14 May 2020
EMA/PRAC/546361/2020
Human Medicines Division

Pharmacovigilance Risk Assessment Committee (PRAC)

Minutes of the meeting on 14 – 17 April 2020

Chair: Sabine Straus – Vice-Chair: Martin Huber

Disclaimers

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

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

Note on access to documents

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

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1. Introduction

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

The Chairperson opened the 14 – 17 April 2020 meeting by welcoming all participants. In light of the current crisis (COVID-19 outbreak), the EMA Business Continuity Plan (BCP) and exceptional measures taken to protect the staff members and all delegates, experts and members of the Committee are maintained. This entails that the participation and the voting from remote are allowed as a temporary measure, based on the current exceptional circumstances. The Chairperson asked for confirmation of the number of participants and once received assurance by the PRAC secretariat, requested participants to state if they had any objection to hold the meeting and to take decisions (by consensus or by voting) in such a way. No objection was raised. In light of the unanimous agreement of all members to hold the meeting in a virtual mode, the Chair confirmed the validity of the notice of the meeting and proceeded to welcome the new members and alternates.

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

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

See also under 12.1.1.

The PRAC Chair welcomed Marek Juracka, replacing Tatiana Magálová, as the new alternate for Slovakia.

1.2. Agenda of the meeting on 14 - 17 April 2020

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 09 - 12 March 2020

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 09 – 12 March 2020 were published on the EMA website on 31 August 2020 (EMA/PRAC/457964/2020).

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

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

3.1. Newly triggered procedures

None

3.2. Ongoing procedures

None

3.3. Procedures for finalisation

3.3.1. Ingenol mebutate - PICATO[1] - EMEA/H/A-20/1489

Applicant: LEO Laboratories Ltd

PRAC Rapporteur: Adam Przybylkowski; PRAC Co-rapporteur: Adrien Inoubli

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

Background

A referral procedure under Article 20 of Regulation (EC) No 726/2004 for Picato (ingenol mebutate) reviewing the possible risk of skin tumour in the treatment area in patients treated with the medicine is to be concluded. In January 2020, the PRAC recommended the provisional suspension of the marketing authorisation(s) for Picato (ingenol mebutate) until the review is finalised. A final assessment of the data submitted was produced by the Rapporteurs according to the agreed timetable. For further background, see PRAC minutes September 2019 and PRAC minutes January 2020.

Discussion

[1] European Commission (EC) decision on marketing authorisation (MA) withdrawal dated 11 February 2020, at the request of the MAH

The PRAC discussed the conclusions reached by the Rapporteurs.

The PRAC reviewed all information available, from clinical trials, post-marketing reports and non-clinical studies, on the risk of skin tumours in the treatment area in patients treated with Picato (ingenol mebutate).

The PRAC considered that the evidence on the risk of skin malignancies with ingenol mebutate from all the available data, including the statistically significant imbalance in skin malignancies with ingenol mebutate compared to imiquimod confirmed in the final results of study LP0041-63[2], raised serious safety concerns. The PRAC also noted study results supporting the previously observed decreasing efficacy of Picato over time.

In addition, the PRAC could not identify measures to minimise the risk of skin tumours in the treatment area to an acceptable level. Furthermore, the PRAC could not identify any sub-group of patients in which benefit from treatment with Picato would outweigh its risks.

As a consequence, the PRAC considered that the benefit-risk balance of Picato (ingenol mebutate) is not favourable.

Summary of recommendation(s)/conclusions

- The PRAC noted the Commission Decision (C(2020) 856 final) on 11 February 2020 withdrawing the marketing authorisation(s) of Picato (ingenol mebutate) at the request of the MAH. Taking into account that the said marketing authorisation(s) was withdrawn, the PRAC did not recommend any regulatory action in this regard – see EMA Press Release (EMA/194393/2020) entitled 'EMA review of Picato concludes medicine's risks outweigh its benefits' published on 17 April 2020.

Post-meeting note 1: the press release entitled 'Risks of Picato for actinic keratosis outweigh benefits' (EMA/228384/2020) representing the outcome agreed by the CHMP was published on the EMA website on 30 April 2020.

Post-meeting note 2: the CHMP opinion was forwarded to the European Commission (EC), which issued a final legally binding decision applicable in all EU Member States on 06 July 2020. The PRAC assessment report (EMA/248352/2020) was published on 08 July 2020.

3.4. Re-examination procedures[3]

None

3.5. Others

None

[2] A phase 4 trial comparing the cumulative incidence of SCC after treatment with ingenol mebutate and imiquimod for multiple actinic keratoses on face and scalp. A multicentre, randomised, two-arm, open label, active-controlled, parallel group, 36-month trial. Completion expected in Q1 2020

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

4. Signals assessment and prioritisation[4]

4.1. New signals detected from EU spontaneous reporting systems

See Annex I 14.1.

4.2. New signals detected from other sources

See Annex I 14.2.

4.3. Signals follow-up and prioritisation

4.3.1. Adalimumab – AMGEVITA (CAP), AMSPARITY (CAP), HALIMATOZ (CAP), HEFIYA (CAP), HULIO (CAP), HUMIRA (CAP) - EMEA/H/C/000481/SDA/116, HYRIMOZ (CAP), IDACIO (CAP), IMRALDI (CAP)

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

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of autoimmune encephalitis

Action: For adoption of PRAC recommendation

EPITT 19483 – Follow-up to November 2019

Background

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

The MAH for Humira (adalimumab) replied to the request for information on the signal of autoimmune encephalitis and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence from EudraVigilance and the literature, as well as the responses from the MAH for Humira (adalimumab), the PRAC agreed that a causal relationship between adalimumab and autoimmune encephalitis cannot be established at this stage. Therefore, the PRAC agreed that no further regulatory actions are warranted at present.

Summary of recommendation(s)

- The MAHs of adalimumab-containing products should continue to monitor autoimmune encephalitis as part of routine safety surveillance.

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

[5] Held 28-31 October 2019

4.3.2. 5 alfa-reductase inhibitors (5ARIs): finasteride (NAP); dutasteride (NAP)

Applicant(s): various

PRAC Rapporteur: Annika Folin

Scope: Signal of type 2 diabetes mellitus (T2DM)

EPITT 19424 – Follow-up to November 2019

Background

For background information, see PRAC minutes November 2019[6].

The MAHs for originator finasteride- and dutasteride-containing products, Merck Sharp & Dohme Ltd and GlaxoSmithKline respectively, replied to the request for information on the signal of type 2 diabetes mellitus (T2DM) and the responses were assessed by the Rapporteur.

Discussion

The PRAC considered the available evidence from the literature and from the data provided by the MAHs of the originator finasteride- and dutasteride-containing products from clinical studies and the literature review on the potential association of new onset of T2DM in men exposed to 5α-reductase inhibitors (dutasteride and finasteride). The PRAC agreed that the data do not suggest an association of the use of finasteride or dutasteride with an increased risk of T2DM. Therefore, the PRAC agreed that no further regulatory actions are warranted at present.

Summary of recommendation(s)

- The MAHs of finasteride- and dutasteride-containing products should continue to closely monitor T2DM as part of routine safety surveillance and submit within the respective PSURs[7] for finasteride and dutasteride an updated cumulative review of the literature and of cases from clinical studies regarding the risk of new onset of T2DM.

4.3.3. Andexanet alfa – ONDEXXYA (CAP) - EMEA/H/C/004108/SDA/010

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

Action: For adoption of PRAC recommendation

EPITT 19493 – Follow-up to December 2019

Background

For background information, see PRAC minutes December 2019[8].

The MAH replied to the request for information on the signal of erroneous assay results for levels of anti-factor Xa activity with use of andexanet alfa and the responses were assessed

[6] Held 28-31 October 2019
[7] Data lock point (DLP) for finasteride: 31/08/2021; DLP for dutasteride: 19/11/2022
[8] Held 25-28 November 2019

by the Rapporteur.

Discussion

Having considered the available evidence, following assessment of EudraVigilance data, literature and data obtained from the MAH of Ondexxya (andexanet alfa), the PRAC agreed on the need to reflect in the product information the risk of erroneous assay results for levels of anti-factor Xa activity with commercial anti-factor Xa-activity assays following the administration of andexanet alfa. In addition, the PRAC agreed that a direct healthcare professional communication (DHPC) was warranted to inform healthcare professionals (HCPs) about this risk.

Summary of recommendation(s)

- The MAH of Ondexxya (andexanet alfa) should submit to the EMA, within 60 days, a variation to amend[9] the product information.
- The MAH should propose a direct healthcare professional communication (DHPC) along with a communication plan for its distribution, based on key elements defined by the PRAC.

For the full PRAC recommendation, see EMA/PRAC/201784/2020 published on 11 May 2020 on the EMA website.

4.3.4. Ceftriaxone (NAP)

Applicant(s): various

PRAC Rapporteur: Zane Neikena

Scope: Signal of encephalopathy

EPITT 19492 – Follow-up to November 2019

Background

For background information, see PRAC minutes November 2019[10].

The MAH for the originator ceftriaxone-containing product, Roche, replied to the request for information on the signal of encephalopathy and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence, including the data submitted by the MAH, the PRAC agreed that further information was required to assess the signal of encephalopathy and requested additional data from the MAH.

Summary of recommendation(s)

- The MAH, Roche, for the originator ceftriaxone-containing product should submit to the EMA, within 90 days, responses to a list of questions (LoQ).
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

[9] Update of sections of 4.4 and 5.1 of the SmPC. The package leaflet is to be updated accordingly
[10] Held 28-31 October 2019

4.3.5. Ibuprofen – PEDEA (CAP); NAP; ketoprofen (NAP) and fixed-dose combinations: chlorphenamine, ibuprofen, phenylephrine (NAP); dimenhydrinate, ibuprofen, caffeine (NAP); ibuprofen, ascorbic acid (NAP); ibuprofen, caffeine (NAP); ibuprofen, codeine (NAP); ibuprofen, hydrocodone (NAP); ibuprofen, paracetamol (NAP); ibuprofen, phenylephrine (NAP); ibuprofen, pseudoephedrine (NAP); ketoprofen, omeprazole (NAP); ketoprofen, sucralfate (NAP)

Applicant(s): Recordati Rare Diseases (Pedea), various

PRAC Rapporteur: Anette Kirstine Stark

Scope: Signal of serious exacerbation of infections

Action: For adoption of PRAC recommendation

EPITT 19415 – Follow-up to November 2019

Background

For background information, see PRAC minutes November 2019[11].

The Rapporteur assessed the responses to the non-urgent information (NUI) on additional information from EU Member States on the existing wording in the product information of ibuprofen- and ketoprofen-containing products, the literature review performed by EMA while taking into account the expert advice from respectively the Paediatric Committee (PDCO) and the CHMP Infectious Disease Working Party (IDWP).

Discussion

Based on the review of the above data, the PRAC concluded that the risk of complications due to masking of symptoms of infection associated with the use of ibuprofen- and ketoprofen-containing products is plausible. The PRAC noted that based on available studies, this risk is clinically relevant in the setting of bacterial community acquired pneumonia (CAP) and complications of varicella. Therefore, the PRAC agreed that an update of the product information of ibuprofen- and ketoprofen-containing products was warranted[12].

Summary of recommendation(s)

- The MAHs for ibuprofen- and ketoprofen-containing products should submit to relevant National Competent Authorities (NCAs) of the EU Member States, within 180 days, a variation to amend[13] the product information.
- The MAH of Pedea (ibuprofen) should continue to closely monitor cases of serious exacerbation of infections via routine safety surveillance.

For the full PRAC recommendation, see EMA/PRAC/201784/2020 published on 11 May 2020 on the EMA website.

4.3.6. Idelalisib – ZYDELIG (CAP) - EMEA/H/C/003843/SDA/018

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Martin Huber

[11] Held 28-31 October 2019
[12] Excluding Pedea (ibuprofen) for which the current warning(s) and contraindication(s) in the product information related to infections and recommendations for the monitoring and clinical management of patent ductus arteriosus (PDA) in preterm newborn infants are considered sufficient
[13] Update of sections 4.2 and 4.4 of the SmPC. The package leaflet is to be updated accordingly

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

EPITT 19500 – Follow-up to December 2019

Background

For background information, see PRAC minutes December 2019[14].

The MAH replied to the request for information on the signal of drug reaction with eosinophilia and systemic symptoms (DRESS) and the responses were assessed by the Rapporteur.

Discussion

Having considered the review of the available data, including the review conducted by the MAH, the PRAC agreed that there is sufficient evidence for establishing causality between the risk of DRESS and the use of idelalisib. Therefore, the PRAC agreed that the product information should be updated accordingly.

Summary of recommendation(s)

- The MAH for Zydelig (idelalisib) should submit to EMA, within 60 days, a variation to amend[15] the product information.
- The MAH should continue to monitor the occurrence of severe cutaneous adverse reactions (SCARs) in association with idelalisib treatment and provide a review as part of the next PSUR[16].

For the full PRAC recommendation, see EMA/PRAC/201784/2020 published on 11 May 2020 on the EMA website.

4.3.7. Insulin: insulin aspart – FIASP (CAP) - EMEA/H/C/004046/SDA/004, NOVOMIX (CAP) - EMEA/H/C/000308/SDA/055, NOVORAPID (CAP) - EMEA/H/C/000258/SDA/050; insulin aspart, insulin degludec – RYZODEG (CAP) - EMEA/H/C/002499/SDA/007; insulin bovine (NAP); insulin degludec – TRESIBA (CAP) - EMEA/H/C/002498/SDA/014; insulin degludec, liraglutide – XULTOPHY (CAP) - EMEA/H/C/002647/SDA/004; insulin determir – LEVEMIR (CAP) - EMEA/H/C/000528/SDA/053; insulin glargine – ABASAGLAR (CAP), LANTUS (CAP), TOUJEO (CAP), SEMGLEE (CAP); insulin glargine, lixisenatide - SULIQUA (CAP) - EMEA/H/C/004243/SDA/007; insulin glulisine – APIDRA (CAP) - EMEA/H/C/000557/SDA/042; insulin human – ACTRAPHANE (CAP) - EMEA/H/C/000427/SDA/025, ACTRAPID (CAP) - EMEA/H/C/000424/SDA/026, INSULATARD (CAP) - EMEA/H/C/000441/SDA/029, INSUMAN (CAP) - EMEA/H/C/000201/SDA/050, MIXTARD (CAP) - EMEA/H/C/000428/SDA/027, PROTAPHANE (CAP) - EMEA/H/C/000442/SDA/029, NAP; insulin lispro – HUMALOG (CAP) - EMEA/H/C/000088/SDA/033, INSULIN LISPRO SANOFI (CAP) - EMEA/H/C/004303/SDA/002, LIPROLOG (CAP) - EMEA/H/C/000393/SDA/026; insulin porcine (NAP)

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

[14] Held 25-28 November 2019
[15] Update of sections 4.4 and 4.8 of the product information. The package leaflet is to be updated accordingly
[16] Data lock point (DLP): 22/07/2021

Lispro Sanofi, Suliqua), various

PRAC Rapporteur: Hans Christian Siersted

Scope: Signal of cutaneous amyloidosis

EPITT 19499 – Follow-up to December 2019

Background

For background information, see PRAC minutes December 2019[17].

The MAHs, Novo Nordisk, Eli Lilly, Sanofi-Aventis and Wockhardt UK Ltd, provided comments on the proposed wording for updating the product information of insulin-containing products on the signal of cutaneous amyloidosis and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence in EudraVigilance and in the literature with regards to the risk of cutaneous amyloidosis with insulins, as well as comments from the MAHs, the PRAC agreed that there is sufficient evidence for a causal association between the use of insulins and cutaneous amyloidosis and that the product information should be updated accordingly.

Summary of recommendation(s)

- The MAHs for insulin-containing products should submit to EMA or to the relevant National Competent Authorities (NCAs) of the Member States, within 60 days, a variation to amend[18] the product information.

For the full PRAC recommendation, see EMA/PRAC/201784/2020 published on 11 May 2020 on the EMA website.

4.3.8. Tumour necrosis factor (TNF) inhibitors: adalimumab - AMGEVITA (CAP), AMSPARITY (CAP), HALIMATOZ (CAP), HEFIYA (CAP), HULIO (CAP), HUMIRA (CAP), HYRIMOZ (CAP), IDACIO (CAP), IMRALDI (CAP); certolizumab pegol - CIMZIA (CAP); etanercept - BENEPALI (CAP), ENBREL (CAP), ERELZI (CAP); golimumab - SIMPONI (CAP); infliximab - FLIXABI (CAP), INFLECTRA (CAP), REMICADE (CAP), REMSIMA (CAP), ZESSLY (CAP)

Applicant(s): AbbVie Deutschland GmbH Co. KG (Humira), Amgen Europe B.V. (Amgevita), Celltrion Healthcare Hungary Kft. (Remsima), Fresenius Kabi Deutschland GmbH (Idacio), Mylan S.A.S. (Hulio), Janssen Biologics B.V. (Simponi, Remicade), Pfizer Europe MA EEIG (Amsparity, Enbrel, Inflectra), Samsung Bioepis NL B.V. (Benepali, Flixabi, Imraldi), Sandoz GmbH (Erelzi, Halimatoz, Hefiya, Hyrimoz, Zessly), UCB Pharma S.A. (Cimzia)

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of Kaposi's sarcoma

EPITT 19480 – Follow-up to November 2019

Background

For background information, see PRAC minutes November 2019[19].

[17] Held 25-28 November 2019
[18] Update of sections 4.2, 4.5 and 4.8 of the product information. The package leaflet is to be updated accordingly
[19] Held 28-31 October 2019

The EMA performed an analysis of EudraVigilance data on cases of Kaposi's sarcoma related to treatment with tumour necrosis factor (TNF)-alfa inhibitors and the responses were assessed by the Rapporteur.

Discussion

Having considered the data in the EudraVigilance and the comments received on the assessment report, including from the MAHs, the PRAC agreed that additional information was required from the MAHs for the assessment of this signal.

Summary of recommendation(s)

- The MAHs for Cimzia (certolizumab pegol), Enbrel (etanercept), Humira (adalimumab) and Remicade (infliximab) as reference TNF-alfa inhibitor products should submit to the EMA, within 30 days, a cumulative review of cases of Kaposi's sarcoma.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

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 I 15.1.

5.1.1. Amikacin - EMEA/H/C/005264, Orphan

Applicant: Insmed Netherlands B.V.

Scope: Treatment of lung infection as part of combination antibacterial drug regiment in adults

5.1.2. Avapritinib - EMEA/H/C/005208, Orphan

Applicant: Blueprint Medicines (Netherlands) B.V.

Scope: Treatment of gastrointestinal stromal tumours

5.1.3. Belantamab mafodotin - EMEA/H/C/004935, Orphan

Applicant: GlaxoSmithKline (Ireland) Limited

Scope (accelerated assessment): Treatment of patients with relapsed or refractory multiple myeloma

5.1.4. Cabazitaxel - EMEA/H/C/005178

Scope: Treatment of adult patients with metastatic castration resistant prostate cancer previously treated with a docetaxel-containing regimen

See PRAC minutes February 2020.

5.1.5. Crizanlizumab - EMEA/H/C/004874, Orphan

Applicant: Novartis Europharm Limited

Scope: Treatment of sickle cell disease

5.1.6. Fostemsavir - EMEA/H/C/005011

Scope (accelerated assessment): Treatment in combination with other antiretrovirals of adults with multidrug resistant human immunodeficiency virus-1 (HIV-1) infection for whom it is otherwise not possible to construct a suppressive anti-viral regimen due to resistance, intolerance or safety considerations

5.1.7. Idebenone - EMEA/H/C/005123, Orphan

Applicant: Santhera Pharmaceuticals (Deutschland) GmbH

Scope: Treatment of respiratory dysfunction in patients with Duchenne muscular dystrophy (DMD) not using glucocorticoids

5.1.8. Luspatercept - EMEA/H/C/004444, Orphan

Applicant: Celgene Europe BV

Scope: Treatment of adult patients with very low- to intermediate-risk myelodysplastic syndromes (MDS)-associated anaemia and treatment of adult patients with beta-thalassaemia (β-thalassaemia)-associated anaemia who require red blood cell (RBC) transfusions

See PRAC minutes February 2020.

5.1.9. Sodium oxybate – HOPVEUS (CAP MAA) - EMEA/H/C/004962

Applicant: D&A Pharma

Scope (re-examination): Medium to long-term maintenance of alcohol abstinence and treatment of mild to moderate alcohol withdrawal syndrome

Previously, PRAC advice was provided in April 2019, December 2019 and February 2020, see PRAC minutes April 2019, PRAC minutes September 2019 and PRAC minutes February 2020.

5.1.10. Valoctocogene roxaparvovec - EMEA/H/C/004749, Orphan

Applicant: BioMarin International Limited, ATMP[20]

Scope (accelerated assessment): Treatment of haemophilia A

[20] Advanced therapy medicinal product

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

See also Annex I 15.2.

5.2.1. Rivastigmine - EXELON (CAP) - EMEA/H/C/000169/WS1773/0128; PROMETAX (CAP) - EMEA/H/C/000255/WS1773/0128

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ghania Chamouni

Scope: Submission of an updated RMP (version 10.0) to reflect the results of study CENA713D2409: a drug utilisation study (DUS) aimed to assess the extent of inappropriate use of Exelon/Prometax (rivastigmine) as per the conclusions of variation WS1557 adopted in July 2019. In addition, the list of safety concerns of the RMP is updated in line with revision 2 of GVP module V on 'Risk management systems' and in line with the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00002654/201901) finalised in September 2019

Background

Rivastigmine is an acetyl- and butyrylcholinesterase inhibitor of the carbamate type indicated, as Exelon and Prometax, for the symptomatic treatment of mild to moderately severe Alzheimer's dementia and symptomatic treatment of mild to moderately severe dementia in patients with idiopathic Parkinson's disease.

The PRAC is evaluating a worksharing variation procedure for Exelon and Prometax, centrally authorised medicines containing rivastigmine, to update the RMP in order to reflect the final results of study CENA713D2409: a drug utilisation study (DUS) that assessed the extent of inappropriate use of Exelon/Prometax (rivastigmine) and to bring it in line with the latest revision of GVP module V on 'Risk management systems' and the outcome of the last PSUSA. The PRAC is responsible for adopting an outcome based on the assessment report from the PRAC Rapporteur, to be further considered at the level of the CHMP, responsible for adopting an opinion on this variation.

Summary of advice

- The RMP (version 10.0) for Exelon/Prometax (rivastigmine) in the context of the variation procedure under evaluation is considered acceptable.
- The MAH should provide at the next regulatory opportunity further justification for the updates to the list of safety concerns, include a summary of the expectation to submit annual reports of medication errors and classify it as ongoing.

5.2.2. Tegafur, gimeracil, oteracil - TEYSUNO (CAP) - EMEA/H/C/001242/II/0042

Applicant: Nordic Group B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Submission of an updated RMP (version 9.0) in order to revise the list of safety concerns in line with revision 2 of GVP module V on 'Risk management systems' as requested in the conclusions of the periodic safety update report single assessment (PSUSA) procedure PSUSA/00002875/201801 adopted in September 2018

Background

Gimeracil is a dihydropyrimidine dehydrogenase (DPD) inhibitor, oteracil potassium, an orotate phosphoribosyltransferase (OPRT) inhibitor and tegafur, a 5-fluorouracil (5-FU) prodrug. In combination, they are indicated, as Teysuno, in adults for the treatment of advanced gastric cancer when given in combination with cisplatin.

The PRAC is evaluating a type II variation procedure for Teysuno, a centrally authorised medicine containing tegafur/gimeracil/oteracil, updating the RMP in order to bring it in line with the latest revision of GVP module V on 'Risk management systems' and to remove study MATEO: a randomised controlled trial of Teysuno (tegafur/gimeracil/oteracil) (S-1) maintenance therapy in metastatic esophagogastric cancer (listed as a category 3 study) and associated evaluation of the effect of tumour microsatellite instability (MSI) status on Teysuno (tegafur/gimeracil/oteracil) efficacy and safety in gastric cancer. The PRAC is responsible for adopting an outcome based on the assessment report from the PRAC Rapporteur, to be further considered at the level of the CHMP, responsible for adopting an opinion on this variation. For further background, see PRAC minutes February 2020.

Summary of advice

- The RMP (version 9.1) for Teysuno (tegafur/gimeracil/oteracil) in the context of the variation procedure under evaluation is considered acceptable.
- Based on the MAH's justification and the Rapporteur's assessment, the PRAC agreed that it is acceptable to terminate study MATEO in light of the slow recruitment of patients due to significant competition by targeted and immunomodulatory therapy trials currently running in advanced gastric cancer and small sample size preventing from drawing meaningful conclusions.
- The MAH should provide a discussion on the safety findings of the study in the next PSUR[21].

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

See also Annex I 15.3.

5.3.1. Catridecacog - NOVOTHIRTEEN (CAP) - EMEA/H/C/002284/II/0026/G

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Ghania Chamouni

Scope: Grouped variations consisting of an extension of indication to include treatment of bleeding episodes in patients with congenital factor XIII A-subunit deficiency as well as minor surgery based on the results of: 1) study NN1841-3868: use of recombinant factor XIII (rFXIII) in treatment of congenital FXIII deficiency, a prospective multi-centre observational study; 2) registry PRO-RBDD: a prospective rare bleeding disorders database registry. As a consequence, sections 4.1, 4.2, 4.4, 4.6, 5.1 and 5.2 of the SmPC are updated. The package leaflet, Annex II-D on 'Conditions or restrictions with regard to the safe and effective use of the medicinal product' and the RMP (version 15) are updated accordingly. Furthermore, the product information is brought in line with the latest quality review of documents (QRD) template (version 10.1). Finally, the MAH took the opportunity to introduce minor editorial changes to the product information

[21] Data lock point (DLP): 24/01/2021

Background

Catridecacog is a recombinant factor XIII A-subunit, indicated as Novothirteen, for the long-term prophylactic treatment of bleeding in patients with congenital factor XIII A-subunit deficiency.

The CHMP is evaluating grouped type II variations for Novothirteen, a centrally authorised product containing catridecacog, consisting of an extension of indication to include treatment of bleeding episodes in patients with congenital factor XIII A-subunit deficiency and a proposal to remove the existing educational material. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this variation.

Summary of advice

- The RMP for Novothirteen (catridecacog) in the context of the variation procedure under evaluation by the CHMP could be considered acceptable provided that an update to RMP version 15.0 is submitted.
- The PRAC agreed with the proposal to remove the existing educational materials consisting of patient educational material and a physician information brochure as all concerned risks are adequately addressed in the product information. The proposed routine risk minimisation measures are sufficient to minimise the risks of the medicinal product in the proposed indications. As a consequence, Annex II-D on 'conditions or restrictions with regard to the safe and effective use of the medicinal product' is to be updated accordingly.

5.3.2. Infliximab - REMSIMA (CAP) - EMEA/H/C/002576/II/0082

Applicant: Celltrion Healthcare Hungary Kft.

PRAC Rapporteur: Kimmo Jaakkola

Scope: Extension of indication to add Crohn's disease, ulcerative colitis, ankylosing spondylitis, psoriatic arthritis and psoriasis to subcutaneous (SC) route of administration presentations in order to bring them in line with the intravenous (IV) route of administration presentations. The RMP (version 12.1) is updated accordingly

Background

Infliximab is a tumour necrosis factor alfa (TNFα) inhibitor indicated, as Remsima, a biosimilar product containing infliximab, for the treatment of rheumatoid arthritis, adult and paediatric Crohn's disease, ulcerative colitis, ankylosing spondylitis, psoriatic arthritis and psoriasis, subject to certain conditions.

The CHMP is evaluating a type II variation for Remsima, a centrally authorised product containing infliximab, consisting of an extension of indication to add Crohn's disease, ulcerative colitis, ankylosing spondylitis, psoriatic arthritis and psoriasis to the subcutaneous (SC) route of administration presentations in line with the intravenous (IV) route of administration presentations. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this variation.

Summary of advice

- The RMP for Remsima (infliximab) in the context of the variation procedure under evaluation by the CHMP could be considered acceptable provided that an update to RMP version 12.1 is submitted.

- The MAH should provide a revised study plan for study CT-P13 SC 4.9[22] to conduct a comparative study and ensure relevant comparisons of observed adverse effects. The study size and patient follow-up time should be defined so that significantly increased occurrence of the adverse events of special interest (AESI) in either group can be detected.

6. Periodic safety update reports (PSURs)

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

See also Annex I 16.1.

6.1.1. Alemtuzumab - LEMTRADA (CAP) - PSUSA/00010055/201909

Applicant: Sanofi Belgium

PRAC Rapporteur: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

Background

Alemtuzumab is a recombinant deoxyribonucleic acid (DNA)-derived humanised monoclonal antibody indicated, as Lemtrada, for the treatment of relapsing remitting multiple sclerosis (RRMS) as a single disease modifying therapy (DMT) in adult patients with highly active disease despite a full and adequate course of treatment with at least one DMT as well as in adult patients with rapidly evolving severe relapsing remitting multiple sclerosis defined by 2 or more disabling relapses in one year, and with 1 or more gadolinium enhancing lesions on brain magnetic resonance imaging (MRI) or a significant increase in T2 lesion load as compared to a previous recent MRI.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Lemtrada, a centrally authorised medicine containing alemtuzumab 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 Lemtrada (alemtuzumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to revise existing warnings on progressive multifocal leukoencephalopathy (PML) and on acquired haemophilia A. In addition, a warning is added on the risk of pericarditis. Therefore, the current terms of the marketing authorisation(s) should be varied[23].
- In the next PSUR, the MAH should provide a detailed analysis of off-label use. Based on the publication by *Lucchini et al.*[24], the MAH should include a discussion on the off-label use of alemtuzumab both as induction therapy and anti-rejection therapy in relation to

[22] An observational, prospective cohort study to evaluate safety of Remsima (infliximab) subcutaneous in patients with ankylosing spondylitis, psoriatic arthritis and psoriasis
[23] Update of SmPC section 4.4. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion
[24] Lucchini E, Luqmani A, Atta M, Deplano S, Layton M, Vladescu C, *et al.* Autoimmune cytopenias following alemtuzumab-induced renal transplant: Clinical features and treatment outcomes. Blood. 2018 Nov 1;132

renal transplantation and other solid organ transplantations. In addition, the MAH should report in detail on administration errors and scheduling errors. The MAH should specify types of scheduling and administration errors observed and discuss preventability, associated risks and need for risk minimisation measures (RMMs). The MAH should also provide an updated review of cases of pneumonitis and propose an update of the product information as warranted. Finally, the MAH should provide a progress update on its retrospective study on haemophagocytic lymphohistiocytosis (HLH) to gather evidence on alternative corticosteroid dosing regimens from literature and real-world setting.

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. Cemiplimab - LIBTAYO (CAP) - PSUSA/00010780/201909

Applicant: Regeneron Ireland Designated Activity Company (DAC)

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

Background

Cemiplimab is a fully human immunoglobulin G4 (IgG4) monoclonal antibody indicated, as Libtayo, for the treatment of adult patients with metastatic or locally advanced cutaneous squamous cell carcinoma who are not candidates for curative surgery or curative radiation.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Libtayo, a centrally authorised medicine containing cemiplimab 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 Libtayo (cemiplimab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning on solid organ transplant rejection. Transplant rejection is also added as an undesirable effect with a frequency not known. In addition, myositis and dyspnoea are added as undesirable effects with a frequency 'rare' and 'common' respectively. Therefore, the current terms of the marketing authorisation(s) should be varied[25].

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. Choriogonadotropin alfa - OVITRELLE (CAP) - PSUSA/00000736/201909

Applicant: Merck Europe B.V.

PRAC Rapporteur: Menno van der Elst

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

Scope: Evaluation of a PSUSA procedure

Background

Choriogonadotropin alfa is a recombinant human chorionic gonadotropin indicated, as Ovitrelle, for the treatment of adult women undergoing superovulation prior to assisted reproductive techniques such as in vitro fertilisation (IVF) and for the treatment of anovulatory or oligo-ovulatory adult women.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Ovitrelle, a centrally authorised medicine containing choriogonadotropin 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 Ovitrelle (choriogonadotropin alfa) 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 monitor cases of systemic lupus erythematosus as updated information from literature is expected and evaluate whether an update of the product information is appropriate.
- The MAH should submit to the EMA, within 60 days, a review of the criteria used to classify events as 'non-reactions' and provide a methodology used to perform causality assessment. The MAH should provide a discussion on the impact on the benefit-risk balance of the medicinal product and a proposal on risk minimisation measures, as warranted.

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

6.1.4. Denosumab[26] - PROLIA (CAP) - PSUSA/00000954/201909

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Background

Denosumab is a human monoclonal immunoglobulin G2 (IgG2) antibody indicated, as Prolia, for the treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures and for the treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures. It is also indicated for treatment of bone loss associated with long-term systemic glucocorticoid therapy in adult patients at increased risk of fracture.

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

[26] Indicated for osteoporosis and for bone loss associated with hormone ablation in prostate cancer only

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Prolia (denosumab) 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 include a summary of the proposed retrospective database study aiming at further evaluating the occurrence of vertebral fractures in the Swedish population.

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

6.1.5. Dexamethasone[27] - NEOFORDEX (CAP) - PSUSA/00010480/201909

Applicant: Laboratoires CTRS

PRAC Rapporteur: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

Background

Dexamethasone is a synthetic glucocorticoid indicated, as Neofordex, for the treatment of symptomatic multiple myeloma in combination with other medicinal products.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Neofordex, a centrally authorised medicine containing dexamethasone 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 Neofordex (dexamethasone) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning on the risk of pheochromocytoma crisis. Therefore, the current terms of the marketing authorisation(s) should be varied[28].
- In the next PSUR, the MAH should provide a detailed review of cases of off-label use. In addition, the MAH should provide a review of new cases of pheochromocytoma crisis with a proposed update of the product information, as appropriate.

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

[27] Indicated in symptomatic multiple myeloma only, centrally authorised product(s) only
[28] Update of SmPC section 4.4. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

6.1.6. Dupilumab - DUPIXENT (CAP) - PSUSA/00010645/201909

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

Background

Dupilumab is a recombinant human immunoglobulin G4 (IgG4) monoclonal antibody indicated, as Dupixent, for the treatment of moderate-to-severe atopic dermatitis in adults and adolescents 12 years and older who are candidates for systemic therapy as well as add-on maintenance treatment in adults and adolescents 12 years and older for severe asthma with type 2 inflammation characterised by raised blood eosinophils and/or raised fractional exhaled nitric oxide (FeNO), who are inadequately controlled with high dose of inhaled corticosteroid (ICS) plus another medicinal product for maintenance treatment. It is also indicated as an add-on therapy with intranasal corticosteroids for the treatment of adults with severe chronic rhinosinusitis with nasal polyposis (CRSwNP) for whom therapy with systemic corticosteroids and/or surgery do not provide adequate disease control.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Dupixent, a centrally authorised medicine containing dupilumab 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 Dupixent (dupilumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the warning on hypersensitivity to reflect cases of anaphylactic reaction and cases of angioedema that can occur from minutes up to 7 days after administration. Anaphylactic reaction and angioedema are added as undesirable effects with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[29].
- In the next PSUR, the MAH should provide a detailed review of cases of medication errors and provide a proposal for risk minimisation measures, as warranted. The MAH should also review data regarding facial dermatitis eruption/new anatomic region dermatitis with predilection for facial site with a proposal for update of the product information, as appropriate. In addition, the MAH should present a cumulative review of corneal disorders and an updated pregnancy data review. Finally, the MAH should provide an updated cumulative review and discussion on inflammatory arthritis and enthesitis.

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. Fremanezumab - AJOVY (CAP) - PSUSA/00010758/201909

Applicant: Teva GmbH

[29] 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

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

Background

Fremanezumab is a humanised immunoglobulin G2Δa/kappa (IgG2Δa/kappa) monoclonal antibody indicated, as Ajovy, for prophylaxis of migraine in adults who have at least 4 migraine days per month.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Ajovy, a centrally authorised medicine containing fremanezumab 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 Ajovy (fremanezumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning on hypersensitivity reactions, including urticaria, pruritus, rash and swelling. In addition, the product information should be updated to include hypersensitivity reactions as an undesirable effect with a frequency 'uncommon'. Therefore, the current terms of the marketing authorisation(s) should be varied[30].
- In the next PSUR, the MAH should provide a detailed review of cases of anaphylactic reactions and consider whether an update to the product information is needed. In addition, the MAH should also provide a review of hypersensitivity reactions from post-marketing cases. To further explore alopecia and constipation among the most commonly reported undesirable effects in post-marketing data, the MAH should perform a detailed review of all available data and consider, whether any updates to the product information are needed based on this analysis. Finally, the MAH should clarify how the collection of the follow-up information on the pregnancy cases is performed.

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

6.1.8. Infliximab - FLIXABI (CAP); INFLECTRA (CAP); REMICADE (CAP); REMSIMA (CAP); ZESSLY (CAP) - PSUSA/00010759/201908

Applicant(s): Celltrion Healthcare Hungary Kft. (Remsima), Janssen Biologics B.V. (Remicade), Pfizer Europe MA EEIG (Inflectra), Samsung Bioepis NL B.V. (Flixabi), Sandoz GmbH (Zessly)

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Background

Infliximab is a tumour necrosis factor alfa (TNFα) inhibitor indicated, as Flixabi, Inflectra, Remicade, Remsima and Zessly, for the treatment of rheumatoid arthritis (RA), Crohn's

[30] 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

disease (CD), ulcerative colitis (UC), ankylosing spondylitis (AS), psoriatic arthritis and psoriasis, subject to certain conditions.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of Flixabi, Inflectra, Remicade, Remsima and Zessly, centrally authorised medicines containing infliximab 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 Flixabi, Inflectra, Remicade, Remsima and Zessly (infliximab) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, all MAHs should provide cumulative reviews (including data from clinical trials, post-marketing experience, literature and a discussion of mechanisms possibly linking the events to infliximab-treatment) of cases of acquired perforating dermatosis and amicrobial pustulosis of the folds.
- The MAH for Remicade (infliximab) should be requested to submit to the EMA, within 60 days, a further cumulative review of cases of abnormal lipid values in clinical studies as well as literature data on lipid derangements following TNFα inhibitor treatment in general and infliximab treatment in particular. The MAH should also conduct a literature review on postnatal clearance of TNFα inhibitors in the newborn, particularly of infliximab, being prolonged up to one year according to the literature, and of cases of disseminated BCG[31] vaccinations associated with administration of BCG after birth. The MAH should also provide a cumulative review of cases of hidradenitis, presenting data from clinical trials, post-marketing experience and literature, and taking into account the intended use (indication or off-label use). The MAH should make proposals for updating the product information, as appropriate.

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

6.1.9. Naltrexone, bupropion - MYSIMBA (CAP) - PSUSA/00010366/201909

Applicant: Orexigen Therapeutics Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Naltrexone is a mu-opioid antagonist and bupropion an inhibitor of neuronal dopamine and norepinephrine reuptake. In combination, naltrexone/bupropion is indicated, as Mysimba, as an adjunct to a reduced-calorie diet and increased physical activity, for the management of weight in adult patients (≥18 years) with an initial body mass index (BMI) of ≥ 30 kg/m^2 (obese), or ≥ 27 kg/m^2 to < 30 kg/m^2 (overweight) in the presence of one or more weight-related co-morbidities.

[31] Bacillus Calmette-Guérin

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Mysimba, a centrally authorised medicine containing naltrexone/bupropion 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 Mysimba (naltrexone/bupropion) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to increase patient awareness on the recommendations for use in pregnancy, by including information that naltrexone/bupropion should not be used in women currently attempting to become pregnant. Therefore, the current terms of the marketing authorisation(s) should be varied[32].
- In the next PSUR, the MAH should provide a cumulative review of cases of hypertensive crisis as well of cases of eating disorders and provide a proposal for updating the product information, as appropriate. In addition, the MAH should provide a detailed discussion of the biological plausibility of a causal association between naltrexone/bupropion and serotonin syndrome. The MAH should also provide an overview of available data on the effect of the medicinal product on sexual function and provide a detailed cumulative review of confirmed panic-related cases. The MAH should provide an assessment on serious gastrointestinal undesirable effects leading to dehydration with a proposal for updating the product information, as appropriate. Finally, the MAH should provide a detailed discussion on pregnancy-related cases.
- The MAH should submit to the EMA, within 60 days, a variation to provide a detailed review of cases of drug-induced lupus erythematosus with naltrexone/bupropion and its individual substances with a proposed update of the product information, as appropriate. In addition, the MAH should submit a variation to update the product information with a warning on the interaction between naltrexone/bupropion and digoxin.

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.

6.1.10. Niraparib - ZEJULA (CAP) - PSUSA/00010655/201909

Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

Background

Niraparib is an inhibitor of poly(ADP-ribose) polymerase (PARP) enzymes 1 and 2 indicated, as Zejula, for the maintenance treatment of adult patients with platinum-sensitive relapsed high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy.

[32] Update of the package leaflet. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Zejula, a centrally authorised medicine containing niraparib 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 Zejula (niraparib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the existing warning on hypertension. In addition, a new warning about posterior reversible encephalopathy syndrome (PRES) should be included. Finally, hypertensive crisis and PRES should be included as undesirable effects with a frequency 'rare'. Therefore, the current terms of the marketing authorisation(s) should be varied[33].
- In the next PSUR, the MAH should provide a detailed discussion on the causality between niraparib and neuropathy. The MAH should also provide a review of cases of recognitive and attention disorders and disturbances, confusion and disorientation, hallucination, interstitial pneumonitis and drug hypersensitivity.

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

6.1.11. Pitolisant - WAKIX (CAP) - PSUSA/00010490/201909

Applicant: Bioprojet Pharma

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

Background

Pitolisant is an active histamine H3-receptor antagonist/inverse agonist indicated, as Wakix, for the treatment of narcolepsy with or without cataplexy.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Wakix, a centrally authorised medicine containing pitolisant 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 Wakix (pitolisant) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include suicidal ideation as an undesirable effect with a frequency 'uncommon' and to amend the existing warning on psychiatric disorders to add that suicidal ideation has been reported. Therefore, the current terms of the marketing authorisation(s) should be varied[34].

[33] 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
[34] 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

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

6.1.12. Vortioxetine - BRINTELLIX (CAP) - PSUSA/00010052/201909

Applicant: H. Lundbeck A/S

PRAC Rapporteur: Laurence de Fays

Scope: Evaluation of a PSUSA procedure

Background

Vortioxetine is an antidepressant agent modulating serotonergic receptor activity and inhibiting serotonin (5-HT) transporter. It is indicated, as Brintellix, for the treatment of major depressive episodes in adults.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Brintellix, a centrally authorised medicine containing vortioxetine 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 Brintellix (vortioxetine) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include warnings on aggression/agitation and on glaucoma as well as a warning on interference with some methadone immunoassays. In addition, insomnia, aggression and agitation should be added as undesirable effects with a frequency 'not known', as well as glaucoma with a frequency 'rare'. Therefore, the current terms of the marketing authorisation(s) should be varied[35].
- In the next PSUR, the MAH should present detailed cumulative reviews of cases of sexual dysfunction, cases of vision blurred, visual impairment and of all cases reporting photosensitivity. The MAH should also provide a review on the potential risk of precipitation of metabolites in kidney and liver and an evaluation of whether the current product information should be updated regarding the potential risk of liver toxicity based on cumulative information. In addition, the MAH should closely monitor cases of withdrawal reactions and propose to update the product information, as appropriate. The MAH should also provide a cumulative review of cases reporting headache and assess the need for an update of the product information. Finally, the MAH should include a cumulative review of information on the use in patients with a history of mania/hypomania and discuss the need for an update of the product information.

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

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

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

See also Annex I 16.2.

6.2.1. Budesonide, formoterol - BIRESP SPIROMAX (CAP); DUORESP SPIROMAX (CAP); NAP - PSUSA/00010585/201908

Applicants: Teva Pharma B.V. (BiResp Spiromax, DuoResp Spiromax), various

PRAC Rapporteur: Hans Christian Siersted

Scope: Evaluation of a PSUSA procedure

Background

Budesonide is a corticosteroid and formoterol is a long-acting β2 adrenoceptor agonist medicine indicated in combination for the treatment of asthma, where use of a combination is appropriate and for the symptomatic treatment of patients with chronic obstructive pulmonary disease (COPD) who have significant symptoms despite regular therapy with long-acting bronchodilators.

Based on the assessment of the PSURs, the PRAC reviewed the benefit-risk balance of BiResp Spiromax and Duoresp Spiromax, centrally authorised medicine(s) containing budesonide/formoterol and nationally authorised medicines containing budesonide/formoterol 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 budesonide/formoterol-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include dysphonia to the existing term of hoarseness as an undesirable effect with a frequency 'common'. Therefore, the current terms of the marketing authorisations should be varied[36].
- In the next PSUR, MAHs should provide a review of the article by *Kim et al*[37] and propose to update the product information, as warranted. The MAH AstraZeneca should present and characterise the important identified risks of 'cardiac disorders', 'hypersensitivity', 'paradoxical bronchospasm' and 'pneumonia in chronic obstructive pulmonary disease (COPD)'. The MAH Teva should closely monitor cases of medication errors.

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

[36] Update of SmPC section 4.8. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

[37] Kim M, Rhee CK, Shim JS, Park SY, Yoo KH, Kim BY, Bae HW, Sim YS, Chang JH, Cho YJ and Lee JH. Inhaled corticosteroids in asthma and the risk of pneumonia. Allergy Asthma Immunol Res. 2019 Nov;11(6):795-805

6.2.2. Thalidomide - THALIDOMIDE CELGENE (CAP); NAP - PSUSA/00002919/201910

Applicants: Celgene Europe BV (Thalidomide Celgene), various

PRAC Rapporteur: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

Background

Thalidomide is an immunomodulator indicated, as Thalidomide Celgene, in combination with melphalan and prednisone as first line treatment of patients with untreated multiple myeloma, aged ≥ 65 years or ineligible for high dose chemotherapy.

Based on the assessment of the PSURs, the PRAC reviewed the benefit-risk balance of Thalidomide Celgene, a centrally authorised medicine(s) containing thalidomide and nationally authorised medicines containing thalidomide 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 thalidomide-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, Annex II of Thalidomide Celgene on 'Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States' is updated to remove the requirement for six-monthly reporting to EMA by Member States of the status of implementation of the pregnancy prevention programme (PPP) within their Member State and usage estimates. Therefore, the current terms of the marketing authorisation(s) should be varied[38]. The current terms of the marketing authorisations for the other medicinal products should be maintained.
- In the next PSUR, all MAHs should provide a description and status of the implementation of the PPP in each Member State, monitoring methodology and timelines for available data and results of monitoring programmes. An estimate of usage in each Member State should also be provided. In addition, all MAHs should provide cumulative reviews of cases of hypothyroidism, hepatitis E, second primary malignancy, fatal cases and off-label use along with a proposal for updating the product information, as appropriate. All MAHs should monitor cases of reactivation of Epstein-Barr virus (EBV), progressive multifocal leukoencephalopathy (PML) and solid organ transplant rejection.

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

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

See also Annex I 16.3.

[38] Update of Annex II. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

6.3.1. Dexamfetamine (NAP) – PSUSA/00000986/201909

Applicant(s): various

PRAC Lead: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

Background

Dexamfetamine is a sympathomimetic amine with central nervous system-stimulating activity indicated for the treatment of attention deficit/hyperactivity disorder (ADHD) in children and adolescents when response to previous methylphenidate treatment is considered clinically inadequate and for the treatment of narcolepsy in adults.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing dexamfetamine 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 dexamfetamine-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to reflect the experience with the use of lisdexamphetamine, amphetamine and dexamfetamine during pregnancy. Therefore, the current terms of the marketing authorisation(s) should be varied[39].
- In the next PSUR, the MAHs should provide a detailed review of the possible interaction between quinolones and dexamphetamine and propose an update of the product information, as appropriate. The MAHs should also provide a cumulative review of cases of trismus, jaw stiffness, jaw joint rigid state of, tightness in jaw or tightness of jaw muscles and a proposal for updating the product information, as appropriate. Finally, the MAH should include a discussion on Raynaud's syndrome as a possible undesirable effect and propose an update of the product information, as appropriate.

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. Hydrocortisone[40] (NAP) – PSUSA/00010328/201908

Applicant(s): various

PRAC Lead: Željana Margan Koletić

Scope: Evaluation of a PSUSA procedure

Background

Hydrocortisone is a naturally occurring adrenocortical steroid-glucocorticoid. It is indicated[41] for the systemic treatment of patients with endocrine disorders, non-endocrine disorders

[39] Update of SmPC section 4.6. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position
[40] Except medicinal product(s) indicated in adrenal insufficiency in a modified release tablet formulation
[41] Except medicinal product(s) indicated in adrenal insufficiency in a modified release tablet formulation

including rheumatic disorders, collagen diseases, dermatologic diseases, allergic states, ophthalmic diseases, gastrointestinal diseases, respiratory diseases, hematologic disorders, neoplastic diseases, oedematous states, tuberculous meningitis, trichinosis, and medical emergencies including shock secondary to adrenocortical insufficiency or shock unresponsive to conventional therapy when adrenal cortical insufficiency may be present. It is also indicated as topical formulations for dermatological conditions of acute and chronic eczema of different origins, various types of dermatitis, anogenital pruritus and inflammation occurring in the rectal mucosa, other types of pruritus, neurodermatitis, discoid lupus erythematosus, insect bite reactions, nettle stings, miliaria, otitis externa, localised burns, psoriasis, disco and other, mild to moderate inflammatory skin disorders not caused by microorganisms. As ophthalmic formulations, it is indicated for allergic blepharitis and conjunctivitis, inflammatory conditions in the outer and frontal parts of the eye. Finally, it is indicated as buccal formulations for local use in aphthous ulceration or ulcerative colitis.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine containing hydrocortisone[42] 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 hydrocortisone[43]-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include hypertrophic cardiomyopathy as an undesirable effect with a frequency 'not known' and as a warning. In addition, weight increased is added as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[44].
- In the next PSUR, the MAHs of systemic formulations should provide a detailed cumulative review of cases of blindness during treatment and of cases reporting cerebellar growth impairment, by reviewing all available data. The MAHs should also discuss a possible mechanism by which hydrocortisone could cause these undesirable effects and propose an update of the product information, as appropriate. In addition, the MAHs of systemic formulations should provide interval analysis of cases reporting spinal epidural lipomatosis and discuss a proposed mechanism of action and provide a proposal for an update of the product information, as appropriate. The MAHs of topical formulations should provide a cumulative review of cases of steroid withdrawal and include a causality assessment as well as information on dechallenge/rechallenge.

The PRAC considered that specific hydrocortisone formulations/indications should be assessed in the future within separate PSUSA procedures. As a consequence, the PRAC recommended splitting the exiting entry of the EURD list into two entries: 'hydrocortisone (systemic formulations except for products indicated in adrenal insufficiency in a modified release tablet formulation and except for centrally authorised products for adrenal insufficiency, paediatric use only)' and 'hydrocortisone (all formulations apart from systemic use)'. The next PSURs should be submitted in accordance with the requirements set out in

[42] Except medicinal product(s) indicated in adrenal insufficiency in a modified release tablet formulation
[43] Except medicinal product(s) indicated in adrenal insufficiency in a modified release tablet formulation
[44] Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC.

6.3.3. Nifuroxazide (NAP) – PSUSA/00002160/201908

Applicant(s): various

PRAC Lead: Jana Lukačišinová

Scope: Evaluation of a PSUSA procedure

Background

Nifuroxazide is an antibacterial agent indicated for the treatment of acute diarrhoea presumably from bacterial origin, in the absence of suspected invasive phenomena.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine containing nifuroxazide 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 nifuroxazide-containing medicinal product(s) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAHs should provide a detailed cumulative review of blood and lymphatic system disorders and a review of cases of acute generalised exanthematous pustulosis (AGEP). The MAH Takeda should provide a cumulative assessment of safety data in children versus adult patients including data from clinical studies, post-marketing and literature.

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

6.3.4. Oxcarbazepine (NAP) – PSUSA/00002235/201908

Applicant(s): various

PRAC Lead: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

Background

Oxcarbazepine is a first-line antiepileptic medicine indicated for the treatment of partial epileptic seizures and generalised tonic-clonic epileptic seizures, in adults and in children.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine containing oxcarbazepine 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 oxcarbazepine-containing medicinal product(s) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAHs should provide a detailed review on the risk of intrauterine growth retardation including low birth weight and pre-term age based on the article by *Hernandez-Diaz et al*[45] and relevant literature, spontaneous case reports and reports from other sources. In addition, the MAHs should provide a cumulative review for the potential risk of decreased fertility with a proposal for updating of the product information, as appropriate.

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

6.3.5. Sotalol (NAP) – PSUSA/00002774/201908

Applicant(s): various

PRAC Lead: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

Background

Sotalol is a non-selective beta-blocking agent indicated for the treatment of ventricular tachyarrhythmias and symptomatic premature ventricular contractions, prophylaxis of paroxysmal atrial tachycardia and paroxysmal atrial fibrillation, the maintenance of normal sinus rhythm following conversion of atrial fibrillation or atrial flutter and treatment of arrhythmias caused by excess circulating catecholamines and those due to increased sensitivity to catecholamines.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine containing sotalol 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 sotalol-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include alopecia, hyperhidrosis and thrombocytopenia as undesirable effects with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[46].

[45] Hernandez-Diaz S et al. Fetal growth and premature delivery in pregnant women on antiepileptic drugs. Ann Neurol. 2017;82(3):457-465. doi: 10.1002/ana.25031
[46] 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

- In the next PSUR, the MAHs should provide, based on literature, reported cases and clinical trial data, a detailed cumulative review of cases of loss of consciousness with a proposal for updating the product information, as appropriate.

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

Additionally, the PRAC noted that the information regarding the interaction between sotalol and fluoroquinolones or quinolones resulting in QT interval prolongation is not reflected in the product information of all sotalol-containing products despite the plausible mechanism of action. The PRAC agreed that the product information of such products should be updated accordingly. Further consideration should be given at the level of CMDh.

6.4. Follow-up to PSUR/PSUSA procedures

6.4.1. Apixaban - ELIQUIS (CAP) - EMEA/H/C/002148/LEG 036

Applicant: Bristol-Myers Squibb / Pfizer EEIG

PRAC Rapporteur: Menno van der Elst

Scope: Cumulative review of cases of angioedema as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00000226/201905) adopted in December 2019

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 (NYHA8class ≥II). It is also indicated for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), as well as for the prevention of recurrent DVT and PE in adults.

Following the evaluation of the most recently submitted PSUR(s) for the above mentioned medicine(s), the PRAC requested the MAH to submit further data on cases of angioedema. For background, see PRAC minutes December 2019[47]. The responses were assessed by the Rapporteur for further PRAC advice.

Summary of advice/conclusion(s)

- Having considered the available data and the assessment report from the PRAC Rapporteur, the PRAC agreed that there is sufficient evidence to support a causal association between apixaban and angioedema.
- The MAH should submit to the EMA, within 60 days, a variation to update the product information[48] to include angioedema as an undesirable effect with a frequency 'not known'.

[47] Held 25-28 November 2019
[48] Update of SmPC section 4.8. The package leaflet is to be updated accordingly

6.4.2. Brodalumab - KYNTHEUM (CAP) - EMEA/H/C/003959/LEG 005.1

Applicant: LEO Pharma A/S

PRAC Rapporteur: Eva Segovia

Scope: MAH's response to LEG 005 [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 the PSUR single assessment (PSUSA) procedure (PSUSA/00010341/201812) for secukinumab adopted in July 2019] as per the request for supplementary information (RSI) adopted in December 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(s) for the above mentioned medicine(s), the PRAC requested the MAH of Kyntheum (brodalumab) as an interleukin 17 (IL17)-inhibitor to submit further data on the risk of inflammatory bowel disease (IBD). For background information, see PRAC minutes July 2019 and PRAC minutes December 2019[49]. The responses were assessed by the Rapporteur for further PRAC advice.

Summary of advice/conclusion(s)

- Having considered the available data and the assessment report from the PRAC Rapporteur, the PRAC agreed that an update of the current warning of IBD was warranted to include risk minimisation measures for this risk.
- The MAH should submit to EMA, within 60 days, a variation to update the product information[50] to include information on the development of IBD after treatment with brodalumab.
- In the next RMP update, the MAH should discuss the possible implications of this finding on the safety concern of 'worsening of Crohn's disease (CD) in subjects with active CD'.

6.4.3. Ixekizumab - TALTZ (CAP) - EMEA/H/C/003943/LEG 004.1

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: MAH's response to LEG 004 [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 the PSUR single assessment (PSUSA) procedure (PSUSA/00010341/201812) for secukinumab adopted in July 2019] as per the request for supplementary information (RSI) adopted in December 2019

Background

[49] Held 25-28 November 2019
[50] Update of SmPC sections 4.4 and 4.8. The package leaflet is to be updated accordingly

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(s) for the above mentioned medicine(s), the PRAC requested the MAH of Taltz (ixekizumab) as an interleukin 17 (IL17)-inhibitor to submit further data on the risk of inflammatory bowel disease. For background information, see PRAC minutes July 2019 and PRAC minutes December 2019[51]. The responses were assessed by the Rapporteur for further PRAC advice.

Summary of advice/conclusion(s)

- Having considered the available data and the assessment report from the PRAC Rapporteur, the PRAC agreed that an update of the current warning of IBD was warranted to include risk minimisation measures for this risk.
- The MAH should submit to EMA, within 60 days, a variation to update the product information[52] to include information about the development of IBD after treatment with ixekizumab.
- In the next RMP update, the MAH should discuss the possible implications of this finding on the safety concern of 'IBD'.

6.4.4. Natalizumab - TYSABRI (CAP) - EMEA/H/C/000603/LEG 070

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Analyses of cumulative data on pregnancy including foetal outcomes as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00002127/201908) adopted in February 2020

Background

Natalizumab is a humanised monoclonal antibody that binds to the α4 chain of the α4β1 and α4β7 integrins. It is indicated, as Tysabri, as single disease modifying therapy in adults with highly active relapsing remitting multiple sclerosis (RRMS) in patients with highly active disease despite a full and adequate course of treatment with at least one disease modifying therapy (DMT) and patients with rapidly evolving severe relapsing remitting multiple sclerosis defined by 2 or more disabling relapses in one year, and with 1 or more gadolinium enhancing lesions on brain magnetic resonance imaging (MRI) or a significant increase in T2 lesion load as compared to a previous recent MRI.

Following the evaluation of the most recently submitted PSURs for the above mentioned medicine(s), the PRAC requested the MAH to submit further data on pregnancy including foetal outcomes. For background, see PRAC minutes February 2020. The responses were assessed by the Rapporteur for further PRAC advice.

Summary of advice/conclusion(s)

[51] Held 25-28 November 2019
[52] Update of SmPC section 4.4. The package leaflet is to be updated accordingly

- Having considered the available data and the assessment report from the PRAC Rapporteur, the PRAC agreed that further clarifications were necessary to obtain a more detailed overview of the effect of Tysabri (natalizumab) on pregnancy outcomes.
- The MAH should submit to EMA, within 60 days, responses to a request for supplementary information (RSI) agreed by the PRAC.

6.4.5. Secukinumab - COSENTYX (CAP) - EMEA/H/C/003729/LEG 007.1

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Eva Segovia

Scope: MAH's response to LEG 007 [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 the PSUR single assessment (PSUSA) procedure (PSUSA/00010341/201812) adopted in July 2019] as per the request for supplementary information (RSI) adopted in December 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(s) for the above mentioned medicine(s), the PRAC requested the MAH to submit further data on the risk of inflammatory bowel disease (IBD). For background information, see PRAC minutes July 2019 and PRAC minutes December 2019[53]. The responses were assessed by the Rapporteur for further PRAC advice.

Summary of advice/conclusion(s)

- Having considered the available data and the assessment report from the PRAC Rapporteur, the PRAC agreed that an update of the current warning of IBD was warranted to include risk minimisation measures for this risk.
- The MAH should submit to EMA, within 60 days, a variation to update the product information[54] to include information about the development of IBD after treatment with secukinumab.
- In the next RMP update, the MAH should discuss the possible implications of this finding on the safety concern of IBD.

[53] Held 25-28 November 2019
[54] Update of SmPC section 4.4. The package leaflet is to be updated accordingly

6.5. Variation procedure(s) resulting from PSUSA evaluation

6.5.1. Docetaxel - TAXOTERE (CAP) - EMEA/H/C/000073/II/0136/G

Applicant: Sanofi Mature IP

PRAC Rapporteur: Ghania Chamouni

Scope: Grouped variations consisting of: 1) update of sections 4.4 and 4.8 of the SmPC to add a warning and safety information about tumour lysis syndrome (TLS) based on a cumulative safety review requested in the conclusions of the latest periodic safety update report single assessment (PSUSA) procedure (PSUSA/00001152/201611) concluded in September 2017. The package leaflet is updated accordingly. In addition, the MAH took the opportunity to make minor corrections to the SmPC and update the list of local representatives in the package leaflet; 2) update of section 4.8 of the SmPC to add safety information about myositis based on cumulative safety review requested in the conclusions of the latest PSUSA procedure (PSUSA/00001152/201611) concluded in September 2017. The package leaflet is updated accordingly

Background

Docetaxel is an antineoplastic agent indicated, as Taxotere, for the treatment of breast cancer, non-small lung cancer, prostate cancer, gastric adenocarcinoma as well as head and neck cancer under certain conditions.

Following the evaluation of the recently submitted PSURs for the above mentioned medicine(s), the PRAC requested the MAH to submit a variation to update the product information about the risk of tumour lysis syndrome (TLS) and to include safety information about myositis. For background information, see PRAC minutes September 2017[55]. The PRAC is responsible for adopting an outcome based on the assessment report from the PRAC Rapporteur, to be further considered at the level of the CHMP, responsible for adopting an opinion on this variation.

Summary of recommendation(s)

- Based on the available data and the Rapporteur's assessment, the PRAC supported to update[56] the product information of Taxotere (docetaxel) by adding a warning and safety information on TLS and by including safety information on myositis.

7. Post-authorisation safety studies (PASS)

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

See Annex I 17.1.

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

See Annex I 17.2.

[55] Held 29 August–01 September 2017
[56] Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly
[57] In accordance with Article 107n of Directive 2001/83/EC
[58] In accordance with Article 107m of Directive 2001/83/EC, supervised by PRAC in accordance with Article 61a (6) of Regulation (EC) No 726/2004

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

None

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

See also Annex I 17.4.

7.4.1. Deferasirox - EXJADE (CAP) - EMEA/H/C/000670/II/0068

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ghania Chamouni

Scope: Submission of the final report related to the physician survey (NO6987) conducted for Exjade (deferasirox) to assess the impact of educational materials on the prescribers' awareness of doses and biological monitoring recommendations and to assess the awareness and appropriate use of both formulations (dispersible tablets and film-coated tablets). The RMP (version 17.1) is updated accordingly

Background

Deferasirox is an orally active chelator that is highly selective for iron (III) indicated, as Exjade, for the treatment of chronic iron overload due to frequent blood transfusions in patients with beta thalassaemia major aged 6 years and older, for the treatment of chronic iron overload due to blood transfusions when deferoxamine therapy is contraindicated or inadequate and in patients with non-transfusion-dependent thalassaemia syndromes aged 10 years and older.

As stated in the RMP of Exjade (deferasirox), the MAH conducted a non-imposed non-interventional PASS (NO6987) to assess the impact of educational materials on the prescribers' awareness of doses and biological monitoring recommendations and to assess the awareness and appropriate use of both formulations. The Rapporteur assessed the final study report together with the MAH's responses to the request for supplementary information (RSI). For further background, see PRAC minutes January 2020.

Summary of advice

- Based on the available data, the MAH's answers to the RSI and the Rapporteur's review, the PRAC agreed that the MAH should provide responses to a further request for supplementary information within 60 days, before a conclusion could be drawn on the assessment of the final study report. In particular, the PRAC considered that the prescriber guide needs to be improved to include a checklist to be used as a prescribing decision tool. In addition, the MAH should propose to evaluate the effectiveness of the revised educational material.

7.4.2. Hydroxycarbamide - SIKLOS (CAP) - EMEA/H/C/000689/II/0045

Applicant: Addmedica S.A.S.

PRAC Rapporteur: Laurence de Fays

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

Scope: Update of sections 4.2, 4.3, 4.4, 4.5, 4.6, 4.8 and 4.9 of the SmPC in order to reflect the final study results of non-interventional cohort study ESCORT-HU (European Sickle Cell Disease Cohort-Hydroxyurea): an observational prospective cohort study to measure the occurrence of adverse events and serious adverse events and to harmonise the product information with other hydroxyurea (HU)-containing products. In addition, Annex II-D on 'Conditions or restrictions with regard to the safe and effective use of the medicinal product' is amended to delete the reference to the treatment guide for physicians. The package leaflet and the RMP (version 20) are updated accordingly

Background

Hydroxycarbamide is an antineoplastic agent indicated, as Siklos, for the prevention of recurrent painful vaso-occlusive crises including acute chest syndrome in adults, adolescents and children older than 2 years suffering from symptomatic sickle cell syndrome (SCS).

As stated in the RMP of Siklos (hydroxycarbamide), the MAH conducted a non-imposed non-interventional PASS (ESCORT-HU (European Sickle Cell Disease Cohort-Hydroxyurea)) to measure the occurrence of adverse events and serious adverse events. The Rapporteur assessed the final study report.

Summary of advice

- Based on the available data and the Rapporteur's review, the PRAC agreed that the MAH should provide responses to a further request for supplementary information within 60 days, before a conclusion could be drawn on the assessment of the final study report. In particular, the PRAC considered that the MAH should provide some key elements to address the risk of dispensing errors as an additional risk minimisation. In addition, the PRAC advised to retain the treatment guide for physicians.

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

See also Annex I 17.5.

7.5.1. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/MEA 022.19

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Rhea Fitzgerald

Scope: Ninth annual report for study C0168Z03 (PSOLAR: PSOriasis Longitudinal Assessment and Registry): an international prospective cohort study/registry programme designed to collect data on psoriasis (PSO) patients that are eligible to receive systemic therapies, including generalised phototherapy and biologics, together with MAH's response to MEA 022.18 [eighth annual report for study C0168Z03] as per the request for supplementary information (RSI) adopted in January 2020

Background

Ustekinumab is an interleukin (IL) inhibitor of IL-12 and IL-23 indicated, as Stelara, subject to certain conditions, for the treatment of adult patients with moderately to severely active Crohn's disease or ulcerative colitis, treatment of moderate to severe plaque psoriasis in adults, children and adolescent patients from the age of 6 years and older, as well as alone

or in combination with methotrexate (MTX) for the treatment of active psoriatic arthritis in adult patients.

The MAH had committed to perform study C0168Z03 (PSOLAR: PSOriasis Longitudinal Assessment and Registry) according to the RMP. The ninth annual report for the study designed to collect data on psoriasis (PSO) patients that are eligible to receive systemic therapies was assessed by the Rapporteur for PRAC review together with the MAH's responses to the request for supplementary information (RSI). For further background, see PRAC minutes January 2020.

Summary of advice

- The PRAC discussed the results from the ninth annual report and agreed that the MAH should provide responses to a request for supplementary information within 60 days, before a conclusion could be drawn on the assessment of the annual report. The MAH should provide additional data on the analyses of cases of major adverse cardiovascular events (MACE) and mortality.

7.6. Others

See Annex I 17.6.

7.7. New Scientific Advice

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

7.8. Ongoing Scientific Advice

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

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

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

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

8.1. Annual reassessments of the marketing authorisation

See Annex I 18.1.

8.2. Conditional renewals of the marketing authorisation

See Annex I 18.2.

8.3. Renewals of the marketing authorisation

See Annex I 18.3.

9. Product related pharmacovigilance inspections

9.1. List of planned pharmacovigilance inspections

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

9.2. Ongoing or concluded pharmacovigilance inspections

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

9.3. Others

None

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

10.1. Safety related variations of the marketing authorisation

None

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

None

10.3. Other requests

None

10.4. Scientific Advice

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

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

11.1. Safety related variations of the marketing authorisation

None

11.2. Other requests

None

12. Organisational, regulatory and methodological matters

12.1. Mandate and organisation of the PRAC

12.1.1. PRAC Rules of Procedure - revision

The EMA Management Board (MB) at its meeting on 19 March 2020 adopted amendments to the existing Rules of Procedure of EMA's scientific committees and MB. These amendments are required to enable those bodies to continue their workings in a virtual emergency setting, as well as to ensure the validity of the various output decisions that each committee will adopt in the coming weeks. A change is also introduced in the quorum required for adoption of scientific opinions or recommendations in case of an emergency situation. To add flexibility to the system, irrespective of an emergency situation, the possibility is introduced to give a proxy vote to another member or to the alternate of a member who is present at the relevant meeting of the body concerned.

The PRAC adopted on 14 April 2020 the amendments to the PRAC Rules of Procedure, as adopted by the EMA Management Board.

Post-meeting note: revision 2 of the PRAC Rules of Procedure (EMA/PRAC/567515/2012 Rev.2) was published on the EMA website on 17 April 2020.

12.2. Coordination with EMA Scientific Committees or CMDh-v

None

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

None

12.4. Cooperation within the EU regulatory network

12.4.1. Coronavirus (COVID-19) pandemic - update

The EMA secretariat updated the PRAC on the activities of the COVID-19 EMA pandemic Task Force (ETF), including an overview of ongoing clinical trials, medicines in development and their safety surveillance.

12.4.2. Heads of Medicines Agencies (HMA)-EMA joint big data taskforce – call for nomination to the steering group

Following a presentation to PRAC in November 2019 (see PRAC minutes November 2019[61]), the EMA Secretariat provided PRAC with further details on the HMA – EMA Joint Big Data Taskforce final report endorsed by the Heads of Medicines Agencies (HMA) in November 2019 and EMA Management Board in December 2019. To implement the recommendations of the task force, a Big Data steering group was established and the PRAC was requested to nominate a representative. The PRAC endorsed Sabine Straus as the PRAC member of the steering group.

[61] Held 28-31 October 2019

12.5. Cooperation with International Regulators

None

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

None

12.7. PRAC work plan

None

12.8. Planning and reporting

12.8.1. Marketing authorisation applications (MAA) forecast for 2020 – planning update dated Q1 2020

The EMA Secretariat presented to PRAC for information a quarterly updated report on marketing authorisation applications planned for submission (the business 'pipeline').

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

The meeting of the GPAG was cancelled.

12.10.3. PSURs repository

None

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

The PRAC endorsed the draft revised EURD list, version March 2020, reflecting the PRAC's comments impacting on the data lock point (DLP) and PSUR submission frequencies of the substances/combinations. The PRAC endorsed the newly allocated Rapporteurs for upcoming PSUSAs in accordance with the principles previously endorsed by the PRAC (see PRAC minutes April 2013).

Post-meeting note: following the PRAC meeting of March 2020, the updated EURD list was adopted by the CHMP and CMDh at their March 2020 meetings and published on the EMA website on 07 May 2020, see:

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

12.11. Signal management

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

PRAC lead: Menno van der Elst

The SMART working group updated the PRAC on the practicalities related to the monitoring of EudraVigilance and scientific literature in the context of COVID-19 treatments.

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 29 April 2020, see: Home>Human Regulatory>Post-authorisation>Pharmacovigilance>Medicines under additional monitoring>List of medicines under additional monitoring

12.13. EudraVigilance database

12.13.1. Activities related to the confirmation of full functionality

None

12.14. Risk management plans and effectiveness of risk minimisations

12.14.1. Risk management systems

None

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

None

12.15. Post-authorisation safety studies (PASS)

12.15.1. Post-authorisation Safety Studies – imposed PASS

None

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

None

12.16. Community procedures

12.16.1. Referral procedures for safety reasons

None

12.17. Renewals, conditional renewals, annual reassessments

None

12.18. Risk communication and transparency

12.18.1. Public participation in pharmacovigilance

None

12.18.2. Safety communication

None

12.19. Continuous pharmacovigilance

12.19.1. Incident management

None

12.20. Others

12.20.1. Strategy on measuring the impact of pharmacovigilance - PRAC interest group (IG) Impact – results and recommendations from case study on stakeholder engagement for valproate

PRAC lead: Antoine Pariente, Daniel Morales

The EMA secretariat and the PRAC interest group (IG) impact updated the PRAC on the results and recommendations from the case study on stakeholder engagement for valproate which will be the basis for further work to establish a process for involvement of patient and healthcare professional (HCP) organisations/bodies and healthcare providers in evaluation of effectiveness of risk minimisation, in line with the PRAC Impact Strategy.

12.20.2. Summary of product characteristics (SmPC) Advisory Group (AG) – call for nomination

The EMA secretariat invited the PRAC to nominate a member for the Summary of Product characteristics (SmPC) Advisory Group (AG). The PRAC endorsed the nominations of Željana Margan Koletić and Adrien Inoubli.

12.20.3. Workshop on the role of registries in the monitoring of cancer therapies based on tumours' genetic and molecular features, 29 November 2019, Amsterdam, the Netherlands – final report: main observation and follow-up actions

The EMA secretariat updated the PRAC on the report of the workshop on the use of registries in the monitoring of cancer therapies based on tumours' genetic and molecular features (EMA/661159/2019) that took place on 29 November 2019.

13. Any other business

None

14. Annex I – Signals assessment and prioritisation[62]

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[63].

14.1.1. Abiraterone – ZYTIGA (CAP)

Applicant(s): Janssen-Cilag International NV

[62] 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

[63] 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

PRAC Rapporteur: Eva Segovia

Scope: Signal of anaphylactic reaction

EPITT 19535 – New signal

Lead Member State(s): ES

14.1.2. Bisoprolol (NAP)

Applicant(s): various

PRAC Rapporteur: Kirsti Villikka

Scope: Signal of angioedema

EPITT 19542 – New signal

Lead Member State(s): FI

14.1.3. Paclitaxel – ABRAXANE (CAP), APEALEA (CAP), PAZENIR (CAP); NAP

Applicant(s): Celgene Europe BV (Abraxane), Oasmia Pharmaceutical AB (Apealea), ratiopharm GmbH (Pazenir), various

PRAC Rapporteur: Menno van der Elst

Scope: Signal of progressive multifocal leukoencephalopathy (PML)

EPITT 19553 – New signal

Lead Member State(s): NL, PT

14.1.4. Pomalidomide – IMNOVID (CAP)

Applicant(s): Celgene Europe BV

PRAC Rapporteur: Eva Segovia

Scope: Signal of progressive multifocal leukoencephalopathy (PML)

EPITT 19546 – New signal

Lead Member State(s): ES

14.2. New signals detected from other sources

14.2.1. Vedolizumab – ENTYVIO (CAP)

Applicant(s): Takeda Pharma A/S

PRAC Rapporteur: Adam Przybylkowski

Scope: Signal of Evans' syndrome, autoimmune haemolytic anaemia, immune thrombocytopenic purpura

EPITT 19547 – New signal

Lead Member State(s): PL

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. Paliperidone - EMEA/H/C/005486

Scope: Treatment of schizophrenia

15.1.2. Teriparatide - EMEA/H/C/005233

Scope: Treatment of osteoporosis

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. Alemtuzumab - LEMTRADA (CAP) - EMEA/H/C/003718/II/0031

Applicant: Sanofi Belgium

PRAC Rapporteur: Anette Kirstine Stark

Scope: Submission of an updated RMP (version 7.0) in order to reflect all amendments and additional activities as per the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 completed in November 2019 (EMEA/H/A-20/1483)

15.2.2. Asparaginase - SPECTRILA (CAP) - EMEA/H/C/002661/II/0017

Applicant: medac Gesellschaft fur klinische Spezialpraparate mbH

PRAC Rapporteur: Jan Neuhauser

Scope: Submission of an updated RMP (version 12) in line with revision 2 of GVP module V on 'Risk management systems' and in line with revision 2.0.1 of the guidance on the format of RMP in the EU (template). The milestones and timelines for study MC-Spectrila.1/ALL: a clinical phase 2 trial to describe pharmacokinetics, pharmacodynamics, safety and immunogenicity of Spectrila (asparaginase) with the pharmaceutical active ingredient recombinant L asparaginase in adult subjects with newly diagnosed acute B-Cell lymphoblastic leukaemia are updated in accordance with the newly applied data lock point (DLP) for the RMP

15.2.3. Dexamethasone - OZURDEX (CAP) - EMEA/H/C/001140/II/0037

Applicant: Allergan Pharmaceuticals Ireland

PRAC Rapporteur: Eva Segovia

Scope: Submission of an updated RMP (version 9.0) in order to reflect increased knowledge of the medicinal product and bring it in line with revision 2 of the guidance on the format of RMP in the EU (template)

15.2.4. Docetaxel - DOCETAXEL ZENTIVA (CAP) - EMEA/H/C/000808/II/0061

Applicant: Zentiva, k.s.

PRAC Rapporteur: Ghania Chamouni

Scope: Submission of an updated RMP (version 1.1) in order to revise the list of safety concerns in line with revision 2 of GVP module V on 'Risk management systems' and to complete Part II modules

15.2.5. Docetaxel - TAXOTERE (CAP) - EMEA/H/C/000073/II/0134

Applicant: Sanofi Mature IP

PRAC Rapporteur: Ghania Chamouni

Scope: Submission of an updated RMP (version 1.1) in order to revise the list of safety concerns in line with revision 2 of GVP module V on 'Risk management systems' and to complete Part II modules

15.2.6. Histamine dihydrochloride - CEPLENE (CAP) - EMEA/H/C/000796/II/0040

Applicant: Noventia Pharma Srl

PRAC Rapporteur: Rhea Fitzgerald

Scope: Submission of an updated RMP (version 8.1) in order to include information about the termination/finalisation of: 1) non-interventional study Ceplene-3290 (listed as a category 3 study in the RMP): an open study designed to gain further knowledge on Ceplene (histamine dihydrochloride) under day to day conditions with special emphasis on tolerability, practicability, usage, and measurable minimal residual disease and course of blast cells and; 2) post-authorisation efficacy study (PAES) Ceplene cohort study 3306: an international, multicentre, observational, non-interventional, registry-based cohort study aiming to describe and evaluate minimal residual disease (MRD) at baseline and follow-up for the assessment of the anti-leukaemic activity of Ceplene (histamine dihydrochloride)/interleukin-2 (IL-2) as remission maintenance therapy in adult patients with acute myeloid leukaemia (AML) in first complete remission (CR1) compared to matched control patients who did not receive Ceplene (histamine dihydrochloride)/IL-2. In addition, the RMP is brought in line with revision 2.0.1 of the guidance on the format of RMP in the EU (template). As a consequence, the list of safety concerns is amended in particular 'drug effect decreased as a consequence of drug interaction' is added as a new important potential risk

15.2.7. Nonacog alfa - BENEFIX (CAP) - EMEA/H/C/000139/II/0163

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Submission of an updated RMP (version 10.0) to remove 'less than therapeutic effect (LETE)' as an important identified risk. In addition, specific patient populations previously identified as missing information are removed from the RMP in line with revision 2 of GVP module V on 'Risk management systems'

15.2.8. Sevelamer - RENAGEL (CAP) - EMEA/H/C/000254/WS1775/0114; Sevelamer carbonate - RENVELA (CAP) - EMEA/H/C/000993/WS1775/0051; SEVELAMER CARBONATE WINTHROP (CAP) - EMEA/H/C/003971/WS1775/0024

Applicant: Genzyme Europe BV

PRAC Rapporteur: Laurence de Fays

Scope: Submission of an updated RMP (version 10) in order to remove from the list of safety concerns 'sevelamer crystals associated with serious gastrointestinal disorders' as an important potential risk as per the conclusions of the renewal procedure for Sevelamer Carbonate Winthrop (R/0022) finalised 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. Andexanet alfa - ONDEXXYA (CAP) - EMEA/H/C/004108/II/0009/G

Applicant: Portola Netherlands B.V.

PRAC Rapporteur: Menno van der Elst

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

15.3.2. Anidulafungin - ECALTA (CAP) - EMEA/H/C/000788/II/0040

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Extension of the approved indication 'treatment of invasive candidiasis (ICC)' to include paediatric patients aged from 1 month to less than 18 years of age. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 4.9, 5.1, 5.2, 5.3 and 6.6 of the SmPC are updated. The package leaflet and the RMP (version 13.0) are updated accordingly. The RMP is also updated in line with revision 2 of GVP module V on 'Risk management systems'. In addition, the MAH took the opportunity to update the information in the product information on fructose in line with the European Commission (EC) guideline on 'excipients in the

labelling and package leaflet of medicinal products for human use'

15.3.3. Avelumab - BAVENCIO (CAP) - EMEA/H/C/004338/II/0015

Applicant: Merck Europe B.V.

PRAC Rapporteur: Hans Christian Siersted

Scope: Update of sections 4.2, 4.4 and 4.8 of the SmPC in order to change posology recommendations, to amend an existing warning and to add myasthenia gravis and myasthenic syndrome as new adverse drug reactions (ADRs) with a frequency uncommon. The update results from an update of the company core data sheet (CCDS) based on the review of cases of myasthenia gravis/myasthenic syndrome. The package leaflet is updated accordingly. The RMP (version 2.2) is updated with a proposal to reclassify 'other immune-related events (myasthenic syndrome)' from an important potential risk to an important identified risk of 'other immune-related events (myasthenia gravis/myasthenic syndrome)'

15.3.4. Bedaquiline - SIRTURO (CAP) - EMEA/H/C/002614/X/0036/G, Orphan

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Grouped application consisting of: 1) extension application to add a new strength (20 mg tablets); 2) extension of the existing indication on pulmonary multidrug-resistant tuberculosis (MDR-TB) to include paediatric patients aged from 5 years to less than 18 years of age and weighing more than 15 kg based on the results of the week 24 analysis of cohort 2 (paediatric subjects aged ≥5 to <12 years) of study TMC207-C211: a phase 2, open-label, multicentre, single-arm study to evaluate the pharmacokinetics, safety, tolerability and antimycobacterial activity of TMC207 (bedaquiline) in combination with a background regimen (BR) of MDR-TB Medications for the treatment of children and adolescents 0 months to <18 years of age who have confirmed or probable pulmonary MDR-TB. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 are updated. The package leaflet and the RMP (version 4.4) are updated in accordance

15.3.5. Binimetinib - MEKTOVI (CAP) - EMEA/H/C/004579/WS1695/0007; encorafenib - BRAFTOVI (CAP) - EMEA/H/C/004580/WS1695/0008

Applicant: Pierre Fabre Medicament

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Extension of indication to include encorafenib in combination with binimetinib and cetuximab, for the treatment of adult patients with metastatic colorectal cancer (CRC) with a BRAF V600E mutation, who have received prior systemic therapy. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The package leaflet and the RMP (version 1.1) are updated accordingly. Furthermore, the product information is brought in line with the latest quality review of documents (QRD) template (version 10.1)

15.3.6. Brodalumab - KYNTHEUM (CAP) - EMEA/H/C/003959/II/0014

Applicant: LEO Pharma A/S

PRAC Rapporteur: Eva Segovia

Scope: Update of sections 4.4 and 4.8 of the SmPC to reflect a signal of anaphylactic reaction detected in post marketing setting. The package leaflet and the RMP (version 1.2) are updated accordingly. The MAH took the opportunity to introduce minor updates throughout the product information

15.3.7. Buprenorphine, naloxone - SUBOXONE (CAP) - EMEA/H/C/000697/X/0042

Applicant: Indivior Europe Limited

PRAC Rapporteur: Martin Huber

Scope: Extension application to introduce a new pharmaceutical form (sublingual film) associated with four new strengths (2/0.5 mg, 4/1 mg, 8/2 mg and 16/4 mg) and a new route of administration (either sublingual or buccal administration). The RMP (version 14.0) is updated accordingly

15.3.8. Canagliflozin - INVOKANA (CAP) - EMEA/H/C/002649/II/0046

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Martin Huber

Scope: Extension of indication to add the treatment of stage 2 or 3 chronic kidney disease (CKD) and albuminuria, as an adjunct to standard of care, in adults with type 2 diabetes mellitus (T2DM), based on new clinical efficacy and safety data from study DNE3001 (CREDENCE): a randomised, double-blind, event-driven, placebo-controlled, multicentre phase 3 study of the effects of canagliflozin on renal and cardiovascular outcomes in subjects with T2DM and diabetic nephropathy. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 8.1) are updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet

15.3.9. Canagliflozin, metformin - VOKANAMET (CAP) - EMEA/H/C/002656/II/0051

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to add the treatment of stage 2 or 3 chronic kidney disease (CKD) and albuminuria, as an adjunct to standard of care, in adults with type 2 diabetes mellitus (T2DM), based on new clinical efficacy and safety data from study DNE3001 (CREDENCE): a randomised, double-blind, event-driven, placebo-controlled, multicentre phase 3 study of the effects of canagliflozin on renal and cardiovascular outcomes in subjects with T2DM and diabetic nephropathy. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 8.1) are updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet

15.3.10. Carfilzomib - KYPROLIS (CAP) - EMEA/H/C/003790/II/0043, Orphan

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Update of section 4.8 of the SmPC in order to include cardiomyopathy as a new adverse drug reaction (ADR) with a frequency uncommon. The RMP (version 11.0) is updated accordingly. In addition, the MAH took the opportunity to introduce minor editorial changes to the product information

15.3.11. Certolizumab pegol - CIMZIA (CAP) - EMEA/H/C/001037/II/0084/G

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of sections 4.8 and 5.1 of the SmPC in order to update the safety and efficacy information following the final results from three studies (listed as category 3 studies in the RMP) namely: 1) study PS0002 (CIMPASI-2): a phase 3, multicentre, randomized, double-blind, parallel-group, study followed by a dose-blind period and open-label follow-up to evaluate the efficacy and safety of certolizumab pegol in subjects with moderate to severe chronic plaque psoriasis; 2) study PS0003 (CIMPACT): a phase 3, multicentre, randomized, double-blind, parallel-group, placebo- and active-controlled study followed by a placebo-controlled maintenance period and open-label follow-up to evaluate the efficacy and safety of certolizumab pegol in subjects with moderate to severe chronic plaque psoriasis; 3) study PS0005 (CIMPASI-1): a phase 3, multicentre, randomized, double-blind, parallel-group, study followed by a dose-blind period and open-label follow-up to evaluate the efficacy and safety of certolizumab pegol in subjects with moderate to severe chronic plaque psoriasis. The RMP (version 16.0) is updated accordingly. In addition, the MAH took the opportunity to bring the product information in line with the latest quality review of documents (QRD) template (version 10.1)

Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

15.3.12. Certolizumab pegol - CIMZIA (CAP) - EMEA/H/C/001037/II/0087

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of sections 4.2, 4.8 and 5.1 of the SmPC in order to introduce a change in posology for axial spondyloarthritis (axSpA) and to update the safety and efficacy information based on the results of study AS0005 (C-OPTIMISE) (listed as a category 3 study in the RMP): a multicentre, open-label (part A) followed by a randomised, double-blind, parallel-group, placebo-controlled study (part B) to evaluate maintenance of remission in subjects with active axSpA receiving either certolizumab pegol 200 mg once every 2 weeks (q2w) or 200 mg once every 4 weeks (q4w) as compared to placebo. The package leaflet and the RMP (version 17.0) are updated accordingly. In addition, the interim study reports for studies AS0006 and AS0007 are submitted to include additional pooled safety data in the SmPC. Study AS0006 is a phase 3, multicentre, randomised, placebo-controlled, double-blind study to evaluate efficacy and safety of certolizumab pegol in subjects with active axSpA without x-ray evidence of ankylosing spondylitis and objective signs of inflammation. Study AS0007 is a multicentre, open-label study to assess the effects of certolizumab pegol on the reduction of anterior uveitis flares in axSpA subjects with a history of anterior uveitis (C-VIEW).

Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

15.3.13. Clopidogrel - ISCOVER (CAP) - EMEA/H/C/000175/WS1769/0140; PLAVIX (CAP) - EMEA/H/C/000174/WS1769/0138

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Extension of indication to include adult patients with high risk transient ischemic attack (TIA) ($ABCD^2$ score ≥4) or minor ischemic stroke (IS) (National Institutes of Health Stroke Scale (NIHSS) ≤3) within 24 hours of either the TIA or IS event. The new indication is based on the results of 1) study POINT: a double-blind, randomised, placebo-controlled phase 3 study on platelet-oriented inhibition in new TIA and minor IS; 2) study CHANCE: a double-blind, randomised, placebo-controlled phase 3 study comparing the effects of a 3-month clopidogrel regimen, combined with acetylsalicylic acid (ASA) during the first 21 days, versus ASA alone for the acute treatment of TIA or minor stroke. As a consequence, sections 4.1, 4.2, 4.4 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 1.0) are updated accordingly

15.3.14. Delamanid - DELTYBA (CAP) - EMEA/H/C/002552/II/0040, Orphan

Applicant: Otsuka Novel Products GmbH

PRAC Rapporteur: Laurence de Fays

Scope: Extension of indication to include adolescents and children above 6 years with a body weight of at least 30 kg. As a consequence, sections 4.1, 4.2, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 3.2) are updated accordingly. Furthermore, the product information is brought in line with the latest quality review of documents (QRD) template (version 10.1)

15.3.15. Dupilumab - DUPIXENT (CAP) - EMEA/H/C/004390/II/0027

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Kimmo Jaakkola

Scope: Extension of indication to include atopic dermatitis patients from 6 years to 11 years. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 5.0) are updated accordingly

15.3.16. Esketamine - SPRAVATO (CAP) - EMEA/H/C/004535/II/0001/G

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Kirsti Villikka

Scope: Grouped variations consisting of: 1) extension of indication to include a new indication for the rapid reduction of depressive symptoms in adult patients with a moderate to severe depressive episode of major depressive disorder (MMD) who have current suicidal ideation with intent. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 the SmPC are updated. The package leaflet and the RMP (version 2.1) are updated accordingly; 2) addition of a new pack size corresponding to 4 weeks of treatment in the new indication.

The package leaflet and labelling are updated in accordance. In addition, the MAH took the opportunity to clarify the wording in Annex II-D on 'Conditions or restrictions with regard to the safe and effective use of the medicinal product'

15.3.17. 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

15.3.18. Herpes zoster vaccine (recombinant, adjuvanted) - SHINGRIX (CAP) - EMEA/H/C/004336/II/0022

Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Sonja Hrabcik

Scope: Extension of indication to include adults of 18 years of age or older at increased risk of herpes zoster, supported by clinical studies: 1) study ZOSTER-002: a phase 3, randomised, observer-blind, placebo-controlled, multicentre, clinical trial to assess the prophylactic efficacy, safety, and immunogenicity of Shingrix (herpes zoster vaccine) when administered intramuscularly on a two-dose schedule to adult autologous haematopoietic stem cell transplant (HCT) recipients (MEA 001); 2) study ZOSTER-039: a phase 3, randomised, observer-blind, placebo-controlled, multicentre study to assess the safety and immunogenicity of Shingrix (herpes zoster vaccine) when administered intramuscularly on a two-dose schedule to adults aged 18 years and older with haematologic malignancies (MEA 002); 3) study ZOSTER-041: a phase 3, randomised, observer-blind, placebo-controlled, multicentre clinical study to assess the immunogenicity and safety of Shingrix (herpes zoster vaccine) when administered intramuscularly on a 0- and 1- to 2-months schedule to adults $\geqslant$ 18 years of age with renal transplant (MEA 003); 4) study ZOSTER-028: a phase 2/3, randomised, observer-blind, placebo-controlled, multicentre, clinical trial to assess the immunogenicity and safety of Shingrix (herpes zoster vaccine) when administered intramuscularly on a 0 and 1 to 2 months schedule to adults of 18 years of age with solid tumours receiving chemotherapy (MEA 004); 5) study ZOSTER-001: a phase 1/2a, randomised, observer-blind, placebo-controlled, multicentre study to evaluate the safety and immunogenicity of Shingrix (herpes zoster vaccine) and to saline (placebo) when administered as 2 doses or 3 doses to autologous HCT recipients ; 6) study ZOSTER-015: a phase 1/2a, randomised, observer-blind, placebo-controlled, multicentre study to evaluate the safety and immunogenicity of Shingrix (herpes zoster vaccine) in comparison to placebo when administered as 3 doses to adult human immunodeficiency virus (HIV)-infected subjects. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated in order to add the indication, delete a warning and add new safety and efficacy information.

The package leaflet and the RMP (version 2.1) are updated in accordance

15.3.19. Ibrutinib - IMBRUVICA (CAP) - EMEA/H/C/003791/II/0059, Orphan

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Extension of indication to add the combination with rituximab or obinutuzumab for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL), based on results from study E1912 (PCYC-1126e-CA): a randomized phase 3 study of ibrutinib-based therapy vs standard fludarabine, cyclophosphamide, and rituximab (FCR) chemoimmunotherapy in untreated younger patients with CLL. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated to include information related to the new indication. The package leaflet and the RMP (version 16.1) are updated accordingly. The MAH took the opportunity to introduce minor editorial changes in Annex II and the labelling (Annex III-A)

15.3.20. Insulin glargine - ABASAGLAR (CAP) - EMEA/H/C/002835/WS1587/0028/G; insulin lispro - HUMALOG (CAP) - EMEA/H/C/000088/WS1587/0178/G

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Annika Folin

Scope: Grouped variations consisting of: 1) introduction of an additional prefilled pen presentation; 2) extension to multipacks. As a consequence, sections 1, 4.2, 4.4, 6.2, 6.4, 6.5, 6.6 and 8 of the SmPC are updated. The package leaflet and labelling are updated accordingly. In addition, the MAH took the opportunity to introduce an editorial change in the Slovakian address of the package leaflet

15.3.21. Ivacaftor - KALYDECO (CAP) - EMEA/H/C/002494/II/0082, Orphan

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Extension of indication to include a new population for Kalydeco (ivacaftor) 150 mg tablets to extend the use to patients with cystic fibrosis (CF) aged 6 years and older and weighing 25 kg or more who have an R117H mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene and for Kalydeco (ivacaftor) granules 75 mg and 50 mg, to add patients with CF aged 12 months and older and weighing 7 kg to less than 25 kg who have an R117H mutation in the CFTR gene. This is based on a clinical trial and literature data, and post-marketing experience with Kalydeco (ivacaftor). As a consequence, sections 4.1, 4.2, 4.4 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 8.5) are updated accordingly

15.3.22. Ixekizumab - TALTZ (CAP) - EMEA/H/C/003943/II/0031

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include the treatment of moderate to severe plaque

psoriasis in children from the age of 6 years and adolescents who are candidates for systemic therapy for Taltz (ixekizumab). As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated with new safety and efficacy information. The package leaflet and the RMP (version 7.1) are updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet

15.3.23. Lacosamide - LACOSAMIDE UCB (CAP) - EMEA/H/C/005243/WS1782/0006; VIMPAT (CAP) - EMEA/H/C/000863/WS1782/0088

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension of indication to include the treatment as adjunctive therapy of primary generalised tonic-clonic seizures in adults, adolescents and children from 4 years of age with idiopathic generalised epilepsy. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 15.0) are updated in accordance. Furthermore, the MAH took the opportunity to bring the product information in line with the latest quality review of documents (QRD) template (version 10.1), to align the product information of Lacosamide UCB (lacosamide) with the product information of Vimpat (lacosamide) and to implement some minor corrections in the Bulgarian, Czech, Danish, French, German, Hungarian, Polish and Spanish versions of the product information

15.3.24. Lenalidomide - REVLIMID (CAP) - EMEA/H/C/000717/II/0112/G

Applicant: Celgene Europe BV

PRAC Rapporteur: Ghania Chamouni

Scope: Grouped variations consisting of: 1) update of sections 4.2, 4.4 and 4.8 of the SmPC with anaphylaxis following a safety review. The package leaflet is updated accordingly; 2) update of section 6.6 of the SmPC in order to include recommendations to minimise the risk of unintended occupational exposures in healthcare professionals. The MAH took the opportunity to include minor updates to section 4.4 of the SmPC and to introduce more clarity in Annex II-D on 'Specific obligation to complete post-authorisation measures for the conditional marketing authorisation' regarding the educational materials, prescribing and dispensing restrictions. Finally, the MAH introduced some editorial changes throughout the product information

15.3.25. Levetiracetam - KEPPRA (CAP) - EMEA/H/C/000277/WS1664/0187

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Laurence de Fays

Scope: Update of section 4.2 of the SmPC to recommend the same dosing for monotherapy and adjunctive therapy based on data from modelling and simulation project. The package leaflet and the RMP (version 9.0) are updated accordingly. The MAH took the opportunity to move Braille to another box section and to review and adapt the German product information in line with the latest quality review of documents (QRD) template (version 10.1)

15.3.26. Lumacaftor, ivacaftor - ORKAMBI (CAP) - EMEA/H/C/003954/II/0055

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Update of section 4.8 of the SmPC following results from study VX16-809-116 (study 106, safety study in children): a phase 3, open-label, rollover extension study evaluating the long-term safety of lumacaftor/ivacaftor in patients with cystic fibrosis aged 2 and older, homozygous for the deletion of phenylalanine in position 508 of the cystic fibrosis transmembrane conductance regulator (F508del-CFTR) mutation, who initiated treatment in parent study 115. The package leaflet and the RMP (version 7.1) are updated accordingly. The MAH took the opportunity to bring the product information in line with the latest quality review of documents (QRD) template (version 10.1)

15.3.27. Methotrexate - NORDIMET (CAP) - EMEA/H/C/003983/II/0016

Applicant: Nordic Group B.V.

PRAC Rapporteur: Martin Huber

Scope: Extension of indication to include the treatment of mild to moderate Crohn's disease either alone or in combination with corticosteroids in patients refractory or intolerant to thiopurines. As a consequence, sections 4.1, 4.2 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 5.0) are updated in accordance. Furthermore, the MAH took the opportunity to update the RMP in line with revision 2.0.1 of the guidance on the format of RMP in the EU (template) and the outcome of the referral procedure for methotrexate-containing products under Article 31 of Directive 2001/83/EC (EMEA/H/A-31/1463) finalised in July 2019

15.3.28. Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/II/0080

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include treatment of adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma (OSCC) after prior fluoropyrimidine- and platinum-based chemotherapy. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 16.0) are updated in accordance

15.3.29. Obinutuzumab - GAZYVARO (CAP) - EMEA/H/C/002799/II/0038, Orphan

Applicant: Roche Registration GmbH

PRAC Rapporteur: Annika Folin

Scope: Submission of final clinical study report (CSR) for study MO28543/GREEN: a multicentre, open-label, single-arm, phase 3b, international study evaluating the safety of obinutuzumab alone or in combination with chemotherapy in patients with previously untreated or relapsed/refractory chronic lymphocytic leukaemia (in fulfilment of the post authorisation commitment MEA 005). The RMP (version 6.1) is updated accordingly

15.3.30. Ocrelizumab - OCREVUS (CAP) - EMEA/H/C/004043/II/0017

Applicant: Roche Registration GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of sections 4.2, 4.8 and 5.1 of the SmPC in order to add the option of a shorter infusion for second and subsequent doses of Ocrevus (ocrelizumab): from the approved 3.5 hours infusion to 2 hours, based on the primary analysis of a therapeutic use substudy MA30143 (shorter infusion substudy (Ensemble Plus)): an open-label, single-arm study to evaluate the effectiveness and safety of ocrelizumab in patients with early stage relapsing remitting multiple sclerosis. The Package Leaflet is updated accordingly. The RMP (version 4.0) is updated accordingly

15.3.31. Olaparib - LYNPARZA (CAP) - EMEA/H/C/003726/II/0033

Applicant: AstraZeneca AB

PRAC Rapporteur: Amelia Cupelli

Scope: Extension of indication to support the use of Lynparza (olaparib) tablets (100 mg and 150 mg) for the maintenance treatment of germline breast cancer gene (BRCA) mutation (gBRCAm) metastatic pancreatic cancer based on the results from the pivotal phase 3 study POLO: a phase 3, randomised, double blind, placebo controlled, multicentre study of maintenance olaparib monotherapy in patients with gBRCA mutated metastatic pancreatic cancer whose disease has not progressed on first line platinum based chemotherapy. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 18) are updated in accordance. In addition, the MAH took the opportunity to update section 4.8 for Lynparza (olaparib) hard capsules (50 mg) to revise the list of adverse drug reactions (ADR) based on a pooled safety data analysis. Furthermore, the product information is brought in line with the latest Annex to the European Commission (EC) guideline on 'excipients in the labelling and package leaflet of medicinal products for human use' on sodium content. The MAH also took the opportunity to include some minor editorial changes in the product information

15.3.32. Pegvaliase - PALYNZIQ (CAP) - EMEA/H/C/004744/II/0007/G, Orphan

Applicant: BioMarin International Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Grouped variations consisting of an update of sections 4.4, 4.8 and 5.1 of the SmPC based on final results from: 1) study 1655-003 (listed as a category 3 study in the RMP): a long-term extension of a phase 2, open-label, dose-finding study; 2) study 165-302 (listed as a category 3 study in the RMP): a phase 3, randomised, double-blind, placebo-controlled, four-arm, discontinuation study to evaluate executive function in adults with phenylketonuria. The RMP (version 2.0) is updated accordingly. In addition, the MAH took the opportunity to introduce minor editorial changes in the product information

15.3.33. 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

15.3.34. Pomalidomide - IMNOVID (CAP) - EMEA/H/C/002682/II/0036/G, Orphan

Applicant: Celgene Europe BV

PRAC Rapporteur: Eva Segovia

Scope: Grouped variations consisting of: 1) update of sections 4.2, 4.4 and 4.8 of the SmPC with information on anaphylaxis and section 4.8 of SmPC with hypothyroidism as an adverse drug reaction (ADR) following a safety review. The package leaflet is updated accordingly; 2) update of section 6.6 of the SmPC in order to include recommendations to minimise the risk of unintended occupational exposures in healthcare professionals. The MAH took the opportunity to include minor updates to section 4.4 of the SmPC and to introduce more clarity in Annex II-D on 'Specific obligation to complete post-authorisation measures for the conditional marketing authorisation' regarding the educational materials, prescribing and dispensing restrictions

15.3.35. Ravulizumab - ULTOMIRIS (CAP) - EMEA/H/C/004954/II/0002

Applicant: Alexion Europe SAS

PRAC Rapporteur: Kimmo Jaakkola

Scope: Extension of indication to include the treatment of patients with atypical haemolytic uremic syndrome (aHUS). As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated. The package leaflet and the RMP (version 1.6) are updated accordingly. In addition, Annex II-D on 'Conditions or restrictions with regard to the safe and effective use of the medicinal product' is updated to include in the educational materials the risk of thrombotic microangiopathy (TMA) with the new indication

15.3.36. Rivaroxaban - XARELTO (CAP) - EMEA/H/C/000944/X/0074/G

Applicant: Bayer AG

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Grouped applications consisting of: 1) extension application to introduce a new pharmaceutical form, granules for oral suspension, 1 mg/mL; 2) extension of indication to include treatment of venous thromboembolism (VTE) and prevention of VTE recurrence in term neonates, infants and toddlers, children and adolescents aged less than 18 years following initiation of standard anticoagulation treatment for Xarelto (rivaroxaban) 15 mg and 20 mg tablets. As a consequence, sections 4.2, 4.4, 4.5, 4.8, 4.9, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 12.1) are updated accordingly. In addition, sections 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated for all other dose strengths (2.5/10 mg and 15/20 mg initiation packs). Furthermore, the MAH took the opportunity to update the product information with regards to 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'

15.3.37. Thalidomide - THALIDOMIDE CELGENE (CAP) - EMEA/H/C/000823/II/0061/G

Applicant: Celgene Europe BV

PRAC Rapporteur: Ghania Chamouni

Scope: Grouped variations consisting of: 1) update of sections 4.2, 4.4 and 4.8 of the SmPC with information on anaphylaxis following a safety review. The package leaflet is updated accordingly; 2) update of section 6.6 of the SmPC in order to include recommendations to minimise the risk of unintended occupational exposures in healthcare professionals. The MAH took the opportunity to include minor updates to section 4.4 of the SmPC and to introduce more clarity in Annex II-D on 'Specific obligation to complete post-authorisation measures for the conditional marketing authorisation' regarding the educational materials, prescribing and dispensing restrictions

15.3.38. Zoledronic acid - ZOMETA (CAP) - EMEA/H/C/000336/II/0091

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Anette Kirstine Stark

Scope: Update of sections 4.4 and 5.1 of the SmPC in order to update the safety information on osteonecrosis of the jaw (ONJ) based on final results from study CZOL446EUS122 (listed as a category 3 study in the RMP): a non-interventional, prospective, observational, multicentre cohort study to assess the incidence of ONJ in cancer patients with bone metastases starting zoledronic acid treatment. The RMP (version 12) 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. Abemaciclib - VERZENIOS (CAP) - PSUSA/00010724/201909

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Evaluation of a PSUSA procedure

16.1.2. Avelumab - BAVENCIO (CAP) - PSUSA/00010635/201909

Applicant: Merck Europe B.V.

PRAC Rapporteur: Hans Christian Siersted

Scope: Evaluation of a PSUSA procedure

16.1.3. Bedaquiline - SIRTURO (CAP) - PSUSA/00010074/201909

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.4. Cariprazine - REAGILA (CAP) - PSUSA/00010623/201910

Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.1.5. Chenodeoxycholic acid[64] - CHENODEOXYCHOLIC ACID LEADIANT (CAP) - PSUSA/00010590/201910

Applicant: Leadiant GmbH

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.6. Cholic acid[65] - ORPHACOL (CAP) - PSUSA/00010208/201909

Applicant: Laboratoires CTRS

PRAC Rapporteur: Sofia Trantza

Scope: Evaluation of a PSUSA procedure

16.1.7. Ciclosporin[66] - IKERVIS (CAP); VERKAZIA (CAP) - PSUSA/00010362/201909

Applicant: Santen Oy

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.1.8. Crizotinib - XALKORI (CAP) - PSUSA/00010042/201908

Applicant: Pfizer Europe MA EEIG

[64] Indicated for the treatment of inborn errors of primary bile acid synthesis due to sterol 27 hydroxylase deficiency (presenting as cerebrotendinous xanthomatosis (CTX)) in infants, children and adolescents aged 1 month to 18 years and adults – centrally authorised product(s) only
[65] Treatment of inborn errors in primary bile acid synthesis due to 3β-hydroxy-Δ5-C27-steroid oxidoreductase deficiency or Δ4-3-oxosteroid-5β-reductase indication(s) only
[66] Topical use only

PRAC Rapporteur: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

16.1.9. Dacomitinib - VIZIMPRO (CAP) - PSUSA/00010757/201909

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.10. Dapagliflozin - EDISTRIDE (CAP); FORXIGA (CAP) - PSUSA/00010029/201910

Applicant: AstraZeneca AB

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

16.1.11. Darunavir, cobicistat, emtricitabine, tenofovir alafenamide - SYMTUZA (CAP) - PSUSA/00010646/201909

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.1.12. Darvadstrocel - ALOFISEL (CAP) - PSUSA/00010676/201909

Applicant: Takeda Pharma A/S, ATMP[67]

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.13. Dulaglutide - TRULICITY (CAP) - PSUSA/00010311/201909

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Ilaria Baldelli

Scope: Evaluation of a PSUSA procedure

16.1.14. Eluxadoline - TRUBERZI (CAP) - PSUSA/00010528/201909

Applicant: Allergan Pharmaceuticals International Limited

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.15. Etravirine - INTELENCE (CAP) - PSUSA/00001335/201909

Applicant: Janssen-Cilag International NV

[67] Advanced therapy medicinal product

PRAC Rapporteur: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

16.1.16. Galcanezumab - EMGALITY (CAP) - PSUSA/00010733/201909

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

16.1.17. Glycopyrronium[68] - SIALANAR (CAP) - PSUSA/00010529/201909

Applicant: Proveca Pharma Limited

PRAC Rapporteur: Zane Neikena

Scope: Evaluation of a PSUSA procedure

16.1.18. Idebenone[69] - RAXONE (CAP) - PSUSA/00010412/201909

Applicant: Santhera Pharmaceuticals (Deutschland) GmbH

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.1.19. Insulin aspart - FIASP (CAP); NOVOMIX (CAP); NOVORAPID (CAP) - PSUSA/00001749/201909

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

16.1.20. Insulin degludec, liraglutide - XULTOPHY (CAP) - PSUSA/00010272/201909

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.21. Isavuconazole - CRESEMBA (CAP) - PSUSA/00010426/201909

Applicant: Basilea Pharmaceutica Deutschland GmbH

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

[68] Indicated for the treatment of severe sialorrhea (chronic pathological drooling), centrally authorised product(s) only
[69] Centrally authorised product(s) only

16.1.22. Lorlatinib - LORVIQUA (CAP) - PSUSA/00010760/201909

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

16.1.23. Lusutrombopag - MULPLEO (CAP) - PSUSA/00010755/201909

Applicant: Shionogi B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.24. Mepolizumab - NUCALA (CAP) - PSUSA/00010456/201909

Applicant: GlaxoSmithKline Trading Services Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.25. Mogamulizumab - POTELIGEO (CAP) - PSUSA/00010741/201909

Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Hans Christian Siersted

Scope: Evaluation of a PSUSA procedure

16.1.26. Naldemedine - RIZMOIC (CAP) - PSUSA/00010753/201909

Applicant: Shionogi B.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

16.1.27. Naloxegol - MOVENTIG (CAP) - PSUSA/00010317/201909

Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Ronan Grimes

Scope: Evaluation of a PSUSA procedure

16.1.28. Netupitant, palonosetron - AKYNZEO (CAP) - PSUSA/00010393/201910

Applicant: Helsinn Birex Pharmaceuticals Limited

PRAC Rapporteur: Ilaria Baldelli

Scope: Evaluation of a PSUSA procedure

16.1.29. Ocrelizumab - OCREVUS (CAP) - PSUSA/00010662/201909

Applicant: Roche Registration GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.30. Panitumumab - VECTIBIX (CAP) - PSUSA/00002283/201909

Applicant: Amgen Europe B.V.

PRAC Rapporteur: David Olsen

Scope: Evaluation of a PSUSA procedure

16.1.31. Raltegravir - ISENTRESS (CAP) - PSUSA/00010373/201909

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

16.1.32. Ribociclib - KISQALI (CAP) - PSUSA/00010633/201909

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Hans Christian Siersted

Scope: Evaluation of a PSUSA procedure

16.1.33. Risankizumab - SKYRIZI (CAP) - PSUSA/00010765/201909

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.34. Ritonavir - NORVIR (CAP) - PSUSA/00002651/201908

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.35. Rivaroxaban - XARELTO (CAP) - PSUSA/00002653/201909

Applicant: Bayer AG

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.36. Sodium zirconium cyclosilicate - LOKELMA (CAP) - PSUSA/00010675/201909

Applicant: AstraZeneca AB

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

16.1.37. Sofosbuvir, ledipasvir - HARVONI (CAP) - PSUSA/00010306/201910

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.1.38. Telbivudine - SEBIVO (CAP) - PSUSA/00002880/201908

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

16.1.39. Tenecteplase - METALYSE (CAP) - PSUSA/00002888/201908

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.40. Tildrakizumab - ILUMETRI (CAP) - PSUSA/00010720/201909

Applicant: Almirall S.A

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.41. Tobramycin[70] - VANTOBRA (CAP) - PSUSA/00010370/201909

Applicant: PARI Pharma GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.42. Trabectedin - YONDELIS (CAP) - PSUSA/00003001/201909

Applicant: Pharma Mar, S.A.

PRAC Rapporteur: Hans Christian Siersted

Scope: Evaluation of a PSUSA procedure

[70] Nebuliser solution, centrally authorised product(s) only

16.1.43. Velmanase alfa - LAMZEDE (CAP) - PSUSA/00010677/201909

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.1.44. Vernakalant hydrochloride - BRINAVESS (CAP) - PSUSA/00003109/201908

Applicant: Correvio

PRAC Rapporteur: Menno van der Elst

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. Anagrelide - ANAGRELIDE MYLAN (CAP); XAGRID (CAP); NAP - PSUSA/00000208/201909

Applicants: Mylan S.A.S (Anagrelide Mylan), Shire Pharmaceuticals Ireland Limited (Xagrid), various

PRAC Rapporteur: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

16.2.2. Octocog alfa - ADVATE (CAP); HELIXATE NEXGEN[71]; KOGENATE BAYER (CAP); KOVALTRY (CAP); NAP - PSUSA/00002200/201908

Applicants: Baxter AG (Advate), Bayer AG (Helixate NexGen, Kogenate Bayer, Kovaltry), various

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.2.3. Trientine - CUFENCE (CAP); CUPRIOR (CAP); NAP - PSUSA/00010637/201909

Applicants: GMP-Orphan SA (Cuprior), Univar Solutions BV (Cufence), various

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.2.4. Zoledronic acid[72] - ZOLEDRONIC ACID HOSPIRA (CAP); ZOLEDRONIC ACID MEDAC (CAP); ZOMETA (CAP); NAP - PSUSA/00003149/201908

Applicants: Medac Gesellschaft fur klinische Spezialpraparate mbH (Zoledronic acid medac), Novartis Europharm Limited (Zometa), Pfizer Europe MA EEIG (Zoledronic acid Hospira), various

[71] European Commission (EC) decision on the marketing authorisation withdrawal granted on 19 December 2019
[72] Indicated for the treatment of cancer and fractures only

PRAC Rapporteur: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

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

16.3.1. Biperiden (NAP) – PSUSA/00000415/201908

Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.3.2. Conjugated estrogens (CE), medroxyprogesterone acetate (MPA) (NAP) – PSUSA/00000582/201908

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.3.3. Dermatophagoides pteronyssinus, dermatophagoides farina[73] [74] [75] (NAP) – PSUSA/00010582/201909

Applicant(s): various

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.3.4. Finasteride (NAP) – PSUSA/00001392/201908

Applicant(s): various

PRAC Lead: Annika Folin

Scope: Evaluation of a PSUSA procedure

16.3.5. Fluocinolone acetonide[76] (NAP) – PSUSA/00010224/201908

Applicant(s): various

PRAC Lead: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Evaluation of a PSUSA procedure

16.3.6. Human plasma protease C1 inhibitor[77] (NAP) – PSUSA/00010163/201908

Applicant(s): various

[73] Allergen for therapy
[74] For oromucosal use only
[75] Medicinal product(s) authorised via mutually recognition procedure and decentralised procedure only
[76] Intravitreal implant(s) in applicator only
[77] Nationally authorised product(s) only

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.3.7. Lercanidipine (NAP) – PSUSA/00001841/201908

Applicant(s): various

PRAC Lead: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

16.3.8. Modafinil (NAP) – PSUSA/00010242/201908

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.3.9. Paricalcitol (NAP) – PSUSA/00002316/201908

Applicant(s): various

PRAC Lead: Eva Segovia

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 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)[78]

17.1.1. Asfotase alfa – STRENSIQ (CAP) – EMEA/H/C/PSA/S/0050

Applicant: Alexion Europe SAS

PRAC Rapporteur: Rhea Fitzgerald

Scope: Substantial amendment to a protocol previously agreed in May 2016 (PSP/0032.1) for study ALX-HPP-501: an observational, longitudinal, prospective, long-term registry of patients with hypophosphatasia to collect information on the epidemiology of the disease, including clinical outcomes and quality of life, and to evaluate safety and effectiveness data in patients treated with Strensiq (asfotase alfa)

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

17.1.2. Rurioctocog alfa pegol – ADYNOVI (CAP) - EMEA/H/C/PSA/S/0045.1

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to PSA/S/0045.1 [substantial amendment to a protocol previously agreed in July 2019 (PSP/S/0077.1) for a study evaluating the long-term safety of Adynovi/Adynovate (rurioctocog alfa pegol) in adults and adolescents ≥12 years of age with haemophilia A] as per the request for supplementary information (RSI) adopted in January 2020

17.1.3. Turoctocog alfa pegol – ESPEROCT (CAP) - EMEA/H/C/PSP/S/0085.1

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Brigitte Keller Stanislawski

Scope: MAH's response to PSP/S/0085 [protocol for a multinational, prospective, open labelled, non-controlled, non-interventional post-authorisation study of turoctocog alfa pegol (N8-GP) including the polyethylene glycol (PEG) moiety during long-term routine prophylaxis and treatment of bleeding episodes in patients with haemophilia A] as per the request for supplementary information (RSI) adopted in January 2020

17.1.4. Volanesorsen – WAYLIVRA (CAP) - EMEA/H/C/PSP/S/0080.2

Applicant: Akcea Therapeutics Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: MAH's response to PSP/S/0080.1 [protocol for a multinational observational registry (WAY4001) of patients treated with volanesorsen to evaluate the safety on severe thrombocytopenia and bleeding in patients with familial chylomicronemia syndrome (FCS)] as per the request for supplementary information (RSI) adopted in January 2020

17.2. Protocols of PASS non-imposed in the marketing authorisation(s)[79]

17.2.1. Cangrelor - KENGREXAL (CAP) - EMEA/H/C/003773/MEA 002.2

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Ilaria Baldelli

Scope: MAH's response to MEA 002.1 [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 December 2019

17.2.2. Dibotermin alfa - INDUCTOS (CAP) - EMEA/H/C/000408/LEG 074.2

Applicant: Medtronic BioPharma B.V.

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

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to LEG 074.1 [detailed evaluation of the effectiveness of the current educational materials as requested in the conclusions of the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00001034/201709) adopted in April 2018, including the submission of a protocol for a survey amongst physicians to assess their knowledge and understanding of selected risks of Inductos (dibotermin alfa) in Europe] as per the request for supplementary information (RSI) adopted in November 2019

17.2.3. Emtricitabine, tenofovir disoproxil - TRUVADA (CAP) - EMEA/H/C/000594/MEA 047.4

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: MAH's response to MEA 047.3 [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) of adults and adolescents in Europe] as per the request for supplementary information (RSI) adopted in December 2019

17.2.4. Flutemetamol (^{18}F) - VIZAMYL (CAP) - EMEA/H/C/002557/MEA 002.3

Applicant: GE Healthcare AS

PRAC Rapporteur: Martin Huber

Scope: Amendment to a previously agreed protocol in December 2015 for study GE067-027 CPR in order to evaluate the effectiveness of Vizamyl (flutemetamol (^{18}F)) reader training in Europe and to assess the frequency of image classification errors in clinical practice

17.2.5. Hydrocortisone - PLENADREN (CAP) - EMEA/H/C/002185/MEA 009.2

Applicant: Shire Services BVBA

PRAC Rapporteur: Annika Folin

Scope: MAH's response to MEA 009.1 [amended protocol for study SHP617-400 (EU AIR) (0918-400): a non-interventional (PASS) registry study: A European multicentre, multi-country, post-authorisation observational study (registry) to monitor the safety of long-term treatment with Plenadren (hydrocortisone) and other glucocorticoid replacement therapies in patients with chronic adrenal insufficiency with a focus on intercurrent illness, adrenal crisis and serious adverse events] as per the request for supplementary information (RSI) adopted in November 2019

17.2.6. Inotersen - TEGSEDI (CAP) - EMEA/H/C/004782/MEA 001.3

Applicant: Akcea Therapeutics Ireland Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: MAH's response to MEA 001.2 [protocol for a long-term observational study to evaluate and further characterise the events of thrombocytopenia, glomerulonephritis and retinal toxicity/eye disease related to vitamin A deficiency when Tegsedi (inotersen) is

prescribed in normal clinical practice, consisting of a protocol for a cohort of inotersen-exposed patients (TEG4001) and a protocol for an external comparator cohort (TEG4003)] as per the request for supplementary information (RSI) adopted in November 2019

17.2.7. Inotersen - TEGSEDI (CAP) - EMEA/H/C/004782/MEA 002.3

Applicant: Akcea Therapeutics Ireland Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: MAH's response to MEA 002.2 [protocol for study TEG4002: a retrospective chart review for evaluating adherence to and effectiveness of the proposed platelet monitoring schedule, proposed cut-off points, dose adaptation, and initiation of corticosteroids on thrombocyte recovery] as per the request for supplementary information (RSI) adopted in November 2019

17.2.8. Interferon beta-1a - AVONEX (CAP) - EMEA/H/C/000102/MEA 088

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Protocol for a joint PASS for study 2600153 (INFORM): an observational study regarding interferon beta exposure in the second and third trimesters of pregnancy - a register-based drug utilisation study (DUS) in Finland and Sweden

17.2.9. Interferon beta-1a - REBIF (CAP) - EMEA/H/C/000136/MEA 045

Applicant: Merck Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Protocol for a joint PASS for study 2600153 (INFORM): an observational study regarding interferon beta exposure in the second and third trimesters of pregnancy - a register-based drug utilisation study (DUS) in Finland and Sweden

17.2.10. Interferon beta-1b - BETAFERON (CAP) - EMEA/H/C/000081/MEA 025

Applicant: Bayer AG

PRAC Rapporteur: Martin Huber

Scope: Protocol for a joint PASS for study 2600153 (INFORM): an observational study regarding interferon beta exposure in the second and third trimesters of pregnancy - a register-based drug utilisation study (DUS) in Finland and Sweden

17.2.11. Interferon beta-1b - EXTAVIA (CAP) - EMEA/H/C/000933/MEA 023

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Martin Huber

Scope: Protocol for a joint PASS for study 2600153 (INFORM): an observational study regarding interferon beta exposure in the second and third trimesters of pregnancy - a register-based drug utilisation study (DUS) in Finland and Sweden

17.2.12. Patisiran - ONPATTRO (CAP) - EMEA/H/C/004699/MEA 002.3

Applicant: Alnylam Netherlands B.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: MAH's response to MEA 002.2 [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 December 2019

17.2.13. Peginterferon beta-1a - PLEGRIDY (CAP) - EMEA/H/C/002827/MEA 010

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Protocol for a joint PASS for study 2600153 (INFORM): an observational study regarding interferon beta exposure in the second and third trimesters of pregnancy - a register-based drug utilisation study (DUS) in Finland and Sweden

17.2.14. Romosozumab - EVENITY (CAP) - EMEA/H/C/004465/MEA 001

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Adrien Inoubli

Scope: Protocol for study OP0005: a European non-interventional PASS to study the adherence to the risk minimisation measures (RMMs) in the product information by estimating the compliance with contraindications and target indication(s) amongst incident romosozumab users, and analysing the utilisation pattern using the EU-adverse drug reactions (EU-ADR) Alliance [final study results expected in March 2026] (from initial opinion/marketing authorisation)

17.2.15. Romosozumab - EVENITY (CAP) - EMEA/H/C/004465/MEA 002

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Adrien Inoubli

Scope: Protocol for study OP0004: a European non-interventional PASS to evaluate potential differences in terms of serious cardiovascular adverse events between romosozumab and currently available therapies used in comparable patients in real-world conditions using the EU-adverse drug reactions (EU-ADR) Alliance [final study results expected in December 2026] (from initial opinion/marketing authorisation)

17.2.16. Romosozumab - EVENITY (CAP) - EMEA/H/C/004465/MEA 003

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Adrien Inoubli

Scope: Protocol for study OP0006: a European non-interventional PASS to evaluate potential differences in terms of serious infection between romosozumab and currently available therapies used in comparable patients in real-world conditions using the EU-

adverse drug reactions (EU-ADR) Alliance [final study results expected in December 2024] (from initial opinion/marketing authorisation)

17.2.17. Ropeginterferon alfa-2b - BESREMI (CAP) - EMEA/H/C/004128/MEA 001.2

Applicant: AOP Orphan Pharmaceuticals AG

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: MAH's response to MEA 001.1 [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 December 2019

17.2.18. Sotagliflozin - ZYNQUISTA (CAP) - EMEA/H/C/004889/MEA 004.1

Applicant: Navigant Germany GmbH

PRAC Rapporteur: Martin Huber

Scope: MAH's response to MEA 004 [protocol for a nested, case-control study to evaluate the risk of malignancies (bladder, renal, breast, Leydig cell, pancreatic, thyroid and prostate cancers) in adult patients with type 1 diabetes mellitus (T1DM) using sotagliflozin in existing healthcare databases in Europe and in the United States [final clinical study report (CSR) expected in April 2030]] as per the request for supplementary information (RSI) adopted in November 2019

17.3. Results of PASS imposed in the marketing authorisation(s)[80]

None

17.4. Results of PASS non-imposed in the marketing authorisation(s)[81]

17.4.1. Agalsidase beta - FABRAZYME (CAP) - EMEA/H/C/000370/II/0113

Applicant: Genzyme Europe BV

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Submission of the final report from study AGALSC08994 (listed as a category 3 study in the RMP): a post-authorisation study on Fabrazyme (agalsidase beta) home infusion educational materials effectiveness evaluation: a survey of healthcare providers and patients/caregivers. The RMP (version 2.0) is updated accordingly. The RMP is also updated in line with revision 2 of the guidance on the format of RMP in the EU (template) and with information on study AGAL02603: a multicentre, multinational study of the effects of Fabrazyme (agalsidase beta) treatment on lactation and infants and study AGAL19211: the Fabry registry/pregnancy sub-registry

[80] In accordance with Article 107p-q of Directive 2001/83/EC
[81] 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

17.4.2. Blinatumomab - BLINCYTO (CAP) - EMEA/H/C/003731/II/0034/G, Orphan

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Eva Jirsová

Scope: Submission of the final reports from studies 20150163 and 20150228 (listed as category 3 studies in the RMP) assessing the effectiveness of the additional risk minimisation measures (aRMM) for healthcare professionals (study 20150163) and patients/caregivers (study 20150228)

17.4.3. Etanercept - ENBREL (CAP) - EMEA/H/C/000262/WS1653/0230; LIFMIOR (CAP) - EMEA/H/C/004167/WS1653/0024

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Eva Segovia

Scope: Submission of the second 5-year report from the British Society for Rheumatology Biologics Register (BSRBR) also referred as study B1801309 (listed as a category 3 study in the RMP). This is a prospective observational cohort study which investigates the long-term outcomes of patients with rheumatoid arthritis treated with etanercept with particular reference to safety

17.4.4. 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

17.4.5. 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

17.4.6. 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

17.4.7. 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

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

17.5.1. Alemtuzumab - LEMTRADA (CAP) - EMEA/H/C/003718/MEA 007.9

Applicant: Sanofi Belgium

PRAC Rapporteur: Anette Kirstine Stark

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

17.5.2. Etanercept - BENEPALI (CAP) - EMEA/H/C/004007/MEA 002.3

Applicant: Samsung Bioepis NL B.V.

PRAC Rapporteur: Eva Segovia

Scope: Fourth annual interim report from an established nationwide register (British Society for Rheumatology Rheumatoid Arthritis Register (BSRBR-RA)) for patients with rheumatological disorders treated with biologic agents, designed as a national prospective study whose primary purpose is to assess long-term toxicity from the use of these agents in routine practice [final report expected in 2027]

17.5.3. Etanercept - BENEPALI (CAP) - EMEA/H/C/004007/MEA 003.3

Applicant: Samsung Bioepis NL B.V.

PRAC Rapporteur: Eva Segovia

Scope: Fourth annual interim report from an established nationwide register (Rheumatoide Arthritis: Beobachtung der Biologika-Therapie (RABBIT)) for patients with rheumatological

disorders treated with biologic agents, designed as a national prospective study whose primary purpose is to assess long-term toxicity from the use of these agents in routine practice [final report expected in 2027]

17.5.4. Etanercept - BENEPALI (CAP) - EMEA/H/C/004007/MEA 004.3

Applicant: Samsung Bioepis NL B.V.

PRAC Rapporteur: Eva Segovia

Scope: Fourth annual interim report for study from ARTIS (Anti-Rheumatic Treatment in Sweden) register: a national prospective, observational, uncontrolled cohort study evaluating the risk of selected adverse events (AEs) in rheumatoid arthritis (RA), juvenile idiopathic arthritis, and other rheumatic disease patients treated with etanercept [final report expected in 2027]

17.5.5. Etanercept - BENEPALI (CAP) - EMEA/H/C/004007/MEA 005.3

Applicant: Samsung Bioepis NL B.V.

PRAC Rapporteur: Eva Segovia

Scope: Fourth annual interim report for study from BADBIR (British Association of Dermatologists Biologic Interventions Register) register: a national prospective, observational, uncontrolled cohort study evaluating the risk of selected adverse events (AEs) in rheumatoid arthritis (RA), juvenile idiopathic arthritis, and other rheumatic disease patients treated with etanercept [final report expected in 2027]

17.5.6. Golimumab - SIMPONI (CAP) - EMEA/H/C/000992/MEA 033.3

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Second annual interim report for study MK-8259-050 (listed as a category 3 study in the RMP): an observational PASS for golimumab in treatment of poly-articular juvenile idiopathic arthritis (pJIA) using the German Biologics JIA registry (BiKeR)

17.5.7. Lonoctocog alfa - AFSTYLA (CAP) - EMEA/H/C/004075/MEA 002.1

Applicant: CSL Behring GmbH

PRAC Rapporteur: Sonja Hrabcik

Scope: Progress report for study CSL627_3001: a multicentre, open-label, phase 3 extension study which will investigate the safety and efficacy of recombinant factor VIII (rVIII)-single chain (CSL627) for prophylaxis and on-demand treatment of bleeding episodes in a total of at least 250 previously treated patients (PTP) with severe congenital haemophilia A

17.5.8. Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/MEA 008.7

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: MAH's response to MEA 008.6 [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] as per the request for supplementary information (RSI) adopted in December 2019

17.5.9. Rivastigmine - EXELON (CAP) - EMEA/H/C/000169/MEA 036.5

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ghania Chamouni

Scope: Annual report (covering the period from 01 February 2018 to 31 January 2019) of the drug utilisation study (DUS) on the effectiveness of risk minimisation measures (RMM) for multiple patch use

17.5.10. Rivastigmine - PROMETAX (CAP) - EMEA/H/C/000255/MEA 037.5

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ghania Chamouni

Scope: Annual report (covering the period from 01 February 2018 to 31 January 2019) of the drug utilisation study (DUS) on the effectiveness of risk minimisation measures (RMM) for multiple patch use

17.5.11. Sirolimus - RAPAMUNE (CAP) - EMEA/H/C/000273/MEA 054.2

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Interim analysis study report for study B1741224: a non-interventional observational population-based cohort study to monitor the safety and effectiveness of sirolimus in patients with sporadic lymphangioleiomyomatosis (S-LAM)

17.6. Others

17.6.1. Deferasirox - EXJADE (CAP) - EMEA/H/C/000670/MEA 075.1

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ghania Chamouni

Scope: MAH's response to MEA 075 [interim study results for study CICL670F2202 (CALYPSO): a randomized, open-label, multicentre, two arm, phase 2 study allowing to evaluate the safety of deferasirox granules in paediatric patients with iron overload [final clinical study report (CSR) expected in June 2021] (from X/54)] as per the request for supplementary information (RSI) adopted in November 2019

Action: For adoption of advice to CHMP

17.6.2. Emicizumab - HEMLIBRA (CAP) - EMEA/H/C/004406/MEA 005

Applicant: Roche Registration GmbH

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of the MAH's assessment of a letter to the editor in the New England Journal of Medicine (NEJM) entitled 'deaths associated with emicizumab in patients with hemophilia A'[82] published in November 2019

17.7. New Scientific Advice

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

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. Afamelanotide - SCENESSE (CAP) - EMEA/H/C/002548/S/0032 (without RMP)

Applicant: Clinuvel Europe Limited

PRAC Rapporteur: Martin Huber

Scope: Annual reassessment of the marketing authorisation

18.1.2. Cholic acid - ORPHACOL (CAP) - EMEA/H/C/001250/S/0033 (without RMP)

Applicant: Laboratoires CTRS

PRAC Rapporteur: Sofia Trantza

Scope: Annual reassessment of the marketing authorisation

[82] N Engl J Med 2019; 381: 1878-1879: DOI 10.1056/nejmC1909742

18.1.3. Susoctocog alfa - OBIZUR (CAP) - EMEA/H/C/002792/S/0028 (without RMP)

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Annual reassessment of the marketing authorisation

18.1.4. Tafamidis - VYNDAQEL (CAP) - EMEA/H/C/002294/S/0055 (without RMP)

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Ghania Chamouni

Scope: Annual reassessment of the marketing authorisation

18.2. Conditional renewals of the marketing authorisation

18.2.1. Ataluren - TRANSLARNA (CAP) - EMEA/H/C/002720/R/0057 (without RMP)

Applicant: PTC Therapeutics International Limited

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Conditional renewal of the marketing authorisation

18.3. Renewals of the marketing authorisation

18.3.1. Aripiprazole - ARIPIPRAZOLE SANDOZ (CAP) - EMEA/H/C/004008/R/0014 (without RMP)

Applicant: Sandoz GmbH

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: 5-year renewal of the marketing authorisation

18.3.2. Carfilzomib - KYPROLIS (CAP) - EMEA/H/C/003790/R/0044 (without RMP)

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: 5-year renewal of the marketing authorisation

18.3.3. Cobimetinib - COTELLIC (CAP) - EMEA/H/C/003960/R/0019 (without RMP)

Applicant: Roche Registration GmbH

PRAC Rapporteur: Menno van der Elst

Scope: 5-year renewal of the marketing authorisation

18.3.4. Everolimus - VOTUBIA (CAP) - EMEA/H/C/002311/R/0065 (without RMP)

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Martin Huber

Scope: 5-year renewal of the marketing authorisation

18.3.5. Glycerol phenylbutyrate - RAVICTI (CAP) - EMEA/H/C/003822/R/0034 (without RMP)

Applicant: Immedica Pharma AB

PRAC Rapporteur: Ilaria Baldelli

Scope: 5-year renewal of the marketing authorisation

18.3.6. Mepolizumab - NUCALA (CAP) - EMEA/H/C/003860/R/0031 (with RMP)

Applicant: GlaxoSmithKline Trading Services Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: 5-year renewal of the marketing authorisation

18.3.7. Pemetrexed - PEMETREXED MEDAC (CAP) - EMEA/H/C/003905/R/0008 (with RMP)

Applicant: medac Gesellschaft fur klinische Spezialpraparate mbH

PRAC Rapporteur: Ghania Chamouni

Scope: 5-year renewal of the marketing authorisation

18.3.8. Pemetrexed - PEMETREXED SANDOZ (CAP) - EMEA/H/C/004011/R/0008 (without RMP)

Applicant: Sandoz GmbH

PRAC Rapporteur: Ghania Chamouni

Scope: 5-year renewal of the marketing authorisation

18.3.9. Phenylephrine, ketorolac - OMIDRIA (CAP) - EMEA/H/C/003702/R/0015 (with RMP)

Applicant: Omeros Ireland Limited

PRAC Rapporteur: Jan Neuhauser

Scope: 5-year renewal of the marketing authorisation

18.3.10. Pregabalin - PREGABALIN ACCORD (CAP) - EMEA/H/C/004024/R/0015 (with RMP)

Applicant: Accord Healthcare S.L.U.

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: 5-year renewal of the marketing authorisation

18.3.11. Pregabalin - PREGABALIN SANDOZ (CAP) - EMEA/H/C/004010/R/0012 (with RMP)

Applicant: Sandoz GmbH

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: 5-year renewal of the marketing authorisation

18.3.12. Pregabalin - PREGABALIN SANDOZ GMBH (CAP) - EMEA/H/C/004070/R/0013 (with RMP)

Applicant: Sandoz GmbH

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: 5-year renewal of the marketing authorisation

18.3.13. Sacubitril, valsartan - ENTRESTO (CAP) - EMEA/H/C/004062/R/0031 (without RMP)

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Anette Kirstine Stark

Scope: 5-year renewal of the marketing authorisation

18.3.14. Tasimelteon - HETLIOZ (CAP) - EMEA/H/C/003870/R/0018 (without RMP)

Applicant: Vanda Pharmaceuticals Germany GmbH

PRAC Rapporteur: Adam Przybylkowski

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 14-17 April 2020 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
Sonja Hrabcik	Alternate	Austria	No interests declared	Full involvement
Jean-Michel Dogné	Member	Belgium	No interests declared	Full involvement
Laurence de Fays	Alternate	Belgium	No restrictions applicable to this meeting	Full involvement
Maria Popova-Kiradjieva	Member	Bulgaria	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Nikica Mirošević Skvrce	Member	Croatia	No interests declared	Full involvement
Željana Margan Koletić	Alternate	Croatia	No interests declared	Full involvement
Helena Panayiotopoulou	Member	Cyprus	No interests declared	Full involvement
Panagiotis Psaras	Alternate	Cyprus	No interests declared	Full involvement
Eva Jirsová	Member	Czech Republic	No interests declared	Full involvement
Jana Lukacisinova	Alternate	Czech Republic	No interests declared	Full involvement
Anette Stark	Member	Denmark	No interests declared	Full involvement
Hans Christian Siersted	Alternate	Denmark	No participation in discussion, final deliberations and voting on:	16.1.24 - Mepolizumab - NUCALA (CAP) 18.3.6 - Mepolizumab - NUCALA (CAP)
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 interests declared	Full involvement
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 restrictions applicable to this meeting	Full involvement
Julia Pallos	Member	Hungary	No participation in final	4.3.5 - Ibuprofen – PEDEA (CAP);

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			deliberations and voting on:	NAP; ketoprofen (NAP) and fixed-dose combinations: chlorphenamine, ibuprofen, phenylephrine (NAP); dimenhydrinate, ibuprofen, caffeine (NAP); ibuprofen, ascorbic acid (NAP); ibuprofen, caffeine (NAP); ibuprofen, codeine (NAP); ibuprofen, hydrocodone (NAP); ibuprofen, paracetamol (NAP); ibuprofen, phenylephrine (NAP); ibuprofen, pseudoephedrine (NAP); ketoprofen, omeprazole (NAP), ketoprofen, sucralfate (NAP)
Guðrún Stefánsdóttir	Member	Iceland	No participation in discussion, final deliberations and voting on:	4.3.8 - Tumour necrosis factor (TNF) inhibitors 6.1.4 -. Denosumab - PROLIA (CAP) 15.3.10 - Carfilzomib -

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				KYPROLIS (CAP) 16.1.30 - Panitumumab - VECTIBIX (CAP) 17.4.2 - Blinatumomab - BLINCYTO (CAP)
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
Ruta Kerpauskiene	Alternate	Lithuania	No interests declared	Full involvement
John Joseph Borg	Member	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 and voting on:	4.3.5 - Ibuprofen – PEDEA (CAP); NAP; ketoprofen (NAP) and fixed-dose combinations: chlorphenamine, ibuprofen, phenylephrine (NAP); dimenhydrinate, ibuprofen, caffeine (NAP); ibuprofen,

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				ascorbic acid (NAP); ibuprofen, caffeine (NAP); ibuprofen, codeine (NAP); ibuprofen, hydrocodone (NAP); ibuprofen, paracetamol (NAP); ibuprofen, phenylephrine (NAP); ibuprofen, pseudoephedrine (NAP); ketoprofen, omeprazole (NAP), ketoprofen, sucralfate (NAP) 15.3.36 - Rivaroxaban - XARELTO (CAP) 16.1.35 - Rivaroxaban - XARELTO (CAP), 16.2.2 -. Octocog alfa - ADVATE (CAP); HELIXATE NEXGEN ; KOGENATE BAYER (CAP); KOVALTRY (CAP); NAP 17.2.10 - Interferon beta-1b - BETAFERON (CAP)

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Karen Pernille Harg	Alternate	Norway	No interests declared	Full involvement
Adam Przybylkowski	Member	Poland	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
Alexandra - Maria Spurni	Alternate	Romania	No interests declared	Full involvement
Michal Radik	Member	Slovakia	No restrictions applicable to this meeting	Full involvement
Marek Juracka	Alternate	Slovakia	No interests declared	Full involvement
Jasmina Klopcic	Alternate	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
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
Livia Puljak	Member	Independent scientific expert	No interests declared	Full involvement
Stefan Weiler	Member	Independent scientific expert	No restrictions	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			applicable to this meeting	
Raymond Anderson	Member	Healthcare Professionals' Representative	No interests declared	Full involvement
Roberto Frontini	Alternate	Healthcare Professionals' Representative	No restrictions applicable to this meeting	Full involvement
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
Martine Sabbe	Expert - via telephone*	Belgium	No interests declared	Full involvement
Sophie Goethals	Expert - via telephone*	Belgium	No restrictions applicable to this meeting	Full involvement
Ivana Kosier	Expert - via telephone*	Croatia	No interests declared	Full involvement
Barbara Kovačić	Expert - via telephone*	Croatia	No interests declared	Full involvement
Petra Vacková	Expert - via telephone*	Czech Republic	No interests declared	Full involvement
Jitka Vokrouhlická	Expert - via telephone*	Czech Republic	No interests declared	Full involvement
Kirsten Egebjerg Juul	Expert - via telephone*	Denmark	No interests declared	Full involvement
Karin Susanne Erneholm	Expert - via telephone*	Denmark	No restrictions applicable to this meeting	Full involvement
Helle Esbjørn Kristensen	Expert - via telephone*	Denmark	No interests declared	Full involvement
Louise Hesselbjerg Rasmussen	Expert - via telephone*	Denmark	No interests declared	Full involvement
Marian Hjortlund Allon	Expert - via telephone*	Denmark	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Peter Horskjær Rose	Expert - via telephone*	Denmark	No interests declared	Full involvement
Pernille Lynge Gammelgaard	Expert - via telephone*	Denmark	No interests declared	Full involvement
Astrid Munch Hestbæk	Expert - via telephone*	Denmark	No restrictions applicable to this meeting	Full involvement
Emma Louise Nautrup Ravn Stadsbjerg	Expert - via telephone*	Denmark	No interests declared	Full involvement
Helle Gerda Olsen	Expert - via telephone*	Denmark	No interests declared	Full involvement
Caroline Marie Voss	Expert - via telephone*	Denmark	No interests declared	Full involvement
Päivi Susanna Worsøe	Expert - via telephone*	Denmark	No restrictions applicable to this meeting	Full involvement
Josiane Uwera	Expert - via telephone*	Denmark	No restrictions applicable to this meeting	Full involvement
Krõõt Aab	Expert - via telephone*	Estonia	No interests declared	Full involvement
Caroline Auriche	Expert - via telephone*	France	No interests declared	Full involvement
Cecile Choquet	Expert - via telephone*	France	No restrictions applicable to this meeting	Full involvement
Emilie Patras-De-Campaigno	Expert – via telephone*	France	No interests declared	Full involvement
Dennis Lex	Expert – via telephone*	Germany	No restrictions applicable to this meeting	Full involvement
Jayne Crowe	Expert - via telephone*	Ireland	No interests declared	Full involvement
Kate Browne	Expert - via telephone*	Ireland	No interests declared	Full involvement
Serena Marchetti	Expert - via telephone*	Netherlands	No restrictions	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			applicable to this meeting	
Eva Malikova	Expert - via telephone*	Slovakia	No interests declared	Full involvement
Ana Fernandez Dueñas	Expert - via telephone*	Spain	No interests declared	Full involvement
Charlotte Backman	Expert – via telephone*	Sweden	No interests declared	Full involvement
A representative from the European Commission attended the meeting				
Meeting run with support from relevant EMA staff				

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

20. Annex III - List of acronyms and abbreviations

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

21. Explanatory notes

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

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

(Items 2 and 3 of the PRAC minutes)

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