1) receptor agonist. Insulin glargine, lixisenatide is indicated, as Suliqua, for the treatment of adults with type 2 diabetes mellitus (T2DM) in combination with metformin to improve glycaemic control when this has not been provided by metformin alone or metformin combined with another oral glucose lowering medicinal product or with basal insulin.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Suliqua, a centrally authorised medicine containing insulin glargine/lixisenatide 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 Suliqua (insulin glargine/lixisenatide) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include cutaneous amyloidosis and lipodystrophy as undesirable effects with a frequency 'not known' and to amend the method of administration instructions accordingly. Therefore, the current terms of the marketing authorisation(s) should be varied[15].

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. Tolvaptan[16] - JINARC (CAP) - PSUSA/00010395/201905

Applicant: Otsuka Pharmaceutical Netherlands B.V.

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

[15] Update of SmPC sections 4.2 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
[16] Indicated for adults with autosomal dominant polycystic kidney disease (ADPKD) only

Background

Tolvaptan is a vasopressin antagonist indicated, as Jinarc, to slow the progression of cyst development and renal insufficiency of autosomal dominant polycystic kidney disease (ADPKD) in adults with chronic kidney disease (CKD) stage 1 to 4 at initiation of treatment with evidence of rapidly progressing disease.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Jinarc, a centrally authorised medicine containing tolvaptan 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 Jinarc (tolvaptan) 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 detailed analyses on the causal relationship between several undesirable effects (dysgeusia, syncope, dry skin, urticaria, arthralgia, myalgia, chest pain, and weight increased) and tolvaptan, and propose to update the product information as warranted.

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

6.1.7. Vedolizumab - ENTYVIO (CAP) - PSUSA/00010186/201905

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

Background

Vedolizumab is a gut-selective immunosuppressive biologic, indicated as Entyvio, for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a tumour necrosis factor-alfa (TNFα) antagonist, as well as for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a TNFα antagonist.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Entyvio, a centrally authorised medicine containing vedolizumab 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 Entyvio (vedolizumab) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.

- In the next PSUR, the MAH should provide cumulative reviews of all cases from all sources of acquired haemophilia and pancreatitis respectively. The MAH should also closely monitor cases of interstitial lung disease.

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

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

See also Annex 16.2.

6.2.1. Olanzapine - OLAZAX DISPERZI (CAP); ZALASTA (CAP); ZYPADHERA (CAP); ZYPREXA (CAP); ZYPREXA VELOTAB (CAP); NAP - PSUSA/00010540/201903

Applicant(s): Eli Lilly Nederland B.V. (Zypadhera, Zyprexa, Zyprexa Velotab), Glenmark Pharmaceuticals s.r.o. (Olazax Disperzi), Krka, d.d., Novo mesto (Zalasta), various

PRAC Rapporteur: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

Background

Olanzapine is an antipsychotic indicated for the treatment of schizophrenia, for the treatment of moderate to severe manic episode and for the prevention of recurrence in patients with bipolar disorder.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Olazax Disperzi, Zalasta, Zypadhera, Zyprexa and Zyprexa Velotab, centrally authorised medicines containing olanzapine, and nationally authorised medicines containing olanzapine 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 olanzapine-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include salivary hypersecretion as an undesirable effect with a frequency 'uncommon'. Therefore, the current terms of the marketing authorisations should be varied[17].
- In the next PSUR, the MAHs should evaluate and discuss the available data on pericarditis, pericardial effusions and other related pericardial disorders, including whether an amendment of the product information is warranted. The MAHs should also provide a cumulative review of cases of pulmonary hypertension including spontaneous reports, literature and clinical trials along with a discussion on biological plausibility.

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

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

6.2.2. Pramipexole - MIRAPEXIN (CAP); SIFROL (CAP); NAP - PSUSA/00002491/201904

Applicant: Boehringer Ingelheim International GmbH (Mirapexin, Sifrol), various

PRAC Rapporteur: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

Background

Pramipexole is a dopamine agonist indicated in adults for the treatment of the signs and symptoms of idiopathic Parkinson's disease, alone or in combination with levodopa, and for symptomatic treatment of moderate to severe idiopathic restless legs syndrome (RLS).

Based on the assessment of the PSURs, the PRAC reviewed the benefit-risk balance of Mirapexin and Sifrol, centrally authorised medicine containing pramipexole, as well as nationally authorised medicine containing pramipexole 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 pramipexole-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include a revised warning on risk factors of dopamine agonist withdrawal syndrome (DAWS) and a warning on DAWS when discontinuing or tapering pramipexole. Therefore, the current terms of the marketing authorisations should be varied[18].
- In the next PSUR, the MAHs should present new information regarding risk factors of DAWS and propose to update the product information as warranted. The MAHs should also discuss the recommendations regarding tapering strategy for pramipexole in context of the occurrence of symptoms of DAWS. Additionally, all MAHs should provide an updated cumulative review of cases of 'stereotypy' (punding) with information on dechallenge or rechallenge.

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

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

See also Annex 16.3.

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

6.3.1. Deoxycholic acid (NAP) – PSUSA/00010525/201904

Applicant(s): various

PRAC Lead: Annika Folin

Scope: Evaluation of a PSUSA procedure

Background

Deoxycholic acid is an endogenous bile acid indicated for the treatment of moderate to severe convexity or fullness associated with submental fat (SMF) in adults when the presence of SMF has an important psychological impact.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of Belkyra, a nationally authorised medicine containing deoxycholic acid 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 deoxycholic acid-containing medicinal product(s) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAH should closely monitor cases of medication errors along with the root cause analysis and evaluation of effectiveness of the risk minimisation measures (RMMs), as well as monitor cases of systemic hypersensitivity and lymphadenopathy. The MAH should also provide cumulative analyses of cases of permanent cutaneous adverse drug reactions (ADRs), cases of injection site mass as well as cases of abscess, cellulitis or infection related to treatment with deoxycholic acid, and propose to update of the product information as warranted. In addition, the MAH should provide a cumulative review of all off-label cases with a detailed review of lack of efficacy.

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

6.3.2. Ethinylestradiol, levonorgestrel (NAP) - PSUSA/00001309/201904

Applicant(s): various

PRAC Lead: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

Background

Ethinylestradiol is an oestrogen and levonorgestrel is a progestogen indicated in combination for the prevention of pregnancy.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing ethinylestradiol/levonorgestrel 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 ethinylestradiol/levonorgestrel-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning on angioedema and to revise the existing contraindication regarding direct-acting antivirals (DAAV). Therefore, the current terms of the marketing authorisation(s) should be varied[19].
- In the next PSUR, the MAHs should present detailed reviews of cases of decidual cast, dysmenorrhea and decidual disorder as well as on cases of loss of libido.

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. Isotretinoin[20] (NAP) - PSUSA/00010488/201905

Applicant(s): various

PRAC Lead: Maia Uusküla

Scope: Evaluation of a PSUSA procedure

Background

Isotretinoin is a stereoisomer of all-trans retinoic acid (tretinoin) indicated for the treatment of severe forms of acne (nodular or conglobate acne, or acne at risk of permanent scarring) and acne which has failed to respond to standard therapies with systemic antibiotics and topical therapy.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of isotretinoin-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include vulvovaginal dryness as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[21].
- In the next PSUR, the MAH should provide detailed reviews of cases of thyroid dysfunction (thyroiditis, hypothyroidism and hyperthyroidism, increased or decreased thyroid function analyses), cases of suicidal ideation/suicide attempt, cases of inflammatory bowel disease (IBD) including ulcerative colitis and Crohn's disease, as well as a cumulative review of cases of hidradenitis suppurativa. In addition, the MAHs

[19] Update of SmPC sections 4.3, 4.4, 4.5 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position
[20] Oral formulation(s) only
[21] Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

should provide a cumulative review of cases reported in infants exposed to isotretinoin, regardless of the presence of congenital abnormalities.

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. Sulfametrole, trimethoprim (NAP); sulfadiazine, trimethoprim (NAP); sulfamethoxazole, trimethoprim (co-trimoxazole) (NAP) - PSUSA/00010593/201903

Applicant(s): various

PRAC Lead: Željana Margan Koletić

Scope: Evaluation of a PSUSA procedure

Background

Sulfametrole, sulfadiazine and sulfamethoxazole are sulfonamide antibiotics and trimethoprim is an inhibitor of dihydrofolate reductase indicated, in combinations, for the treatment of infections caused by susceptible organisms, including urinary tract infections (UTIs), respiratory tract infections, genital tract infections, gastrointestinal tract infections, treatment and prevention of *Pneumocystis jiroveci*, nocardiosis, toxoplasmosis, brucellosis and melioidosis.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing sulfametrole/trimethoprim, sulfadiazine/trimethoprim and sulfamethoxazole/trimethoprim (co-trimoxazole) 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 sulfametrole/trimethoprim-, sulfadiazine/trimethoprim- and sulfamethoxazole/trimethoprim (co-trimoxazole)-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include Sweet's syndrome as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[22].
- In the next PSUR, all MAHs should provide a cumulative analysis of cases of psychotic disorders, a cumulative analysis of cases of cardiac arrhythmias, a cumulative analysis of all available data on hyperkalaemia as well as possible interactions with angiotensin system inhibitors and spironolactone. In addition, the MAHs should closely monitor respiratory toxicity and provide an analysis of cases from all available sources with a special focus on children and adolescents, and propose to update the product information as warranted.

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

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

6.4. Follow-up to PSUR/PSUSA procedures

6.4.1. Brodalumab - KYNTHEUM (CAP) - EMEA/H/C/003959/LEG 005

Applicant: LEO Pharma A/S

PRAC Rapporteur: Eva Segovia

Scope: Review of all available data from clinical trials, spontaneous reports and published literature relating to the risk of inflammatory bowel disease (IBD) and potential mechanism/biological plausibility of the occurrence of IBD as requested in the conclusions of PSUSA/00010341/201812 for secukinumab adopted in July 2019

Background

Brodalumab is a recombinant fully human monoclonal immunoglobulin G2 (IgG2) antibody that binds with high affinity to human interleukin 17RA (IL-17RA), indicated for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy.

Following the evaluation of the most recently submitted PSUR for secukinumab-containing medicine, the PRAC requested the MAH of Kyntheum (brodalumab) as an interleukin 17 (IL17)-inhibitor to submit further data. For background information, see PRAC minutes July 2019. The responses were assessed by the Rapporteur for further PRAC advice.

Summary of advice/conclusion(s)

- The MAH should submit to EMA, within 60 days, further information on cases of inflammatory bowel disease (IBD) identified in clinical trials together with information on whether patients with active IBD including ulcerative colitis (UC) were allowed to enter clinical trials. The MAH should also provide an updated proposed wording for the warning on IBD.

6.4.2. Ixekizumab - TALTZ (CAP) - EMEA/H/C/003943/LEG 004

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Review of all available data from clinical trials, spontaneous reports and published literature relating to the risk of inflammatory bowel disease (IBD) and potential mechanism/biological plausibility of the occurrence of IBD as requested in the conclusions of PSUSA/00010341/201812 for secukinumab adopted in July 2019

Background

Ixekizumab is an immunoglobulin G4 (IgG4) monoclonal antibody that binds with high affinity and specificity to interleukin 17A (both IL-17A and IL-17A/F), indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy and, alone or in combination with methotrexate, for the treatment of active psoriatic arthritis in adult patients subject to certain conditions.

Following the evaluation of the most recently submitted PSUR for secukinumab-containing medicine, the PRAC requested the MAH of Taltz (ixekizumab) as an interleukin 17 (IL17)-inhibitor to submit further data. For background information, see PRAC minutes July 2019. The responses were assessed by the Rapporteur for further PRAC advice.

Summary of advice/conclusion(s)

- The MAH should submit to EMA, within 60 days, an updated proposed wording for the warning on inflammatory bowel disease (IBD).

6.4.3. Secukinumab - COSENTYX (CAP) - EMEA/H/C/003729/LEG 007

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Eva Segovia

Scope: Review of cases of inflammatory bowel disease (IBD) in order to revise the existing warning on IBD in the product information as requested in the conclusions of PSUSA/00010341/201812 adopted in July 2019

Background

Secukinumab is a fully human immunoglobulin G, subclass 1, κ light chain (IgG1/κ) monoclonal antibody that selectively binds to and neutralises the pro-inflammatory cytokine interleukin-17A (IL-17A). It is indicated, as Cosentyx, for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy as well as for the treatment of active ankylosing spondylitis in adults who have responded inadequately to conventional therapy. It is also indicated alone or in combination with methotrexate (MTX) for the treatment of active psoriatic arthritis in adult patients when the response to previous disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate.

Following the evaluation of the most recently submitted PSUR for the above mentioned medicine(s), the PRAC requested the MAH to submit further data. For background information, see PRAC minutes July 2019. The responses were assessed by the Rapporteur for further PRAC advice.

Summary of advice/conclusion(s)

- The MAH should submit to EMA, within 60 days, an updated wording for the warning on inflammatory bowel disease (IBD). In addition, the MAH should provide a summary of cases of IBD identified from all available sources, including the number of cases of the different types of IBD, number of patients who did and did not discontinue treatment with secukinumab (dechallenge) and number of patients who were re-exposed to secukinumab after recovering from a first event of IBD (rechallenge). The MAH should also provide further details of the cases in patients who discontinued secukinumab after developing IBD while being treated and who had a pre-existing history of IBD. In patients who experienced IBD while receiving secukinumab, the MAH should confirm if any action was taken with secukinumab (e.g. temporarily interruption) after development of IBD.

7. Post-authorisation safety studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)[23]

See Annex 17.1.

[23] In accordance with Article 107n of Directive 2001/83/EC

7.2. Protocols of PASS non-imposed in the marketing authorisation(s)[24]

See Annex 17.2.

7.3. Results of PASS imposed in the marketing authorisation(s)[25]

None

7.4. Results of PASS non-imposed in the marketing authorisation(s)[26]

See Annex 17.4.

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

See also Annex 17.5.

7.5.1. 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 004.2

Applicant: Orchard Therapeutics (Netherlands) BV, ATMP[27]

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to ANX 004.1 [biennial progress report for study GSK2696273 entitled 'adenosine deaminase severe combined immunodeficiency (ADA-SCID) registry for patients treated with Strimvelis gene therapy: long-term prospective, non-interventional follow-up of safety and effectiveness' (PSP/004) [final clinical study report (CSR) after the 50th patient has 15 year follow-up visit - Q4 2037] as per the request for supplementary information (RSI) adopted in June 2019 and discussion at the November 2019 PRAC meeting

Background

Autologous CD34$^+$ enriched cell fraction that contains CD34$^+$ cells transduced with retroviral vector that encodes for the human adenosine deaminase (ADA) cDNA sequence is an advanced therapy medicinal product (ATMP) indicated, as Strimvelis, for the treatment of patients with severe combined immunodeficiency due to adenosine deaminase deficiency (ADA-SCID), for whom no suitable human leukocyte antigen (HLA)-matched related stem cell donor is available.

As part of the conditions or restrictions with regard to the safe and effective use of the medicinal product (Annex II-D of the marketing authorisation(s)), the MAH conducts a non-interventional PASS entitled 'adenosine deaminase severe combined immunodeficiency (ADA-SCID) registry for patients treated with Strimvelis gene therapy: long-term prospective, non-interventional follow-up of safety and effectiveness'. The PRAC is responsible for evaluating

[24] 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
[25] In accordance with Article 107p-q of Directive 2001/83/EC
[26] In accordance with Article 61a (6) of Regulation (EC) No 726/2004, in line with the revised variations regulation for any submission as of 4 August 2013
[27] Advanced therapy medicinal product

the PASS interim results. For further background see PRAC minutes June 2019 and PRAC minutes November 2019[28].

Summary of advice

- The PRAC discussed the Rapporteur's review of the PASS interim study report and agreed that the benefit-risk balance of autologous $CD34^+$ enriched cell fraction that contains $CD34^+$ cells transduced with retroviral vector that encodes for the human ADA cDNA sequence remains unchanged.
- The MAH should continue to conduct the study in accordance with the approved protocol.

7.6. Others

See Annex I 17.6.

7.7. New Scientific Advice

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

7.8. Ongoing Scientific Advice

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

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

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

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

8.1. Annual reassessments of the marketing authorisation

See Annex 18.1.

8.2. Conditional renewals of the marketing authorisation

See Annex 18.2.

8.3. Renewals of the marketing authorisation

See Annex 18.3.

[28] Held 28-31 October 2019

9. Product related pharmacovigilance inspections

9.1. List of planned pharmacovigilance inspections

None

9.2. Ongoing or concluded pharmacovigilance inspections

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

9.3. Others

None

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

10.1. Safety related variations of the marketing authorisation

10.1.1. Nomegestrol acetate, estradiol – ZOELY (CAP) – EMEA/H/C/001213/II/0050

Applicant: Theramex Ireland Limited

PRAC Rapporteur: Adrien Inoubli

Scope: PRAC consultation on a type II variation updating sections 4.3 and 4.4 of the SmPC in order to add a new contraindication and a new warning regarding meningioma, as requested in the conclusions of LEG 014 finalised in March 2019. The package leaflet is updated accordingly. In addition, the MAH took the opportunity to update the contact details of the local representatives in the Netherlands and Portugal in the package leaflet

Background

Nomegestrol acetate is a progestogen and estradiol is a natural oestrogen identical to the endogenous human 17β-estradiol. In combination, estradiol/nomegestrol acetate is indicated, as Zoely, for oral contraception.

A type II variation proposing to update the product information of Zoely (nomegestrol acetate/estradiol) to add a new contraindication and a new warning regarding meningioma is under evaluation at the CHMP. The PRAC was requested to provide advice on this variation. For further background, see PRAC minutes March 2019.

Summary of advice

- Based on the review of the available information, the PRAC discussed the request for PRAC advice and considered whether an update of the RMP was warranted and whether to recommend the use of follow-up questionnaires (FUQ) to collect further data on reported cases of meningioma. The PRAC advised that meningioma fulfils the criteria of revision 2 of GVP module V on 'Risk management systems' and should be included as an

important potential risk in the RMP. The PRAC also advised that the MAH uses FUQ to collect further relevant information.

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

None

10.3. Other requests

None

10.4. Scientific Advice

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

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

11.1. Safety related variations of the marketing authorisation

None

11.2. Other requests

None

12. Organisational, regulatory and methodological matters

12.1. Mandate and organisation of the PRAC

None

12.2. Coordination with EMA Scientific Committees or CMDh-v

None

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

12.3.1. Scientific advice working party (SAWP) – re-nomination of PRAC representative(s)

The EMA secretariat informed the PRAC that a re-examination and re-nomination of the PRAC Scientific Advice Working Party (SAWP) composition is planned for CHMP adoption in March 2020, i.e. one year after the election of the new SAWP Chair as per the working party mandate. The EMA Secretariat launched a call for nominating PRAC member(s) as a joint PRAC-SAWP representative to the SAWP. PRAC members were invited to express nomination interest by 16 December 2020. Follow-up discussion is scheduled in February 2020.

12.4. Cooperation within the EU regulatory network

12.4.1. European Network Training Centre (EU NTC) - Pharmacoepidemiology - Training curriculum (TC)

The EMA secretariat presented to the PRAC a proposal to establish a pharmacoepidemiology curriculum in the context of the European Network Training Centre (EU NTC). This aims at increasing within the EU network the cooperation and capacity in the assessment and interpretation of study protocols and results of non-interventional studies performed for regulatory purposes. PRAC members were invited to provide comments by 17 January 2020.

12.5. Cooperation with International Regulators

None

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

None

12.7. PRAC work plan

12.7.1. PRAC work plan 2020 – preparation

PRAC lead: Sabine Straus, Martin Huber

The EMA secretariat provided an overview of planned topics to be included in the PRAC work plan 2020. PRAC members were invited to provide comments by 13 December 2019. Further discussion is planned in January 2020.

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

12.10.3. PSURs repository

None

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

The PRAC endorsed the draft revised EURD list, version December 2019, reflecting the PRAC's comments impacting on the data lock point (DLP) and PSUR submission frequencies of the substances/combinations. The PRAC endorsed the newly allocated Rapporteurs for upcoming PSUSAs in accordance with the principles previously endorsed by the PRAC (see PRAC minutes April 2013).

Post-meeting note: following the PRAC meeting of December 2019, the updated EURD list was adopted by the CHMP and CMDh at their December 2019 meetings and published on the EMA website on 18/12/2019, see:

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

12.10.5. Periodic safety update reports single assessment (PSUSA) – updates to the assessment report template

PRAC lead: Ulla Wändel Liminga, Menno van der Elst (NL), Jana Lukačišinová (CZ), Ana Sofia Martins (PT)

As a follow-up to the PRAC discussion held in November 2019 (for further background, see PRAC minutes November 2019[29]), the EMA Secretariat presented to the PRAC the consolidated proposal to simplify and clarify the PSUSA assessment report (AR) template. The PRAC endorsed the proposal.

12.11. Signal management

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

PRAC lead: Menno van der Elst

[29] Held 28-31 October 2019

12.12. Adverse drug reactions reporting and additional monitoring

12.12.1. Management and reporting of adverse reactions to medicinal products

None

12.12.2. Additional monitoring

None

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

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

Post-meeting note: The updated additional monitoring list was published on the EMA website on 12/12/2019, see: Home>Human Regulatory>Post-authorisation>Pharmacovigilance>Medicines under additional monitoring>List of medicines under additional monitoring

12.13. EudraVigilance database

12.13.1. Activities related to the confirmation of full functionality

None

12.14. Risk management plans and effectiveness of risk minimisations

12.14.1. Risk management systems

None

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

None

12.15. Post-authorisation safety studies (PASS)

12.15.1. Post-authorisation Safety Studies – imposed PASS

None

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

None

12.16. Community procedures

12.16.1. Referral procedures for safety reasons

None

12.17. Renewals, conditional renewals, annual reassessments

None

12.18. Risk communication and transparency

12.18.1. Public participation in pharmacovigilance

None

12.18.2. Safety communication

None

12.18.3. Direct healthcare professional communication (DHPC) – proposal for publication on the EMA website

The EMA secretariat presented to the PRAC a proposal for publication of agreed direct healthcare professional communications (DHPCs) on the EMA website. The PRAC supported the proposal.

Post-meeting note: As of February 2020, the EMA started the publication of DHPCs agreed at EU level, together with their respective communication plans at the time of national dissemination as agreed by PRAC, CHMP or CMDh as appropriate. See: https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/direct-healthcare-professional-communications

12.19. Continuous pharmacovigilance

12.19.1. Incident management

None

12.20. Others

12.20.1. Biosimilar medicines and identification – update

Further to an update provided to the PRAC in October 2019 (for further background, see PRAC minutes October 2019[30]), the EMA secretariat informed the PRAC of the most recent findings of the identification of biosimilar medicines in EudraVigilance, using their brand name and batch number.

12.20.2. EMA – future proofing exercise

The EMA secretariat provided an update to the PRAC on the EMA re-organisational aspects including the organisational structure to be implemented in Q1 2020. Further update will be presented to the PRAC in due course.

[30] Held 30 September – 03 October 2019

12.20.3. EMA relocation, Amsterdam, the Netherlands – move to the new building

The EMA secretariat provided further updates on the move to the new EMA building in Amsterdam, due in January 2020.

12.20.4. Strategy on measuring the impact of pharmacovigilance - PRAC interest group (IG) Impact – impact guidance

PRAC Lead: Antoine Pariente

The EMA secretariat together with the PRAC lead presented to the PRAC the draft guidance on pharmacovigilance impact research developed by the PRAC interest group (IG), which includes product, population or healthcare setting targeted by the regulatory action and also includes the potential unintended consequences of regulatory actions. PRAC members were invited to provide written comments by 6 February 2020. Further discussion is scheduled in February 2020.

13. Any other business

None

14. Annex I – Signals assessment and prioritisation[31]

14.1. New signals detected from EU spontaneous reporting systems

As per agreed criteria for new signal(s), the PRAC adopted without further plenary discussion the recommendation of the Rapporteur to request MAH(s) to submit a cumulative review following standard timetables[32].

14.1.1. Idelalisib – ZYDELIG (CAP)

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Martin Huber

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

EPITT 19500 – New signal

Lead Member State(s): DE

14.1.2. Nilotinib – TASIGNA (CAP)

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Hans Christian Siersted

[31] [31] 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

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

Scope: Signal of anaphylactic reaction

EPITT 19497 – New signal

Lead Member State(s): DK

14.2. New signals detected from other sources

None

15. Annex I – Risk management plans

15.1. Medicines in the pre-authorisation phase

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

15.1.1. Arsenic trioxide - EMEA/H/C/005235

Scope: Treatment of relapsed acute promyelocytic leukaemia (APL)

15.1.2. Azacitidine - EMEA/H/C/004984

Scope: Treatment of adult patients who are not eligible for haematopoietic stem cell transplantation (HSCT)

15.1.3. Doxorubicin - EMEA/H/C/005194

Scope: Treatment of breast cancer, ovarian cancer, progressive multiple myeloma and acquired immune deficiency syndrome (AIDS)-related Kaposi’s sarcoma

15.1.4. Rituximab - EMEA/H/C/004696

Scope: Treatment of non-Hodgkin's lymphoma (NHL), chronic lymphocytic leukaemia (CLL) and rheumatoid arthritis (RA)

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

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

15.2.1. Blinatumomab - BLINCYTO (CAP) - EMEA/H/C/003731/II/0033, Orphan

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Eva Jirsová

Scope: Submission of an updated RMP (version 11) in line with revision 2 of GVP module V

on 'Risk management systems'. The protocol for study 20150136 (listed as a category 1 in the RMP/Annex II): an observational study of blinatumomab safety and effectiveness, utilisation, and treatment practices is updated and the enrolment period extended by 1 year. As a consequence, the milestones in the RMP are updated accordingly. In addition, the RMP includes a proposed update to the milestone of study 20180138 (listed as a category 3 study in the RMP): long-term follow-up of patients enrolled in TOWER study (a phase 3, randomized, open label study investigating the efficacy of the bispecific T-cell engager (BiTE) antibody blinatumomab versus standard of care chemotherapy in adult subjects with relapsed/refractory B-precursor acute lymphoblastic leukaemia (ALL))

15.2.2. Dinutuximab beta - QARZIBA (CAP) - EMEA/H/C/003918/II/0015, Orphan

Applicant: EUSA Pharma (Netherlands) B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Submission of an updated RMP (version 9.0) in order to remove as missing information drug-drug interaction, use in adolescents, adults and elderly, use in patients with an ethnic origin other than Caucasian, use in patients with hepatic and renal impairment as well as potential harm from overdose

15.2.3. Fentanyl - INSTANYL (CAP) - EMEA/H/C/000959/II/0052

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Ghania Chamouni

Scope: Submission of an updated RMP (version 19.2) in order to update information relating to educational material to include greater emphasis on off label use and the risk of misuse and abuse. In addition, the MAH submitted a synopsis of a protocol for a PASS (as a category 3 study in the RMP) to assess the impact of the updated educational material

15.2.4. Irinotecan hydrochloride trihydrate – ONIVYDE PEGYLATED LIPOSOMAL (CAP) - EMEA/H/C/004125/II/0015, Orphan

Applicant: Les Laboratoires Servier

PRAC Rapporteur: David Olsen

Scope: Submission of an updated RMP (version 2.7) in order to update the RMP in line with the conclusions of periodic safety update report single assessment (PSUSA) procedures PSUSA/00010534/201804 finalised in November 2018 and PSUSA procedure PSUSA/00010534/201810 finalised in May 2019. The RMP is also updated in line with revision 2 of GVP module V on 'Risk management systems'

15.2.5. Lenvatinib - KISPLYX (CAP) - EMEA/H/C/004224/II/0030

Applicant: Eisai GmbH

PRAC Rapporteur: David Olsen

Scope: Submission of an updated RMP (version 11.3) as a result of interim analysis and updated final report submission dates for study E7080-G000-307: a multicentre, open-label, randomized, phase 3 trial to compare the efficacy and safety of lenvatinib in

combination with everolimus or pembrolizumab versus sunitinib alone in first-line treatment of subjects with advanced renal cell carcinoma (CLEAR). The protocol is also updated to include an interim analysis for profession-free survival and overall survival

15.2.6. Lopinavir, ritonavir - ALUVIA (Art 58[33]) - EMEA/H/W/000764/WS1711/0112; KALETRA (CAP) - EMEA/H/C/000368/WS1711/0181

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Adrien Inoubli

Scope: Submission of an updated RMP (version 9.0) in order to bring it in line with revision 2 of the guidance on the format of RMP in the EU (template). The MAH took the opportunity to review the safety information contained in the RMP, removed an important potential risk of drug interaction with telaprevir and boceprevir (hepatitis C virus (HCV) protease inhibitors) and missing information regarding use of lopinavir/ritonavir (LPV/r) in elderly patients

15.2.7. Lutropin alfa - LUVERIS (CAP) - EMEA/H/C/000292/II/0082

Applicant: Merck Europe B.V.

PRAC Rapporteur: Hans Christian Siersted

Scope: Submission of an updated RMP (version 3.1) in order to bring it in line with revision 2 of GVP module V on 'Risk management systems' and to remove 'ovarian hyperstimulation syndrome (OHSS)' and 'mild to severe hypersensitivity reactions including anaphylactic reactions and shock' as important identified risks and well as 'thromboembolic (TE) events', 'reproductive system cancer', 'ectopic pregnancy', 'multiple pregnancies', 'congenital anomaly' and 'off label use' as important potential risks. In addition, the age for missing information 'hypogonadotropic hypogonadal women with severe luteinizing hormone (LH) and follicle-stimulating hormone (FSH) deficiency of advanced maternal age (older than 40 years)' is changed from 40 to 42 years. Finally, the sections on epidemiology and non-clinical sections are updated as per the most recent data

15.2.8. Measles, mumps and rubella vaccine (live) - M-M-RVAXPRO (CAP) - EMEA/H/C/000604/II/0096

Applicant: MSD Vaccins

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Submission of an updated RMP (version 4.1) in order to bring it in line with revision 2 of GVP module V on 'Risk management systems' and with revision 2 of the guidance on the format of RMP in the EU (template). The MAH took the opportunity to remove the important potential risk of 'a potential change in the safety profile related to the replacement of human serum albumin (HAS) with recombinant human albumin (rHA)' and to remove the missing information related to 'exposure during pregnancy'

[33] 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)

15.2.9. Pioglitazone - ACTOS (CAP) - EMEA/H/C/000285/WS1680/0082; GLUSTIN (CAP) - EMEA/H/C/000286/WS1680/0081 pioglitazone, glimepiride - TANDEMACT (CAP) - EMEA/H/C/000680/WS1680/0060 pioglitazone, metformin - COMPETACT (CAP) - EMEA/H/C/000655/WS1680/0074; GLUBRAVA (CAP) - EMEA/H/C/000893/WS1680/0060

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Rhea Fitzgerald

Scope: Submission of an updated RMP (version 27) in order to update and consolidate within a single RMP the RMPs for pioglitazone-containing product(s), pioglitazone/metformin-fixed dose combination (FDC) and pioglitazone/glimepiride-FDC. The list of safety concerns is revised in line with the conclusions of periodic safety update report single assessment (PSUSA) procedure PSUSA/00002417/201807 finalised in March 2019 with regards to the discontinuation of the additional risk minimisation measures (aRMMs)

15.2.10. Ponatinib - ICLUSIG (CAP) - EMEA/H/C/002695/II/0053, Orphan

Applicant: Incyte Biosciences Distribution B.V.

PRAC Rapporteur: Annika Folin

Scope: Submission of an updated RMP (version 20) in order to remove study AP24534-14-401: a post-marketing observational registry to evaluate the incidence of and risk factors for vascular occlusive events associated with Iclusig (ponatinib) in routine clinical practice in the US (OMNI) from the pharmacovigilance plan. In addition, the MAH took the opportunity to remove the distribution of the educational material in line with the conclusions of variation II/51 adopted in September 2019

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

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

15.3.1. Abatacept - ORENCIA (CAP) - EMEA/H/C/000701/II/0134

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Kimmo Jaakkola

Scope: Update of sections 4.8 and 5.1 of the SmPC for the solution for injection in pre-filled syringe and update of section 4.8 of the SmPC for the powder for concentrate for solution for infusion based on the final 24 month-results from study IM101301:an open-label study to assess pharmacokinetics (PK), safety, and efficacy of subcutaneous (SC) abatacept in polyarticular juvenile idiopathic arthritis (pJIA) with no formal hypothesis testing. The package leaflet for the solution for injection in pre-filled syringe is also updated to reflect the removal of the instructions for use (IFU) booklet as requested by the CHMP in the conclusion of procedure X/0117/G adopted in January 2019. The RMP (version 27.0) is updated accordingly. In addition, the MAH took the opportunity to update Annex II and section 4.4 of the SmPC in line with the latest quality review of documents (QRD) template (version 10.1). In addition, the list of local representatives in the package leaflet is updated

15.3.2. Afatinib - GIOTRIF (CAP) - EMEA/H/C/002280/II/0031

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Annika Folin

Scope: Update of sections 4.4 and 4.8 of the SmPC in order to add gastrointestinal (GI) perforation as an additional side effect based on summaries of clinical trial and post-marketing safety data. The package leaflet is updated accordingly. In addition, the RMP (version 8.0) is updated accordingly and in line with revision 2 of the guidance on the format of RMP in the EU (template), taking also into consideration recommendations part of the conclusions of renewal procedure R/0026 adopted in March 2018. Furthermore, the MAH took the opportunity to correct some typographical errors in the German, Austrian and Spanish product information and to update the list of the local representatives for Austria in the package leaflet

15.3.3. Alglucosidase alfa - MYOZYME (CAP) - EMEA/H/C/000636/II/0075

Applicant: Genzyme Europe BV

PRAC Rapporteur: Adrien Inoubli

Scope: Update of sections 4.4 and 5.1 of the SmPC in order to reflect changes in the existing warning on immunogenicity and immunomodulation and to add new clinical information on infantile onset Pompe disease (IOPD) patients' immune tolerance induction based on data on use of immune tolerance induction in IOPD patients from two exploratory phase 4 studies, namely: study AGLU03707/MSC12817: an exploratory study of the safety and efficacy of immune tolerance induction (ITI) in patients with Pompe disease who have previously received Myozyme (alglucosidase alfa); companion study AGLU03807/MSC12892: open-label, exploratory study of the safety and efficacy of prophylactic ITI in alglucosidase alfa-naïve cross reactive immunologic material (CRIM)(-) patients with IOPD, as well as the Duke Center of Excellence observational study (01562): open-label, retrospective cohort study of ITI regimens in combination with alglucosidase alfa in patients with CRIM(-) IOPD. The RMP (version 9.0) is updated accordingly

15.3.4. Alogliptin, pioglitazone - INCRESYNC (CAP) - EMEA/H/C/002178/II/0029

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Menno van der Elst

Scope: Submission of an updated RMP (version 10.0) in order to remove additional risk minimisation measures (aRMMs) as requested in the outcome of periodic safety update report single assessment (PSUSA) procedure PSUSA/00002417/201807 for pioglitazone, glimepiride/pioglitazone and metformin/pioglitazone adopted in March 2019 and consequently removal of the drug utilisation study (DUS) on the utilisation of pioglitazone-alogliptin containing medicinal product(s) in clinical practice with regard to diabetic treatment regimen and comorbidities as well as the removal of relevant commitments as per the conclusions of LEG 008 adopted in September 2015. In addition, the RMP is brought in line with revision 2 of the guidance on the format of RMP in the EU (template) reflecting changes in the categorisation of safety concerns. Furthermore, the targeted adverse event (AE) follow-up questionnaires related to AEs of severe hypersensitivity skin reactions, hepatic events, pancreatitis, bladder cancer, malignancies (including pancreatic cancer),

bone fractures, and macular oedema are removed. Finally, the RMP is updated to reflect the removal of the additional monitoring inverted black triangle as per the conclusion of the renewal procedure R/0023 finalised in March 2018. Annex II is updated accordingly

15.3.5. Andexanet alfa - ONDEXXYA (CAP) - EMEA/H/C/004108/II/0002

Applicant: Portola Netherlands B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Submission of the final study report for study ANNEXA-4 (listed as a category 2 study in Annex II and the RMP): an interventional non-randomized, multicentre, prospective, open-label, single-group study in andexanet alfa patients receiving a factor Xa inhibitor with acute major bleeding. The RMP (version 1.1) is updated accordingly

15.3.6. Apalutamide - ERLEADA (CAP) - EMEA/H/C/004452/II/0001

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Ghania Chamouni

Scope: Extension of indication to include the treatment of metastatic hormone-sensitive prostate cancer (mHSPC) in combination with androgen deprivation therapy (ADT) based on the results of study 56021927PCR3002 (TITAN study): a randomised, double-blind, placebo-controlled phase 3 study comparing apalutamide plus ADT versus ADT in patients with mHSPC. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated in order to add a warning on ischaemic cardiovascular events and to reflect new safety and efficacy information. The package leaflet and the RMP (version 2.0) are updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet and to make editorial update to the product information

15.3.7. Belimumab - BENLYSTA (CAP) - EMEA/H/C/002015/II/0073

Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of the final report from study BEL116027 (listed as a category 3 study in the RMP): a multicentre, open-label, non-randomized, efficacy and safety study to evaluate treatment holidays and rebound phenomenon after treatment with belimumab 10 mg/kg in subjects with low systemic lupus erythematosus (SLE) disease activity. The RMP (version 34) is updated accordingly

15.3.8. Budesonide - JORVEZA (CAP) - EMEA/H/C/004655/X/0007/G, Orphan

Applicant: Dr. Falk Pharma GmbH

PRAC Rapporteur: Zane Neikena

Scope: Grouped application consisting of: 1) extension application to add a new strength of 0.5 mg for budesonide orodispersible tablets; 2) extension of indication to include the maintenance of remission for the 0.5 mg and 1 mg orodispersible tablets. As a consequence, sections 4.2, 4.8 and 5.1 of the SmPC are updated to reflect the

recommended daily dose and duration of treatment of Jorveza (budesonide) for the maintenance of remission, to update the list of adverse reactions and the clinical efficacy and safety information based on the results of study BUL-2/EER: a double-blind, randomized, placebo-controlled, phase 3 study on the efficacy and tolerability of a 48-week treatment with two different doses of budesonide effervescent tablets vs. placebo for maintenance of clinico-pathological remission in adult patients with eosinophilic esophagitis. The package leaflet is updated accordingly. In addition, the RMP (version 2.0) is updated accordingly and is brought in line with revision 2 of the guidance on the format of RMP in the EU (template). The MAH also took the opportunity to bring the product information in line with the latest quality review of documents (QRD) template (version 10.1); 3) addition of a new pack-size of 200 x 1 orodispersible tablets (unit dose) in a blister for Jorveza (budesonide) 1 mg orodispersible tablet

15.3.9. Daratumumab - DARZALEX (CAP) - EMEA/H/C/004077/X/0032, Orphan

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Extension application to introduce a new pharmaceutical form (solution for injection), a new strength (1800 mg) and a new route of administration (subcutaneous route). The RMP (version 7.0) is updated accordingly

15.3.10. Darunavir, cobicistat, emtricitabine, tenofovir alafenamide - SYMTUZA (CAP) - EMEA/H/C/004391/II/0021/G

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Grouped variations consisting of: 1) submission of the final report from study GS-US-311-1717 (listed as a category 3 study in the RMP): a randomized, double-blind, active-controlled study to evaluate the safety and efficacy of switching to emtricitabine/tenofovir alafenamide (F/TAF) versus continuing abacavir/lamivudine (ABC/3TC) in human immunodeficiency virus type 1 (HIV-1) infected subjects who were virologically suppressed (HIV-1 ribonucleic acid (RNA) < 50 copies/mL) on a stable regimen containing ABC/3TC after 96 weeks. The RMP (version 6.1) is updated accordingly; 2) Submission of an updated RMP (version 6.1) in order to postpone the due date of the final report from study GS-US-292-0109: a phase 3, open-label study to evaluate switching from a tenofovir disoproxil fumarate (TDF)-containing combination regimen to a TAF-containing combination single tablet regimen (STR) in virologically-suppressed HIV-1 positive subjects, from Q4 2019 to Q2 2021

15.3.11. Emtricitabine, tenofovir alafenamide - DESCOVY (CAP) - EMEA/H/C/004094/II/0044

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Submission of the final report from study GS-US-311-1717 (listed as a category 3 in the RMP): a phase 3b, randomized, double-blind, switch study to evaluate emtricitabine/tenofovir alafenamide (F/TAF) in human immunodeficiency virus type 1 (HIV-1) infected subjects who are virologically suppressed on regimens containing

abacavir/lamivudine (ABC/3TC). The RMP (version 4.1) is updated accordingly

15.3.12. Fidaxomicin - DIFICLIR (CAP) - EMEA/H/C/002087/X/0034/G

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Grouped application consisting of: 1) extension application to introduce a new pharmaceutical form associated with a new strength (40 mg/mL granules for oral suspension); 2) extension of indication to include paediatric use of Dificlir (fidaxomicin) in children from birth to less than 18 years of age. The SmPC of Dificlir 200 mg film-coated tablet, labelling and the, package leaflet are updated accordingly. In addition, the MAH took the opportunity to update the package leaflet with the statement on 'sodium-free' in accordance with the European Commission (EC) guideline on 'excipients in the labelling and package leaflet of medicinal products for human use'. Furthermore, the MAH updated the details of the local representative in Czech Republic

15.3.13. Fremanezumab - AJOVY (CAP) - EMEA/H/C/004833/II/0003

Applicant: Teva GmbH

PRAC Rapporteur: Kirsti Villikka

Scope: Update of section 4.8 of the SmPC in order to update the safety information based on final results from study TV48125-CNS-30051 (listed as a category 3 study in the RMP): a multicentre, randomized, double-blind, parallel-group study evaluating the long-term safety, tolerability, and efficacy of subcutaneous administration of TEV-48125 (fremanezumab) for the preventive treatment of migraine. The package leaflet and the RMP (version 2.0) are updated accordingly

15.3.14. Human papillomavirus vaccine [types 6, 11, 16, 18, 31, 33, 45, 52, 58] (recombinant, adsorbed) - GARDASIL 9 (CAP) - EMEA/H/C/003852/II/0033

Applicant: MSD Vaccins

PRAC Rapporteur: Jean-Michel Dogné

Scope: Update of sections 4.2, 4.6, 4.8 and 5.1 of the SmPC in order to update the safety and immunogenicity information based on final results from study V503-P004 (listed as a category 3 study in the RMP): an open-label phase 3 clinical trial to study the immunogenicity and tolerability of Gardasil 9 in adult women (27 to 45 year-olds) compared to young adult women (16 to 26 year-olds) (in fulfilment of MEA 007). The package leaflet and the RMP (version 4.1) are updated accordingly. In addition, the MAH took the opportunity to update section 4.4 of the SmPC in line with the 'Guideline on quality aspects included in the product information for vaccines for human use (EMA/CHMP/BWP/133540/2017)' and to include editorial changes in section 5.1 of the SmPC

15.3.15. Ixekizumab - TALTZ (CAP) - EMEA/H/C/003943/II/0030

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include treatment of adult patients with active axial spondyloarthritis. 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 10.1) are updated accordingly. The product information is also brought in line with the latest quality review of documents (QRD) template (version 10.1)

15.3.16. Lidocaine, prilocaine - FORTACIN (CAP) - EMEA/H/C/002693/II/0030

Applicant: Recordati Ireland Ltd

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Change in the legal status from 'medicinal product subject to medical prescription' to 'medicinal product not subject to medical prescription' in view of the safety profile of Fortacin (lidocaine/prilocaine), the post-marketing experience already available with other medicinal products containing amide local anaesthetics and in view of making the medicinal product more accessible to the target population. The RMP (version 3.1) is updated accordingly. Furthermore, the product information is also brought in line with the latest quality review of documents (QRD) template (version 10.1)

15.3.17. Necitumumab - PORTRAZZA (CAP) - EMEA/H/C/003886/II/0017

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Rugile Pilviniene

Scope: Submission of the exploratory biomarker analysis from 4 clinical studies (listed as a category 3 studies in the RMP) namely: 1) study I4X-MC-JFCU: a single-arm, multicentre, phase 1b study with an expansion cohort to evaluate safety and efficacy of necitumumab in combination with abemaciclib in treatment of patients with stage IV non-small cell lung cancer (NSCLC); 2) study I4X-MC-JFCQ: an open-label, multicentre, phase 1b study with an expansion cohort to evaluate safety and efficacy of the combination of necitumumab with pembrolizumab in patients with stage IV NSCLC; 3) study I4X-MC-JFCP: a single-arm, multicentre, open-label, phase 2 study of nab-paclitaxel and carboplatin chemotherapy plus necitumumab (LY3012211) in the first-line treatment of patients with stage IV NSCLC; 4) study I6A-MC-CBBE: a phase 2 study of the combination of LY3023414 (oral phosphatidylinositol-3-kinase (PI3K)/ mammalian target of rapamycin (mTOR) dual inhibitor) and necitumumab after first-line chemotherapy for metastatic squamous non-small cell carcinoma of the lung. The RMP (version 8.1) is updated accordingly

15.3.18. Nintedanib - OFEV (CAP) - EMEA/H/C/003821/II/0027, Orphan

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Extension of indication to include the treatment of other chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype based on the results of pharmacology studies and the double-blind, randomised, placebo-controlled phase 3 trial (INBUILD). 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 9.0) are updated accordingly. In addition, the MAH took the opportunity to introduce minor formatting changes in the product information. Furthermore, the product information is brought in line with the latest quality review of

documents (QRD) template (version 10.1)

15.3.19. Nomegestrol acetate, estradiol - ZOELY (CAP) - EMEA/H/C/001213/II/0051

Applicant: Theramex Ireland Limited

PRAC Rapporteur: Adrien Inoubli

Scope: Submission of an updated RMP (version 9.1) as requested in the outcome of the imposed PASS protocol adopted by the PRAC in June 2019 for a prospective observational study to assess the risk of venous thromboembolic events (VTE) and arterial thromboembolic events (ATE) in nomegestrel/estradiol users compared with the risk of VTE in users of combined oral contraceptives (COCs)-containing levonorgestrel. The RMP is also updated in line with revision 2 of the guidance on the format of RMP in the EU (template) including an update of the due date for the PASS (from June 2020 to April 2021). As a consequence, Annex II is updated. The MAH also took the opportunity to amend the package leaflet in order to update the list of local representatives in The Netherlands and Portugal

15.3.20. Obinutuzumab - GAZYVARO (CAP) - EMEA/H/C/002799/II/0036, Orphan

Applicant: Roche Registration GmbH

PRAC Rapporteur: Annika Folin

Scope: Update of sections 4.8 and 5.1 of the SmPC based on data from the final clinical study report (CSR) of pivotal study GA04753g/GO01297 (GADOLIN) (listed as category 3 study in the RMP): an open-label, multicentre, randomized, phase 3 Study to investigate the efficacy and safety of bendamustine compared with bendamustine+ obinutuzumab (RO5072759 (GA101)) in patients with rituximab-refractory, indolent non-Hodgkin's lymphoma. The package leaflet and the RMP (version 6.0) are updated accordingly

15.3.21. Pemetrexed - ALIMTA (CAP) - EMEA/H/C/000564/WS1704/0058; PEMETREXED LILLY (CAP) - EMEA/H/C/004114/WS1704/0010

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Ghania Chamouni

Scope: Update of section 4.8 of the SmPC to reorganise the section as requested in the conclusions of periodic safety update report single assessment (PSUSA) procedure PSUSA/00002330/201802 finalised in October 2018. The package leaflet is updated accordingly. The product information is also brought in line with the latest quality review of documents (QRD) template (version 10.1). In addition, the RMP (version 6.1) is updated accordingly and in line with revision 2 of the guidance on the format of RMP in the EU (template)

15.3.22. Perampanel - FYCOMPA (CAP) - EMEA/H/C/002434/II/0047

Applicant: Eisai GmbH

PRAC Rapporteur: Ghania Chamouni

Scope: Extension of indication to include adjunctive treatment in paediatric patients from 2

to 11 years of age in partial-onset (focal) seizures with or without secondary generalisation and primary generalised tonic-clonic seizures with idiopathic generalised epilepsy. As a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 4.3) are updated accordingly

15.3.23. Propranolol - HEMANGIOL (CAP) - EMEA/H/C/002621/II/0019

Applicant: Pierre Fabre Dermatologie

PRAC Rapporteur: Eva Segovia

Scope: Submission of the results of a drug utilisation study (DUS) performed in Germany and France to evaluate off-label use and effectiveness of risk minimisation measures (RMM) in a real-life clinical setting (in fulfilment of MEA 002). As a consequence, the package leaflet is updated to strengthen the warning on hypoglycaemia and bronchospasm. The RMP (version 3.1) is updated accordingly. In addition, the MAH took the opportunity to introduce some editorial changes in section 4.4 of the SmPC as well as changes in the package leaflet in accordance with the latest quality review document (QRD) template (version 10.0)

15.3.24. Ramucirumab - CYRAMZA (CAP) - EMEA/H/C/002829/II/0033

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include Cyramza (ramucirumab) in combination with erlotinib for the first-line treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) with activating epidermal growth factor receptor (EGFR) mutations. 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 9.0) are updated accordingly

15.3.25. Regadenoson - RAPISCAN (CAP) - EMEA/H/C/001176/II/0034/G

Applicant: GE Healthcare AS

PRAC Rapporteur: Eva Segovia

Scope: Grouped variations consisting of: 1) update of sections 4.4 and 4.8 of the SmPC regarding myocardial ischaemia (myocardial infarction, ventricular arrhythmias and cardiac arrest) based on a review of the safety database and company core safety datasheet (CCDS) update; 2) update of sections 4.4, 4.5, 4.8, 4.9 and 5.1 of the SmPC regarding co-administration with methylxanthine due to the risk of seizure and hypersensitivity including anaphylaxis based on a review of the safety database and CCDS update; 3) update of section 5.1 of the SmPC regarding the use of regadenoson in patients with inadequate stress test based on results from study 3606-CL-3004: a phase 3b, open-label, parallel group, randomized, multicentre study to assess regadenoson administration following an inadequate exercise stress test as compared to regadenoson alone for myocardial perfusion imaging (MPI) using single photon emission computed tomography (SPECT); and CCDS update. The RMP (version 11.1) is updated accordingly (in fulfilment of LEG 016)

15.3.26. Secukinumab - COSENTYX (CAP) - EMEA/H/C/003729/II/0053/G

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Eva Segovia

Scope: Grouped variations consisting of: 1) extension of indication to include the treatment of non-radiographic axial spondyloarthritis (nr-axSpA)/axial spondyloarthritis (axSpA) without radiographic evidence. As a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1 of the SmPC are amended. The package leaflet and the RMP (version 5.0) are updated accordingly; 2) change in the due date of the psoriasis registry (listed as a category 3 study in the RMP)

15.3.27. Sodium oxybate - XYREM (CAP) - EMEA/H/C/000593/II/0076

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Extension of indication to include adolescents and children older than 7 years to the existing indication of treatment of narcolepsy with cataplexy in adults. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The package leaflet and the RMP (version 9.0) are updated accordingly

15.3.28. Sodium zirconium cyclosilicate - LOKELMA (CAP) - EMEA/H/C/004029/II/0013

Applicant: AstraZeneca AB

PRAC Rapporteur: Kirsti Villikka

Scope: Update of sections 4.2, 4.4 and 5.1 of the SmPC in order to update the clinical information based on final results from study DIALIZE: a Phase 3b, multicentre, prospective, randomised, double-blind, placebo-controlled study to reduce incidence of pre-dialysis hyperkalaemia with sodium zirconium cyclosilicate. The package leaflet, labelling and the RMP (version 2.1) are updated accordingly. In addition, the MAH took the opportunity to reflect information on sodium content in line with the Annex to the European Commission (EC) guideline on 'excipients in the labelling and package leaflet of medicinal products for human use'. Furthermore, minor editorial changes were introduced in the package leaflet

15.3.29. Tafamidis - VYNDAQEL (CAP) - EMEA/H/C/002294/X/0049/G, Orphan

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Ghania Chamouni

Scope: Grouped application consisting of: 1) extension application to introduce a new strength (61 mg soft capsules, pack-size of 30 and 90 capsules) including an extension of indication to include treatment of transthyretin amyloidosis in adult patients with wild-type or hereditary cardiomyopathy to reduce all-cause mortality and cardiovascular-related hospitalisation (ATTR-CM); 2) update of section 4.6 of the SmPC of 20 mg soft capsules to reflect some wording pertaining to the Tafamidis Enhanced Surveillance for Pregnancy Outcomes (TESPO) programme. The RMP (version 9.0) is updated accordingly, including proposed new dosage/indication, review of the additional data collected from the ATTR-CM clinical programme and post marketing reporting, a reclassification of the safety concerns and the removal of healthcare professional (HCP) educational leaflet. Annex II is updated in accordance. In addition, the MAH proposed to update the information in Braille of Annex III-A on 'labelling' to differentiate between the dosage forms

15.3.30. Tisagenlecleucel - KYMRIAH (CAP) - EMEA/H/C/004090/II/0013/G, Orphan

Applicant: Novartis Europharm Limited, ATMP[34]

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Grouped variations consisting of: 1) update of sections 4.4, 4.8, 5.1 and 5.2 of the SmPC to implement 24 month follow-up results from study CCTL019C2201: a phase 2, single arm, multicentre trial to determine the efficacy and safety of CTL019 (tisagenlecleucel) in adult patients with relapsed or refractory diffuse large b-cell lymphoma (DLBCL); 2) update of sections 4.4, 4.8, 5.1 and 5.2 of the SmPC based on interim results from study CCTL019B2202: a phase 2, single arm, multicentre trial to determine the efficacy and safety of CTL019 in paediatric patients with relapsed and refractory b-cell acute lymphoblastic leukaemia; 3) update of section 5.2 of the SmPC based on interim results from study CCTL019B2205J: a phase 2, single arm, multicentre trial to determine the efficacy and safety of CTL019 in paediatric patients with relapsed and refractory b-cell acute lymphoblastic leukaemia. Annex II, the package leaflet and the RMP (version 2.0) are updated accordingly. In addition, the MAH took the opportunity to clarify the wording of the indication in order to reflect that patients of 25 years of age are being included and to introduce some minor editorial corrections throughout the SmPC and the package leaflet

15.3.31. Trastuzumab emtansine - KADCYLA (CAP) - EMEA/H/C/002389/II/0048/G

Applicant: Roche Registration GmbH

PRAC Rapporteur: Hans Christian Siersted

Scope: Grouped variations consisting of: 1) update of sections 4.4 and 4.8 of the SmPC in order to update the safety information on the risk of left ventricular dysfunction (LVD) based on the final results from study BO39807 (listed as a category 3 study in the RMP): an observational study of cardiac events in patients with epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer who have a left ventricular ejection fraction (LVEF) between 40%-49% prior to initiating treatment with Kadcyla (trastuzumab emtansine). The RMP (version 10.0) is updated accordingly; 2) submission of the final report from study BO28408 (listed as a category 3 study in the RMP): a randomised, multicentre, open-label, two-arm, phase 3 neoadjuvant study evaluating the efficacy and safety of trastuzumab emtansine plus pertuzumab compared with chemotherapy plus trastuzumab and pertuzumab for patients with HER2-positive breast cancer

15.3.32. Trifluridine, tipiracil - LONSURF (CAP) - EMEA/H/C/003897/II/0016

Applicant: Les Laboratoires Servier

PRAC Rapporteur: Annika Folin

Scope: Update of sections 4.2, 4.4 and 5.2 of the SmPC in order to update information on patients with severe renal impairment based on final results from study TO-TAS-102-107: a phase 1, open-label study to evaluate the safety, tolerability, and pharmacokinetics of TAS-102 (trifluridine/tipiracil) in patients with advanced solid tumours and varying degrees of renal impairment. The package leaflet and the RMP (version 6.3) are updated accordingly. In addition, the MAH took the opportunity to bring the RMP in line with revision 2 of the

[34] Advanced therapy medicinal product

guidance on the format of RMP in the EU (template)

15.3.33. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/II/0073

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Rhea Fitzgerald

Scope: Extension of indication to include a new population for Stelara (ustekinumab) solution for injection in children aged 6 to 12 years with moderate to severe psoriasis based on the results of study CNTO1275PSO3013: a phase 3 open-label study to assess the efficacy, safety, and pharmacokinetics of subcutaneously administered ustekinumab in the treatment of moderate to severe chronic plaque psoriasis in paediatric subjects greater than or equal to 6 to less than 12 years of age. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. Section 4.8 of the SmPC for Stelara (ustekinumab) concentrate for solution for infusion is updated accordingly. The package leaflet and the RMP (version 15.0) are updated accordingly. The MAH also updated the RMP to add 'follow-up of pregnancy registry'. The MAH took the opportunity to introduce minor editorial changes to section 4.5 for both formulations and to update the list of local representatives in the package leaflet

15.3.34. Vedolizumab - ENTYVIO (CAP) - EMEA/H/C/002782/X/0040

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Adam Przybylkowski

Scope: Extension application to introduce a new pharmaceutical form (solution for injection) associated with a new strength (108 mg) and a new route of administration (subcutaneous use). The RMP (version 5.0) is updated accordingly

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

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

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

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

16.1.1. Anakinra - KINERET (CAP) - PSUSA/00000209/201905

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Hans Christian Siersted

Scope: Evaluation of a PSUSA procedure

16.1.2. Atezolizumab - TECENTRIQ (CAP) - PSUSA/00010644/201905

Applicant: Roche Registration GmbH

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Evaluation of a PSUSA procedure

16.1.3. Benralizumab - FASENRA (CAP) - PSUSA/00010661/201905

Applicant: AstraZeneca AB

PRAC Rapporteur: David Olsen

Scope: Evaluation of a PSUSA procedure

16.1.4. Brigatinib - ALUNBRIG (CAP) - PSUSA/00010728/201904

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Evaluation of a PSUSA procedure

16.1.5. Brinzolamide, timolol - AZARGA (CAP) - PSUSA/00000433/201904

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

16.1.6. Cetrorelix - CETROTIDE (CAP) - PSUSA/00000633/201904

Applicant: Merck Europe B.V.

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.7. Darunavir, cobicistat - REZOLSTA (CAP) - PSUSA/00010315/201905

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Ilaria Baldelli

Scope: Evaluation of a PSUSA procedure

16.1.8. Dinutuximab beta - QARZIBA (CAP) - PSUSA/00010597/201905

Applicant: EUSA Pharma (Netherlands) B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.9. Dolutegravir, rilpivirine - JULUCA (CAP) - PSUSA/00010689/201905

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

16.1.10. Emicizumab - HEMLIBRA (CAP) - PSUSA/00010668/201905

Applicant: Roche Registration GmbH

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.1.11. Fexinidazole - FEXINIDAZOLE WINTHROP (Art 58[35]) - EMEA/H/W/002320/PSUV/0001

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUR procedure

16.1.12. Gemtuzumab ozogamicin - MYLOTARG (CAP) - PSUSA/00010688/201905

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Evaluation of a PSUSA procedure

16.1.13. Letermovir - PREVYMIS (CAP) - PSUSA/00010660/201905

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

16.1.14. Lidocaine, prilocaine[36] - FORTACIN (CAP) - PSUSA/00010110/201905

Applicant: Recordati Ireland Ltd

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

16.1.15. Lumacaftor, ivacaftor - ORKAMBI (CAP) - PSUSA/00010455/201905

Applicant: Vertex Pharmaceuticals (Ireland) Limited

[35] 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)
[36] Centrally authorised product(s) only

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

16.1.16. Meningococcal group B vaccine (recombinant, adsorbed) - TRUMENBA (CAP) - PSUSA/00010607/201904

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

16.1.17. Midostaurin - RYDAPT (CAP) - PSUSA/00010638/201904

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Evaluation of a PSUSA procedure

16.1.18. Padeliporfin - TOOKAD (CAP) - PSUSA/00010654/201905

Applicant: Steba Biotech S.A

PRAC Rapporteur: Maia Uusküla

Scope: Evaluation of a PSUSA procedure

16.1.19. Pandemic influenza vaccine (H5N1) (live attenuated, nasal) - PANDEMIC INFLUENZA VACCINE H5N1 ASTRAZENECA (CAP) - PSUSA/00010501/201905

Applicant: AstraZeneca AB

PRAC Rapporteur: Sonja Hrabcik

Scope: Evaluation of a PSUSA procedure

16.1.20. Pandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) - ADJUPANRIX (CAP); prepandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) - PREPANDRIX (CAP) - PSUSA/00002281/201905

Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.21. Pixantrone - PIXUVRI (CAP) - PSUSA/00009261/201905

Applicant: Les Laboratoires Servier

PRAC Rapporteur: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

16.1.22. Prasterone[37] - INTRAROSA (CAP) - PSUSA/00010672/201905

Applicant: Endoceutics S.A.

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.23. Radium (^{223}Ra) dichloride - XOFIGO (CAP) - PSUSA/00010132/201905

Applicant: Bayer AG

PRAC Rapporteur: Rugile Pilviniene

Scope: Evaluation of a PSUSA procedure

16.1.24. Rurioctocog alfa pegol - ADYNOVI (CAP) - PSUSA/00010663/201905

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.25. Shingles (herpes zoster) vaccine (live) - ZOSTAVAX (CAP) - PSUSA/00009289/201905

Applicant: MSD Vaccins

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.26. Sunitinib - SUTENT (CAP) - PSUSA/00002833/201904

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.1.27. Susoctocog alfa - OBIZUR (CAP) - PSUSA/00010458/201905

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.28. Tafamidis - VYNDAQEL (CAP) - PSUSA/00002842/201905

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

[37] Pessary, for vaginal use only

16.1.29. Temoporfin - FOSCAN (CAP) - PSUSA/00002885/201904

Applicant: Biolitec Pharma Ltd

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.30. Tilmanocept - LYMPHOSEEK (CAP) - PSUSA/00010313/201905

Applicant: Norgine B.V.

PRAC Rapporteur: Rugile Pilviniene

Scope: Evaluation of a PSUSA procedure

16.1.31. Tolvaptan[38] - SAMSCA (CAP) - PSUSA/00002994/201905

Applicant: Otsuka Pharmaceutical Netherlands B.V.

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.1.32. Vestronidase alfa - MEPSEVII (CAP) - PSUSA/00010709/201905

Applicant: Ultragenyx Germany GmbH

PRAC Rapporteur: Eva Segovia

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. Bortezomib - BORTEZOMIB ACCORD (CAP); BORTEZOMIB HOSPIRA (CAP); BORTEZOMIB SUN (CAP); VELCADE (CAP); NAP - PSUSA/00000424/201904

Applicant(s): Accord Healthcare S.L.U. (Bortezomib Accord), Janssen-Cilag International NV (Velcade), Pfizer Europe MA EEIG (Bortezomib Hospira), Sun Pharmaceutical Industries Europe B.V. (Bortezomib Sun), various

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.2.2. Efavirenz - STOCRIN (CAP); SUSTIVA (CAP), NAP - PSUSA/00001200/201904

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

PRAC Rapporteur: Ana Sofia Diniz Martins

[38] Indicated for adults with hyponatraemia secondary to syndrome of inappropriate antidiuretic hormone secretion (SIADH) only

Scope: Evaluation of a PSUSA procedure

16.2.3. Hydrochlorothiazide, telmisartan - KINZALKOMB (CAP), MICARDISPLUS (CAP), PRITORPLUS (CAP); telmisartan - KINZALMONO (CAP), MICARDIS (CAP), PRITOR (CAP); NAP - PSUSA/00002882/201904

Applicant(s): Bayer AG (Kinzalkomb, Kinzalmono, Pritor, PritorPlus), Boehringer Ingelheim International GmbH (Micardis, MicardisPlus), various

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.2.4. Mycophenolate mofetil - CELLCEPT (CAP), MYCLAUSEN (CAP), MYCOPHENOLATE MOFETIL TEVA (CAP), MYFENAX (CAP); NAP; mycophenolic acid (NAP) - PSUSA/00010550/201905

Applicant(s): Passauer Pharma GmbH (Myclausen), Roche Registration GmbH (CellCept), Teva B.V. (Mycophenolate mofetil Teva, Myfenax), various

PRAC Rapporteur: Hans Christian Siersted

Scope: Evaluation of a PSUSA procedure

16.2.5. Tacrolimus[39] - PROTOPIC (CAP); NAP - PSUSA/00002840/201903

Applicant: LEO Pharma A/S (Protopic), various

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

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

16.3.1. Carteolol (NAP) - PSUSA/00000574/201903

Applicant(s): various

PRAC Lead: Tatiana Magalova

Scope: Evaluation of a PSUSA procedure

16.3.2. Carvedilol, ivabradine (NAP) - PSUSA/00010586/201904

Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.3.3. Cytarabine (NAP) - PSUSA/00000911/201903

Applicant(s): various

[39] Topical formulation(s) only

PRAC Lead: Julia Pallos

Scope: Evaluation of a PSUSA procedure

16.3.4. Ivermectin[40] (NAP) - PSUSA/00010377/201904

Applicant(s): various

PRAC Lead: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

16.3.5. Ivermectin[41] (NAP) - PSUSA/00010376/201904

Applicant(s): various

PRAC Lead: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

16.3.6. Nefopam (NAP) - PSUSA/00002131/201903

Applicant(s): various

PRAC Lead: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

16.3.7. Triamcinolone[42] (NAP) - PSUSA/00010292/201903

Applicant(s): various

PRAC Lead: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Evaluation of a PSUSA procedure

16.3.8. Varicella vaccine (live) (NAP) - PSUSA/00010473/201903

Applicant(s): various

PRAC Lead: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

16.4. Follow-up to PSUR/PSUSA procedures

None

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

Based on the assessment of the following PASS protocol(s), result(s), interim result(s) or feasibility study(ies), and following endorsement of the comments received, the PRAC

[40] Systemic use only
[41] Topical use only
[42] Intraocular formulation(s) only

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)[43]

17.1.1. Damoctocog alfa pegol - JIVI (CAP) - EMEA/H/C/PSP/S/0070.2

Applicant: Bayer AG

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to PSP/S/0070.1 [protocol for an observational study to assess the effectiveness and long term safety of prophylaxis with damoctocog alfa pegol in real-world settings through the collection of total bleeding events and analysis of the annualised bleeding rate (ABR) in the different prophylaxis regimens (following approved local label or any other regimen prescribed by the physician as part of normal clinical practice) in patients with haemophilia A] as per the request for supplementary information (RSI) adopted in July 2019

17.1.2. Levofloxacin - QUINSAIR (CAP) - EMEA/H/C/PSA/S/0039.1

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Maria del Pilar Rayon

Scope: MAH's response to PSA/S/0039 [amendment to a protocol initially endorsed by PRAC in April 2017 (EMEA/H/C/PSP/S/0049.2) for a post-marketing, observational safety study in patients with cystic fibrosis to evaluate the long-term safety of Quinsair (levofloxacin) over a five-year period (2017 to 2021) compared to other inhaled approved antibiotic therapies in cystic fibrosis (CF) patients who are enrolled in the United Kingdom (UK) CF registry. The primary objective is extended to evaluate the safety profile of Quinsair (levofloxacin) over a three-year period (2019 to 2021) compared to other inhaled approved antibiotic therapies in CF patients who are enrolled in the German CF registry] as per the request for supplementary information (RSI) adopted in July 2019

17.1.3. Radium (Ra^{223}) – XOFIGO (CAP) - EMEA/H/C/PSP/S/0076.2

Applicant: Bayer AG

PRAC Rapporteur: Rugile Pilviniene

Scope: MAH's response to PSP/S/0076.1 [protocol for a PASS to estimate the incidence rate of symptomatic bone fractures among users of Xofigo (radium-223) in routine clinical practice] as per the request for supplementary information (RSI) adopted in July 2019

17.1.4. Valproate (NAP) - EMEA/H/N/PSP/J/0072.2

Applicant: Sanofi-Aventis Recherche & Développement

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: MAH's response to PSP/J/0072.1 [protocol for a retrospective observational study to

[43] In accordance with Article 107n of Directive 2001/83/EC

investigate the association between paternal exposure to valproate and the risk of congenital anomalies and neurodevelopmental disorders including autism in offspring, as required in the outcome of the referral procedure under Article 31 of Directive 2001/83/EC on valproate-containing products completed in February 2018 (EMEA/H/A-31/1454)] as per the request for supplementary information (RSI) adopted in July 2019

17.1.5. Valproate (NAP) - EMEA/H/N/PSP/J/0073.2

Applicant: Sanofi-Aventis Recherche & Développement

PRAC Rapporteur: Liana Gross-Martirosyan

Scope MAH's response to PSP/J/0073.1 [protocol for a survey among healthcare professionals (HCP) to assess the knowledge of HCP and behaviour with regard to the pregnancy prevention programme (PPP), the receipt/use of direct healthcare professional communication (DHPC) and educational materials as well as for a survey among patients to assess the knowledge of patients with regards to PPP and receipt/use of educational materials, as required in the outcome of the referral procedure under Article 31 of Directive 2001/83/EC on valproate-containing products completed in February 2018 (EMEA/H/A-31/1454)] as per the request for supplementary information (RSI) adopted in July 2019

17.1.6. Valproate (NAP) - EMEA/H/N/PSP/J/0075.2

Applicant: Sanofi-Aventis Recherche & Développement

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: MAH's response to PSP/J/0075.1 [protocol for a drug utilisation study (DUS) to assess the effectiveness of the new risk minimisation measures (RMMs) and to further characterise the prescribing patterns for valproate as required in the outcome of the referral procedure under Article 31 of Directive 2001/83/EC on valproate-containing products completed in February 2018 (EMEA/H/A-31/1454)] as per the request for supplementary information (RSI) adopted in July 2019

17.2. Protocols of PASS non-imposed in the marketing authorisation(s)[44]

17.2.1. Cangrelor - KENGREXAL (CAP) - EMEA/H/C/003773/MEA 002.1

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Ilaria Baldelli

Scope: MAH's response to MEA 002 [Protocol for study DFIDM-1801 (ARCANGELO (itAlian pRospective study on CANGrELOr)): a multicentre prospective observational study of acute coronary syndrome patients undergoing percutaneous coronary intervention (PCI) who receive cangrelor and transition to either clopidogrel, prasugrel or ticagrelor] as per the request for supplementary information (RSI) adopted in July 2019

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

17.2.2. Empagliflozin - JARDIANCE (CAP) - EMEA/H/C/002677/MEA 004.4

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Eva Segovia

Scope: MAH's response to MEA 004.3 [amendment to a previously agreed protocol in September 2016 for study 1245.97: a study to assess the risk of urinary tract malignancies in relation to empagliflozin exposure in patients with type 2 mellitus diabetes (T2DM): a multi-database European study to add Finnish national registries to the study as additional data sources to evaluate the main study outcomes] as per the request for supplementary information (RSI) adopted in June 2019

17.2.3. Empagliflozin, metformin - SYNJARDY (CAP) - EMEA/H/C/003770/MEA 006.4

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Eva Segovia

Scope: MAH's response to MEA 006.3 [amendment to a previously agreed protocol in September 2016 for study 1245.97: a study to assess the risk of urinary tract malignancies in relation to empagliflozin exposure in patients with type 2 mellitus diabetes (T2DM): a multi-database European study to add Finnish national registries to the study as additional data sources to evaluate the main study outcomes] as per the request for supplementary information (RSI) adopted in June 2019

17.2.4. Emtricitabine, tenofovir disoproxil - TRUVADA (CAP) - EMEA/H/C/000594/MEA 047.3

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: MAH's response to MEA 047.2 [protocol for study No GS EU 276 4487: a prospective, longitudinal, observational registry of emtricitabine/tenofovir disoproxil fumarate for human immunodeficiency virus 1 (HIV-1) pre-exposure prophylaxis (PrEP) in the European Union] as per the request for supplementary information (RSI) adopted in June 2019

17.2.5. Estrogens conjugated, bazedoxifene - DUAVIVE (CAP) - EMEA/H/C/002314/MEA 002.13

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Martin Huber

Scope: MAH's response to MEA 02.12 [Substantial amendment to a protocol previously agreed in May 2015 for ongoing US study B2311060 (listed as a category 3 study in the RMP): a study to estimate the incidence and to compare the risks of endometrial hyperplasia and endometrial cancer in postmenopausal women initiating either Duavive (estrogens conjugated/bazedoxifene) or estrogen + progestin (E+P) combination hormone replacement therapy (HRT)] as per the request for supplementary information (RSI) adopted in July 2019

17.2.6. Lenalidomide - REVLIMID (CAP) - EMEA/H/C/000717/MEA 046.3

Applicant: Celgene Europe BV

PRAC Rapporteur: Ghania Chamouni

Scope: Substantial amendment (version 4.0) to a protocol previously endorsed in November 2017 for study CC-5013-MCL-005 to further investigate and characterise the association of lenalidomide and tumour flare reaction (TFR)/high tumour burden following the extension of indication for the treatment of adult patients with relapsed and/or refractory mantle cell lymphoma (RRMCL) [final clinical study report (CSR) expected in December 2022]

17.2.7. Naldemedine - RIZMOIC (CAP) - EMEA/H/C/004256/MEA 001

Applicant: Shionogi B.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Protocol for an observational PASS of patients with chronic opioid use for non-cancer and cancer pain who have opioid-induced constipation (OIC) [final clinical study report (CSR) expected in January 2026)] (from opinion/MA)

17.2.8. Patisiran - ONPATTRO (CAP) - EMEA/H/C/004699/MEA 002.2

Applicant: Alnylam Netherlands B.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: MAH's response to MEA 002.1 [protocol for study ALN-TTR02-0009: a prospective observational study to monitor and assess the safety of Onpattro (patisiran) in a real-world cohort of hereditary transthyretin amyloidosis (hATTR) patients] as per the request for supplementary information (RSI) adopted in July 2019

17.2.9. Ropeginterferon alfa-2b - BESREMI (CAP) - EMEA/H/C/004128/MEA 001.1

Applicant: AOP Orphan Pharmaceuticals AG

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: MAH's response to MEA 001 [protocol for EUPAS29462 study: a prospective, multicentre, non-interventional observational PASS to further investigate the safety and tolerability of ropeginterferon alfa-2b in polycythaemia vera patients with a special focus on hepatotoxicity to evaluate the effectiveness of risk minimisation measures and to evaluate cardiovascular safety during titration phase [final study report expected in Q3 2023]] as per the request for supplementary information (RSI) adopted in July 2019

17.3. Results of PASS imposed in the marketing authorisation(s)[45]

None

[45] In accordance with Article 107p-q of Directive 2001/83/EC

17.4. Results of PASS non-imposed in the marketing authorisation(s)[46]

17.4.1. Cladribine - MAVENCLAD (CAP) - EMEA/H/C/004230/II/0009

Applicant: Merck Europe B.V.

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Submission of the final clinical study report (CSR) for study EMR700568-012 (PREMIERE registry) (listed as a category 3 study in the RMP): a prospective, observational, long-term safety registry of multiple sclerosis (MS) patients who have participated in cladribine clinical studies. It collected long-term safety data from patients previously participating in 1 out of 5 clinical trials, namely: 1) study 25643 (CLARITY): a phase 3, randomized, double-blind, three-arm, placebo-controlled, multi-center study to evaluate the safety and efficacy of oral cladribine in subjects with relapsing-remitting multiple sclerosis (RRMS); 2) study 26593 (ONWARD): a phase 2, multicentre, randomized, double blind, placebo controlled, safety, tolerability and efficacy study of add-on cladribine tablet therapy with interferon-beta (IFN-β) treatment in MS subjects with active disease; 3) study 27820: a phase 3b, double-blind, placebo-controlled, multicentre, parallel group, extension trial to evaluate the safety and tolerability of oral cladribine in subjects with relapsing-remitting multiple sclerosis who have completed trial 25643 (CLARITY); 4) study 27967: an open-label, cross over study, to assess the interactions of pantoprazole with oral cladribine administered in subjects with MS; 5) study 28821: a phase 3, randomized, double-blind, placebo-controlled, multicentre clinical trial of oral cladribine in subjects with a first clinical event at high risk of converting to MS

17.4.2. Daratumumab - DARZALEX (CAP) - EMEA/H/C/004077/II/0033, Orphan

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Submission of final study results of non-interventional study L01XC24 investigating the effectiveness of the educational materials of Darzalex (daratumumab) concerning the potential risk of daratumumab to interfere with blood typing analysis. This commitment was requested as PAM 001. The RMP (version 5.4) is updated accordingly

17.4.3. Infliximab - INFLECTRA (CAP) - EMEA/H/C/002778/II/0079

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Kimmo Jaakkola

Scope: Submission of the final clinical study report (CSR) for study C1231002 (PERSIST): an observational cohort study designed to evaluate real life drug persistence in biologic naive rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis patients receiving CT-P13 (infliximab biosimilar) or those switched to CT-P13 from stable treatment with the reference medicinal product containing infliximab

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

17.4.4. Infliximab - INFLECTRA (CAP) - EMEA/H/C/002778/II/0080

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Kimmo Jaakkola

Scope: Submission of the final clinical study report (CSR) for study C1231001 (CONNECT-IBD): a non-interventional study designated as a PASS conducted voluntarily to capture data from real-world clinical practice to characterise the population and document drug utilisation patterns. In addition, available safety data and data on the effectiveness of CT-P13 (infliximab biosimilar) was collected in patients with Crohn's disease or ulcerative colitis in the context of standard of care utilisation of the reference medicinal product containing infliximab

17.4.5. Infliximab - REMSIMA (CAP) - EMEA/H/C/002576/II/0073

Applicant: Celltrion Healthcare Hungary Kft.

PRAC Rapporteur: Kimmo Jaakkola

Scope: Submission of the final clinical study report (CSR) for study C1231001 (CONNECT-IBD): a non-interventional study designated as a PASS conducted voluntarily to capture data from real-world clinical practice to characterise the population and document drug utilisation patterns. In addition, available safety data and data on the effectiveness of CT-P13 (infliximab biosimilar) was collected in patients with Crohn's disease or ulcerative colitis in the context of standard of care utilisation of the reference medicinal product containing infliximab

17.4.6. Infliximab - REMSIMA (CAP) - EMEA/H/C/002576/II/0074

Applicant: Celltrion Healthcare Hungary Kft.

PRAC Rapporteur: Kimmo Jaakkola

Scope: Submission of the final clinical study report (CSR) for study C1231002 (PERSIST): an observational cohort study designed to evaluate real life drug persistence in biologic naive rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis patients receiving CT-P13 (infliximab biosimilar) or those switched to CT-P13 from stable treatment with the reference medicinal product containing infliximab

17.4.7. Linaclotide - CONSTELLA (CAP) - EMEA/H/C/002490/II/0043

Applicant: Allergan Pharmaceuticals International Limited

PRAC Rapporteur: Martin Huber

Scope: Submission of the final report from study 'linaclotide utilisation study in selected European populations' (listed as a category 3 study in the RMP): a drug utilisation study (DUS) addressing the potential for off-label use and abuse/excessive use, the extent of use in pregnancy and lactation, and male patients as well as assessing the extent of off-label use and the extent of use in males and in pregnant females

17.4.8. Nalmefene - SELINCRO (CAP) - EMEA/H/C/002583/II/0025

Applicant: H. Lundbeck A/S

PRAC Rapporteur: Martin Huber

Scope: Submission for the final study reports for: 1) study 15649A on the use of Selincro (nalmefene) using European databases: a cohort design study using longitudinal electronic medical records or claims databases; 2) study 14910A: a non-interventional multi-country prospective cohort study to investigate the pattern of use of Selincro (nalmefene) and frequency of selected adverse reactions in routine clinical practice

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

17.5.1. Adalimumab - HUMIRA (CAP) - EMEA/H/C/000481/MEA 046.9

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Tenth annual interim report for study P10-262, a registry study in juvenile idiopathic arthritis (JIA) patients: a long term, multicentre, longitudinal post-marketing, observational study to assess long term safety and effectiveness of Humira (adalimumab) in children with moderately to severely active polyarticular or polyarticular-course JIA – STRIVE [final study report due date: 31 December 2024]

17.5.2. Adalimumab - HUMIRA (CAP) - EMEA/H/C/000481/MEA 075.8

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Seventh annual interim study report for Humira ulcerative colitis registry P11-282: a long-term non-interventional post-marketing study to assess safety and effectiveness of Humira (adalimumab) in patients with moderately to severely active ulcerative colitis (UC)

17.5.3. Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/MEA 008.6

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Third annual interim report for study CA209234 (listed as a category 3 study in the RMP): a PASS exploring the pattern of use, safety, and effectiveness of nivolumab in routine oncology practice [final clinical study report (CSR) expected in December 2024]

17.5.4. Simoctocog alfa - NUWIQ (CAP) - EMEA/H/C/002813/MEA 004.5

Applicant: Octapharma AB

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Progress report for study GENA-99: a prospective, multinational, non-interventional post-authorisation study to document the long-term immunogenicity, safety, and efficacy of simoctocog alfa in patients with haemophilia A treated in routine clinical practice [final

report due date expected in 2020]

17.5.5. Simoctocog alfa - VIHUMA (CAP) - EMEA/H/C/004459/MEA 004.4

Applicant: Octapharma AB

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Progress report for study GENA-99: a prospective, multinational, non-interventional post-authorisation study to document the long-term immunogenicity, safety, and efficacy of simoctocog alfa in patients with haemophilia A treated in routine clinical practice [final report due date expected in 2020]

17.5.6. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/MEA 023.12

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Rhea Fitzgerald

Scope: MAH's response to MEA 023.11 [ninth annual interim report for study CNTO1275PSO4005 (Nordic database initiative): a prospective cohort registry, five-year observational study of adverse events (AEs) observed in patients exposed to ustekinumab] as per the request for supplementary information (RSI) adopted in July 2019

17.5.7. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/MEA 024.13

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Rhea Fitzgerald

Scope: MAH's response to MEA 024.12 [ninth annual interim report for study CNTO1275PSO4007 (Nordic pregnancy research initiative) (C0743T): exposure to ustekinumab during pregnancy in patients with psoriasis: a review and analysis of birth outcomes from the Swedish, Danish, and Finnish medical birth registers] as per the request for supplementary information (RSI) adopted in July 2019

17.5.8. Venetoclax - VENCLYXTO (CAP) - EMEA/H/C/004106/MEA 006.1

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Eva Jirsová

Scope: MAH's reponse to MEA 006 [interim study report for study M12-175: a phase 1 study evaluating the safety and pharmacokinetics of venetoclax (ABT-199) in subjects with relapsed or refractory chronic lymphocytic leukaemia and non-Hodgkin lymphoma] as per the request for supplementary information (RSI) adopted in July 2019

17.6. Others

17.6.1. Evolocumab - REPATHA (CAP) - EMEA/H/C/003766/MEA 009.1

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Kimmo Jaakkola

Scope: Feasibility/futility report for study 20150162 (listed as a category 3 study in the

RMP) with a protocol previously agreed in March 2016: a multi-national observational study to evaluate the safety of Repatha (evolocumab) in pregnancy [final report expected in Q2 2027] (from initial opinion/MA)

17.7. New Scientific Advice

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

17.8. Ongoing Scientific Advice

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

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

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

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

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

18.1. Annual reassessments of the marketing authorisation

18.1.1. Asfotase alfa - STRENSIQ (CAP) - EMEA/H/C/003794/S/0041 (without RMP)

Applicant: Alexion Europe SAS

PRAC Rapporteur: Rhea Fitzgerald

Scope: Annual reassessment of the marketing authorisation

18.1.2. Cerliponase alfa - BRINEURA (CAP) - EMEA/H/C/004065/S/0018 (without RMP)

Applicant: BioMarin International Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Annual reassessment of the marketing authorisation

18.2. Conditional renewals of the marketing authorisation

18.2.1. Bosutinib - BOSULIF (CAP) - EMEA/H/C/002373/R/0039 (without RMP)

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Martin Huber

Scope: Conditional renewal of the marketing authorisation

18.2.2. Parathyroid hormone - NATPAR (CAP) - EMEA/H/C/003861/R/0022 (without RMP)

Applicant: Shire Pharmaceuticals Ireland Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Conditional renewal of the marketing authorisation

18.3. Renewals of the marketing authorisation

18.3.1. Aripiprazole - ARIPIPRAZOLE MYLAN PHARMA (CAP) - EMEA/H/C/003803/R/0013 (without RMP)

Applicant: Mylan S.A.S

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: 5-year renewal of the marketing authorisation

18.3.2. Atazanavir, cobicistat - EVOTAZ (CAP) - EMEA/H/C/003904/R/0031 (without RMP)

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Adrien Inoubli

Scope: 5-year renewal of the marketing authorisation

18.3.3. Duloxetine - DULOXETINE MYLAN (CAP) - EMEA/H/C/003981/R/0021 (without RMP)

Applicant: Mylan S.A.S

PRAC Rapporteur: Maria del Pilar Rayon

Scope: 5-year renewal of the marketing authorisation

18.3.4. Edoxaban - LIXIANA (CAP) - EMEA/H/C/002629/R/0023 (with RMP)

Applicant: Daiichi Sankyo Europe GmbH

PRAC Rapporteur: Adrien Inoubli

Scope: 5-year renewal of the marketing authorisation

18.3.5. Lenvatinib - LENVIMA (CAP) - EMEA/H/C/003727/R/0031 (with RMP)

Applicant: Eisai GmbH

PRAC Rapporteur: Annika Folin

Scope: 5-year renewal of the marketing authorisation

18.3.6. Levofloxacin - QUINSAIR (CAP) - EMEA/H/C/002789/R/0022 (with RMP)

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Maria del Pilar Rayon

Scope: 5-year renewal of the marketing authorisation

18.3.7. Lutetium (^{177}Lu) chloride - LUMARK (CAP) - EMEA/H/C/002749/R/0014 (with RMP)

Applicant: I.D.B. Holland B.V.

PRAC Rapporteur: Ronan Grimes

Scope: 5-year renewal of the marketing authorisation

18.3.8. Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/R/0074 (with RMP)

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: 5-year renewal of the marketing authorisation

18.3.9. Pembrolizumab - KEYTRUDA (CAP) - EMEA/H/C/003820/R/0081 (without RMP)

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: 5-year renewal of the marketing authorisation

18.3.10. Pregabalin - PREGABALIN MYLAN (CAP) - EMEA/H/C/004078/R/0014 (without RMP)

Applicant: Mylan S.A.S

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: 5-year renewal of the marketing authorisation

18.3.11. Pregabalin - PREGABALIN MYLAN PHARMA (CAP) - EMEA/H/C/003962/R/0012 (without RMP)

Applicant: Mylan S.A.S

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: 5-year renewal of the marketing authorisation

18.3.12. Voriconazole - VORICONAZOLE HIKMA (CAP) - EMEA/H/C/003737/R/0010 (with RMP)

Applicant: Hikma Farmaceutica (Portugal), S.A.

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: 5-year renewal of the marketing authorisation

19. Annex II – List of participants

including any restrictions with respect to involvement of members / alternates / experts following evaluation of declared interests for the 25-28 November 2019 meeting.

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Sabine Straus	Chair	The Netherlands	No interests declared	Full involvement
Jan Neuhauser	Member	Austria	No interests declared	Full involvement
Jean-Michel Dogné	Member	Belgium	No interests declared	Full involvement
Laurence de Fays	Alternate	Belgium	No participation in final deliberations and voting on:	4.3.1. Thiazide and thiazide-like diuretics: bendroflumethiazide; chlortalidone; cicletanine; clopamide; cyclopenthiazide; hydrochlorothiazide; hydroflumethiazide; indapamide; metipamid; metolazone; xipamide (NAP)
Maria Popova-Kiradjieva	Member	Bulgaria	No interests declared	Full involvement
Željana Margan Koletić	Alternate	Croatia	No interests declared	Full involvement
Helena Panayiotopoulou	Member	Cyprus	No interests declared	Full involvement
Eva Jirsovà	Member	Czech Republic	No interests declared	Full involvement
Anette Stark	Member	Denmark	No interests declared	Full involvement
Hans Christian Siersted	Alternate	Denmark	No restrictions applicable to this meeting	Full involvement
Maia Uusküla	Member	Estonia	No interests declared	Full involvement
Kirsti Villikka	Member	Finland	No interests declared	Full involvement
Kimmo Jaakkola	Alternate	Finland	No interests declared	Full involvement
Ghania Chamouni	Member	France	No participation in discussion,	17.1.2. Levofloxacin - QUINSAIR (CAP)

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			final deliberations and voting on:	18.3.6. Levofloxacin - QUINSAIR (CAP)
Adrien Inoubli	Alternate	France	No interests declared	Full involvement
Martin Huber	Member (Vice-Chair)	Germany	No interests declared	Full involvement
Brigitte Keller-Stanislawski	Alternate	Germany	No interests declared	Full involvement
Sophia Trantza	Alternate	Greece	No participation in discussion, final deliberations and voting on:	4.3.1. Thiazide and thiazide-like diuretics: bendroflumethiazide; chlortalidone; cicletanine; clopamide; cyclopenthiazide; hydrochlorothiazide; hydroflumethiazide; indapamide; metipamid; metolazone; xipamide (NAP)
Julia Pallos	Member	Hungary	No interests declared	Full involvement
Rhea Fitzgerald	Member	Ireland	No restrictions applicable to this meeting	Full involvement
Ronan Grimes	Alternate	Ireland	No interests declared	Full involvement
Amelia Cupelli	Member	Italy	No interests declared	Full involvement
Ilaria Baldelli	Alternate	Italy	No interests declared	Full involvement
Zane Neikena	Member	Latvia	No interests declared	Full involvement
Rugile Pilviniene	Member	Lithuania	No interests declared	Full involvement
Marcel Bruch	Member	Luxembourg	No interests declared	Full involvement
Benjamin Micallef	Alternate	Malta	No interests declared	Full involvement
Menno van der Elst	Member	Netherlands	No interests declared	Full involvement
Liana Gross-Martirosyan	Alternate	Netherlands	No interests declared	Full involvement
David Olsen	Member	Norway	No participation in final deliberations	4.3.1. Thiazide and thiazide-like diuretics: bendroflumethia

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			and voting on:	zide; chlortalidone; cicletanine; clopamide; cyclopenthiazide; hydrochlorothiazide; hydroflumethiazide; indapamide; metipamid; metolazone; xipamide (NAP) 6.3.2. Ethinylestradiol, levonorgestrel (NAP) 16.1.23. Radium (223Ra) dichloride - XOFIGO (CAP) 16.2.3. Hydrochlorothiazide, telmisartan - KINZALKOMB (CAP); MICARDISPLUS (CAP); PRITORPLUS (CAP); Telmisartan - KINZALMONO (CAP); MICARDIS (CAP); PRITOR (CAP); NAP 17.1.1. Damoctocog alfa pegol - JIVI (CAP) 17.1.3. Radium (Ra223) – XOFIGO (CAP)
Karen Pernille Harg	Alternate	Norway	No interests declared	Full involvement
Katarzyna Ziolkowska	Alternate	Poland	No interests declared	Full involvement
Ana Diniz Martins	Member	Portugal	No interests declared	Full involvement
Marcia Silva	Alternate	Portugal	No interests declared	Full involvement
Roxana Stefania Stroe	Member	Romania	No interests declared	Full involvement
Michal Radik	Member	Slovakia	No restrictions applicable to	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			this meeting	
Gabriela Jazbec	Member	Slovenia	No interests declared	Full involvement
Eva Segovia	Member	Spain	No interests declared	Full involvement
Maria del Pilar Rayon	Alternate	Spain	No interests declared	Full involvement
Ulla Wändel Liminga	Member	Sweden	No interests declared	Full involvement
Annika Folin	Alternate	Sweden	No interests declared	Full involvement
Patrick Batty	Alternate	United Kingdom	No interests declared	Full involvement
Birgitta Grundmark	Member	Independent scientific expert	No interests declared	Full involvement
Daniel Morales	Member	Independent scientific expert	No interests declared	Full involvement
Hedvig Nordeng	Member	Independent scientific expert	No interests declared	Full involvement
Antoine Pariente	Member	Independent scientific expert	No restrictions applicable to this meeting	Full involvement
Stefan Weiler	Member	Independent scientific expert	No restrictions applicable to this meeting	Full involvement
Raymond Anderson	Member	Healthcare Professionals' Representative	No interests declared	Full involvement
Roberto Frontini	Alternate	Healthcare Professionals' Representative	No participation in final deliberations and voting on:	17.5.4. Simoctocog alfa - NUWIQ (CAP) 17.5.5. Simoctocog alfa - VIHUMA (CAP)
Cathalijne van Doorne	Member	Patients' Organisation Representative	No interests declared	Full involvement
Virginie Hivert	Alternate	Patients' Organisation Representative	No restrictions applicable to this meeting	Full involvement
Christelle Bizimungu	Expert - via telephone*	Belgium	No restrictions applicable to this meeting	Full involvement
Flora Musuamba Tshinanu	Expert - in person*	Belgium	No interests declared	Full involvement
Charlotte Selvais	Expert - via telephone*	Belgium	No interests declared	Full involvement
Françoise Wuillaume	Expert - via telephone*	Belgium	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Ivona Bahnik Bisevac	Expert - via telephone*	Croatia	No restrictions applicable to this meeting	Full involvement
Marian Hjortlund Allon	Expert - in person*	Denmark	No interests declared	Full involvement
Helle Esbjørn Kristensen	Expert - via telephone*	Denmark	No restrictions applicable to this meeting	Full involvement
Astrid Munch Hestbæk	Expert - via telephone*	Denmark	No restrictions applicable to this meeting	Full involvement
Pernille Lynge Gammelgaard	Expert - in person*	Denmark	No interests declared	Full involvement
Peter Horskjær Rose	Expert - in person*	Denmark	No interests declared	Full involvement
Kroot Aab	Expert - in person*	Estonia	No interests declared	Full involvement
Matthew Burbank	Expert - in person*	France	No restrictions applicable to this meeting	Full involvement
Pauline Dayani	Expert - via telephone*	France	No restrictions applicable to this meeting	Full involvement
Emiliano Gemma	Expert - in person*	France	No interests declared	Full involvement
Emilie Patras de Campaigno	Expert - in person*	France	No interests declared	Full involvement
Norontsoa Rasolondramanitra	Expert - via telephone*	France	No interests declared	Full involvement
Faustine Vidil	Expert - in person*	France	No interests declared	Full involvement
Dennis Lex	Expert - in person*	Germany	No restrictions applicable to this meeting	Full involvement
Kerstin Löschcke	Expert - in person*	Germany	No interests declared	Full involvement
Beate Mosl	Expert - via telephone*	Germany	No restrictions applicable to this meeting	Full involvement
Martina Schüßler-Lenz	Expert - via telephone*	Germany	No interests declared	Full involvement
Elena Wolff-Holz	Expert - in person*	Germany	No interests declared	Full involvement
Sinead Curran	Expert - in person*	Ireland	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
Carmela Macchiarulo	Expert - via telephone*	Italy	No interests declared	Full involvement
Giuseppe Pimpinella	Expert - via telephone*	Italy	No restrictions applicable to this meeting	Full involvement
Johannes Hendrikus Ovelgonne	Expert - in person*	Netherlands	No interests declared	Full involvement
Raquel Granados	Expert - in person*	Spain	No interests declared	Full involvement
Charlotte Backman	Expert - in person*	Sweden	No interests declared	Full involvement
Jonas Bergh	Expert - via telephone*	Sweden	No restrictions applicable to this meeting	Full involvement
Rolf Gedeborg	Expert - via telephone*	Sweden	No interests declared	Full involvement
Jolanta Gulbinovic	Expert - in person*	Sweden	No interests declared	Full involvement
Johanna Henriksnäs	Expert - via telephone*	Sweden	No restrictions applicable to this meeting	Full involvement
Kristofer Olofsson	Expert - via telephone*	Sweden	No restrictions applicable to this meeting	Full involvement
A representative from the European Commission attended the meeting				
Meeting run with support from relevant EMA staff				

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

20. Annex III - List of acronyms and abbreviations

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

21. Explanatory notes

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

EU Referral procedures for safety reasons: Urgent EU procedures and Other EU referral procedures
(Items 2 and 3 of the PRAC minutes)

A referral is a procedure used to resolve issues such as concerns over the safety or benefit-risk balance of a medicine or a class of medicines. In a referral, 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:
http://www.ema.europa.eu/ema/