03 October 2019
EMA/PRAC/60629/2020
Inspections, Human Medicines Pharmacovigilance and Committees Division

Pharmacovigilance Risk Assessment Committee (PRAC)

Minutes of the meeting on 02-05 September 2019

Chair: Sabine Straus – Vice-Chair: Martin Huber

Health and safety information

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

Disclaimers

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

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

Note on access to documents

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

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1. Introduction

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

The Chairperson opened the 02 – 05 September 2019 meeting by welcoming all participants.

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

Discussions, deliberations and voting took place in full respect of the restricted involvement of Committee members and experts in line with the relevant provisions the Rules of Procedure (EMA/PRAC/567515/2012 Rev.1). All decisions taken at this meeting were made in the presence of a quorum of members (i.e. 24 or more members were present in the room). All decisions, recommendations and advice were agreed unanimously, unless otherwise specified.

1.2. Agenda of the meeting on 02 - 05 September 2019

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

1.3. Minutes of the previous meeting on 08 – 11 July 2019

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

Post-meeting note: the PRAC minutes of the meeting held on 08 – 11 July 2019 were published on the EMA website on 19 December 2019 (EMA/PRAC/692665/2019).

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

3.1.1. Ingenol mebutate - PICATO (CAP) - 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

The European Commission (EC) sent a letter of notification dated 3 September 2019 triggering a procedure under Article 20 of Regulation (EC) No 726/2004 for the review of Picato (ingenol mebutate). Picato is a centrally authorised medicine containing ingenol mebutate indicated for the cutaneous treatment of non-hyperkeratotic, non-hypertrophic actinic keratosis (AK) in adults.

At the time of the initial marketing authorisation (MA) in 2012, the risk of AK progressing to squamous cell carcinoma (SCC) was reflected in the RMP as an important potential risk and the MAH was requested to conduct a phase 4 study assessing the long term cumulative incidence of SCC after treatment with ingenol mebutate gel 0.015% or imiquimod cream 5% for multiple AKs on face and scalp (study LP0041-63[1]). In 2017, the product information of Picato (ingenol mebutate) was updated to reflect an excess of keratoacanthoma (KA) following the results of study LP0105-1020[2] comparing ingenol mebutate 0.06% to placebo. In parallel, an imbalance in the incidence of SCC between the ingenol mebutate and imiquimod arms was observed in the preliminary results of study LP0041-63. In addition, as part of the recommendation for periodic safety update report single assessment (PSUSA) procedure (PSUSA/00010035/201807) adopted in February 2019, the PRAC concluded there was a reasonable possibility that ingenol esters may be tumour promoting in some patients. The important potential risk of AK to SCC progression was updated to 'new skin tumours in treatment areas' and two safety studies[3] [4] were imposed to characterise the risk and provide reassurance on long term safety. In 2019, the CHMP Scientific Advice Working Party (SAWP) reviewed the protocol for the recently imposed interventional study, and considered that a substantially larger study than proposed by the MAH would be required to generate meaningful data regarding the incidence of treatment area skin malignancy. This led to concerns on the conduct and finalisation of the study in a reasonable timeframe.

[1] 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
[2] Efficacy and safety of ingenol mebutate gel 0.06% when applied once daily for 2, 3 or 4 consecutive days to a treatment area of approximately 250 cm^2 on trunk and extremities in subjects with AK
[3] A randomised, double-blind trial in patients treated with ingenol mebutate compared with vehicle control, over at least 18 months of follow-up to further investigate the incidence of treatment area skin malignancy
[4] A cohort non-interventional PASS comparing patients treated with ingenol mebutate with patients exposed to other AK treatments to investigate the rate of skin malignancies

During the evaluation of the latest PSUSA for Picato (ingenol mebutate) (PSUSA/00010035/201901) a new case of SCC was assessed in addition to the known safety profile of ingenol mebutate. See under 6.1.10. In light of the conclusion of the PSUSA procedure regarding the potential risk of new skin tumour in the treatment area, and the difficulty to generate appropriate data to address the uncertainty about this important risk, the PRAC concluded a review of all available data (including from ongoing studies) and its impact on the benefit-risk balance of Picato (ingenol mebutate) in its authorised indication was necessary.

Therefore, the EC requested the EMA to give its opinion on whether the marketing authorisation(s) for Picato (ingenol mebutate) should be maintained, varied, suspended or revoked. In addition, the EC requested the EMA to give its opinion, as soon as possible, as to whether provisional measures were necessary to ensure the safe and effective use of the medicinal product.

Discussion

The PRAC noted the notification letter from the EC and appointed Adam Przybylkowski as Rapporteur and Adrien Inoubli as Co-Rapporteur for the procedure.

The PRAC discussed a list of questions (LoQ) to be addressed during the procedure together with a timetable for conducting the review. In addition, the PRAC reviewed the need for provisional measures to protect public health. The PRAC also discussed the need for a public hearing.

Summary of recommendation(s)/conclusions

- The Committee adopted a LoQ to the MAH (EMA/PRAC/484308/2019) and a timetable for the procedure (EMA/PRAC/484544/2019).
- The PRAC also considered the need for provisional measures to ensure the safe and effective use of the medicinal product while the review is ongoing. Taking into account the conclusion and recommendation of the PSUSA procedure (PSUSA/00010035/201901), the PRAC agreed that the latter was sufficient and that no additional measures were needed at this stage.
- The PRAC also discussed the option to conduct a public hearing in the context of the current procedure according to the pre-defined criteria set out in the rules of procedure[5] (EMA/363479/2015). It was agreed by the Committee that at this stage of the procedure, in light of the currently available data and the need to determine the appropriate approach to stakeholder engagement, a public hearing would not be appropriate. The PRAC can reconsider this at a later stage of the procedure as needed.

See EMA press release (EMA/484093/2019) entitled 'Review of data on skin cancer with Picato'.

3.2. Ongoing procedures

3.2.1. Estradiol[6] (NAP) - EMEA/H/A-31/1482

Applicant(s): various

[5] Rules of procedure on the organisation and conduct of public hearings at the PRAC
[6] 0.01%, topical use only

PRAC Rapporteur: Eva Jirsova; PRAC Co-rapporteur: Menno van der Elst

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

Background

A referral procedure under Article 31 of Directive 2001/83/EC is ongoing for estradiol-containing medicines (0.01% w/w) for topical use, reviewing data showing plasma levels of estradiol similar to those associated with the use of estradiol in systemic hormone replacement therapy (HRT). This follows the partial annulment of the scientific conclusions reached in 2014 in a previous EU review based on procedural grounds and the concerns that the safety risks for those medicinal products are no longer addressed adequately and that patients are put at risk. Therefore, a further review was initiated in April 2019 to review the data assessed in the previous referral procedure for medicinal products containing estradiol for topical use as well as any data that would have become available since 2014. For further background, see PRAC minutes April 2019 and PRAC minutes July 2019.

Summary of recommendation(s)/conclusions

- The PRAC adopted the list of experts for the ad-hoc expert group meeting organised on 17 September 2019.

3.2.2. Tofacitinib - XELJANZ (CAP) - EMEA/H/A-20/1485

Applicant(s): Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan; PRAC Co-rapporteur: Amelia Cupelli

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 is ongoing for Xeljanz (tofacitinib) following an increased risk of pulmonary embolism (PE) and overall mortality arising from study A3921133[7] in patients with cardiovascular risk factors treated for rheumatoid arthritis with tofacitinib 10 mg twice daily (BID). The review assesses the impact of the risk of thromboembolic events, in particular PE and deep venous thrombosis (DVT) as well as increased mortality in the context of the benefit-risk balance of the medicinal product in the authorised indications and doses. In May 2019, the PRAC recommended, until a thorough review is finalised, provisional measures to amend the product information. For further background, see PRAC minutes May 2019.

Summary of recommendation(s)/conclusions

- The PRAC discussed the assessment reports produced by the Rapporteurs.
- The PRAC adopted a list of outstanding issues (LoOI), to be addressed by the MAHs in accordance with a revised timetable (EMA/PRAC/269913/2019 – Rev. 1).

[7] A phase 3B/4 randomised safety endpoint study of 2 doses of tofacitinib (tofacitinib 5 mg twice daily (BID) and tofacitinib 10 mg BID) in comparison to a tumour necrosis factor (TNF) inhibitor in subjects with rheumatoid arthritis

- The PRAC adopted a list of questions (LoQ) for an ad-hoc expert group meeting organised on 10 October 2019.
- PRAC members were invited to nominate experts to participate in the expert group meeting until 15 September 2019.

3.3. Procedures for finalisation

None

3.4. Re-examination procedures[8]

None

3.5. Others

None

4. Signals assessment and prioritisation[9]

4.1. New signals detected from EU spontaneous reporting systems

See also Annex I 14.1.

4.1.1. Durvalumab – IMFINZI (CAP)

Applicant(s): AstraZeneca AB

PRAC Rapporteur: David Olsen

Scope: Signal of myasthenia gravis

EPITT 19451 – New signal

Lead Member State(s): NO

Background

Durvalumab is a fully human, immunoglobulin G1 kappa (IgG1 κ) monoclonal antibody that selectively blocks the interaction of programmed death-ligand 1 (PD-L1) with programmed cell death protein 1 (PD-1) and cluster of differentiation 80 (CD80). Imfinzi (durvalumab) is a centrally authorised product indicated for the treatment of locally advanced, unresectable non-small cell lung cancer (NSCLC) in adults whose tumours express PD-L1 on $\geq$ 1% of tumour cells and whose disease has not progressed following platinum-based chemoradiation therapy.

The exposure for Imfinzi (durvalumab) is estimated to have been more than 10,163 patient-years worldwide, in the period from first authorisation in 2018 to 2019.

[8] Re-examination of PRAC recommendation under Article 32 of Directive 2001/83/EC
[9] 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

During routine signal detection activities, a signal of myasthenia gravis was identified by the EMA, based on 11 cases retrieved from EudraVigilance. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

Having considered the evidence from the case reports in EudraVigilance and in the literature, the PRAC agreed that a causal association between durvalumab and myasthenia gravis is plausible, considering the known association of immune-checkpoint inhibitors with a range of immune-related adverse events including neurological toxicities.

Summary of recommendation(s)

- The MAH for Imfinzi (durvalumab) should submit to the EMA, within 30 days, comments on the proposal agreed by the PRAC regarding amendments of the product information.

4.1.2. Immune checkpoint inhibitors: atezolizumab – TECENTRIQ (CAP); avelumab-BAVENCIO (CAP); cemiplimab – LIBTAYO (CAP); durvalumab – IMFINZI (CAP); ipilimumab – YERVOY (CAP); nivolumab – OPDIVO (CAP); pembrolizumab - KEYTRUDA (CAP)

Applicant(s): AstraZeneca AB (Imfinzi), Bristol-Myers Squibb Pharma (Opdivo), Bristol-Myers Squibb Pharma EEIG (Yervoy), Merck Europe B.V. (Bavencio), Merck Sharp & Dohme B.V. (Keytruda), Regeneron Ireland U.C. (Libtayo), Roche Registration GmbH (Tecentriq)

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Signal of tuberculosis

EPITT 19464 – New signal

Lead Member State(s): DK, NL, NO, PT

Background

Atezolizumab, avelumab, cemiplimab, durvalumab, ipilimumab, nivolumab and pembrolizumab are centrally-authorised medicines containing immune checkpoint inhibitors. Tecentriq (atezolizumab) is indicated for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma, in combination with bevacizumab, paclitaxel and carboplatin for the first-line treatment of adult patients with metastatic non-squamous non-small cell lung cancer (NSCLC) and as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic NSCLC, subject to certain conditions. Bavencio (avelumab) indicated for the treatment of adult patients with metastatic Merkel cell carcinoma (MCC). Libtayo (cemiplimab) is indicated for the treatment of adult patients with metastatic or locally advanced cutaneous squamous cell carcinoma (SCC), subject to certain conditions. Imfinzi (durvalumab) is indicated for the treatment of locally advanced, unresectable NSCLC in adults whose tumours express PD-L1 on $\geq$ 1% of tumour cells and whose disease has not progressed following platinum-based chemoradiation therapy. Yervoy (ipilimumab) is indicated as monotherapy for the treatment of advanced (unresectable or metastatic) melanoma and in combination with nivolumab is indicated for the treatment of advanced (unresectable or metastatic) melanoma and for the first-line treatment of adult patients with intermediate/poor-risk advanced renal cell carcinoma. Opdivo (nivolumab) is indicated as monotherapy or in combination with ipilimumab for the treatment of advanced (unresectable or metastatic) melanoma, for the adjuvant treatment of adults with melanoma with involvement of lymph nodes or metastatic disease, for the treatment of locally advanced

or metastatic NSCLC and advanced renal cell carcinoma, for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL), for the treatment of recurrent or metastatic squamous cell cancer of the head and neck and for the treatment of locally advanced unresectable or metastatic urothelial carcinoma, subject to certain conditions. Keytruda (pembrolizumab) is indicated for the treatment of advanced (unresectable or metastatic) melanoma, stage III melanoma and lymph node involvement in patients who have undergone complete resection, first-line treatment of metastatic NSCLC in adults whose tumours express PD-L1 with a ≥ 50% tumour proportion score (TPS) or metastatic non-squamous NSCLC in adults whose tumours have no endothelial growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) positive mutations. It is also indicated for the treatment of relapsed or refractory cHL, locally advanced or metastatic urothelial carcinoma and recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) in adults whose tumours express PD-L1 with a ≥ 50% TPS, subject to certain conditions.

The exposure for Tecentriq (atezolizumab) is estimated to have been more than 46,699 patients worldwide, in the period from first authorisation in 2016 to 2019. The exposure for Bavencio (avelumab) is estimated to have been more than 1,499 patient-years worldwide, in the period from first authorisation in 2017 to 2019. The exposure for Imfinzi (durvalumab) is estimated to have been more than 10,163 patient-years worldwide, in the period from first authorisation in 2018 to 2019. The exposure for Yervoy (ipilimumab) is estimated to have been more than 62,495 patients worldwide, in the period from first authorisation in 2011 to 2019. The exposure for Opdivo (nivolumab) is estimated to have been more than 346,304 patients worldwide, in the period from first authorisation in 2015 to 2019. The exposure for Keytruda (pembrolizumab) is estimated to have been more than 99,173 patient-years worldwide, in the period from first authorisation in 2015 to 2018.

During routine signal detection activities, a signal of tuberculosis was identified by the EMA, based on 54 cases retrieved from EudraVigilance for the preferred terms tuberculosis and pulmonary tuberculosis. Germany confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

Having considered the available evidence from case reports in EudraVigilance and the literature, the PRAC agreed that the signal should be further investigated and agreed to request a cumulative review of all cases of tuberculosis.

The PRAC appointed Brigitte Keller-Stanislawski as Rapporteur for the signal.

Summary of recommendation(s)

- The MAHs for Tecentriq (atezolizumab), Bavencio (avelumab), Libtayo (cemiplimab), Imfinzi (durvalumab), Yervoy (ipilimumab), Opdivo (nivolumab) and Keytruda (pembrolizumab) should submit to the EMA, within 60 days, a cumulative review of all cases from published literature and data from spontaneous reports and reports from studies, including an analysis of all case reports of tuberculosis and related terms as well as of tuberculosis reactivation.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.2. New signals detected from other sources

See also Annex I 14.2.

4.2.1. Sitagliptin – JANUVIA (CAP), RISTABEN (CAP), TESAVEL (CAP), XELEVIA (CAP); NAP
sitagliptin, ertugliflozin – STEGLUJAN (CAP)
sitagliptin, metformin – EFFICIB (CAP), JANUMET (CAP), VELMETIA (CAP); NAP

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

PRAC Rapporteur: Menno van der Elst

Scope: Signal of rhabdomyolysis

EPITT 19466 – New signal

Lead Member State(s): NL

Background

Sitagliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor, authorised alone or in combination with ertugliflozin, a sodium glucose co-transporter-2 (SGLT2) inhibitor or metformin, a biguanide oral anti-diabetic. Januvia, Ristaben, Tesavel and Xelevia (sitagliptin), Steglujan (sitagliptin/ertugliflozin) and Efficib, Janumet and Velmetia (sitagliptin/metformin) are centrally authorised products indicated for the treatment of adult patients with type 2 diabetes mellitus (T2DM) to improve glycaemic control subject to certain conditions.

The exposure for Januvia, Ristaben, Tesavel and Xelevia (sitagliptin) is estimated to have been more than 47,573,639 patient-years worldwide, in the period from first authorisations in 2007 to 2017. The exposure for Steglujan (sitagliptin/ertugliflozin) is estimated to have been more than 4,260 patient-years worldwide, in the period from first authorisation in 2018 to 2018. The exposure for Efficib, Janumet and Velmetia (sitagliptin/metformin) is estimated to have been more than 23,180,041 patient years worldwide, in the period from first authorisations in 2008 to 2017.

Based on information received from another regulatory authority and a review of 260 cases retrieved from EudraVigilance, a signal of rhabdomyolysis was validated by the Netherlands, based on. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

Having considered the evidence from the cases in EudraVigilance, the PRAC agreed that further evaluation of the signal on sitagliptin and rhabdomyolysis is warranted. Additionally, the PRAC agreed that this evaluation should be extended to cover the whole class of DPP-4 inhibitors.

The PRAC appointed Menno van der Elst as Rapporteur for the signal.

Summary of recommendation(s)

- The MAHs for the originator-containing products of the DPP-4 inhibitor class (alogliptin, linagliptin, saxagliptin, sitagliptin and vildagliptin) should submit to the EMA, within 60 days, a cumulative review of the signal, including an analysis of all case reports of rhabdomyolysis and related terms from MEdDRA SMQ[10] on rhabdomyolysis/myopathy from clinical trials and post-marketing sources. The MAHs should provide a proposal to amend the product information as appropriate.

[10] Medical Dictionary for Regulatory Activities – Standard MedDRA queries

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

4.3. Signals follow-up and prioritisation

4.3.1. Ibrutinib - IMBRUVICA (CAP) - EMEA/H/C/003791/SDA/029

Applicant(s): Janssen-Cilag International NV

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Signal of ischemic stroke

EPITT 19369 – Follow-up to April 2019

Background

For background information, see PRAC minutes April 2019.

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

Discussion

Having considered the available evidence and following the assessment of the data submitted by the MAH, including the number of suggestive cases, seriousness of the issue and a plausible mechanism, the PRAC agreed that the product information of Imbruvica (ibrutinib) should be updated to reflect the risk of ischemic central nervous vascular conditions.

Summary of recommendation(s)

- The MAH for Imbruvica (ibrutinib) should submit to EMA, within 60 days, a variation for amending the product information[11].

For the full PRAC recommendation, see EMA/PRAC/474667/2019 published on 30 September 2019 on the EMA website.

4.3.2. Ibuprofen (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)

Applicant(s): various

PRAC Rapporteur: Anette Kirstine Stark

Scope: Signal of acute generalised exanthematous pustulosis (AGEP)

EPITT 19409 – Follow-up to May 2019

Background

For background information, see PRAC minutes May 2019.

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

The brandleader MAH for ibuprofen-containing products Reckitt Benckiser replied to the request for information on the signal of acute generalised exanthematous pustulosis (AGEP) and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence in EudraVigilance and in the literature on the risk of AGEP, including several well-documented cases associating ibuprofen with AGEP including cases with a positive dechallenge, rechallenge and positive testing for hypersensitivity, the PRAC agreed that the product information of ibuprofen-containing products should be updated to reflect the risk of AGEP.

Summary of recommendation(s)

- The MAHs for ibuprofen-containing products[12] should submit to the relevant National Competent Authorities (NCAs) of the Member States, within 60 days, a variation for amending the product information[13].

For the full PRAC recommendation, see EMA/PRAC/474667/2019 published on 30 September 2019 on the EMA website.

4.3.3. Omalizumab - XOLAIR (CAP) - EMEA/H/C/000606/SDA/068

Applicant(s): Novartis Europharm Limited

PRAC Rapporteur: Annika Folin

Scope: Signal of acquired haemophilia

EPITT 19385 – Follow-up to April 2019

Background

For background information, see PRAC minutes April 2019.

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

Discussion

Having considered the available evidence, including data provided by the MAH, the PRAC agreed that an association between omalizumab therapy and acquired haemophilia cannot be established at this stage. Therefore, the PRAC agreed that no further regulatory actions were warranted at present.

Summary of recommendation(s)

- The MAH for Xolair (omalizumab) should continue to monitor acquired haemophilia through routine safety surveillance.

4.3.4. Pembrolizumab - KEYTRUDA (CAP) - EMEA/H/C/003820/SDA/022

Applicant(s): Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

[12] Including ibuprofen monotherapy and ibuprofen in fixed-drug combination products
[13] Update of SmPC sections 4.4 and 4.8. The package leaflet is to be updated accordingly

Scope: Signal of optic neuritis

EPITT 19381 – Follow-up to April 2019

Background

For background information, see PRAC minutes April 2019.

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

Discussion

Having considered the available evidence from case reports in EudraVigilance and in the literature, including the cumulative review provided by the MAH, the PRAC agreed that the number of possible cases of optic neuritis with a temporal relationship to pembrolizumab is low and that the causal relationship between treatment with pembrolizumab and optic neuritis cannot be established at this stage. Therefore, the PRAC agreed that no further action was warranted at this stage.

Summary of recommendation(s)

- The MAH for Keytruda (pembrolizumab) should continue to monitor these events as part of routine safety surveillance.

4.3.5. Perampanel - FYCOMPA (CAP) - EMEA/H/C/002434/SDA/018

Applicant(s): Eisai GmbH

PRAC Rapporteur: Ghania Chamouni

Scope: Signal of hepatotoxicity

EPITT 19383 – Follow-up to April 2019

Background

For background information, see PRAC minutes April 2019.

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

Discussion

Having considered the evidence from case reports in EudraVigilance, the literature, clinical trials and the cumulative review provided by the MAH, the PRAC agreed that further information was required and requested a cumulative review from the MAH.

Summary of recommendation(s)

- The MAH for Fycompa (perampanel) should submit to the EMA, in the next PSUR[14], a cumulative review of all post-marketing cases of hepatic disorders, with a specific focus on cases with positive de-challenge including cases of patients with concomitant use of hepatotoxic drugs.

4.3.6. Sodium-glucose co-transporter 2 (SGLT2) inhibitors: canagliflozin – INVOKANA (CAP) - EMEA/H/C/002649/SDA/018; canagliflozin,

[14] Data lock point (DLP): 22/07/2019

metformin – VOKANAMET (CAP) - EMEA/H/C/002656/SDA/016; dapagliflozin – EDISTRIDE (CAP) - EMEA/H/C/004161/SDA/014; dapagliflozin – FORXIGA (CAP) - EMEA/H/C/002322/SDA/027; dapagliflozin, metformin – EBYMECT (CAP) - EMEA/H/C/004162/SDA/013; dapagliflozin, metformin – XIGDUO (CAP) - EMEA/H/C/002672/SDA/016; empagliflozin – JARDIANCE (CAP) - EMEA/H/C/002677/SDA/017; empagliflozin, metformin – SYNJARDY (CAP) - EMEA/H/C/003770/SDA/011; empagliflozin, linagliptin – GLYXAMBI (CAP) - EMEA/H/C/003833/SDA/008; ertugliflozin – STEGLATRO (CAP) - EMEA/H/C/004315/SDA/006; ertugliflozin, metformin – SEGLUROMET (CAP) - EMEA/H/C/004314/SDA/005; ertugliflozin, sitagliptin - STEGLUJAN (CAP) - EMEA/H/C/004313/SDA/006; saxagliptin, dapagliflozin - QTERN (CAP) - EMEA/H/C/004057/SDA/002

Applicant(s): AstraZeneca AB (Ebymect, Edistride, Forxiga, Qtern, Xigduo), Boehringer Ingelheim (Glyxambi), Boehringer Ingelheim International GmbH (Jardiance, Synjardy), Janssen-Cilag International NV (Invokana, Vokanamet), Merck Sharp & Dohme B.V. (Segluromet, Steglatro, Steglujan)

PRAC Rapporteur: Martin Huber

Scope: New information on the known association between sodium-glucose co-transporter 2 (SGLT2) inhibitors and diabetic ketoacidosis (DKA) in surgical patients

EPITT 19355 – Follow-up to March 2019

Background

For background information, see PRAC minutes March 2019.

The MAHs for Edistride/Forxiga (dapagliflozin), Ebymect/Xigduo (dapagliflozin/metformin) and Qtern (saxagliptin/dapagliflozin); for Jardiance (empagliflozin) and Glyxambi/Synjardy (empagliflozin/linagliptin); for Invokana (canagliflozin) and Vokanamet (canagliflozin/metformin); and for Steglatro (ertugliflozin), Segluromet (ertugliflozin/metformin) and Steglujan (ertugliflozin/sitagliptin) replied to the request for information on the signal of diabetic ketoacidosis (DKA) in surgical patients and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence in EudraVigilance and in the literature, the known association of sodium-glucose co-transporter 2 inhibitors (SGLT2i) with diabetic ketoacidosis as well as the replies from the MAHs of SGLT2i-containing medicinal products, the PRAC agreed that further information is necessary in the product information to further mitigate the risk of DKA in surgical patients.

Summary of recommendation(s)

- The MAHs for all SGLT2i-containing medicinal products should submit to the EMA, within 60 days, a variation for amending the product information[15].

For the full PRAC recommendation, see EMA/PRAC/474667/2019 published on 30 September 2019 on the EMA website.

[15] Update of SmPC section 4.4

4.3.7. Teriflunomide - AUBAGIO (CAP) - EMEA/H/C/002514/SDA/007

Applicant(s): Sanofi-aventis groupe

PRAC Rapporteur: Martin Huber

Scope: Signal of psoriasis

EPITT 19366 – Follow-up to April 2019

Background

For background information, see PRAC minutes April 2019.

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

Discussion

Having considered the available evidence in EudraVigilance, the literature, clinical trials and the cumulative review provided by the MAH, including cases of new onset psoriasis or worsening of pre-existing psoriasis as well as cases with a positive de-challenge and a case of positive re-challenge, the PRAC agreed that a causal association between teriflunomide and psoriasis can be established. The PRAC agreed that the product information of Aubagio (teriflunomide) should be updated accordingly.

Summary of recommendation(s)

- The MAH for Aubagio (teriflunomide) should submit to the EMA, within 60 days, a variation for amending the product information[16].

For the full PRAC recommendation, see EMA/PRAC/474667/2019 published on 30 September 2019 on the EMA website.

4.3.8. Ticagrelor - BRILIQUE (CAP) - EMEA/H/C/001241/SDA/025

Applicant(s): AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Signal of severe cutaneous adverse reactions (SCARs)

EPITT 19375 – Follow-up to April 2019

Background

For background information, see PRAC minutes April 2019.

The MAH replied to the request for information on the signal of severe cutaneous adverse reactions (SCARs) and the responses were assessed by the Rapporteur.

Discussion

Having considered the evidence including the cumulative review of cases of SCARs and the medical literature provided by the MAH, the PRAC agreed that the causal relationship between ticagrelor and severe cutaneous adverse reactions (SCARs) could not be established at this stage. Therefore, the PRAC agreed that no further regulatory action is warranted at

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

present. Nevertheless, the PRAC recommended that the MAH should closely monitor reports of SCARs.

Summary of recommendation(s)

- The MAH for Brilique (ticagrelor) should closely monitor cases of SCARs in future PSURs. It should include an analysis of all reports of SCARs in association with ticagrelor and a discussion on the need for further risk minimisation measures (RMMs). In addition, SCARs should be added as an 'important potential risk' in the PSUR summary of safety concerns.

For the full PRAC recommendation, see EMA/PRAC/474667/2019 published on 30 September 2019 on the EMA website.

4.3.9. Tocilizumab - ROACTEMRA (CAP) - EMEA/H/C/000955/SDA/058

Applicant(s): Roche Registration GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

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

EPITT 19360 – Follow-up to March 2019

Background

For background information, see PRAC minutes March 2019.

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 available evidence from the literature, EudraVigilance and from the cumulative review provided by the MAH, the PRAC agreed that considering the low number of possible cases of DRESS with a temporal relationship to tocilizumab, the causal relationship between treatment with tocilizumab and DRESS cannot be established at this stage. Therefore, the PRAC agreed that no further regulatory actions is warranted at present.

Summary of recommendation(s)

- The MAH for RoActemra (tocilizumab) should continue to monitor cases of DRESS as part of routine safety surveillance.

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(s). 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. Alpelisib - EMEA/H/C/004804

Scope: Treatment of postmenopausal women, and men, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, advanced breast cancer with a phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alfa (PIK3CA) mutation in combination with fulvestrant after disease progression following an endocrine-based regimen

5.1.2. Sodium oxybate - EMEA/H/C/004962

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

Previous PRAC advice was provided in April 2019, see PRAC minutes April 2019.

5.1.3. Upadacitinib - EMEA/H/C/004760

Scope: Treatment of moderate to severe active rheumatoid arthritis

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

See Annex I 15.2.

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

See also Annex I 15.3.

5.3.1. Belimumab - BENLYSTA (CAP) - EMEA/H/C/002015/II/0062

Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension of indication to include patients aged 5 years and older in the current approved indication for the powder for solution for infusion 120 mg/mL and 400 mg/mL based on the results of study BEL114055 (PLUTO): a multicentre, randomised parallel group, placebo-controlled double-blind trial to evaluate the safety, efficacy, and pharmacokinetics of belimumab, a human monoclonal anti-BLyS antibody, plus standard therapy in paediatric patients with systemic lupus erythematosus (SLE). As a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated with safety and efficacy information. In addition, sections 4.2, 5.1 and 5.2 of the SmPC for the solution for injection in pre-filled pen and pre-filled syringe 200 mg are updated to reflect the paediatric data available for the intravenous formulation. The package leaflet is updated accordingly. Furthermore, the RMP (version 28.0) is updated accordingly and with revision 2 of the guidance on the format of RMP in the EU (template). Finally, the MAH took the opportunity to introduce some editorial changes in the product information and bring it in line with the latest quality review document (QRD) template (version 10.0)

Background

Belimumab is a human immunoglobulin (Ig) G1 monoclonal antibody specific for soluble human B lymphocyte stimulator protein (BLyS). It is indicated, as Benlysta, as add-on therapy in adult patients with active, autoantibody-positive systemic lupus erythematosus (SLE) with a high degree of disease activity despite standard therapy.

The CHMP is evaluating a type II variation for Benlysta, a centrally authorised product containing belimumab, consisting of an extension of indication to include patients aged 5 years and older in the current approved indication based on the results of study BEL114055 (PLUTO): an interventional study on safety, efficacy and pharmacokinetics. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this variation. For further background, see PRAC minutes February 2019 and PRAC minutes June 2019.

Summary of advice

- The RMP for Benlysta (belimumab) in the context of the variation procedure under evaluation by the CHMP could be considered acceptable provided that an update to RMP version 33.0 is submitted.
- In view of the limited safety data in paediatric patients from 5 years of age and older, the PRAC considered that there is a safety concern regarding infections. Therefore, the PRAC supported the addition of the open label continuation of the PLUTO study as a category 3 study in the RMP. In addition, the MAH is requested to review the possibility to undertake a PASS within established registries, to further characterise the safety of Benlysta (belimumab) treatment in children with SLE, with a particular focus on infections. The MAH is requested to conduct a feasibility assessment and submit the results to EMA within 60 days of the variation Commission Decision (CD). Pending its feasibility, the study should be added to the RMP as a category 3 study.

5.3.2. Bosentan - STAYVEER (CAP) - EMEA/H/C/002644/II/0028

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Adrien Inoubli

Scope: Update of Annex II-D on 'Conditions or restrictions with regard to the safe and effective use of the medicinal product' in order to remove the 'prescriber kit' from the additional risk minimisation measures (aRMM) and also to remove the obligation to implement a formal 'controlled distribution system' in EU countries as requested in the conclusions of LEG 10.2 adopted by PRAC in March 2019. Section 4.2 of the SmPC is updated to include the statement that patients should be given the package leaflet and the patient alert card which are included in the pack. The RMP (version 11) is updated accordingly. In addition, the MAH took the opportunity to align the product information with the European Commission (EC) guideline on 'excipients in the labelling and package leaflet of medicinal products for human use'

Background

Bosentan is a dual endothelin receptor antagonist (ERA) with affinity for both endothelin A and B (ETA and ETB) receptors. It is indicated, as Stayveer, for the treatment of pulmonary arterial hypertension (PAH) to improve exercise capacity and symptoms in patients with

WHO[17] functional class III. It is also indicated to reduce the number of new digital ulcers in patients with systemic sclerosis and ongoing digital ulcer disease.

The CHMP is evaluating a type II variation for Stayveer, a centrally authorised product containing bosentan, to update Annex II-D on 'Conditions or restrictions with regard to the safe and effective use of the medicinal product' to remove the prescriber kit from the additional risk minimisation measures (aRMM) and remove the obligation to implement a formal 'controlled distribution system' in EU countries as requested in the conclusions of post authorisation measure LEG 10.2 adopted by PRAC in March 2019. In addition, the product information is updated to reflect that patients should be given the package leaflet and the patient alert card which are included in the pack. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this variation. For further background, see PRAC minutes March 2019.

Summary of advice

- The RMP (version 11) for Stayveer (bosentan) in the context of the variation procedure under evaluation by the CHMP is considered acceptable.
- The PRAC confirmed its support for the removal of the prescriber kit and the control distribution system. The PRAC agreed that routine risk minimisation measures are sufficient to mitigate the risks, and considered that the patient alert card alone is sufficient to ensure that new patients are fully aware of the risk of hepatotoxicity associated with bosentan and of the recommendation to perform monthly liver tests and to use an adequate contraceptive method while on treatment. Therefore, Annex II should be updated accordingly.

5.3.3. Bosentan - TRACLEER (CAP) - EMEA/H/C/000401/II/0092

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Adrien Inoubli

Scope: Update of Annex II-D on 'Conditions or restrictions with regard to the safe and effective use of the medicinal product' in order to remove the 'prescriber kit' from the additional risk minimisation measures (aRMM) and also to remove the obligation to implement a formal 'controlled distribution system' in EU countries as requested in the conclusions of LEG 86.2 adopted in March 2019. Section 4.2 of the SmPC is updated to include the statement that patients should be given the package leaflet and the patient alert card which are included in the pack. The RMP (version 11) is updated accordingly. In addition, the MAH took the opportunity to align the product information with the European Commission (EC) guideline on 'excipients in the labelling and package leaflet of medicinal products for human use'

Background

Bosentan is a dual endothelin receptor antagonist (ERA) with affinity for both endothelin A and B (ETA and ETB) receptors. It is indicated, as Tracleer, for the treatment of pulmonary arterial hypertension (PAH) to improve exercise capacity and symptoms in patients with WHO[18] functional class III. It is also indicated to reduce the number of new digital ulcers in patients with systemic sclerosis and ongoing digital ulcer disease.

[17] World Health Organization
[18] World Health Organization

The CHMP is evaluating a type II variation for Tracleer, a centrally authorised product containing bosentan, to update Annex II-D on 'Conditions or restrictions with regard to the safe and effective use of the medicinal product' to remove the prescriber kit from the additional risk minimisation measures (aRMM) and remove the obligation to implement a formal 'controlled distribution system' in EU countries as requested in the conclusions of post authorisation measure LEG 86.2 adopted in March 2019. In addition, the product information is updated to reflect that patients should be given the package leaflet and the patient alert card which are included in the pack. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this variation. For further background, see PRAC minutes March 2019.

Summary of advice

- The RMP (version 11) for Tracleer (bosentan) in the context of the variation procedure under evaluation by the CHMP is considered acceptable.
- The PRAC confirmed its support for the removal of the prescriber kit and the control distribution system. The PRAC agreed that routine risk minimisation measures are sufficient to mitigate the risks, and considered that the patient alert card alone is sufficient to ensure that new patients are fully aware of the risk of hepatotoxicity associated with bosentan and of the recommendation to perform monthly liver tests and to use an adequate contraceptive method while on treatment. Therefore, Annex II should be updated accordingly.

5.3.4. Interferon beta-1a - REBIF (CAP) - EMEA/H/C/000136/II/0137/G

Applicant: Merck Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Grouped variations consisting of: 1) update of sections 4.3, 4.6 and 5.3 of the SmPC in order to add information on pregnancy following the completion of the European interferon beta (IFN-β) pregnancy registry (eighth annual and final report) and the final clinical study report (CSR) of the register-based study in the Nordic countries EUPAS13054: multiple sclerosis pregnancy study - pregnancy outcomes in multiple sclerosis populations exposed and unexposed to interferon beta - a register-based study in the Nordic countries; 2) update of section 4.6 of the SmPC in order to update the statement regarding breast-feeding following a review of studies, case reports and literature articles (in fulfilment of MEA 043.2 and MEA 039). The package leaflet is updated accordingly. The RMP (version 10.0) is updated accordingly, including the deletion of the important potential risk 'pregnancy outcomes'. The RMP is also updated to bring it in line with revision 2 of the guidance on the format of RMP in the EU (template)

Background

Interferon beta-1a is a recombinant interferon, glycoproteins endowed with immunomodulatory, antiviral and antiproliferative properties. It is indicated, as Rebif, for the treatment of relapsing multiple sclerosis, as well as in patients with a single demyelinating event with an active inflammatory process, if alternative diagnoses have been excluded, and if they are determined to be at high risk of developing clinically definite multiple sclerosis.

The CHMP is evaluating grouped variations for Rebif, a centrally authorised product containing interferon beta-1a, including the assessment of the final annual report of the EU interferon (IFN)-beta pregnancy registry, the final report for the registry-based study in

Nordic countries (EUPAS13054) and update of the product information regarding use in pregnancy and breastfeeding. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this application. For further background, see PRAC minutes February 2019 and PRAC minutes May 2019.

See also under 10.1.1.

Summary of advice

- The RMP for Rebif (interferon beta-1a) in the context of the variation procedure under evaluation by the CHMP could be considered acceptable provided that an update to RMP version 10.1 and satisfactory responses to the request for supplementary information (RSI) are submitted.
- The PRAC advised to continue to address 'use during second and third trimesters of pregnancy' as missing information in the RMP. In addition, within the same Nordic data sources, the MAH should evaluate whether usage patterns have changed after implementation of the label change. The MAH should also review the number of pregnancies with long exposure to interferon beta during pregnancy after 3 and 5 years. The PRAC also agreed with requesting the MAHs to further study exposure during pregnancy and to provide further details on the methodology after completion of the variation procedure.

5.3.5. Mecasermin - INCRELEX (CAP) - EMEA/H/C/000704/II/0060

Applicant: Ipsen Pharma

PRAC Rapporteur: Kirsti Villikka

Scope: Update of sections 4.1, 4.2, 4.3, 4.4, 4.8 and 4.9 of the SmPC in order to update the safety information on benign or malignant neoplasia based on the EU registry study: the Ipsen global safety database and based on a literature review. The package leaflet and the RMP (version 11.1) are updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet

Background

Mecasermin is a human insulin-like growth factor-1 (rhIGF-1) produced by recombinant deoxyribonucleic acid (DNA) technology. It is indicated, as Increlex, for the long-term treatment of growth failure in children and adolescents from 2 to 18 years with severe primary insulin-like growth factor-1 deficiency (primary IGFD).

The CHMP is evaluating a type II variation for Increlex, a centrally authorised product containing mecasermin, consisting of an update of the safety information on benign or malignant neoplasia based on the results of an EU registry study. The MAH is proposing to update the existing key elements of the educational materials (physician and patient information) on the risk of benign or malignant neoplasia as well as to communicate the update via a direct healthcare professional communication (DHPC). 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 Increlex (mecasermin) in the context of the variation procedure under evaluation by the CHMP could be considered acceptable provided that an update to RMP version 11.1 is submitted.
- The PRAC discussed the inclusion of 'benign and malignant neoplasia' as an important identified risk in the safety specification of the RMP taking into consideration the biological plausibility and the current proposal for inclusion of this risk to the product information as an undesirable effect (ADR). This will be further considered in the next round of assessment. The PRAC agreed with the proposed updated targeted follow up questionnaires on cases of neoplasia. In addition, the proposed additional pharmacovigilance activity to further characterise the risk of benign and malignant neoplasia, with the commitment to submit by December 2019 a study feasibility report is supported. With regard to the proposed updates to the existing key elements of the educational materials (physician information pack and patient information pack) to include information on the risk of neoplasia, and the proposal for a DHPC, the PRAC considered that they need to be further considered following review by the CHMP of the proposed product information updates.

5.3.6. Peginterferon beta-1a - PLEGRIDY (CAP) - EMEA/H/C/002827/II/0052/G

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Grouped variations consisting of: 1) update of sections 4.3 and 4.6 of the SmPC in order to add information on pregnancy and update the statement regarding breast-feeding following the completion of the European interferon beta (IFN-β) pregnancy registry (eighth annual and final report) and the final clinical study report (CSR) of the register-based study in the Nordic countries EUPAS13054: multiple sclerosis pregnancy study - pregnancy outcomes in multiple sclerosis populations exposed and unexposed to interferon beta - a register-based study in the Nordic countries; 2) update of section 4.6 of the SmPC in order to update the statement regarding breast-feeding following a review of studies, case reports and literature articles (in fulfilment of MEA 08.2 and MEA 002). The package leaflet is updated accordingly. The RMP (version 4.1) is updated accordingly, including the deletion of the important potential risk 'pregnancy outcomes'. The RMP is also updated to bring it in line with revision 2 of the guidance on the format of RMP in the EU (template)

Background

Peginterferon beta-1a is a pegylated recombinant interferon, glycoproteins endowed with immunomodulatory, antiviral and antiproliferative properties. It is indicated, as Plegridy, in adult patients for the treatment of relapsing remitting multiple sclerosis (RRMS).

The CHMP is evaluating grouped variations for Plegridy, a centrally authorised product containing peginterferon beta-1a, including the assessment of the final annual report of the EU interferon (IFN)-beta pregnancy registry, the final report for the registry-based study in Nordic countries (EUPAS13054) and update of the product information regarding use in pregnancy and breastfeeding. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this application. For further background, see PRAC minutes February 2019 and PRAC minutes May 2019.

See also under 10.1.1.

Summary of advice

- The RMP for Plegridy (peginterferon beta-1a) in the context of the variation procedure under evaluation by the CHMP could be considered acceptable provided that an update to RMP version 4.2 and satisfactory responses to the request for supplementary information (RSI) are submitted.
- The PRAC advised to continue to address 'use during second and third trimesters of pregnancy' as missing information in the RMP. In addition, within the same Nordic data sources, the MAH should evaluate whether usage patterns have changed after implementation of the label change. The MAH should also review the number of pregnancies with long exposure to interferon beta during pregnancy after 3 and 5 years. The PRAC also agreed with requesting the MAHs to further study exposure during pregnancy and to provide further details on the methodology after completion of the variation procedure.

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

Applicant: Pierre Fabre Dermatologie

PRAC Rapporteur: Eva Segovia

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

Background

Propranolol is a beta-blocker and has shown a local haemodynamic effect, an antiangiogenic effect, an apoptosis-triggering effect on capillary endothelial cells as well as a reduction of both vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) signalling pathways and subsequent angiogenesis/proliferation. It is indicated, as Hemangiol, in the treatment of proliferating infantile haemangioma requiring systemic therapy, namely: life- or function-threatening haemangioma, ulcerated haemangioma with pain and/or lack of response to simple wound care measures as well as haemangioma with a risk of permanent scars or disfigurement.

The CHMP is evaluating a type II variation for Hemangiol, a centrally authorised product containing propranolol, assessing the results of a drug utilisation study (DUS) performed in Germany and France to evaluate off-label use and effectiveness of risk minimisation measures (RMM) in a real-life clinical setting. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this variation. For further background, see PRAC minutes February 2019 and PRAC minutes May 2019.

Summary of advice

- The RMP for Hemangiol (propranolol) in the context of the variation procedure under evaluation by the CHMP could be considered acceptable provided that an update to RMP version 3.4 is submitted.
- The PRAC supported changes to the risk minimisation measures (RMMs) in order to minimise and prevent the important identified risk of 'hypoglycaemia and related

seizures'. The Committee supported new key message to reflect that the risk is equally prominent during the whole period of treatment. In addition, the RMMs for the important identified risk of 'bronchospasm and bronchial hyperreactivity reactions', are considered appropriate. With regard to 'hypotension and bradycardia', current risk minimisation measures are considered sufficient. Finally, the PRAC advised to request the MAH to further adjust the list of safety concerns in line with revision 2 of GVP module V on 'Risk management systems'.

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. Axitinib - INLYTA (CAP) - PSUSA/00010022/201901

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: David Olsen

Scope: Evaluation of a PSUSA procedure

Background

Axitinib is a potent and selective tyrosine kinase inhibitor of vascular endothelial growth factor receptors (VEGFR)-1, VEGFR-2 and VEGFR-3. It is indicated, as Inlyta, for the treatment of adult patients with advanced renal cell carcinoma (RCC) after failure of prior treatment with sunitinib or a cytokine.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Inlyta, a centrally authorised medicine containing axitinib 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 Inlyta (axitinib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add cholecystitis as an undesirable effect with a frequency 'common'. Therefore, the current terms of the marketing authorisation(s) should be varied[19].
- In the next PSUR, the MAH should provide causality assessments taking into account the effect of axitinib on the treated patient population and whether administering axitinib to a patient at risk may have contributed to an adverse drug reaction (ADR). In addition, the MAH should provide a detailed review of cases of fractures distinguishing high and low impact trauma.

The frequency of PSUR submission should be revised from yearly to three-yearly and the next PSUR should be submitted to the EMA within 90 days of the data lock point. The list of

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

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

6.1.2. Baricitinib - OLUMIANT (CAP) - PSUSA/00010578/201902

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

Background

Baricitinib is a selective and reversible inhibitor of Janus kinase (JAK)1 and JAK2. It is indicated, as Olumiant, for the treatment of moderate to severe active rheumatoid arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drugs (DMARDs).

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Olumiant, a centrally authorised medicine containing baricitinib 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 Olumiant (baricitinib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add a warning on hypersensitivity and to add rash as an undesirable effect with a frequency 'common' and swelling of the face/urticaria with a frequency 'uncommon'. In addition, the existing warning on venous thromboembolism should be amended to state that in case of clinical features of deep vein thrombosis (DVT)/pulmonary embolism (PE) treatment with baricitinib should be discontinued. DVT and PE should be added as undesirable effects with a frequency 'uncommon'. Therefore, the current terms of the marketing authorisation(s) should be varied[20].
- In the next PSUR, the MAH should provide detailed information on cases of possible drug-drug interaction (DDI) as additive immunosuppressant effect of baricitinib.

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. Carfilzomib - KYPROLIS (CAP) - PSUSA/00010448/201901

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

Background

[20] 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

Carfilzomib is a tetrapeptide epoxyketone proteasome inhibitor. It is indicated, as Kyprolis, in combination with either lenalidomide and dexamethasone or dexamethasone alone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Kyprolis, a centrally authorised medicine containing carfilzomib 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 Kyprolis (carfilzomib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add new warnings on hepatitis virus B (HVB) reactivation and progressive multifocal leukoencephalopathy (PML) and to amend the existing warnings on cardiac disorders and hypertension. HVB reactivation and PML are added as undesirable effects with a frequency 'uncommon' and 'rare' respectively. Therefore, the current terms of the marketing authorisation(s) should be varied[21].
- In the next PSUR, the MAH should provide a detailed review of cases of gastrointestinal obstruction and propose to update the product information as warranted. The MAH should also provide a review on the risk of hepatic toxicity together with a discussion on risk factors and propose to update the product information as warranted. In addition, the MAH should include detailed reviews on cases of cardio-respiratory arrest, cardiogenic shock, ventricular fibrillation and sudden cardiac death including a discussion on possible pathophysiological mechanisms. Finally, the MAH should closely monitor cases of hypertension and cases of cardiac toxicity.

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. Collagenase clostridium histolyticum[22] - XIAPEX (CAP) - PSUSA/00000871/201902

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Collagenases are proteinases that hydrolyse collagen under physiological conditions. Collagenase clostridium histolyticum is a mixture of class I (AUX-I) and class II (AUX-II) clostridial collagenases in a defined mass ratio. It is indicated, as Xiapex, for the treatment of Dupuytren's contracture in adult patients with a palpable cord and for the treatment of adult men with Peyronie's disease with a palpable plaque and curvature deformity of at least 30 degrees at the start of therapy.

[21] Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion
[22] Indicated for the treatment of Dupuytren's contracture and treatment of Peyronie's disease

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Xiapex, a centrally authorised medicine containing collagenase clostridium histolyticum 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 Xiapex (collagenase clostridium histolyticum) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add warnings on finger necrosis and on digital phalangeal fractures for the indication on Dupuytren's contracture. In addition, a new warning is added on the time span before resuming sexual activity and caution to be taken when resuming sexual activity for the indication of Peyronie's disease. Digital necrosis and digital fracture should be added as undesirable effects with a frequency 'not known' for the indication on Dupuytren's contracture. Therefore, the current terms of the marketing authorisation(s) should be varied[23].
- In the next PSUR, the MAH should closely monitor cases of finger fracture and evaluate whether there is any pattern with regards to the concerned fingers or any other important information on finger fractures related to collagenase clostridium histolyticum and the finger extension procedure. In addition, the MAH should provide a detailed review of cases of penile fractures. Information on long-term outcome with regard to erectile dysfunction or urinary dysfunction or remaining pain is of special interest.

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. Dolutegravir - TIVICAY (CAP); dolutegravir, abacavir, lamivudine - TRIUMEQ (CAP) - PSUSA/00010075/201901

Applicant(s): ViiV Healthcare B.V.

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Dolutegravir is an inhibitor of human immunodeficiency virus (HIV) integrase indicated, as Tivicay, and in combination with abacavir/lamivudine as Triumeq, for the treatment of HIV infection, subject to certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Tivicay and Triumeq, centrally authorised medicines containing dolutegravir and dolutegravir/abacavir/lamivudine respectively, and issued a recommendation on their marketing authorisation(s).

Summary of recommendation(s) and conclusions

[23] 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

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Tivicay (dolutegravir) and Triumeq (dolutegravir/abacavir/lamivudine) 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 cumulatively review and provide a causality assessment of all cases of thrombocytopenia, anaemia, myocarditis, hepatic events and alopecia in association with dolutegravir treatment.
- The MAH should submit to EMA, within 60 days, a comprehensive review of weight gain, focusing on all available data.

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

6.1.6. Etanercept[24] - BENEPALI (CAP); ERELZI (CAP) - PSUSA/00010452/201901

Applicant(s): Samsung Bioepis NL B.V. (Benepali), Sandoz GmbH (Erelzi)

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

Background

Etanercept is a tumour necrosis factor alfa (TNF-α) inhibitor indicated, as Benepali and Erelzi, alone or in combination with methotrexate for the treatment of moderate to severe active rheumatoid arthritis in adults, treatment of polyarthritis (rheumatoid factor positive or negative) and extended oligoarthritis in children and adolescents from the age of 2 years, psoriatic arthritis in adolescents from the age of 12 years, enthesitis-related arthritis in adolescents from the age of 12 years, treatment of active and progressive psoriatic arthritis in adults, treatment of adults with severe active ankylosing spondylitis, adults with severe non-radiographic axial spondyloarthritis with objective signs of inflammation, treatment of adults with moderate to severe plaque psoriasis and chronic severe plaque psoriasis in children and adolescents from the age of 6 years, subject to certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Benepali and Erelzi, centrally authorised medicines containing etanercept 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 Benepali and Erelzi (etanercept) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include inflammatory bowel disease (IBD) as an undesirable effect with a frequency 'uncommon'. Therefore, the current terms of the marketing authorisations should be varied[25].
- In the next PSUR, the MAHs should provide a cumulative review of cases of autoimmune encephalitis which occurs after switching etanercept-containing product(s) as well as

[24] Biosimilar product(s) only
[25] Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

cumulative reviews of pyoderma gangrenosum, pancreatitis and alopecia. In addition, the MAHs should further propose an update of the product information regarding IBD in light of the available evidence including recommendation on patients' management. Finally, the MAH Samsung Bioepis NL B.V. should provide a summary of the review of hepatotoxicity profile.

The PRAC considered that PSURs for 'etanercept (all except biosimilar(s))'- and 'etanercept (biosimilar(s) only'-containing products should be assessed in the future within the same PSUSA procedure. Therefore the list of Union reference dates (EURD list) should be updated accordingly. The next PSUR should be submitted in accordance with the requirements set out in the EURD list provided for under Article 107c(7) of Directive 2001/83/EC.

6.1.7. Etanercept[26] - ENBREL (CAP) - PSUSA/00001295/201902

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

Background

Etanercept is a tumour necrosis factor alfa (TNF-α) inhibitor indicated, as Enbrel, alone or in combination with methotrexate for the treatment of moderate to severe active rheumatoid arthritis in adults, treatment of polyarthritis (rheumatoid factor positive or negative) and extended oligoarthritis in children and adolescents from the age of 2 years, psoriatic arthritis in adolescents from the age of 12 years, enthesitis-related arthritis in adolescents from the age of 12 years, treatment of active and progressive psoriatic arthritis in adults, treatment of adults with severe active ankylosing spondylitis, adults with severe non-radiographic axial spondyloarthritis with objective signs of inflammation, treatment of adults with moderate to severe plaque psoriasis and chronic severe plaque psoriasis in children and adolescents from the age of 6 years, subject to certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Enbrel, a centrally authorised medicine containing etanercept 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 Enbrel (etanercept) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include inflammatory bowel disease (IBD) as an undesirable effect with a frequency 'uncommon'. Therefore, the current terms of the marketing authorisation(s) should be varied[27].
- In the next PSUR, the MAH should closely monitor cases of human papillomavirus (HPV) infection, cervical dysplasia and cervical cancer. In addition, the MAH should provide cumulative reviews and causality assessment of cases of autoimmune encephalitis. Furthermore, cumulative reviews of cases of pyoderma gangrenosum, pancreatitis and alopecia should be submitted.

[26] All except biosimilar product(s)
[27] Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

The PRAC considered that PSURs for 'etanercept (all except biosimilar(s))'- and 'etanercept (biosimilar(s) only)'-containing products should be assessed in the future within the same PSUSA procedure. Therefore the list of Union reference dates (EURD list) should be updated accordingly. The next PSUR should be submitted in accordance with the requirements set out in the EURD list provided for under Article 107c(7) of Directive 2001/83/EC.

6.1.8. Evolocumab - REPATHA (CAP) - PSUSA/00010405/201901

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

Background

Evolocumab is an inhibitor of proprotein convertase subtilisin/kexin type 9 (PCSK9). IT is indicated, as Repatha, for the treatment of adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet in combination with a statin or statin with other lipid-lowering therapies and alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated. It is also indicated in adults and adolescents aged 12 years and over with homozygous familial hypercholesterolaemia in combination with other lipid-lowering therapies and in adults with established atherosclerotic cardiovascular disease to reduce cardiovascular risk by lowering low-density lipoprotein cholesterol (LDL-C) levels, subject to certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Repatha, a centrally authorised medicine containing evolocumab 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 Repatha (evolocumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include hypersensitivity reaction as an undesirable effect with a frequency 'common'. Therefore, the current terms of the marketing authorisation(s) should be varied[28].
- In the next PSUR, the MAH should provide a cumulative review of cases of headache and should discuss cases of neoplasms, including the available non-clinical, clinical, post marketing and epidemiological data to evaluate whether there are data indicating a malignancy risk associated with evolocumab.

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

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

6.1.9. Ferric maltol - FERACCRU (CAP) - PSUSA/00010476/201902

Applicant: Norgine B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

Background

Ferric maltol is an iron complex with a trimaltol ligand indicated, as Feraccru, for the treatment of iron deficiency.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Feraccru, a centrally authorised medicine containing ferric maltol 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 Feraccru (ferric maltol) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include discoloured faeces as an undesirable effect with a frequency 'common'. Therefore, the current terms of the marketing authorisation(s) should be varied[29].

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. Ingenol mebutate - PICATO (CAP) - PSUSA/00010035/201901

Applicant: LEO Laboratories Ltd

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

Background

Ingenol mebutate has shown *in vivo* and *in vitro* models a dual mechanism of action for the effects of induction of local lesion cell death and for promoting an inflammatory response characterised by local production of pro-inflammatory cytokines and chemokines and infiltration of immunocompetent cells. Ingenol mebutate is indicated, as Picato, for the cutaneous treatment of non-hyperkeratotic, non-hypertrophic actinic keratosis in adults.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Picato, a centrally authorised medicine containing ingenol mebutate and issued a recommendation on its marketing authorisation(s). For further background, see PRAC minutes July 2019.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Picato (ingenol mebutate) in the approved indication(s) remains unchanged.

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

- Nevertheless, the product information should be updated to add a warning on cutaneous malignancies, namely basal cell carcinoma, Bowen's disease and squamous cell carcinoma (SCC). Therefore, the current terms of the marketing authorisation(s) should be varied[30].
- The PRAC agreed on the distribution of a direct healthcare professional communication (DHPC) together with a communication plan.

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.

In light of the outcome of the current PSUSA procedure and considering the potential risk of new skin tumour in the treatment area and the difficulty to generate appropriate data to address the uncertainty about this risk, the PRAC considered a review of all available data, including from ongoing studies and its impact on the benefit-risk balance of Picato (ingenol mebutate) in its authorised indication was necessary. The European Commission (EC) initiated on 3 September 2019 a referral procedure under Article 20 of Regulation (EC) No 726/2004.

The recommendation is without prejudice to the final conclusions of the referral procedure under Article 20 of Commission Regulation (EC) No 726/2004. See under 3.1.1.

6.1.11. Nilotinib - TASIGNA (CAP) - PSUSA/00002162/201901

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Hans Christian Siersted

Scope: Evaluation of a PSUSA procedure

Background

Nilotinib is an inhibitor of the Abelson murine leukaemia viral oncogene (ABL) tyrosine kinase activity. It is indicated, as Tasigna, for the treatment of adult and paediatric patients with newly diagnosed Philadelphia chromosome positive chronic myelogenous leukaemia (CML) in the chronic phase, adult patients with chronic phase and accelerated phase Philadelphia chromosome positive CML with resistance or intolerance to prior therapy and paediatric patients with chronic phase Philadelphia chromosome positive CML with resistance or intolerance to prior therapy.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Tasigna, a centrally authorised medicine containing nilotinib 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 Tasigna (nilotinib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include growth retardation in the paediatric population as a warning and as an undesirable effect with a frequency

[30] 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

'very common'. Therefore, the current terms of the marketing authorisation(s) should be varied[31].

- In the next PSUR, the MAH should add thrombotic microangiopathy (TMA) as an important potential risk in the safety concerns and provide a discussion on new information concerning the risk of hepatotoxicity and present the details on cases of sudden death.

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.

Given the association of nilotinib with growth retardation in the paediatric population and a similar risk for imatinib and dasatinib being already known, the PRAC considered there is a potential class effect for BCR[32]-ABL targeting tyrosine kinase inhibitors (TKIs). The PRAC agreed that MAHs of other BCR-ABL TKIs, bosutinib- and ponatinib-containing products, should provide in their next PSURs cumulative reviews of data on of growth retardation in the paediatric population from all sources. Further consideration is to be given at the level of CHMP.

6.1.12. Ospemifene - SENSHIO (CAP) - PSUSA/00010340/201902

Applicant: Shionogi B.V.

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

Background

Ospemifene is a non-steroidal selective oestrogen receptor modulator (SERM) indicated, as Senshio, for the treatment of moderate to severe symptomatic vulvar and vaginal atrophy (VVA) in post-menopausal women who are not candidates for local vaginal oestrogen therapy.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Senshio, a centrally authorised medicine containing ospemifene 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 Senshio (ospemifene) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include vaginal haemorrhage as an undesirable effect with a frequency 'common'. Therefore, the current terms of the marketing authorisation(s) should be varied[33].

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.

[31] 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
[32] Breakpoint cluster region protein
[33] Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

6.1.13. Paclitaxel albumin - ABRAXANE (CAP) - PSUSA/00010123/201901

Applicant: Celgene Europe BV

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

Background

Paclitaxel albumin corresponds to nanoparticles of human serum albumin-paclitaxel, an antimicrotubule agent. It is indicated, as Abraxane, for the treatment of metastatic breast cancer in adult patients who have failed first-line treatment for metastatic disease and for whom standard, anthracycline containing therapy is not indicated; in combination with gemcitabine for the first-line treatment of adult patients with metastatic adenocarcinoma of the pancreas as well in combination with carboplatin for the first-line treatment of non-small cell lung cancer (NSCLC) in adult patients who are not candidates for potentially curative surgery and/or radiation therapy.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Abraxane, a centrally authorised medicine containing paclitaxel albumin 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 Abraxane (paclitaxel albumin) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include scleroderma as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[34].

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

6.1.14. Pegfilgrastim - FULPHILA (CAP); NEULASTA (CAP); PELGRAZ (CAP); PELMEG (CAP); UDENYCA (CAP); ZIEXTENZO (CAP) - PSUSA/00002326/201901

Applicant(s): Accord Healthcare S.L.U. (Pelgraz), Amgen Europe B.V. (Neulasta), Cinfa Biotech S.L. (Pelmeg), ERA Consulting GmbH (Udenyca), Mylan S.A.S (Fulphila), Sandoz GmbH (Ziextenzo)

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

Background

Pegfilgrastim is a pegylated human granulocyte colony stimulating factor (G-CSF) indicated, as Fulphila, Neulasta, Pelgraz, Pelmeg, Udenyca and Ziextenzo, for the reduction in the duration of neutropenia and the incidence of febrile neutropenia in adult patients treated with cytotoxic chemotherapy for malignancy with the exception of chronic myeloid leukaemia and myelodysplastic syndromes.

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

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Fulphila, Neulasta, Pelgraz, Pelmeg, Udenyca and Ziextenzo, centrally authorised medicines containing pegfilgrastim 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 Fulphila, Neulasta, Pelgraz, Pelmeg, Udenyca and Ziextenzo (pegfilgrastim) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include Stevens-Johnson syndrome (SJS) as a warning and as an undesirable effect with a frequency 'rare'. Therefore, the current terms of the marketing authorisation(s) should be varied[35].
- In the next PSUR, the MAH Amgen should provide a cumulative review and discussion of cases of medication errors with the on-body injector (OBI).

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.

6.1.15. Pirfenidone - ESBRIET (CAP) - PSUSA/00002435/201902

Applicant: Roche Registration GmbH

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

Background

Pirfenidone is an immunosuppressant indicated in adults, as Esbriet, for the treatment of mild to moderate idiopathic pulmonary fibrosis (IPF).

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Esbriet, a centrally authorised medicine containing pirfenidone 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 Esbriet (pirfenidone) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add anaphylaxis as a warning and as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[36].
- The MAH should submit to EMA, within 60 days, a detailed review of cases of serious hepatic reactions, including all available evidence and review the adequacy of the current risk minimisation measures (RMM) of the product information. In addition, the MAH should provide a detailed review of cases of hyponatraemia together with a

[35] 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
[36] 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

discussion on possible mechanisms. The MAH should include a proposal for updating the product information as warranted.

- In the next PSUR, the MAH should provide a cumulative review of cases of serious severe cutaneous adverse reactions (SCARs) with an evaluation of data from other sources including a review of the literature. The MAH should include a proposal for updating the product information as warranted. In addition, a review of data on atrial fibrillation, cerebrovascular accident and myocardial infarction with consideration to data from all relevant sources should be included.

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.

6.1.16. Telotristat - XERMELO (CAP) - PSUSA/00010639/201902

Applicant: Ipsen Pharma

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

Background

Telotristat ethyl and its active metabolite telotristat are inhibitors of L-tryptophan hydroxylases (TPH1 and TPH2). It is indicated, as Xermelo, for the treatment of carcinoid syndrome diarrhoea in combination with somatostatin analogue (SSA) therapy in adults inadequately controlled by SSA therapy.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Xermelo, a centrally authorised medicine containing telotristat 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 Xermelo (telotristat) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include nausea, depression and intestinal obstruction as undesirable effects with a frequency 'very common', 'common' and 'uncommon' respectively. The existing warning on depressive disorders is adjusted accordingly. Therefore, the current terms of the marketing authorisation(s) should be varied[37].
- In the next PSUR, the MAH should provide detailed reviews of cases of vomiting, arthralgia and back pain and dizziness.

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.

[37] 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

6.1.17. Vismodegib - ERIVEDGE (CAP) - PSUSA/00010140/201901

Applicant: Roche Registration GmbH

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

Background

Vismodegib is an orally available small-molecule inhibitor of the Hedgehog pathway. It is indicated, as Erivedge, for the treatment of adult patients with symptomatic metastatic basal cell carcinoma and for the treatment of adult patients with locally advanced basal cell carcinoma inappropriate for surgery or radiotherapy.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Erivedge, a centrally authorised medicine containing vismodegib 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 Erivedge (vismodegib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add a warning on serious cutaneous adverse reactions (SCARs) and to include Stevens Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalised exanthematous pustulosis (AGEP) as undesirable effects with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[38].
- In the next PSUR, the MAH should provide a cumulative review of cases of muscular weakness, muscle atrophy and rhabdomyolysis from clinical trials, post marketing and the literature. The causality should be discussed for all cases. In addition, the MAH should include a review of pregnancy cases as part of the important identified risk of teratogenicity.

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

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

See Annex I 16.2.

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

See also Annex I 16.3.

[38] 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

6.3.1. 5-fluorouracil[39] (NAP) - PSUSA/00010000/201901

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

5-fluorouracil is an antineoplastic and antimetabolite agent indicated, for topical use, for the treatment of superficial pre-malignant and malignant skin lesions, keratoses including senile, actinic and arsenical forms, keratoacanthoma (KA), Bowen's disease, erythroplasia of Queyrat, superficial basal-cell carcinoma and acuminated condyloma.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing 5-fluorouracil 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 5-fluorouracil-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include application site haemorrhage as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[40].
- In the next PSUR, the MAH should provide a detailed review of cases of blood and lymphatic system disorders.

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. Botulinum neurotoxin type A (150 kD) free from complexing proteins (NAP) - PSUSA/00009084/201812

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Botulinum neurotoxin type A (150 kD) free from complexing proteins blocks cholinergic transmission at the neuromuscular junction by inhibiting the release of acetylcholine. It is indicated for the symptomatic treatment of blepharospasm, cervical dystonia of a predominantly rotational form, spasticity of the upper limb in adults and chronic sialorrhoea due to neurological disorders in adults. It is also indicated for the temporary improvement in the appearance of upper facial lines in adults below 65 years when the severity of these lines has an important psychological impact for the patient, moderate to severe vertical lines

[39] For topical formulation(s) only
[40] 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

between the eyebrows seen at maximum frown (glabellar frown lines), and/or moderate to severe lateral periorbital lines seen at maximum smile (crow's feet lines), and/or moderate to severe horizontal forehead lines seen at maximum contraction.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing botulinum neurotoxin type A (150 kD) free from complexing proteins 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 botulinum neurotoxin type A (150 kD) free from complexing proteins-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include muscle atrophy as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[41].
- In the next PSUR, the MAH(s) should assess whether the information in the product information is sufficient to address the potential of medication errors and to prevent their occurrence. The MAH(s) should closely monitor the use in the pediatric population and update the review on muscle atrophy with recent information, including a reasonable mechanism of action. The MAHs should present the available information on drug-induced seizures and present the new available information on antitoxin administration in the management of iatrogenic botulism.

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

6.3.3. Botulinium toxin A (NAP) - PSUSA/00000426/201812

Applicant(s): various

PRAC Lead: Ronan Grimes

Scope: Evaluation of a PSUSA procedure

Background

Botulinium toxin A is a purified botulinum neurotoxin complex. It is indicated for the treatment of spasticity associated with neurologic disorders, blepharospasm, hemifacial spasm, cervical dystonia, chronic migraine, idiopathic overactive bladder (with symptoms of urinary incontinence, urgency and frequency), urinary incontinence in adults with neurogenic detrusor overactivity resulting from neurogenic bladder due to stable sub-cervical spinal cord injury, or multiple sclerosis, persistent severe primary hyperhidrosis of the axillae. It is also indicated for the temporary improvement in the appearance moderate to severe vertical lines between the eyebrows seen at maximum frown, moderate to severe lateral canthal lines (crow's feet lines) and moderate to severe forehead lines seen at maximum eyebrow elevation, subject to certain conditions.

[41] 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

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing botulinium toxin A 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 botulinium toxin A-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include eyelid oedema as an undesirable effect in the 'additional information' section on post-marketing experience. Therefore, the current terms of the marketing authorisation(s) should be varied[42].
- In the next PSUR, the MAH should present the new available information on antitoxin administration in the management of iatrogenic botulism and propose updates 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.

6.3.4. Botulinum toxin A-haemagglutinin complex (NAP) - PSUSA/00000427/201812

Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Background

Botulinum toxin A-haemagglutinin complex is a botulinum neurotoxin complex indicated for the symptomatic treatment of focal spasticity affecting the upper and/or lower limbs. It is also indicated for the treatment of spasmodic torticollis, blepharospasm, hemifacial spasm and axillary hyperhidrosis. In addition, it is indicated for the treatment of moderate to severe glabellar lines and moderate to severe lateral canthal lines.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing botulinum toxin A-haemagglutinin complex 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 botulinum toxin A-haemagglutinin complex-containing medicinal product(s) in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to remove the existing reference to the absence of a specific antidote (antitoxin) in case of overdose. Therefore, the current terms of the marketing authorisation(s) should be varied[43].

[42] 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
[43] Update of SmPC section 4.9. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

- In the next PSUR, the MAH should continue monitoring and discuss the appearance of the neutralizing antibodies in patients treated with botulinum toxin type A. In addition, the MAH(s) should continue monitoring cardiac disorders, life-threatening and fatal events, ear and labyrinthine disorders, and safety in patients with neuromuscular disease. Furthermore, the MAH(s) should continue monitoring cases of overdosing and botulism in all indications.

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

6.3.5. Bupropion (NAP) - PSUSA/00000461/201812

Applicant(s): various

PRAC Lead: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

Background

Bupropion is a selective inhibitor of the neuronal re-uptake of noradrenaline and dopamine indicated for the treatment of major depressive disorder (MDD) and for the treatment of nicotine dependence as an aid to smoking cessation.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing bupropion 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 bupropion-containing medicinal products in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAH(s) should provide further reviews of neurosensory deafness and deafness, including cases with co-reported tinnitus and provide an overall discussion including a discussion on a potential mechanism of action.
- The PRAC considered that increased sexual function with bupropion use should be further reviewed. The detailed review should include all available information including cases published in the literature, data from non-clinical studies, clinical and epidemiological studies and post marketing spontaneous reports. Further consideration is to be given at the level of the CMDh.
- The PRAC also considered that a detailed review of serotonin syndrome, including cases from clinical trials and post-marketing sources together with a discussion of the relevant literature is necessary. Further consideration is to be given at the level of the CMDh.

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

6.3.6. Testosterone[44] (NAP) - PSUSA/00010631/201812

Applicant(s): various

PRAC Lead: Maia Uusküla

Scope: Evaluation of a PSUSA procedure

Background

Testosterone is an androgen indicated[45] as testosterone replacement therapy for male hypogonadism.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing testosterone[46] 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 testosterone-containing medicinal product(s)[47] in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to revise the existing warning on clotting disorders by adding the need for exercising caution in patients with venous thromboembolism (VTE) risk factors. In addition, a new warning should be added to mention that VTE cases have been reported in thrombophilic patients despite anticoagulation treatment and recommending careful evaluation of continuous testosterone treatment after the first thrombotic event. Therefore, the current terms of the marketing authorisation(s) should be varied[48].
- In the next PSUR, all MAHs should provide a review of cases of VTE from all sources including the scientific literature. The MAH Bayer should also provide a review of cases of inappropriate schedule of drug administration as well as an evaluation of the effectiveness of the educational materials in the next PSUR.

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.

6.3.7. Testosterone[49] (NAP) - PSUSA/00002908/201812

Applicant(s): various

PRAC Lead: Maia Uusküla

Scope: Evaluation of a PSUSA procedure

Background

[44] For all formulations (apart from topical use)
[45] For all formulations (apart from topical use)
[46] For all formulations (apart from topical use)
[47] For all formulations (apart from topical use)
[48] Update of SmPC section 4.4. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position
[49] For topical use only

Testosterone is an androgen indicated for topical use as testosterone replacement therapy for male hypogonadism.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing testosterone for topical use 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 testosterone-containing medicinal product(s) for topical use in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to revise the existing warning on clotting disorders by adding the need for exercising caution in patients with venous thromboembolism (VTE) risk factors. In addition, a new warning should be added to mention that VTE cases have been reported in thrombophilic patients despite anticoagulation treatment and recommending careful evaluation of continuous testosterone treatment after the first thrombotic event. Therefore, the current terms of the marketing authorisation(s) should be varied[50].

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.

6.3.8. Zafirlukast[51] - PSUSA/00003138/201812

Applicant(s): various

PRAC Lead: Ronan Grimes

Scope: Evaluation of a PSUSA procedure

Background

Zafirlukast is an orally active selective competitive receptor antagonist for the leukotriene peptide C_4, D_4 and E_4 components of slow reacting substance of anaphylaxis indicated for the prophylaxis and chronic treatment of asthma in adults and children aged 5 years and older.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of medicinal product(s) containing zafirlukast.

Following the submission and start of the PSUSA procedure, the PRAC was informed that all marketing authorisation(s) for zafirlukast-containing product(s) had been withdrawn for commercial reasons throughout the European Union (EU) as of 26 August 2019. In line with the 'Guidance on handling of PSUR procedures for suspended or withdrawn / non-renewed / revoked marketing authorisations' (EMA/576230/2015) (see PRAC minutes January 2016), the PRAC also reviewed the need for further/ad-hoc PSUR(s).

Summary of recommendation(s) and conclusions

[50] Update of SmPC section 4.4. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position
[51] Last marketing authorisation(s) valid in the EU withdrawn on 26 August 2019

- Based on the review of the data on safety and efficacy, the benefit-risk balance of zafirlukast-containing medicinal product(s) in the approved indications remains unchanged.
- The PRAC discussed the assessment report produced by the lead Member State and noted the preliminary recommendation to add warning on neuropsychiatric effects.

The PRAC agreed that no further PSURs are necessary in light of the current context. The list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC is updated accordingly.

6.4. Follow-up to PSUR/PSUSA procedures

See also Annex I 16.4.

6.4.1. Interferon beta-1a - REBIF (CAP) - EMEA/H/C/000136/LEG 044.1

Applicant: Merck Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: MAH's response to LEG 044 [detailed justification regarding the decrease of spontaneous reports during the period covered by the PSUSA procedure together with a cumulative review of cases of panniculitis, as requested in the conclusions of periodic single assessment procedure PSUSA/00009198/201805 adopted at the December 2018 PRAC (held on 26-29 November 2018)] as per the conclusions adopted in April 2019

Background

Interferon beta-1a is a recombinant interferon, glycoproteins endowed with immunomodulatory, antiviral and antiproliferative properties. It is indicated, as Rebif, for the treatment of relapsing multiple sclerosis, as well as in patients with a single demyelinating event with an active inflammatory process, if alternative diagnoses have been excluded, and if they are determined to be at high risk of developing clinically definite multiple sclerosis.

Following the evaluation of the most recently submitted PSURs for the above-mentioned medicine(s), the PRAC requested the MAH to submit a variation to include injection site panniculitis as an undesirable effect with a frequency 'not known'. For background, see PRAC minutes December 2018 (held 26-29 November 2018) and PRAC minutes April 2019. The MAH provided a justification for not submitting the variation requested in the conclusions of LEG 044 and the response was assessed by the Rapporteur for further PRAC advice.

Summary of advice/conclusion(s)

- The PRAC supported that there is a reasonable possibility of a causal relationship between interferon treatment and panniculitis in patients treated with Rebif (interferon beta-1a).
- The PRAC agreed that the MAH should submit to EMA, within 60 days, a variation to update the product information to include injection site panniculitis as an undesirable effect with a frequency 'not known'.

7. Post-authorisation safety studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)[52]

See also Annex I 17.1.

7.1.1. Axicabtagene ciloleucel - YESCARTA (CAP) - EMEA/H/C/PSP/S/0079.1

Applicant: Kite Pharma EU B.V., ATMP[53]

PRAC Rapporteur: Anette Kirstine Stark

Scope: MAH's response to PSP/S/0079 [protocol for a long-term, non-interventional study in patients taking Yescarta (axicabtagene ciloleucel) for the treatment of relapsed or refractory diffuse large B-cell lymphoma and primary mediastinal B-cell lymphoma to evaluate the safety of patients, including secondary malignancies, cytokine release syndrome (CRS), neurologic events, serious infections, prolonged cytopenias, hypogammaglobulinaemia and pregnancy outcomes in female patients of childbearing potential] as per the request for supplementary information (RSI) adopted in May 2019

Background

Yescarta is a centrally authorised medicine containing axicabtagene ciloleucel, an engineered autologous T-cell immunotherapy product. Yescarta (axicabtagene ciloleucel) is indicated for treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma (PMBCL), after two or more lines of systemic therapy.

As part of the conditions or restrictions with regard to the safe and effective use of the medicinal product (Annex II-D of the marketing authorisation(s)) a non-interventional PASS based on a registry should be conducted to assess the safety profile including long term safety in patients with B-lymphocyte malignancies treated with axicabtagene ciloleucel in the post marketing setting. In accordance with Article 107n(3) of Directive 2001/83/EC, the MAH submitted a protocol for a PASS entitled: 'long term, non-interventional study of recipients of Yescarta for treatment of relapsed or refractory diffuse large B-cell lymphoma and primary mediastinal B-cell lymphoma' for which PRAC adopted in May 2019 a request for supplementary information (RSI). The PRAC is responsible for evaluating the PASS protocol. For further background, see PRAC minutes May 2019.

Endorsement/Refusal of the protocol

- The PRAC discussed several outstanding aspects of the post-marketing safety surveillance of chimeric antigen receptor T (CAR-T) cells therapy products using disease registries, in context of the currently ongoing imposed PASS protocol procedure, which is due to be discussed further at the October 2019 PRAC meeting.

7.1.2. Dapagliflozin – EDISTRIDE (CAP); FORXIGA (CAP) - EMEA/H/C/PSP/S/0083

Applicant(s): AstraZeneca AB

PRAC Rapporteur: Annika Folin

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

Scope: Protocol for a non-interventional PASS: an observational cohort study using existing data sources in European countries to estimate the incidence of diabetic ketoacidosis (DKA) in type 1 diabetes mellitus (T1DM) dapagliflozin users following implementation of risk minimisation measures (RMMs) in Europe, as required in the outcome of the extension of indication procedure on type 1 diabetes mellitus (T1DM) (EMEA/H/C/WS1344) finalised in January 2019

Background

Edistride and Forxiga are centrally authorised medicines containing dapagliflozin, a selective and reversible inhibitor of sodium glucose cotransporter type 2 (SGLT2). Edistride and Forxiga (dapagliflozin) are indicated in adults for the treatment of insufficiently controlled type 2 diabetes mellitus (T2DM) as an adjunct to diet and exercise as monotherapy when metformin is considered inappropriate due to intolerance and in addition to other medicinal products for the treatment of T2DM. They are also indicated in adults for the treatment of insufficiently controlled type 1 diabetes mellitus (T1DM) as an adjunct to insulin in patients with body mass index (BMI) $\geq$ 27 kg/m^2, when insulin alone does not provide adequate glycaemic control despite optimal insulin therapy.

As part of the conditions or restrictions with regard to the safe and effective use of the medicinal products (Annex II-D of the marketing authorisation(s) for Edistride, Annex II-D of the marketing authorisation(s) for Forxiga) a non-interventional observational cohort PASS using existing data sources in European countries should be conducted in order to estimate the incidence of DKA in T1DM dapagliflozin users following implementation of risk minimisation measures (RMMs) in Europe. In accordance with Article 107n(3) of Directive 2001/83/EC, the MAH submitted protocol version 1.0 entitled: 'evaluation of effectiveness of dapagliflozin risk minimisation measures in T1DM in Europe: a retrospective cohort study on the risk of DKA'. The PRAC is responsible for evaluating the PASS protocol.

Endorsement/Refusal of the protocol

- The PRAC, having considered protocol version 1.0 in accordance with Article 107n of Directive 2001/83/EC, objected to the draft protocol for Edistride and Forxiga (dapagliflozin). The PRAC agreed that the PASS is non-interventional but the study design does not fulfil the study objectives at this stage. In particular, the PRAC considered that the information on actual exposure to RMMs should be made accessible, and reassurance given on the validity of the T1DM and DKA diagnoses.
- The MAH should submit a revised PASS protocol within 60 days to the EMA. A 60 day-assessment timetable will be followed.

7.1.3. Ingenol mebutate – PICATO (CAP) - EMEA/H/C/PSP/S/0081

Applicant: LEO Laboratories Ltd

PRAC Rapporteur: Adam Przybylkowski

Scope: Protocol for an observational comparative safety study (POCKET) of patients with actinic keratosis in German claims database to evaluate the safety of ingenol mebutate gel treatment

Background

Ingenol mebutate has shown in *in vivo* and *in vitro* models a dual mechanism of action for the effects of induction of local lesion cell death and for promoting an inflammatory response

characterised by local production of pro-inflammatory cytokines and chemokines and infiltration of immunocompetent cells. Ingenol mebutate is indicated, as Picato, for the cutaneous treatment of non-hyperkeratotic, non-hypertrophic actinic keratosis (AK) in adults.

As part of the conditions or restrictions with regard to the safe and effective use of the medicinal product (Annex II-D of the marketing authorisation(s)) a non-interventional cohort PASS should be conducted in order to investigate the rate of skin malignancies (squamous cell carcinoma, Bowen's disease, basal cell carcinoma, keratoacanthoma, malignant melanoma) in patients with AK treated with ingenol mebutate compared to patients with AK treated with other AK treatments. In accordance with Article 107n(3) of Directive 2001/83/EC, the MAH submitted protocol version 0.1 for a study entitled 'Picato observational comparative safety study of AK patients in German claims database (POCKET)'. The PRAC is responsible for evaluating the PASS protocol.

Endorsement/Refusal of the protocol

- The PRAC, having considered protocol version 0.1 in accordance with Article 107n of Directive 2001/83/EC, objected to the draft protocol for Picato (ingenol mebutate). The PRAC agreed that the PASS is non-interventional but the study design does not fulfil the study objectives at this stage. In particular, the MAH should justify its choice of comparator based on expected efficacy. The MAH should also discuss potential for off-label use of ingenol mebutate gel 0.015% in other treatment areas than face and scalp. In addition, the MAH is requested to discuss in the study protocol the extent of comparability between treatment cohorts, taking into account follow-up treatment, biopsy rate and disease severity.
- The MAH should submit a revised PASS protocol within 60 days to the EMA. A 60 day-assessment timetable will be followed.

7.1.4. Nonacog beta pegol – REFIXIA (CAP) - EMEA/H/C/PSA/S/0041

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Amendment to a protocol previously agreed in June 2018 (PSP/S/0059) for a non-interventional PASS in male haemophilia B patients receiving nonacog beta pegol (N9-GP) prophylaxis treatment to investigate safety of N9-GP during long-term routine use

Background

Nonacog beta pegol is a purified recombinant human factor IX (rFIX). Nonacog beta pegol is indicated, as Refixia, for the treatment and prophylaxis of bleeding in patients 12 years and above with haemophilia B (congenital factor IX deficiency).

As part of the conditions or restrictions with regard to the safe and effective use of the medicinal product (Annex II-D of the marketing authorisation(s)) a non-interventional PASS deriving from a registry of haemophilia patients should be conducted in order to investigate the potential effects of polyethylene glycol (PEG) accumulation in the choroid plexus of the brain and other tissues/organs. In accordance with Article 107n(3) of Directive 2001/83/EC, the MAH submitted protocol version 2.0 for a study entitled 'a non-interventional PASS in male haemophilia B patients receiving nonacog beta pegol (N9-GP) prophylaxis treatment'. The PRAC is responsible for evaluating the PASS protocol.

Endorsement/Refusal of the protocol

- The PRAC, having considered protocol version 2.0 in accordance with Article 107n of Directive 2001/83/EC, objected to the draft protocol for Refixia (nonacog beta pegol). The PRAC agreed that the PASS is non-interventional but the study design does not fulfil the study objectives at this stage. In particular, the PRAC did not support the proposed diary and alternative solution should be made. Inhibitor testing prior to baseline and immunogenicity/hypersensitivity questionnaire can be removed as these will be reported as adverse event(s) of special interest (AESI).
- The MAH should submit a revised PASS protocol within 30 days to the EMA. A 30 day-assessment timetable will be followed.

7.1.5. Sotagliflozin – ZYNQUISTA (CAP) - EMEA/H/C/PSP/S/0084

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Martin Huber

Scope: Protocol for an observational retrospective cohort study using existing data sources on the incidence of diabetic ketoacidosis (DKA) in adult patients with type 1 diabetes mellitus (T1DM) treated with sotagliflozin as an adjunct to insulin versus insulin alone, as required in the outcome of the initial opinion/marketing authorisation (EMEA/H/C/004889) finalised in February 2019

Background

Zynquista, is a centrally authorised medicine containing sotagliflozin, a dual inhibitor of sodium glucose cotransporter type 1 (SGLT1) and SGLT2. Zynquista (sotagliflozin) is indicated for treatment as an adjunct to insulin therapy to improve glycaemic control in adults with type 1 diabetes mellitus (T1DM) with a body mass index (BMI) $\geqslant$ 27 kg/m^2, who have failed to achieve adequate glycaemic control despite optimal insulin therapy.

As part of the conditions or restrictions with regard to the safe and effective use of the medicinal product (Annex II-D of the marketing authorisation(s)) a non-interventional cohort PASS should be conducted in order to estimate the incidence of DKA in T1DM sotagliflozin treated patients to assess the effectiveness of the risk minimisation measures (RMMs) implemented in Europe. In accordance with Article 107n(3) of Directive 2001/83/EC, the MAH submitted protocol version 2.0 for a study entitled 'incidence of DKA in adult patients with T1DM treated with sotagliflozin as an adjunct to insulin versus insulin alone'. The PRAC is responsible for evaluating the PASS protocol.

Endorsement/Refusal of the protocol

- The PRAC, having considered protocol version 2.0 in accordance with Article 107n of Directive 2001/83/EC, objected to the draft protocol for Zynquista (sotagliflozin). The PRAC agreed that the PASS is non-interventional but the study design does not fulfil the study objectives at this stage. In particular, the PRAC considered that the MAH should better identify data sources considered suitable for the conduct of this study. In this respect, the MAH should submit a feasibility assessment as an additional annex to the protocol. The MAH should also revise the sample size estimation and patients should be matched by age, sex and BMI.
- The MAH should submit a revised PASS protocol within 60 days to the EMA. A 60 day-assessment timetable will be followed.

7.1.6. Tisagenlecleucel - KYMRIAH (CAP) - EMEA/H/C/PSP/S/0066.1

Applicant: Novartis Europharm Ltd, ATMP[54]

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: MAH's response to PSA/S/0066 [protocol for non-interventional study CCTL019B2401 with secondary use of data from two registries conducted by the 'European Society for Blood and Marrow Transplantation' (EBMT) and 'Centre for International Blood and Marrow Transplant Research' (CIBMTR) to evaluate the long term safety of patients with B lymphocyte malignancies treated with tisagenlecleucel (chimeric antigen receptor (CAR)-T cell therapy) in a real-world setting] as per the request for supplementary information (RSI) adopted in April 2019

Background

Kymriah is a centrally authorised medicine containing tisagenlecleucel, an engineered autologous T-cell immunotherapy product. Kymriah (tisagenlecleucel) is indicated for treatment of paediatric and young adult patients up to 25 years of age with B-cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant or in second or later relapse and treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy.

As part of the conditions or restrictions with regard to the safe and effective use of the medicinal product (Annex II-D of the marketing authorisation(s)) a non-interventional PASS based on a registry should be conducted to further characterise the safety, including long-term safety. In accordance with Article 107n(3) of Directive 2001/83/EC, the MAH submitted a protocol for study CCTL019B2401 with secondary use of data from two registries conducted by the 'European Society for Blood and Marrow Transplantation' (EBMT) and 'Centre for International Blood and Marrow Transplant Research' (CIBMTR) to evaluate the long term safety of patients with B lymphocyte malignancies treated with tisagenlecleucel (chimeric antigen receptor (CAR)-T cell therapy) in a real-world setting. In April 2019, the PRAC adopted a further request for supplementary information (RSI). The PRAC is responsible for evaluating the PASS protocol. For further background, see PRAC minutes December 2018 (held 26-29 November 2018) and PRAC minutes May 2019.

Endorsement/Refusal of the protocol

- The PRAC discussed several outstanding aspects of the post-marketing safety surveillance of CAR-T cells therapy products using disease registries, in context of the currently ongoing imposed PASS protocol procedure, which is due to be discussed at the following PRAC meeting. Further discussion is planned at the October 2019 PRAC meeting.

7.1.7. Vestronidase alfa – MEPSEVII (CAP) - EMEA/H/C/PSP/S/0082

Applicant: Ultragenyx Germany GmbH

PRAC Rapporteur: Eva Segovia

Scope: Protocol for a PASS to obtain long-term data on effectiveness and safety of treatment with Mepsevii (vestronidase alfa) and to characterise the entire

[54] Advanced therapy medicinal product

mucopolysaccharidosis VII, including variability of clinical manifestation, progression and natural history

Background

Mepsevii is a centrally authorised medicine containing vestronidase alfa, a recombinant form of human beta-glucuronidase (GUS). Mepsevii (vestronidase alfa) is indicated for treatment of non-neurological manifestations of mucopolysaccharidosis VII (MPS VII; Sly syndrome).

As part of the conditions or restrictions with regard to the safe and effective use of the medicinal product (Annex II-E of the marketing authorisation(s) under exceptional circumstances) a non-interventional PASS based on adequate source of data deriving from a disease monitoring programme of patients with MPS VII should be conducted to obtain long-term data on effectiveness and safety of treatment with Mepsevii and to characterise the entire MPS VII, including variability of clinical manifestation, progression and natural history. In accordance with Article 107n(3) of Directive 2001/83/EC, the MAH submitted a protocol version amendment 3/Europe for study UX003-CL401 to the EMA. The PRAC is responsible for evaluating the PASS protocol.

Endorsement/Refusal of the protocol

- The PRAC, having considered protocol amendment 3/Europe in accordance with Article 107n of Directive 2001/83/EC, considered that study UX003-CL401 is non-interventional and endorsed the PASS protocol for vestronidase alfa (Mepsevii).

7.1.8. Volanesorsen – WAYLIVRA (CAP) - EMEA/H/C/PSP/S/0080

Applicant: Akcea Therapeutics Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: 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)

Background

Waylivra is a centrally authorised medicine containing volanesorsen, an antisense oligonucleotide designed to inhibit the formation of apolipoprotein C-III (apoC-III). Waylivra (volanesorsen) is indicated an adjunct to diet in adult patients with genetically confirmed familial chylomicronemia syndrome (FCS) and at high risk for pancreatitis, in whom response to diet and triglyceride lowering therapy has been inadequate.

As part of the conditions or restrictions with regard to the safe and effective use of the medicinal product (Annex II-E of the conditional marketing authorisation(s)) a non-interventional PASS based on a registry should be conducted in order to evaluate the safety, including long term follow-up, of Waylivra on thrombocytopenia and bleeding (including incidence rate, severity and outcomes) in FCS patients according to the dose recommendation and dose algorithm and investigate adherence with platelet monitoring and dose adjustment requirements. In accordance with Article 107n(3) of Directive 2001/83/EC, the MAH submitted PASS protocol version 1.0 to the EMA. The PRAC is responsible for evaluating the PASS protocol.

Endorsement/Refusal of the protocol

- The PRAC, having considered protocol version 1.0 in accordance with Article 107n of Directive 2001/83/EC, objected to the draft protocol for Waylivra (volanesorsen). The PRAC considered that the PASS is non-interventional but the study design does not fulfil the study objectives at this stage. The PRAC considered that the study aims should be transferred into measurable objectives and further stratified analyses included. In addition, the observation of efficacy endpoints should be taken into account within the framework of the registry study.
- The MAH should submit a revised PASS protocol within 60 days to the EMA. A 60 day-assessment timetable will be followed.

7.2. Protocols of PASS non-imposed in the marketing authorisation(s)[55]

See Annex I 17.2.

7.3. Results of PASS imposed in the marketing authorisation(s)[56]

None

7.4. Results of PASS non-imposed in the marketing authorisation(s)[57]

See Annex I 17.4.

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

See Annex I 17.5.

7.6. Others

See Annex 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.

[55] 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
[56] In accordance with Article 107p-q of Directive 2001/83/EC
[57] In accordance with Article 61a (6) of Regulation (EC) No 726/2004, in line with the revised variations regulation for any submission as of 4 August 2013

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

8.1. Annual reassessments of the marketing authorisation

See Annex I 18.1.

8.2. Conditional renewals of the marketing authorisation

See Annex I 18.2.

8.3. Renewals of the marketing authorisation

See also Annex I 18.3.

8.3.1. Naltrexone hydrochloride, bupropion hydrochloride - MYSIMBA (CAP) - EMEA/H/C/003687/R/0033 (without RMP)

Applicant: Orexigen Therapeutics Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: 5-year renewal of the marketing authorisation

Background

Naltrexone is a mu-opioid antagonist and bupropion, a weak 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 (e.g. type 2 diabetes, dyslipidaemia, or controlled hypertension).

Mysimba, a centrally authorised medicine containing naltrexone/bupropion, was authorised in 2015.

The MAH submitted an application for renewal of the marketing authorisation for opinion by the CHMP. The PRAC is responsible for providing advice to the CHMP on this renewal with regard to safety and risk management aspects.

Summary of advice

- Based on the review of the available pharmacovigilance data for Mysimba (naltrexone/bupropion) and the CHMP Rapporteur's assessment report, the PRAC considered that the MAH's responses to the request for supplementary information (RSI) in relation to the submission of the annual interim report on PASS NB-CVOT 2[58] (listed as a category 1 study in Annex II), clarification on its progress and expected completion date should be assessed before providing an advice to the CHMP on the renewal procedure.

[58] A multicentre, randomised, double-blind, placebo-controlled, phase 4 study to assess the effect of naltrexone extended release (ER) /bupropion ER on the occurrence of major adverse cardiovascular events (MACE) in overweight and obese subjects with cardiovascular disease

9. Product related pharmacovigilance inspections

9.1. List of planned pharmacovigilance inspections

None

9.2. Ongoing or concluded pharmacovigilance inspections

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

9.3. Others

None

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

10.1. Safety related variations of the marketing authorisation

10.1.1. Interferon beta-1a – AVONEX (CAP) - EMEA/H/C/000102/II/0182/G, REBIF (CAP) - EMEA/H/C/000136/II/0137/G; Interferon beta-1b - BETAFERON (CAP) - EMEA/H/C/000081/II/0124/G; EXTAVIA (CAP) - EMEA/H/C/000933/II/0096/G peginterferon beta-1a - PLEGRIDY (CAP) - EMEA/H/C/002827/II/0052/G

Applicant(s): Bayer AG (Betaferon), Biogen Netherland (Avonex, Plegridy), Merck Europe B.V. (Rebif), Novartis Europharm Limited (Extavia)

PRAC Rapporteur: Ulla Wändel Liminga

Scope: PRAC consultation on individual variations for (peg)interferon beta-containing products on use in pregnancy, namely grouped variations consisting of: 1) update of sections 4.3 and 4.6 of the SmPC in order to add information on pregnancy following the completion of the European interferon beta (IFN-β) pregnancy registry (eighth annual and final report) and the final clinical study report (CSR) of the register-based study in the Nordic countries EUPAS13054: multiple sclerosis pregnancy study - pregnancy outcomes in multiple sclerosis populations exposed and unexposed to interferon beta - a register-based study in the Nordic countries; 2) update of section 4.6 of the SmPC in order to update the statement regarding breast-feeding following a review of studies, case reports and literature articles (in fulfilment of MEA 024.2 and MEA 021). The package leaflet is updated accordingly. The RMP (version 4.1) is updated accordingly, including the deletion of the important potential risk 'pregnancy outcomes'. The RMP is also updated to bring it in line with revision 2 of the guidance on the format of RMP in the EU (template)

Background

Interferon beta-1a, interferon beta-1b and peginterferon beta-1a are endogenous glycoproteins with immunomodulatory, antiviral and antiproliferative properties indicated for the treatment of patients with a single demyelinating event with an active inflammatory

process and patients with relapsing multiple sclerosis (MS), patients with relapsing-remitting MS and patients with secondary progressive MS subject to certain conditions.

Parallel individual type II variations proposing to update the product information for Avonex (interferon beta-1a), Rebif (interferon beta-1a), Betaferon (interferon beta-1b), Extavia (interferon beta-1b) and Plegridy (peginterferon beta-1a) on the use during pregnancy and breastfeeding is under evaluation at the CHMP. The PRAC was requested to provide advice on these variations. For further background, see PRAC minutes February 2019 and PRAC minutes May 2019.

See also under 5.3.4. , 5.3.6. ,15.3.17. and 15.3.18.

Summary of advice

- Based on the review of the available information, the PRAC agreed with the proposed updates of the product information consisting in lifting the contraindication against initiation of treatment in pregnancy, removing the recommendation that women of child bearing potential should use adequate contraception and removing the information in relation to discontinuation in relation to potential risk for spontaneous abortion. The PRAC supported to update the available information of the product information on exposure during pregnancy and to revise the recommendation regarding use in pregnancy to, that if clinically needed, interferon beta may be used during pregnancy.
- The PRAC agreed with requesting the MAHs to further study exposure during pregnancy and to provide further details of the methodology after completion of the type II variation procedures.

10.1.2. Dimethyl fumarate – TECFIDERA (CAP) - EMEA/H/C/002601/II/0063

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Martin Huber

Scope: PRAC consultation on an update of sections 4.4 and 4.8 of the SmPC to reflect progressive multifocal leukoencephalopathy (PML) in the setting of mild lymphopenia based on data submitted in the ongoing PSUSA/00010143/201903 due for recommendation at the November 2019 PRAC meeting. The package leaflet is updated accordingly. Additionally, the Product Information has been updated in line with the quality review of documents (QRD) template (version 10.1)

Background

Dimethyl fumarate is an immune-modulating agent indicated, as Tecfidera a centrally authorised medicine, for the treatment of adult patients with relapsing remitting multiple sclerosis (RRMS).

A type II variation proposing to update the product information of Tecfidera (dimethyl fumarate) on progressive multifocal leukoencephalopathy (PML) is under evaluation at the CHMP. The PRAC was requested to provide advice on this variation.

Summary of advice

- Based on the review of the available information, the PRAC agreed that the current risk minimisation measures (RMMs) including periodical absolute lymphocyte count (ALC) monitoring and the proposed product information by the MAH are insufficient to cover the broad range of lymphocytopenia observed in PML-confirmed subjects and that the

current risk stratification is not sufficient to adequately reduce the risk of PML. The PRAC advised to request the MAH to provide further clarifications, including a re-analysis of risk factors for PML to enable adequate risk stratification as well as an in-depth discussion on additional measures beyond ALC monitoring to manage the risk of PML.

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

11.2.1. Ranitidine (NAP)

Applicant(s): GlaxoSmithKline, various

PRAC Lead: Amelia Cupelli

Scope: PRAC advice on a review on ranitidine and a potential risk of N-nitrosodimethylamine (NDMA) formation in-vivo

Background

Ranitidine is a competitive and reversible inhibitor of the action of histamine, released by enterochromaffin-like (ECL) cells, at the histamine H2-receptors on parietal cells in the stomach. It is indicated for the treatment of peptic ulceration, gastroesophageal reflux disease (GERD), reflux oesophagitis, Zollinger-Ellison syndrome, chronic episodic dyspepsia, peptic ulcer hemorrhage, prophylaxis of stress ulceration, Mendelson's syndrome, duodenal ulcers, benign gastric ulcers, post-operative ulcer, symptomatic relief of heart burn, dyspepsia (acid indigestion), hyperacidity, and prevention of symptoms associated with consuming food and drink.

The EMA was informed on the potential for ranitidine tablets to produce N-nitrosodimethylamine (NDMA) through the metabolism of ranitidine *in vivo* in the human stomach.

In the context of the evaluation of the available data and from the MAH of the originator

medicinal product containing ranitidine, Italy as the lead Member State (LMS) for ranitidine requested PRAC advice on its assessment.

Summary of advice

- Based on the review of the available information, the PRAC considered that this issue merits a thorough assessment at EU level and was also of the view that this assessment should involve expertise from quality and non-clinical experts. The PRAC considered it important to obtain human data, specifically to investigate excretion data, and complement those results with *in vitro* testing. The PRAC agreed that before an update of the RMP is considered, it should be clarified whether this is a manufacturing issue or whether the formation of NDMA is associated with the degradation of ranitidine in the product or formation in vivo.

Post-meeting note: a review of ranitidine-containing medicines was initiated in September 2019 at the request of the European Commission (EC) under Article 31 of Directive 2001/83/EC (EMEA/H/A-31/1491). The review is being carried out by the Committee for Medicinal Products for Human Use (CHMP).

12. Organisational, regulatory and methodological matters

12.1. Mandate and organisation of the PRAC

12.1.1. PRAC working group - Best practice guide on using PRAC plenary time efficiently and effectively – update on the implementation of quantitative goals

PRAC lead: Martin Huber, Ulla Wändel Liminga, Menno van der Elst, Tatiana Magálová, Ghania Chamouni, Jan Neuhauser

In line with the adopted PRAC best practice guidance (BPG) on Committee efficiency (see PRAC minutes May 2016 and PRAC minutes June 2018) and the adopted implementation plan for the BPG including goals to measure compliance with the recommendations (see PRAC minutes June 2016 and PRAC minutes June 2018), the PRAC was updated at the organisational matters teleconference held on 19 September 2019 on quantitative measures collected for the second quarter of 2019 of PRAC meetings. For previous update, see PRAC minutes April 2019.

12.2. Coordination with EMA Scientific Committees or CMDh-v

None

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

12.3.1. Working Party with Patients' and Consumers' Organisations (PCWP) and Working Party with Healthcare Professionals' Organisations (HCPWP) - work plan 2019-2022

The PRAC endorsed the work plan 2019-2022 for the Working Party with Patients' and Consumers' Organisations (PCWP) and Working Party with Healthcare Professionals' Organisations (HCPWP).

12.4. Cooperation within the EU regulatory network

12.4.1. PRAC strategic review and learning meeting (SRLM) under the Finnish presidency of the European Union (EU) Council – Helsinki, Finland, 22-23 October 2019 - agenda

PRAC lead: Kirsti Villikka, Kimmo Jaakkola

The PRAC was presented with a draft agenda for the 'PRAC strategic review and learning meeting (SRLM)', to be held jointly with the Committee for Medicinal Products for Human Use (CHMP) on 22-23 October 2019 in Helsinki, Finland, under the Finnish presidency of the Council of the European Union (EU).

12.4.2. PRAC strategic review and learning meeting (SRLM) under the Romanian presidency of the European Union (EU) Council - Bucharest, Romania, 22-23 May 2019 - report

PRAC lead: Roxana Stroe, Alexandra Spurni

The PRAC was presented with the conclusions and proposed actions from the 'PRAC strategic review and learning meeting (SRLM)' held on 22-23 May 2019 in Bucharest, Romania, under the Romanian presidency of the Council of the European Union (EU).

12.5. Cooperation with International Regulators

12.5.1. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)-E2D on 'post-approval safety data management' and reflection paper - pharmacoepidemiology discussion group (PEpi-DG): call for nominations

The EMA Secretariat updated PRAC on the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E2D guideline on 'post-approval safety data management' and the reflection paper on 'strategic approach to international harmonisation of technical scientific requirements for pharmacoepidemiological studies submitted to regulatory agencies to advance more effective utilisation of real-world data' which was endorsed by the ICH Assembly in June 2019. It was proposed to establish a pharmacoepidemiology discussion group (PEpi-DG) to exchange information on existing guidance, identify the need for harmonisation and propose the scope for guidance. The PRAC agreed with the nomination of Brigitte Keller-Stanislawski.

12.5.2. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)-E19 on 'optimisation of safety data collection' – draft guideline

As a follow-up to the discussion in May 2019 (for background, see PRAC minutes May 2019), the PRAC was updated on the status of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E19 guideline on 'optimisation of safety data collection'. The PRAC discussed its draft response to the public consultation on this guideline. PRAC members were invited to send final comments by 27 September 2019. The PRAC responses are due for adoption at its October 2019 meeting.

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

None

12.7. PRAC work plan

12.7.1. PRAC work plan 2019 – mid-year report

PRAC lead: Sabine Straus, Martin Huber

At the organisational matters teleconference held on 19 September 2019, the EMA Secretariat presented to PRAC a mid-year status update on the activities described in the PRAC work plan 2019. The PRAC will initiate its work plan for 2020 taking into account the activities completed, progress made, priorities identified at the level of the Committee, EMA, Heads of Medicines Agencies (HMA) and EU network as well as the EMA business continuity plan (BCP).

12.8. Planning and reporting

12.8.1. EU Pharmacovigilance system – quarterly workload measures and performance indicators – Q2 2019 and predictions

At the organisational matters teleconference held on 19 September 2019, the EMA Secretariat presented quarterly figures on the EMA pharmacovigilance system-related workload and performance indicators. For previous update, see PRAC minutes April 2019.

12.8.2. PRAC workload statistics – Q2 2019

The EMA secretariat presented, at the organisational matters teleconference held on 19 September 2019, quarterly and cumulative figures to estimate the evolution of the workload of the PRAC, by reflecting on the number of procedures and agenda items covered at each PRAC plenary meeting. For previous update, see PRAC minutes April 2019.

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 PRAC was updated on the activities of the GPAG, focussing on harmonising and streamlining the EURD list, and noted the GPAG progress highlights. In particular, the PRAC was updated on the development of the EURD tool.

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

Post-meeting note: following the PRAC meeting of September 2019, the updated EURD list was adopted by the CHMP and CMDh at their September 2019 meetings and published on the EMA website on 02/10/2019, see:

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

12.11. Signal management

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

PRAC lead: Menno van der Elst

The PRAC was updated on the progress from the Signal Management Review Technical (SMART) Working Group meeting held on 2 September 2019. The SMART WG discussed the evaluation of the pilot of monitoring EudraVigilance data by MAHs, the process for recommending the circulation of a direct healthcare professional communication (DHPC) and the practicalities of information exchange with other EU bodies in the context of signal assessments.

12.11.2. Signal management - monitoring of EudraVigilance data by MAHs – experience from the pilot period

As a follow-up to the last discussion in July 2019 (see PRAC minutes July 2019), the EMA Secretariat presented the PRAC with an update on the pilot on signal detection in EudraVigilance (EV) by MAHs. The report to the European Commission (EC) on the pilot was under finalisation taking into account comments from PRAC members. The Secretariat also informed PRAC about a joint paper shared by the European Federation of Pharmaceutical Industries and Associations (EFPIA) and other industry associations highlighting their experience with the pilot and preferred way forward. The EMA intends to provide the European Commission (EC) with the final report on the pilot and suggestions by the end of September 2019. A decision on the next steps should be communicated in December 2019.

Post-meeting note: In December 2019, the EC and EMA agreed to extend the pilot until the end of 2021 to generate more robust data after reviewing the experience gained in the first year of the pilot.

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 07/10/2019, see: Home>Human Regulatory>Post-authorisation>Pharmacovigilance>Medicines under additional monitoring>List of medicines under additional monitoring

12.13. EudraVigilance database

12.13.1. Activities related to the confirmation of full functionality

None

12.14. Risk management plans and effectiveness of risk minimisations

12.14.1. Risk management systems

None

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

None

12.15. Post-authorisation safety studies (PASS)

12.15.1. Post-authorisation Safety Studies – imposed PASS

None

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

None

12.16. Community procedures

12.16.1. Referral procedures for safety reasons

None

12.17. Renewals, conditional renewals, annual reassessments

None

12.18. Risk communication and transparency

12.18.1. Public participation in pharmacovigilance

None

12.18.2. Safety communication

None

12.19. Continuous pharmacovigilance

12.19.1. Incident management

None

12.20. Others

12.20.1. EMA relocation to new building, Amsterdam, the Netherlands – update on planned timelines

The EMA Secretariat updated the PRAC on the planned timelines for the new permanent EMA headquarters. The Committee was provided with practical information relating to PRAC meetings in the context of the EMA relocation to its future new building in Amsterdam, the Netherlands.

12.20.2. Good Pharmacovigilance Practice (GVP) Guideline on product or population specific considerations III: pregnancy and breastfeeding – key areas for discussion following comments on the draft guideline

PRAC lead: Ulla Wändel Liminga

In line with the PRAC work plan 2019, the PRAC was presented with a consolidated draft guideline on good pharmacovigilance practices (GVP) Product- or Population-Specific Considerations III: pregnant and breastfeeding women. PRAC members were invited to send final comments by 11 October 2019 for a final discussion at the PRAC ORGAM teleconference scheduled on 17 October 2019 before adoption.

12.20.3. Patient registry initiative and cross-committee task force on registries – call for additional volunteers

PRAC lead: Ulla Wändel Liminga

The EMA Secretariat launched a call for additional PRAC volunteers for the 'Cross-Committee Task Force on Registries' in the context of the preparation of guidance on registries for industry, registry holders, regulators and other stakeholders. PRAC members were invited to send expression of interest to join the task force by 16 September 2019.

Post-meeting note: the following members volunteered to join the 'Cross-Committee Task Force on Registries': Jean-Michel Dogné, Nikica Mirošević Skvrce, Daniel Morales and Antoine Pariente.

12.20.4. Process for nomination of Rapporteurs for referral procedures – revised principles

The EMA Secretariat updated the PRAC on the judgment delivered on 27 March 2019 in case C-680/16 P (August Wolff GmbH and Remedia vs. European Commission) which led to the partial annulment of the Commission Implementing Decision C(2014) 6030 f concerning marketing authorisations for high concentration of estradiol containing human medicinal products for topical use. The EMA Secretariat and PRAC discussed the impact on the appointment of (co-)Rapporteurs in order to guarantee objective impartiality of the Committee.

13. Any other business

None

14. Annex I – Signals assessment and prioritisation[59]

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[60].

[59] 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

14.1.1. Adalimumab – AMGEVITA (CAP); HALIMATOZ (CAP); HEFIYA (CAP); HULIO (CAP); HUMIRA (CAP); HYRIMOZ (CAP); IMRALDI (CAP)

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

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of pericarditis

EPITT 19457 – New signal

Lead Member State(s): SE

14.1.2. Anastrozole (NAP)

Applicant(s): various

PRAC Rapporteur: Zane Neikena

Scope: Signal of hallucinations

EPITT 19449 – New signal

Lead Member State(s): LV

14.1.3. Ibrutinib – IMBRUVICA (CAP)

Applicant(s): Janssen-Cilag International NV

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Signal of neutrophilic dermatoses

EPITT 19444 – New signal

Lead Member State(s): HR

14.1.4. Prasugrel – EFIENT (CAP), PRASUGREL MYLAN (CAP), NAP

Applicant(s): Daiichi Sankyo Europe GmbH (Effient), Mylan S.A.S (Prasugrel Mylan), various

PRAC Rapporteur: Anette Kirstine Stark

Scope: Signal of severe cutaneous adverse reactions (SCARs)

EPITT 19463 – New signal

Lead Member State(s): DK

14.1.5. Sacubitril, valsartan – ENTRESTO (CAP); NEPARVIS (CAP)

Applicant(s): Novartis Europharm Limited

PRAC Rapporteur: Anette Kirstine Stark

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

Scope: Signal of ventricular arrhythmia

EPITT 19448 – New signal

Lead Member State(s): DK

14.2. New signals detected from other sources

14.2.1. Abiraterone – ZYTIGA (CAP); Sulphonylureas: glibenclamide – AMGLIDIA (CAP), NAP; gliclazide (NAP); gliquidone (NAP); glimepiride (NAP); glimepiride, pioglitazone – TANDEMACT (CAP); glipizide (NAP); tolbutamide (NAP)

Applicant(s): Ammtek (Amglidia), Janssen-Cilag International NV (Zytiga), Takeda Pharma A/S (Tandemact), various

PRAC Rapporteur: Eva Segovia

Scope: Signal of interaction with sulphonylureas leading to hypoglycaemia

EPITT 19445 – New signal

Lead Member State(s): BE, DK, ES, FR, HR, IE, IS, NL

14.2.2. Golimumab – SIMPONI (CAP)

Applicant(s): Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of inflammatory myopathy

EPITT 19460 – New signal

Lead Member State(s): SE

14.3. New signals detected from other sources

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. Deferasirox - EMEA/H/C/005156

Scope: Treatment of chronic iron overload

15.1.2. Dexmedetomidine - EMEA/H/C/005152

Scope: Sedation of adult intensive care unit (ICU) patients requiring a sedation level not deeper than arousal in response to verbal stimulation, and sedation of non-intubated adult

patients prior to and/or during diagnostic or surgical procedures requiring sedation

15.1.3. Selinexor - EMEA/H/C/005127, Orphan

Applicant: Karyopharm Europe GmbH

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

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. Aliskiren - RASILEZ (CAP) - EMEA/H/C/000780/WS1581/0123; Aliskiren, hydrochlorothiazide - RASILEZ HCT (CAP) - EMEA/H/C/000964/WS1581/0093

Applicant: Noden Pharma DAC

PRAC Rapporteur: Ilaria Baldelli

Scope: Submission of an updated RMP (version 14) in order to reflect changes in the categorisation of safety concerns in line with revision 2 of GVP module V on 'Risk management systems' and in line with revision 2 of the guidance on the format of RMP in the EU (template). The update also includes the addition of the new important potential risk of non-melanoma skin cancer (related to Rasilez HCT (aliskiren/hydrochlorothiazide) only) as per the final recommendation of the signal on hydrochlorothiazide-containing products and skin cancer (EPITT 19138) adopted in September 2018

15.2.2. Brinzolamide, brimonidine - SIMBRINZA (CAP) - EMEA/H/C/003698/II/0019

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Submission of an updated RMP (version 3.0) in order to remove 'metabolic acidosis/renal impairment' as an important potential risk from the list of safety concerns and to bring it in line with revision 2 of GVP module V on 'Risk management systems'

15.2.3. Guselkumab - TREMFYA (CAP) - EMEA/H/C/004271/II/0013

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Submission of an updated RMP (version 4.0-s1) to remove 'exposure during lactation' as missing information based on a literature review

15.2.4. Human normal immunoglobulin - KIOVIG (CAP) - EMEA/H/C/000628/II/0091

Applicant: Baxter AG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Submission of an updated RMP (version 9.0) in order to include 'chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)' as a new indication and update the list of safety concerns to bring it in line with revision 2 of GVP module V on 'Risk management systems'

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

Applicant: Merck Europe B.V.

PRAC Rapporteur: Hans Christian Siersted

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

15.2.6. Melatonin - SLENYTO (CAP) - EMEA/H/C/004425/II/0010

Applicant: RAD Neurim Pharmaceuticals EEC SARL

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Submission of an updated RMP (version 1.3) to remove 'delay of sexual maturation and development' as an important potential risk based on the results of study NEUCH7911 showing a lack of effect on sexual maturation and growth after 2 years of continuous treatment, and temporary recommendation for use (RTU) data demonstrating a lack of effect on growth after continuous use of up to 3 years

15.2.7. Pazopanib - VOTRIENT (CAP) - EMEA/H/C/001141/II/0054

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Anette Kirstine Stark

Scope: Submission of an updated RMP (version 17.0) in order to postpone the submission due date for the clinical study report (CSR) for study VEG108844 (COMPARZ): a study of pazopanib versus sunitinib in the treatment of subjects with locally advanced and/or metastatic renal cell carcinoma, and its sub-studies. In addition, the RMP is updated to reflect PRAC recommendations for additional assessments of some risks and to revise the categorisation of the safety concerns in line with revision 2 of the guidance on the format of RMP in the EU (template)

15.2.8. Ponatinib - ICLUSIG (CAP) - EMEA/H/C/002695/II/0051, Orphan

Applicant: Incyte Biosciences Distribution B.V.

PRAC Rapporteur: Annika Folin

Scope: Submission of an updated RMP (version 19) in order to reflect deletion/changes in the categorisation of safety concerns in line with revision 2 of GVP module V on 'Risk management systems'. In addition, the RMP is updated to reflect the change of categorisation of posterior reversible encephalopathy syndrome (PRES) as requested in the conclusions of PSUSA/00010128/201712 procedure adopted in July 2018; to correct the categorisation of study AP24534-14-203: a randomised, open-label, phase 2 trial of ponatinib in patients with resistant chronic phase chronic myeloid leukaemia to characterise the efficacy and safety of a range of doses, from a category 3 study to category 1 study in the RMP and Annex II and to revise the due date for the submission of its study report to August 2021, as described in the product information and as agreed in the conclusions of ANX 016 procedure adopted by CHMP in September 2017

15.2.9. Safinamide - XADAGO (CAP) - EMEA/H/C/002396/II/0031

Applicant: Zambon S.p.A.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Submission of an updated RMP (version 6.0) in order to implement changes in line with revision 2 of the guidance on the format of RMP in the EU (template) and to introduce changes to pre-clinical, clinical and post-marketing exposure information, and to update the due date of drug utilisation study (DUS) Z7219N02: a European multicentre retrospective-prospective cohort study to observe safinamide safety profile and pattern of use in clinical practice during the first post-commercialisation phase; from July 2019 to 28 February 2020

15.2.10. Talimogene laherparepvec - IMLYGIC (CAP) - EMEA/H/C/002771/II//0034

Applicant: Amgen Europe B.V., ATMP[61]

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Submission of an updated RMP (version 7.0) in order to add two studies listed as category 3 studies in the RMP, namely: study 20180062: a multinational, non-interventional, cross-sectional survey in patients ≥18 years of age who have received talimogene laherparepvec at least once in the 3 months before completion of the survey to evaluate the effectiveness of the patient-directed additional risk minimisation measures (RMMs); and study 20180099: a multinational, non-interventional, cross-sectional survey in physicians who completed the required talimogene laherparepvec training as part of the controlled distribution program to evaluate the effectiveness of the HCP-directed additional RMMs. In addition, the RMP is updated to include an internal evaluation of managed distribution process metrics, to evaluate the effectiveness of additional risk minimisation measures (aRMM)

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).

[61] Advanced Therapy Medicinal Product

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

Applicant: Portola Netherlands B.V.

PRAC Rapporteur: Menno van der Elst

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

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

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Ghania Chamouni

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

15.3.4. Avelumab - BAVENCIO (CAP) - EMEA/H/C/004338/II/0009/G, Orphan

Applicant: Merck Europe B.V.

PRAC Rapporteur: Hans Christian Siersted

Scope: Grouped variations consisting of: 1) extension of indication to include a new indication as the first-line combination treatment with avelumab and axitinib in adult patients with advanced renal cell carcinoma (aRCC). As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 1.7) are updated accordingly; 2) change in section 4.2 of the SmPC to support the switch of

avelumab dosing regimen from 10 mg/kg every two weeks (weight-based) to a flat dose of 800 mg every two weeks applicable to the new proposed indication aRCC and the existing one on Merkel cell carcinoma (MCC). The MAH took the opportunity to introduce some editorial changes in the product information

15.3.5. Bedaquiline - SIRTURO (CAP) - EMEA/H/C/002614/II/0033/G, Orphan

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Grouped variations consisting of: 1) extension of indication to include patients 12 years of age and older based on week 24 analysis of cohort 1 (adolescent subjects aged ≥12 to <18 years) for study TMC207-TIDP59-C211: a phase 2, open-label, multicentre, single-arm study to evaluate the pharmacokinetics, safety, tolerability and anti-mycobacterial activity of bedaquiline (TMC207) in combination with a background regimen (BR) of multidrug resistant tuberculosis (MDR-TB) medications for the treatment of children and adolescents 0 month to <18 years of age who have confirmed a probable pulmonary MDR-TB. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 3.2) are updated accordingly; 2) update of section 4.9 of the SmPC to remove reference to the use of activated charcoal as an aid to remove unabsorbed bedaquiline in case of overdose

15.3.6. Bevacizumab - AVASTIN (CAP) - EMEA/H/C/000582/II/0110

Applicant: Roche Registration GmbH

PRAC Rapporteur: Hans Christian Siersted

Scope: Submission of the final report from study NEJ026 (listed as a category 1/obligation in Annex II): an open-label, randomised, phase 3 study conducted in Japan to compare erlotinib + bevacizumab combination therapy versus erlotinib monotherapy as first-line therapies for patients with non-small-cell lung carcinoma (NSCLC) with epidermal growth factor receptor (EGFR) gene mutations (exon 19 deletion or exon 21 L858R substitution). The RMP (version 30.0) is updated accordingly. In addition, the package leaflet is updated to reflect information on sodium content in line with the Annex to the European Commission (EC) guideline on 'excipients in the labelling and package leaflet of medicinal products for human use'

15.3.7. Brigatinib - ALUNBRIG (CAP) - EMEA/H/C/004248/II/0003

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Extension of indication to include first-line treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) previously untreated with an ALK inhibitor for Alunbrig (brigatinib). The addition of a new indication is supported by data from study AP26113-13-301 (ALTA 1L): a phase 3, randomised, open label, comparative, multicentre, international phase 3 study of brigatinib versus crizotinib in patients With ALK-positive advanced lung cancer. As a consequence, sections 4.1, 4.8 and 5.1 of the SmPC are updated. The package leaflet, labelling and the RMP (version (version 5.1) are updated accordingly. The MAH took the opportunity to

introduce minor editorial corrections in the product information

15.3.8. Defibrotide - DEFITELIO (CAP) - EMEA/H/C/002393/II/0043, Orphan

Applicant: Gentium S.r.l.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of a systematic literature analysis to fulfil a specific obligation (SOB) to provide comparative data on efficacy, including pooled outcomes of patients with veno-occlusive disease (VOD) treated with defibrotide; VOD incidence and outcomes in patients not treated with defibrotide. As a consequence, Annex II and the RMP (version 6.1) are updated. In addition, the due date of the observational DefiFrance study (listed as a category 3 study in the RMP): a national, post-registration, observational study of the long term safety and health outcome of patients treated with Defitelio (defibrotide) including patients with severe hepatic VOD after haematopoietic stem cell transplantation (HSCT), is revised. Finally, the RMP is updated in line with revision 2 of the guidance on the format of RMP in the EU (template). The MAH took the opportunity to introduce minor editorial corrections

15.3.9. Docetaxel - DOCETAXEL ZENTIVA (CAP) - EMEA/H/C/000808/WS1550/0058; Docetaxel - TAXOTERE (CAP) - EMEA/H/C/000073/WS1550/0131

Applicant: Aventis Pharma S.A.

PRAC Rapporteur: Ghania Chamouni

Scope: Extension of indication to include combination with androgen-deprivation therapy (ADT), with or without prednisone or prednisolone, for the treatment of patients with metastatic hormone-sensitive prostate cancer for Taxotere (docetaxel) and Docetaxel Zentiva (docetaxel). As a consequence, sections 4.1, 4.2, 4.4 and 4.8 of the SmPC are updated. The package leaflet and the RMP (version 1.0) are updated accordingly. In addition, the MAH took the opportunity to update information impacting the local representatives in the package leaflet

15.3.10. Dulaglutide - TRULICITY (CAP) - EMEA/H/C/002825/II/0040

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Ilaria Baldelli

Scope: Extension of indication to include a new indication to reduce the risk of major adverse cardiovascular events (MACE) (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with type 2 diabetes mellitus (T2DM) who have multiple cardiovascular risk factors without established cardiovascular disease, and in adults with T2DM with established cardiovascular disease. The data supporting this new indication is derived from study GBDJ (researching cardiovascular events with a weekly incretin in diabetes (REWIND)): a single pivotal phase 3 long-term cardiovascular outcomes study, which assessed the efficacy and safety of treatment with once-weekly injection of dulaglutide 1.5 mg when added to glucose-lowering regimen of patients with T2DM, compared to the addition of a once weekly placebo injection (in fulfilment of post-authorisation measure (PAM) (MEA 004)). 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 3.1) are updated

accordingly. In addition, the MAH took the opportunity to update the wording of the existing indication in section 4.1 of the SmPC and to implement a minor change in section 5.1 of the SmPC, in the glycaemic control summary subsection based on the results from the dulaglutide study as add-on to sodium-glucose co-transporter 2 (SGLT2) inhibitor therapy which was assessed as part of variation II/25 concluded in April 2018

15.3.11. Dupilumab - DUPIXENT (CAP) - EMEA/H/C/004390/II/0017

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Kimmo Jaakkola

Scope: Extension of indication to include a new indication in adult patients with chronic rhinosinusitis with nasal polyposis. 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 4.0) are updated accordingly

15.3.12. Fosnetupitant, Netupitant, palonosetron - AKYNZEO (CAP) - EMEA/H/C/003728/X/0018

Applicant: Helsinn Birex Pharmaceuticals Limited

PRAC Rapporteur: Ilaria Baldelli

Scope: Extension application to introduce a new pharmaceutical form 'powder for concentrate for solution for infusion' and a new strength for the fixed combination of fosnetupitant (pro-drug of netupitant)/palonosetron of 235 mg/0.25 mg, to be administered intravenously (new route of administration). The RMP (version 2.4) is updated accordingly

15.3.13. Idelalisib - ZYDELIG (CAP) - EMEA/H/C/003843/II/0047

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Martin Huber

Scope: Submission of the final clinical study report for study 101-09 (listed as a category 1 study in Annex II and the RMP): a phase 2 study to assess the efficacy and safety of idelalisib in subjects with indolent B-cell non-Hodgkin lymphomas refractory to rituximab and alkylating agents. This submission is an Annex II post-authorisation measure (ANX 002) and a category 1 commitment in the RMP. This submission also includes an update to the product information

15.3.14. Infliximab - REMSIMA (CAP) - EMEA/H/C/002576/X/0062

Applicant: Celltrion Healthcare Hungary Kft.

PRAC Rapporteur: Kimmo Jaakkola

Scope: Extension application to introduce a solution for injection as a new pharmaceutical form, 120 mg as a new strength and subcutaneous use as a new route of administration. The RMP (version 9.1) is updated accordingly

15.3.15. Insulin lispro - HUMALOG (CAP) - EMEA/H/C/000088/X/0169

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Annika Folin

Scope: Extension application. The RMP is updated (version 9.3) accordingly and in line with revision 2 of GVP module V on 'Risk management systems'

15.3.16. Insulin lispro - LIPROLOG (CAP) - EMEA/H/C/000393/X/0130

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Annika Folin

Scope: Extension application. The RMP is updated (version 9.3) accordingly and in line with revision 2 of GVP module V on 'Risk management systems'

15.3.17. Interferon beta-1b - BETAFERON (CAP) - EMEA/H/C/000081/II/0124/G

Applicant: Bayer AG

PRAC Rapporteur: Martin Huber

Scope: Grouped variations consisting of: 1) update of sections 4.3 and 4.6 of the SmPC in order to add information on pregnancy and update the statement regarding breast-feeding following the completion of the European interferon beta (IFN-β) pregnancy registry (eighth annual and final report) and the final clinical study report (CSR) of the register-based study in the Nordic countries EUPAS13054: multiple sclerosis pregnancy study - pregnancy outcomes in multiple sclerosis populations exposed and unexposed to interferon beta - a register-based study in the Nordic countries; 2) update of section 4.6 of the SmPC in order to update the statement regarding breast-feeding following a review of studies, case reports and literature articles (in fulfilment of MEA 024.2 and MEA 021). The package leaflet is updated accordingly. The RMP (version 4.1) is updated accordingly, including the deletion of the important potential risk 'pregnancy outcomes'. The RMP is also updated to bring it in line with revision 2 of the guidance on the format of RMP in the EU (template)

See also under 10.1.1.

15.3.18. Interferon beta-1b - EXTAVIA (CAP) - EMEA/H/C/000933/II/0096/G

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Martin Huber

Scope: Grouped variations consisting of: 1) update of sections 4.3 and 4.6 of the SmPC in order to add information on pregnancy and update the statement regarding breast-feeding following the completion of the European interferon beta (IFN-β) pregnancy registry (eighth annual and final report) and the final clinical study report (CSR) of the register-based study in the Nordic countries EUPAS13054: multiple sclerosis pregnancy study - pregnancy outcomes in multiple sclerosis populations exposed and unexposed to interferon beta - a register-based study in the Nordic countries; 2) update of section 4.6 of the SmPC in order to update the statement regarding breast-feeding following a review of studies, case reports and literature articles (in fulfilment of MEA 022.2 and MEA 019). The package leaflet is updated accordingly. The RMP (version 4.1) is updated accordingly, including the deletion of the important potential risk 'pregnancy outcomes'. The RMP is also updated to bring it in line with revision 2 of the guidance on the format of RMP in the EU (template)

See also under 10.1.1.

15.3.19. Lenalidomide - REVLIMID (CAP) - EMEA/H/C/000717/II/0107, Orphan

Applicant: Celgene Europe BV

PRAC Rapporteur: Ghania Chamouni

Scope: Extension of indication to include Revlimid (lenalidomide) in combination with rituximab for the treatment of adult patients with previously treated follicular lymphoma or marginal zone lymphoma. 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 36.2) are updated accordingly

15.3.20. Lumacaftor, ivacaftor - ORKAMBI (CAP) - EMEA/H/C/003954/II/0049

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Updated of section 4.8 of the SmPC with safety data from study 109: a phase 3, double blind, placebo controlled, parallel group study to evaluate the efficacy and safety of lumacaftor in combination with ivacaftor in subjects aged 6 through 11 years with cystic fibrosis (CF), homozygous for the deletion of phenylalanine in position 508 of the cystic fibrosis transmembrane conductance regulator (F508del-CFTR) mutation; and study 011 Part B (study 011B): a phase 3, open-label study to evaluate the pharmacokinetics, safety, and tolerability of lumacaftor in combination with ivacaftor in subjects 6 through 11 years of age with CF, homozygous for the F508del-CFTR mutation (receiving lumacaftor 200 mg in fixed-dose combination with ivacaftor 250 mg orally q12h for 24 weeks). The RMP (version 7.0) is updated accordingly

15.3.21. Moroctocog alfa - REFACTO AF (CAP) - EMEA/H/C/000232/II/0151

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Anette Kirstine Stark

Scope: Update of sections 4.8 and 5.1 of the SmPC based on the final results from study 3082B2-313 (B1831001) (listed as a category 3 study in the RMP): an open-label study to evaluate prophylaxis treatment, and to characterise the efficacy, safety, and pharmacokinetics of b-domain deleted recombinant factor VIII albumin free (moroctocog alfa [AF_CC]) in children with haemophilia A (in fulfilment of MEA 116). The RMP (version 13.0) is updated accordingly. In addition, the SmPC is brought in line with revision 3 of the 'Guideline on core SmPC for human plasma derived and recombinant coagulation factor VIII products' (EMA/CHMP/BPWP/1619/1999 rev. 3)

15.3.22. Nusinersen - SPINRAZA (CAP) - EMEA/H/C/004312/II/0014, Orphan

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of the final report from study SM202 (EMBRACE or CS7) (listed as a category 3 study in the RMP): a phase 2, randomised, double-blind, sham-procedure-controlled study to assess the safety and tolerability and explore the efficacy of nusinersen (ISIS 396443 (BIIB058)) administered intrathecally in subjects with spinal muscular atrophy who are not eligible to participate in study ISIS 396443-CS3B: a phase 3,

randomised, double-blind, sham-procedure controlled study to assess the clinical efficacy and safety of nusinersen administered intrathecally in patients with infantile-onset spinal muscular atrophy; or study ISIS 396443-CS4: a phase 3, randomised, double-blind, sham-procedure controlled study to assess the clinical efficacy and safety of nusinersen administered intrathecally in patients with later-onset spinal muscular atrophy; due to age at screening and/or survival motor neuron 2 (SMN2) copy number. The RMP (version 10.1) is updated accordingly

15.3.23. Osimertinib - TAGRISSO (CAP) - EMEA/H/C/004124/II/0029

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Update of sections 4.2 and 5.2 of the SmPC in order to reflect the outcome of study D5160C00035 (listed as a category 3 study in the RMP): an open-label, phase 1 study to assess the pharmacokinetics, safety and tolerability of osimertinib following a single oral 80 mg dose to patients with advanced solid tumours and normal renal function or severe renal impairment. The RMP (version 13) is updated accordingly

15.3.24. Pegfilgrastim - UDENYCA (CAP) - EMEA/H/C/004413/II/0003

Applicant: ERA Consulting GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Update of section 4.6 of the SmPC to amend the safety information based on feasibility data regarding the pregnancy and lactation registry (listed as a category 3 study in the RMP). The package leaflet and the RMP (version 1.5) are updated accordingly

15.3.25. Pembrolizumab - KEYTRUDA (CAP) - EMEA/H/C/003820/II/0065

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to include Keytruda (pembrolizumab) as monotherapy or in combination with platinum and 5-fluorouracil (5-FU) chemotherapy, first-line treatment of recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) in adults; based on the results from KEYNOTE-048: a randomised, multicentre, open-label phase 3 study investigating pembrolizumab, or pembrolizumab plus platinum plus 5-FU chemotherapy versus platinum plus 5-FU plus cetuximab in subjects with first-line recurrent or metastatic HNSCC. 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 22.1) are updated accordingly

15.3.26. Pemetrexed - PEMETREXED FRESENIUS KABI (CAP) - EMEA/H/C/003895/X/0009

Applicant: Fresenius Kabi Deutschland GmbH

PRAC Rapporteur: Ghania Chamouni

Scope: Extension application to introduce a new pharmaceutical form (concentrate for solution for infusion) associated with new strength 25 mg/mL. The RMP (version 2.0) is updated accordingly

15.3.27. Ranibizumab - LUCENTIS (CAP) - EMEA/H/C/000715/II/0076

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension of indication to include treatment of moderately severe to severe non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR) in adults. As a consequence, sections 4.1, 4.2, 4.4, 4.8, and 5.1 of the SmPC are updated with. The package leaflet and the RMP (version 19.0) are updated accordingly

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

Applicant: GE Healthcare AS

PRAC Rapporteur: Eva Segovia

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

15.3.29. Rituximab - MABTHERA (CAP) – EMEA/H/C/000165/II/0168

Applicant: Roche Registration GmbH

PRAC Rapporteur: Hans Christian Siersted

Scope: Extension of indication in previously untreated, advanced stage paediatric B-cell Non-Hodgkin's lymphoma (B-NHL). The RMP (version 21.0) is updated accordingly

15.3.30. Rituximab - RIXATHON (CAP) - EMEA/H/C/003903/WS1599/0020; RIXIMYO (CAP) - EMEA/H/C/004729/WS1599/0020

Applicant: Sandoz GmbH

PRAC Rapporteur: Hans Christian Siersted

Scope: Submission of the final report from study GP13-301 (listed as a category 3 study in the RMP): a randomised, controlled double-blind phase 3 trial to compare the efficacy, safety and pharmacokinetics of Rixathon/Riximyo (GP2013 – rituximab biosimilars) plus cyclophosphamide, vincristine, prednisone *vs.* MabThera (rituximab) plus cyclophosphamide, vincristine, prednisone, followed by Rixathon/Riximyo (GP2013 - rituximab biosimilars) or MabThera (rituximab) maintenance therapy in patients with previously untreated advanced stage follicular lymphoma. The RMP (version 4.0) is updated accordingly

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

Applicant: AstraZeneca AB

PRAC Rapporteur: Kirsti Villikka

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

15.3.32. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/X/0012

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Extension application to introduce a new pharmaceutical form (prolonged-release tablet) associated with a new strength (11 mg), and presented in pack sizes of 28, 30, 90 and 91 tablets. The line extension includes a change in pharmacokinetics. The RMP (version 4.0) is updated accordingly

15.3.33. Trastuzumab emtansine - KADCYLA (CAP) - EMEA/H/C/002389/II/0045

Applicant: Roche Registration GmbH

PRAC Rapporteur: Hans Christian Siersted

Scope: Extension of indication to include the adjuvant treatment of adult patients with human epidermal growth factor receptor 2 (HER2)-positive early breast cancer. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 9.0) are updated accordingly. In addition, the MAH took the opportunity to introduce some editorial changes

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

Applicant: Roche Registration GmbH

PRAC Rapporteur: Hans Christian Siersted

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

safety of trastuzumab emtansine plus pertuzumab compared with chemotherapy plus trastuzumab and pertuzumab for patients with HER2-positive breast cancer

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

Applicant: Les Laboratoires Servier

PRAC Rapporteur: Annika Folin

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

15.3.36. Turoctocog alfa - NOVOEIGHT (CAP) - EMEA/H/C/002719/II/0030/G

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Grouped variations consisting of submission of: 1) results of study NN7008-3809 (Guardian 4): safety and efficacy of turoctocog alfa in prevention and treatment of bleeds in paediatric previously untreated patients (PUPs) with haemophilia A and; 2) results of study NN7008-4239 (Guardian 9): a multicentre, open-label trial evaluating the pharmacokinetics (PK) of NovoEight (turoctocog alfa) in relation to body mass index (BMI) in subjects with haemophilia A. In addition, the product information is brought in line with revision 3 of the 'Guideline on core SmPC for human plasma derived and recombinant coagulation factor VIII products' (EMA/CHMP/BPWP/1619/1999 rev. 3) and 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'. Sections 2, 4.2, 4.4, 4.5, 4.6, 4.8, 5.1 and 5.2 of the SmPC and the package leaflet are updated accordingly. Furthermore, the MAH took the opportunity to introduce some administrative updates in the product information

15.3.37. Vemurafenib - ZELBORAF (CAP) - EMEA/H/C/002409/II/0054

Applicant: Roche Registration GmbH

PRAC Rapporteur: Annika Folin

Scope: Update of sections 4.4 and 4.5 of the SmPC in order to add information and a precaution regarding concomitant use of strong cytochrome P450 3A4 (CYP3A4) inhibitors based on final results from study GO29475 (MEA-011) (listed as a category 3 study in the RMP): a two-part, phase 1, open-label, multicentre, two-period, one-sequence study to investigate the effect of itraconazole and rifampin on the pharmacokinetic (PK) of vemurafenib at steady state. The package leaflet and the RMP (version 12.0) are updated accordingly. In addition, the package leaflet is updated to reflect information on sodium content in line with the Annex to the European Commission (EC) guideline on 'excipients in the labelling and package leaflet of medicinal products for human use'

15.3.38. Vernakalant - BRINAVESS (CAP) - EMEA/H/C/001215/II/0035

Applicant: Correvio

PRAC Rapporteur: Menno van der Elst

Scope: Update of sections 4.4 and 4.8 of the SmPC in order to add a warning and update the safety information following updates to the company core safety datasheet (CCDS) based on the results of an integrated safety analysis performed on data of existing clinical studies with a stronger emphasis on treatment-related adverse drug reactions (ADRs) and an incidence rate above one percent. The package leaflet and the RMP (version 7.0) are updated accordingly. In addition, the RMP is updated in line with the results from the completed observational cohort SPECTRUM study (study 6621-049): a prospective observational registry study to characterise normal conditions of use, dosing and safety following administration of vernakalant intravenous (IV) sterile concentrate currently under assessment in variation II/34. Furthermore, the MAH took the opportunity to update sections 4.2, 4.4, 4.6, 4.7, 4.8, 5.1, 5.2, 5.3, 6.4 of the SmPC, Annex II, labelling and package leaflet in order to include editorial changes, to correct typographical errors and to bring the product information in line with the latest quality review of documents (QRD) template (version 10). The package leaflet is also updated in line with the European Commission (EC) guideline on 'excipients in the labelling and package leaflet of medicinal products for human use' and the EMA Annex to the EC guideline

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. Albutrepenonacog alfa - IDELVION (CAP) - PSUSA/00010497/201901

Applicant: CSL Behring GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.2. Allogeneic T cells genetically modified with a retroviral vector encoding for a truncated form of the human low affinity nerve growth factor receptor (ΔLNGFR) and the herpes simplex I virus thymidine kinase (HSV-TK Mut2) - ZALMOXIS (CAP) - PSUSA/00010530/201902

Applicant: MolMed S.p.A, ATMP[62]

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.3. Atazanavir, cobicistat - EVOTAZ (CAP) - PSUSA/00010404/201901

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

16.1.4. Besilesomab - SCINTIMUN (CAP) - PSUSA/00000385/201901 (with RMP)

Applicant: Cis Bio International

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

16.1.5. Bevacizumab - AVASTIN (CAP); MVASI (CAP); ZIRABEV (CAP) - PSUSA/00000403/201902

Applicant(s): Amgen Europe B.V. (Mvasi), Pfizer Europe MA EEIG (Zirabev), Roche Registration GmbH (Avastin)

PRAC Rapporteur: Hans Christian Siersted

Scope: Evaluation of a PSUSA procedure

16.1.6. Bictegravir, emtricitabine, tenofovir alafenamide - BIKTARVY (CAP) - PSUSA/00010695/201902

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.7. Brentuximab vedotin - ADCETRIS (CAP) - PSUSA/00010039/201902

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

[62] Advanced therapy medicinal product

16.1.8. Brexpiprazole - RXULTI (CAP) - PSUSA/00010698/201901

Applicant: Otsuka Pharmaceutical Netherlands B.V.

PRAC Rapporteur: Tatiana Magalova

Scope: Evaluation of a PSUSA procedure

16.1.9. Brimonidine[63] - MIRVASO (CAP) - PSUSA/00010093/201902

Applicant: Galderma International

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

16.1.10. Brivaracetam - BRIVIACT (CAP) - PSUSA/00010447/201901

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.11. Burosumab - CRYSVITA (CAP) - PSUSA/00010669/201902

Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.12. Ceftazidime, avibactam - ZAVICEFTA (CAP) - PSUSA/00010513/201902

Applicant: Pfizer Ireland Pharmaceuticals

PRAC Rapporteur: Rugile Pilviniene

Scope: Evaluation of a PSUSA procedure

16.1.13. Chlormethine - LEDAGA (CAP) - PSUSA/00010587/201902

Applicant: Helsinn Birex Pharmaceuticals Limited

PRAC Rapporteur: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

16.1.14. Colistimethate sodium[64] - COLOBREATHE (CAP) - PSUSA/00009112/201902

Applicant: Teva B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

[63] Centrally authorised product(s) only
[64] Dry inhalation powder only

16.1.15. Dapagliflozin, metformin - EBYMECT (CAP); XIGDUO (CAP) - PSUSA/00010294/201901

Applicant(s): AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.16. Daunorubicin, cytarabine - VYXEOS (CAP) - PSUSA/00010701/201902

Applicant: Jazz Pharmaceuticals Ireland Limited

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Evaluation of a PSUSA procedure

16.1.17. Dexamethasone[65] - OZURDEX (CAP) - PSUSA/00000985/201901

Applicant: Allergan Pharmaceuticals Ireland

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

16.1.18. Diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA), poliomyelitis (inactivated), haemophilus type b conjugate vaccine (adsorbed) - VAXELIS (CAP) - PSUSA/00010469/201904

Applicant: MCM Vaccine B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.19. Elbasvir, grazoprevir - ZEPATIER (CAP) - PSUSA/00010519/201901

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.1.20. Elosulfase alfa - VIMIZIM (CAP) - PSUSA/00010218/201902

Applicant: BioMarin International Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

16.1.21. Entacapone - COMTAN (CAP); COMTESS (CAP); ENTACAPONE ORION (CAP) - PSUSA/00001223/201901

Applicant(s): Novartis Europharm Limited (Comtan), Orion Corporation (Comtess,

[65] Centrally authorised product(s) only, indicated in the treatment of uveitis and macular oedema

Entacapone Orion)

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

16.1.22. Eravacycline - XERAVA (CAP) - PSUSA/00010718/201902

Applicant: Tetraphase Pharmaceuticals Ireland Limited

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.23. Ex vivo expanded autologous human corneal epithelial cells containing stem cells - HOLOCLAR (CAP) - PSUSA/00010352/201902

Applicant: Chiesi Farmaceutici S.p.A., ATMP[66]

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

16.1.24. Fenofibrate, simvastatin - CHOLIB (CAP) - PSUSA/00010096/201902

Applicant: Mylan IRE Healthcare Limited

PRAC Rapporteur: Maia Uusküla

Scope: Evaluation of a PSUSA procedure

16.1.25. Florbetaben (^{18}F) - NEURACEQ (CAP) - PSUSA/00010094/201902

Applicant: Life Radiopharma Berlin GmbH

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.26. Fluticasone, salmeterol[67] - AERIVIO SPIROMAX (CAP); AIREXAR SPIROMAX (CAP) - PSUSA/00010531/201902

Applicant(s): Teva B.V.

PRAC Rapporteur: Ilaria Baldelli

Scope: Evaluation of a PSUSA procedure

16.1.27. Glecaprevir, pibrentasvir - MAVIRET (CAP) - PSUSA/00010620/201901

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

[66] Advanced therapy medicinal product
[67] Centrally authorised products only

16.1.28. Glycerol phenylbutyrate - RAVICTI (CAP) - PSUSA/00010454/201901

Applicant: Immedica Pharma AB

PRAC Rapporteur: Ilaria Baldelli

Scope: Evaluation of a PSUSA procedure

16.1.29. Hydrocortisone[68] - ALKINDI (CAP) - PSUSA/00010674/201902

Applicant: Diurnal Europe BV

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

16.1.30. Lanadelumab - TAKHZYRO (CAP) - PSUSA/00010743/201902

Applicant: Shire Pharmaceuticals Ireland Limited

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

16.1.31. Lenvatinib - KISPLYX (CAP); LENVIMA (CAP) - PSUSA/00010380/201902

Applicant(s): Eisai GmbH

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

16.1.32. Mercaptamine[69] - CYSTADROPS (CAP) - PSUSA/00010574/201901

Applicant: Recordati Rare Diseases

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

16.1.33. Metreleptin - MYALEPTA (CAP) - PSUSA/00010700/201901

Applicant: Aegerion Pharmaceuticals B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.34. Modified vaccinia Ankara virus - IMVANEX (CAP) - PSUSA/00010119/201901

Applicant: Bavarian Nordic A/S

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

[68] Centrally authorised product(s) for adrenal insufficiency, paediatric use only
[69] Indicated for treatment of corneal cystine

16.1.35. Nitisinone - ORFADIN (CAP) - PSUSA/00002169/201902

Applicant: Swedish Orphan Biovitrum International AB

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.1.36. Palbociclib - IBRANCE (CAP) - PSUSA/00010544/201902

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Hans Christian Siersted

Scope: Evaluation of a PSUSA procedure

16.1.37. Patisiran - ONPATTRO (CAP) - PSUSA/00010715/201902

Applicant: Alnylam Netherlands B.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

16.1.38. Perflutren - LUMINITY (CAP); OPTISON (CAP) - PSUSA/00002350/201812

Applicant(s): GE Healthcare AS (Optison), Lantheus EU Limited (Luminity)

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

16.1.39. Phenylephrine, ketorolac - OMIDRIA (CAP) - PSUSA/00010419/201901

Applicant: Omeros Ireland Limited

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.1.40. Pomalidomide - IMNOVID (CAP) - PSUSA/00010127/201902

Applicant: Celgene Europe BV

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

16.1.41. Reslizumab - CINQAERO (CAP) - PSUSA/00010523/201902

Applicant: Teva B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.42. Rivastigmine - EXELON (CAP); PROMETAX (CAP); RIVASTIGMINE 1A PHARMA (CAP); RIVASTIGMINE HEXAL (CAP); RIVASTIGMINE SANDOZ (CAP) - PSUSA/00002654/201901

Applicant(s): 1 A Pharma GmbH (Rivastigmine 1A Pharma), Hexal AG (Rivastigmine Hexal), Novartis Europharm Limited (Exelon, Prometax), Sandoz GmbH (Rivastigmine Sandoz)

PRAC Rapporteur: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

16.1.43. Ruxolitinib - JAKAVI (CAP) - PSUSA/00010015/201902

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

16.1.44. Safinamide - XADAGO (CAP) - PSUSA/00010356/201902

Applicant: Zambon S.p.A.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

16.1.45. Samarium (^{153}Sm) lexidronam - QUADRAMET (CAP) - PSUSA/00002682/201902

Applicant: Cis Bio International

PRAC Rapporteur: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

16.1.46. Silodosin - SILODYX (CAP); UROREC (CAP) - PSUSA/00002701/201901

Applicant(s): Recordati Ireland Ltd

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.1.47. Simoctocog alfa - NUWIQ (CAP); VIHUMA (CAP) - PSUSA/00010276/201901

Applicant(s): Octapharma AB

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.48. Sodium phenylbutyrate - AMMONAPS (CAP); PHEBURANE (CAP) - PSUSA/00002758/201812

Applicant(s): Eurocept International B.V. (Pheburane), Immedica Pharma AB (Ammonaps)

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

16.1.49. Sugammadex - BRIDION (CAP) - PSUSA/00002799/201901

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

16.1.50. Tezacaftor, ivacaftor - SYMKEVI (CAP) - PSUSA/00010730/201902

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

16.1.51. Tisagenlecleucel - KYMRIAH (CAP) - PSUSA/00010702/201902

Applicant: Novartis Europharm Limited, ATMP[70]

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.52. Tivozanib - FOTIVDA (CAP) - PSUSA/00010636/201902

Applicant: EUSA Pharma (Netherlands) B.V.

PRAC Rapporteur: Rugile Pilviniene

Scope: Evaluation of a PSUSA procedure

16.1.53. Trastuzumab emtansine - KADCYLA (CAP) - PSUSA/00010136/201902

Applicant: Roche Registration GmbH

PRAC Rapporteur: Hans Christian Siersted

Scope: Evaluation of a PSUSA procedure

16.1.54. Ulipristal acetate[71] - ESMYA (CAP); ULIPRISTAL ACETATE GEDEON RICHTER (CAP) - PSUSA/00009325/201902

Applicant(s): Gedeon Richter Plc.

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

16.1.55. Verteporfin - VISUDYNE (CAP) - PSUSA/00003110/201812

Applicant: Novartis Europharm Limited

[70] Advanced therapy medicinal product
[71] Indicated for treatment of moderate to severe symptoms of uterine fibroids

PRAC Rapporteur: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

16.1.56. Voretigene neparvovec - LUXTURNA (CAP) - PSUSA/00010742/201901

Applicant: Novartis Europharm Limited, ATMP[72]

PRAC Rapporteur: Brigitte Keller-Stanislawski

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. Lenalidomide - LENALIDOMIDE ACCORD (CAP); REVLIMID (CAP); NAP - PSUSA/00001838/201812

Applicant(s): Accord Healthcare S.L.U. (Lenalidomide Accord), Celgene Europe BV (Revlimid), various

PRAC Rapporteur: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

16.2.2. Pregabalin - LYRICA (CAP); PREGABALIN PFIZER (CAP); NAP - PSUSA/00002511/201901

Applicant(s): Pfizer Europe MA EEIG (Lyrica, Pregabalin Pfizer), various

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

16.2.3. Rasagiline - AZILECT (CAP); RASAGILINE RATIOPHARM (CAP); NAP - PSUSA/00002612/201901

Applicant(s): Teva B.V. (Azilect, Rasagiline ratiopharm), various

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

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

16.3.1. Alitretinoin[73] (NAP) – PSUSA/00010710/201901

Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

[72] Advanced therapy medicinal product
[73] For oral use only

16.3.2. Ambrosia artemisiifolia[74] [75] [76] (NAP) – PSUSA/00010693/201901

Applicant(s): various

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.3.3. Amino acid combinations[77] [78](NAP) – PSUSA/00010187/201901

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.3.4. Amlodipine, losartan (NAP) – PSUSA/00010512/201901

Applicant(s): various

PRAC Lead: Julia Pallos

Scope: Evaluation of a PSUSA procedure

16.3.5. Benzydamine, cetylpyridine (NAP) – PSUSA/00000378/201901

Applicant(s): various

PRAC Lead: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.3.6. Bezafibrate (NAP) – PSUSA/00000405/201901

Applicant(s): various

PRAC Lead: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.3.7. Biotin (NAP) – PSUSA/00000414/201901

Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.3.8. Bisoprolol, hydrochlorothiazide (NAP) - PSUSA/00000420/201811

Applicant(s): various

PRAC Lead: Adrien Inoubli

[74] For sublingual use only
[75] Medicinal product(s) authorised via decentralised procedure
[76] Allergen for therapy
[77] Combinations of pure amino acids or amino acids with mineral compounds/electrolytes only
[78] Intravenous (I.V.) formulation(s) only

Scope: Evaluation of a PSUSA procedure

16.3.9. Caffeine, ergotamine (NAP) - PSUSA/00000485/201811

Applicant(s): various

PRAC Lead: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

16.3.10. Camellia sinensis[79] [80] (NAP) - PSUSA/00010569/201812

Applicant(s): various

PRAC Lead: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.3.11. Carboplatin (NAP) - PSUSA/00000559/201901

Applicant(s): various

PRAC Lead: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.3.12. Ciclosporin[81] (NAP) - PSUSA/00000745/201812

Applicant(s): various

PRAC Lead: Maia Uusküla

Scope: Evaluation of a PSUSA procedure

16.3.13. Dexketoprofen, tramadol (NAP) - PSUSA/00010468/201901

Applicant(s): various

PRAC Lead: Eva Segovia

Scope: Evaluation of a PSUSA procedure

16.3.14. Flumazenil (NAP) - PSUSA/00001413/201812

Applicant(s): various

PRAC Lead: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

16.3.15. Flunitrazepam (NAP) - PSUSA/00001418/201901

Applicant(s): various

[79] Leaf, dry extract refined, derived from Camellia sinensis, L. O. Kuntze
[80] For topical use only
[81] For systemic use only

PRAC Lead: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

16.3.16. Hepatitis A vaccine (inactivated, adsorbed) (NAP) - PSUSA/00001596/201901

Applicant(s): various

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.3.17. Ketoprofen[82] (NAP) - PSUSA/00009205/201901

Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.3.18. Landiolol (NAP) - PSUSA/00010570/201902

Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.3.19. Niflumic acid (NAP) - PSUSA/00002157/201812

Applicant(s): various

PRAC Lead: Julia Pallos

Scope: Evaluation of a PSUSA procedure

16.3.20. Pentoxyverine (NAP) - PSUSA/00002345/201812

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.3.21. Protirelin (NAP) - PSUSA/00009273/201901

Applicant(s): various

PRAC Lead: Jana Lukačišinová

Scope: Evaluation of a PSUSA procedure

16.3.22. Roxithromycin (NAP) - PSUSA/00002669/201812

Applicant(s): various

[82] For topical use only

PRAC Lead: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.4. Follow-up to PSUR/PSUSA procedures

16.4.1. Fluticasone furoate - AVAMYS (CAP) - EMEA/H/C/000770/LEG 027.1

Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Adam Przybylkowski

Scope: MAH's response to LEG 027 [cumulative review of cases of respiratory, thoracic and mediastinal disorders together with a cumulative review of lower respiratory tract infections, as requested in the conclusions of PSUSA/009154/201804 adopted in December 2018] as per the request for supplementary information (RSI) adopted in May 2019

16.4.2. Lacosamide - VIMPAT (CAP) - EMEA/H/C/000863/LEG 035

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Cumulative review of cases of metabolic/toxic encephalopathy as requested in the conclusions of periodic safety update single assessment procedure PSUSA/00001816/201808 adopted in April 2019

16.4.3. Zoledronic acid - ACLASTA (CAP) - EMEA/H/C/000595/LEG 037

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Detailed review on rheumatological/immune-mediated syndrome (RIMS) following intravenous bisphosphonate therapy from pooled controlled clinical studies, non-clinical data and post-marketing cases, as requested in the conclusions of periodic safety update single assessment procedure PSUSA/00009334/201808 adopted in April 2019

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)[83]

None

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

17.2. Protocols of PASS non-imposed in the marketing authorisation(s)[84]

17.2.1. Empagliflozin - JARDIANCE (CAP) - EMEA/H/C/002677/MEA 002.8

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Eva Segovia

Scope: MAH's response to MEA 002.7 [amendment to previously agreed protocol for study 1245.96: an observational cohort study using existing data including urinary tract infection (UTI) as a safety topic of interest assessing a number of risks in patients treated with empagliflozin compared with patients treated with other sodium-glucose cotransporter-2 (SGLT2) inhibitors or with dipeptidyl peptidase-4 (DPP-4) inhibitors] as per the request for supplementary information (RSI) adopted in April 2019

17.2.2. Empagliflozin, metformin - SYNJARDY (CAP) - EMEA/H/C/003770/MEA 003.5

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Eva Segovia

Scope: MAH's response to MEA 003.4 [amendment to previously agreed protocol for study 1245.96: an observational cohort study using existing data including urinary tract infection (UTI) as a safety topic of interest assessing a number of risks in patients treated with empagliflozin compared with patients treated with other sodium-glucose cotransporter-2 (SGLT2) inhibitors or with dipeptidyl peptidase-4 (DPP-4) inhibitors] as per the request for supplementary information (RSI) adopted in April 2019

17.2.3. Ertugliflozin - STEGLATRO (CAP) - EMEA/H/C/004315/MEA 002.1

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to MEA 002 [protocol for study 8835-062/000: a PASS to assess the risk of diabetic ketoacidosis (DKA) among patients with type 2 diabetes mellitus (T2DM) treated with ertugliflozin compared to patients treated with other antihyperglycemic agents [final study report due date: December 2023]] as per the request for supplementary information (RSI) adopted in March 2019

17.2.4. Ertugliflozin, metformin hydrochloride - SEGLUROMET (CAP) - EMEA/H/C/004314/MEA 002.1

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to MEA 002 [protocol for study 8835-062/000: a PASS to assess the risk of diabetic ketoacidosis (DKA) among patients with type 2 diabetes mellitus (T2DM) treated with ertugliflozin compared to patients treated with other antihyperglycemic agents [final study report due date: December 2023]] as per the request for supplementary information (RSI) adopted in March 2019

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

17.2.5. Ertugliflozin, sitagliptin - STEGLUJAN (CAP) - EMEA/H/C/004313/MEA 002.1

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to MEA 002 [protocol for study 8835-062/000: a PASS to assess the risk of diabetic ketoacidosis (DKA) among patients with type 2 diabetes mellitus (T2DM) treated with ertugliflozin compared to patients treated with other antihyperglycemic agents [final study report due date: December 2023]] as per the request for supplementary information (RSI) adopted in March 2019

17.2.6. Follitropin alfa - OVALEAP (CAP) - EMEA/H/C/002608/MEA 002.5

Applicant: Theramex Ireland Limited

PRAC Rapporteur: Menno van der Elst

Scope: Protocol for extension to study XM17-WH-50005 (SOFIA): safety of Ovaleap (follitropin alfa) in infertile women undergoing superovulation for assisted reproductive technologies: a multi-national, comparative, prospective, non-interventional, observational cohort study [final clinical study report (CSR) expected in Q1 2021]

17.2.7. Fremanezumab - AJOVY (CAP) - EMEA/H/C/004833/MEA 002

Applicant: Teva GmbH

PRAC Rapporteur: Kirsti Villikka

Scope: Protocol for observational cohort study TV48125-MH-50037: a pregnancy registry assessing pregnancy outcomes in patients treated with Ajovy (fremanezumab) (from initial opinion/MA)

17.2.8. Fremanezumab - AJOVY (CAP) - EMEA/H/C/004833/MEA 003

Applicant: Teva GmbH

PRAC Rapporteur: Kirsti Villikka

Scope: Protocol for observational cohort study TV48125-MH-50038: a pregnancy database study assessing pregnancy outcomes in patients treated with Ajovy (fremanezumab) (from initial opinion/MA)

17.2.9. Galcanezumab - EMGALITY (CAP) - EMEA/H/C/004648/MEA 002

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Kirsti Villikka

Scope: Protocol for study I5Q-MC-B003 (listed as a category 3 study in the RMP): a cohort study to actively monitor exposure to galcanezumab during pregnancy among women with migraine, using administrative (secondary) data and to study the incidence of pregnancy outcomes (including hypertension during pregnancy and pre-eclampsia) among women exposed to galcanezumab during pregnancy in comparison to women receiving other prophylactic migraine medication [final clinical study report (CSR) expected in Q4 2024] (from initial opinion/MA)

17.2.10. Galcanezumab - EMGALITY (CAP) - EMEA/H/C/004648/MEA 003

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Kirsti Villikka

Scope: Protocol for study I5Q-MC-B002 (listed as a category 3 study in the RMP): galcanezumab European drug utilisation and safety outcomes study to describe, in real-world clinical practice the utilisation of galcanezumab in Europe, and the incidence of important safety outcomes such as serious hypersensitivity and long-term safety including serious cardio-vascular events, and malignancies [final clinical study report (CSR) expected in Q4 2026] (from initial opinion/MA)

17.2.11. Galcanezumab - EMGALITY (CAP) - EMEA/H/C/004648/MEA 004

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Kirsti Villikka

Scope: Protocol for study I5Q-MC-B001: galcanezumab US drug utilisation and safety outcomes study to describe, in real-world clinical practice, the utilisation of galcanezumab in the US, and the incidence of important safety outcomes such as serious hypersensitivity and long-term safety including serious cardiovascular events, and malignancies final clinical study report (CSR) expected in Q4 2026] (from initial opinion/MA)

17.2.12. Linaclotide - CONSTELLA (CAP) - EMEA/H/C/002490/MEA 009.3

Applicant: Allergan Pharmaceuticals International Limited

PRAC Rapporteur: Martin Huber

Scope: Amendment to a protocol previously agreed in November 2015 for a PASS: linaclotide safety study assessing the complications of diarrhoea and associated risk factors in selected European populations with irritable bowel syndrome with constipation (IBS-C) for Constella (linaclotilde) 290µg capsules

17.2.13. Tildrakizumab - ILUMETRI (CAP) - EMEA/H/C/004514/MEA 003.1

Applicant: Almirall S.A

PRAC Rapporteur: Adam Przybylkowski

Scope: MAH's response to MEA 003 [protocol for study M-14745-40: European psoriasis registry to collect long-term safety data for tildrakizumab and to further characterise the long-term safety profile of tildrakizumab in the treatment of psoriasis under conditions of routine clinical practice (from initial MAA/opinion)] as per the request for supplementary information (RSI) adopted in April 2019

17.2.14. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/MEA 045.4

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Rhea Fitzgerald

Scope: MAH's response to MEA-045.3 [protocol for study RRA-20745: a PASS to investigate the long-term safety in adult patients with moderately to severely active Crohn's disease]

as per the request for supplementary information (RSI) adopted in April 2019

17.2.15. Venetoclax - VENCLYXTO (CAP) - EMEA/H/C/004106/MEA 002.5

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Eva Jirsová

Scope: MAH response to MEA 002.4 [amendment to protocol (version 3.0) for study P16-562: a prospective observational study to assess the long term safety profile of venetoclax in a Swedish cohort of chronic lymphocytic leukaemia (CLL) patients [final clinical study report (CSR) planned in December 2025]] as adopted in June 2019

17.3. Results of PASS imposed in the marketing authorisation(s)[85]

None

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

17.4.1. Certolizumab pegol - CIMZIA (CAP) - EMEA/H/C/001037/II/0081

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of the final report from study RA0022 from the British Society for Rheumatology Biologics Register (BSRBR) (listed as a category 3 study in the RMP): a UK registry which aims to monitor the long term safety of tumour necrosis factor-alfa (TNF-α) inhibitor drugs and other targeted therapies in rheumatoid arthritis patients; together with the interim report from study RA0020 from the German Register for Rheumatoid Arthritis Observation of Biologic Therapy (RABBIT) (listed as a category 3 study in the RMP): a long-term observational cohort study of the safety and effectiveness of biologic agent in rheumatoid arthritis (RA)

17.4.2. Desloratadine - AERIUS (CAP) - EMEA/H/C/000313/WS1655/0091; AZOMYR (CAP) - EMEA/H/C/000310/WS1655/0095; NEOCLARITYN (CAP) - EMEA/H/C/000314/WS1655/0089

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Jean-Michel Dogné

Scope: Submission of the final report from study EUPAS15038 (listed as a category 3 study in the RMP): a non-interventional non-imposed PASS study designed to assess the potential risk of desloratadine exposure on seizures, supraventricular tachycardia, and atrial fibrillation or flutter

17.4.3. Dexamethasone - OZURDEX (CAP) - EMEA/H/C/001140/II/0035

Applicant: Allergan Pharmaceuticals Ireland

[85] In accordance with Article 107p-q of Directive 2001/83/EC
[86] 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

PRAC Rapporteur: Eva Segovia

Scope: Submission of the final report from study CMO-EPI-EYE-0522 (listed as a category 3 study in the RMP): an observational, cross-sectional study conducted in France, Germany, Spain, and the UK aiming at assessing the effectiveness of the educational material provided to treating physicians

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

Applicant: H. Lundbeck A/S

PRAC Rapporteur: Martin Huber

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

17.4.5. Teriflunomide - AUBAGIO (CAP) - EMEA/H/C/002514/II/0025

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Martin Huber

Scope: Submission of the final survey reports (listed as a category 3 study in the RMP) for patients and healthcare professionals (HCPs) to assess the effectiveness of the education materials. As part of the submission, the MAH proposes a revised patient card

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

17.5.1. Aclidinium - BRETARIS GENUAIR (CAP) - EMEA/H/C/002706/ANX 001.6

Applicant: AstraZeneca AB

PRAC Rapporteur: Adam Przybylkowski

Scope: Second interim report for study D6560R00004, formerly M/34273/44, (listed as a category 1 in Annex II and the RMP): an observational study evaluating the risk of cardiovascular endpoints of aclidinium bromide-containing products versus other chronic obstructive pulmonary disease (COPD) medications in COPD patients in the UK. This is a sub-study report addressing the heart failure component of the PASS programme. It also includes stroke and acute myocardial infarction (AMI) incidence rate descriptive analysis

17.5.2. Aclidinium - EKLIRA GENUAIR (CAP) - EMEA/H/C/002211/ANX 001.6

Applicant: AstraZeneca AB

PRAC Rapporteur: Adam Przybylkowski

Scope: Second interim report for study D6560R00004 (formerly M/34273/44) (listed as a category 1 in Annex II and the RMP): an observational study evaluating the risk of cardiovascular endpoints of aclidinium bromide-containing products versus other chronic obstructive pulmonary disease (COPD) medications in COPD patients in the UK. This is a

sub-study report addressing the heart failure component of the PASS programme. It also includes stroke and acute myocardial infarction (AMI) incidence rate descriptive analysis

17.5.3. Aclidinium, formoterol fumarate dihydrate - BRIMICA GENUAIR (CAP) - EMEA/H/C/003969/ANX 003.3

Applicant: AstraZeneca AB

PRAC Rapporteur: Adam Przybylkowski

Scope: Second interim report for study D6560R00004 (formerly M/34273/44) (listed as a category 1 in Annex II and the RMP): an observational study evaluating the risk of cardiovascular endpoints of aclidinium bromide-containing products versus other chronic obstructive pulmonary disease (COPD) medications in COPD patients in the UK. This is a sub-study report addressing the heart failure component of the PASS programme. It also includes stroke and acute myocardial infarction (AMI) incidence rate descriptive analysis

17.5.4. Aclidinium, formoterol fumarate dihydrate - DUAKLIR GENUAIR (CAP) - EMEA/H/C/003745/ANX 003.3

Applicant: AstraZeneca AB

PRAC Rapporteur: Adam Przybylkowski

Scope: Second interim report for study D6560R00004 (formerly M/34273/44) (listed as a category 1 in Annex II and the RMP): an observational study evaluating the risk of cardiovascular endpoints of aclidinium bromide-containing products versus other chronic obstructive pulmonary disease (COPD) medications in COPD patients in the UK. This is a sub-study report addressing the heart failure component of the PASS programme. It also includes stroke and acute myocardial infarction (AMI) incidence rate descriptive analysis

17.5.5. Dolutegravir - TIVICAY (CAP) - EMEA/H/C/002753/MEA 001.5

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Martin Huber

Scope: MAH’s response to MEA 001.4 [fourth annual interim report for EuroSIDA PASS study 201177 (listed as a category 3 study in the RMP): a prospective observational cohort study in patients receiving dolutegravir to investigate the risk of hypersensitivity reactions (HSR), hepatotoxicity and serious rash (division of acquired immune deficiency syndrome (DAIDS) grading scale category 3 or 4] as per the request for supplementary information (RSI) adopted in May 2019

17.5.6. Dolutegravir, abacavir, lamivudine - TRIUMEQ (CAP) - EMEA/H/C/002754/MEA 007.5

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Martin Huber

Scope: MAH’s response to MEA 007.4 [fourth annual interim report for EuroSIDA PASS study 201177 (listed as a category 3 study in the RMP): a prospective observational cohort study in patients receiving dolutegravir to investigate the risk of hypersensitivity reactions (HSR), hepatotoxicity and serious rash (division of acquired immune deficiency syndrome

(DAIDS) grading scale category 3 or 4] as per the request for supplementary information (RSI) adopted in May 2019

17.5.7. Empagliflozin - JARDIANCE (CAP) - EMEA/H/C/002677/MEA 002.9

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Eva Segovia

Scope: First interim report for study 1245.96: an observational cohort study using existing data assessing the risks of acute liver injury, acute kidney injury and chronic kidney disease, severe complications of urinary tract infection, genital infection, and diabetic ketoacidosis in patients with type 2 diabetes mellitus (T2DM) treated with empagliflozin compared with patients treated with other sodium-glucose cotransporter-2 (SGLT2) inhibitors or with dipeptidyl peptidase-4 (DPP-4) inhibitors [final clinical study report (CSR) expected in Q3 2021]

17.5.8. Empagliflozin, metformin - SYNJARDY (CAP) - EMEA/H/C/003770/MEA 003.6

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Eva Segovia

Scope: First interim report for study 1245.96: an observational cohort study using existing data assessing the risks of acute liver injury, acute kidney injury and chronic kidney disease, severe complications of urinary tract infection, genital infection, and diabetic ketoacidosis in patients with type 2 diabetes mellitus (T2DM) treated with empagliflozin compared with patients treated with other sodium-glucose cotransporter-2 (SGLT2) inhibitors or with dipeptidyl peptidase-4 (DPP-4) inhibitors [final clinical study report (CSR) expected in Q3 2021]

17.5.9. Golimumab - SIMPONI (CAP) - EMEA/H/C/000992/MEA 026.7

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Fourth progress report for study MK-8259-013, the ulcerative colitis (UC) Nordic registry: a non-interventional observational longitudinal PASS of Simponi (golimumab) in the treatment of UC using Nordic national health registries

17.5.10. Guanfacine - INTUNIV (CAP) - EMEA/H/C/003759/MEA 005.3

Applicant: Shire Pharmaceuticals Ireland Limited

PRAC Rapporteur: Maria del Pilar Rayon

Scope: First annual progress report for a drug utilisation study (DUS) of Intuniv (guanfacine extended release) in European countries: a non-imposed, non-interventional, multi-country DUS using retrospective database analysis (DUS-database: EUPAS18735) and a prescriber survey (DUS-survey: EUPAS18739) (version 1.0)

17.5.11. Idelalisib - ZYDELIG (CAP) - EMEA/H/C/003843/MEA 015.3

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Martin Huber

Scope: Interim results for study GS-EU-313-4172: a non-interventional study to assess the safety profile of idelalisib in patients with refractory follicular lymphoma (FL)

17.5.12. Infliximab - INFLECTRA (CAP) - EMEA/H/C/002778/MEA 007.5

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Kimmo Jaakkola

Scope: Annual safety and efficacy interim analysis report for registry CT-P13 4.2: an observational, prospective cohort study to evaluate safety and efficacy of Inflectra (infliximab) in patients with rheumatoid arthritis (EU and Korea) [final clinical study report (CSR) expected: May 2026]

17.5.13. Infliximab - INFLECTRA (CAP) - EMEA/H/C/002778/MEA 010.5

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Kimmo Jaakkola

Scope: Annual safety and efficacy interim analysis report for registry CT-P13 4.3: an observational, prospective cohort study to evaluate the safety and efficacy of Inflectra (infliximab) in patients with Crohn’s disease (CD), and ulcerative colitis (UC) (EU and Korea) [final clinical study report (CSR) expected: May 2026]

17.5.14. Infliximab - REMSIMA (CAP) - EMEA/H/C/002576/MEA 007.5

Applicant: Celltrion Healthcare Hungary Kft.

PRAC Rapporteur: Kimmo Jaakkola

Scope: Annual safety and efficacy interim analysis report for registry CT-P13 4.2: an observational, prospective cohort study to evaluate safety and efficacy of Remsima (infliximab) in patients with rheumatoid arthritis (EU and Korea) [final clinical study report (CSR) expected: May 2026]

17.5.15. Infliximab - REMSIMA (CAP) - EMEA/H/C/002576/MEA 010.5

Applicant: Celltrion Healthcare Hungary Kft.

PRAC Rapporteur: Kimmo Jaakkola

Scope: Annual safety and efficacy interim analysis report for registry CT-P13 4.3: an observational, prospective cohort study to evaluate the safety and efficacy of Remsima (infliximab) in patients with Crohn’s disease (CD), and ulcerative colitis (UC) (EU and Korea) [final clinical study report (CSR) expected: May 2026]

17.5.16. Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/MEA 021

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Interim clinical study report for study CA209835 (listed as a category 3 study in the RMP): a registry study to analyse transplant-related complications after an allogeneic haematopoietic stem cell transplantation (HCT), among patients with classical Hodgkin lymphoma (cHL) who were previously treated with nivolumab (from variation II/12)

17.5.17. Octocog alfa - KOVALTRY (CAP) - EMEA/H/C/003825/MEA 005.1

Applicant: Bayer AG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Annual interim results 2018 for epidemiological study 15689: an evaluation of adverse events of special interest (AESI) in the PEDiatric NETwork (PedNet) haemophilia registry (from MA/opinion)

17.5.18. Ospemifene - SENSHIO (CAP) - EMEA/H/C/002780/ANX 001.7

Applicant: Shionogi B.V.

PRAC Rapporteur: Kirsti Villikka

Scope: Fourth annual interim report for a PASS (ENCEPP/SDPP/8585) (listed as a category 1 study in Annex II and the RMP): an observational retrospective cohort study of ospemifene utilising existing databases in Germany, Italy, Spain, and the United States to evaluate the incidence of venous thromboembolism and other adverse events in vulvar and vaginal atrophy (VVA) patients treated with ospemifene as compared to: 1) patients newly prescribed selective oestrogen receptor modulators (SERM) for oestrogen-deficiency conditions or breast cancer prevention and; 2) the incidence in untreated VVA patients [final report expected in February 2021]

17.5.19. Roflumilast - DAXAS (CAP) - EMEA/H/C/001179/ANX 002.8

Applicant: AstraZeneca AB

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Third interim report for PASS D7120R00003 (previously RO-2455-403-RD): a long-term post-marketing observational study exploring the safety of roflumilast in the treatment of chronic obstructive pulmonary disease (COPD), combined data results from Sweden, Germany and the US (Annex II-D on 'Conditions or restrictions with regard to the safe and effective use of the medicinal product') [final clinical study report (CSR) expected in March 2021]

17.5.20. Sacubitril, valsartan - ENTRESTO (CAP) - EMEA/H/C/004062/MEA 004.6

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Anette Kirstine Stark

Scope: Amendment to protocol previously agreed in March 2017 for study LCZ696B2015 (listed as a category 3 study in the RMP): a non-interventional post-authorisation European multi-database safety study to assess the risk of myotoxicity, hepatotoxicity and acute pancreatitis in statin-exposed heart failure patients with or without concomitant use of

Entresto/Neparvis (sacubitril/valsartan) together with MAH's response to MEA 004.5 as per the request for supplementary information (RSI) adopted in June 2019

17.5.21. Sacubitril, valsartan - NEPARVIS (CAP) - EMEA/H/C/004343/MEA 003.3

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Anette Kirstine Stark

Scope: Amendment to protocol previously agreed in March 2017 for study LCZ696B2015 (listed as a category 3 study in the RMP): a non-interventional post-authorisation European multi-database safety study to assess the risk of myotoxicity, hepatotoxicity and acute pancreatitis in statin-exposed heart failure patients with or without concomitant use of Entresto/Neparvis (sacubitril/valsartan) together with MAH's response to MEA 004.5 as per the request for supplementary information (RSI) adopted in June 2019

17.5.22. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/MEA 022.17

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Rhea Fitzgerald

Scope: MAH's response to MEA 022.16 [eighth 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] as per the request for supplementary information (RSI) adopted in April 2019

17.5.23. Vonicog alfa - VEYVONDI (CAP) - EMEA/H/C/004454/MEA 001.2

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Interim report for study VON (BAX0111) VWF-500 COL (also called ATHN-9 study) (listed as a category 3 study in the RMP): a real world safety and effectiveness study of factor replacement for clinically severe von Willebrand disease (VWD) [final report due date: 30/06/2022] (from initial opinion/MA)

17.5.24. Voriconazole - VFEND (CAP) - EMEA/H/C/000387/MEA 091.3

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: MAH's response to MEA 091.2 [second interim report for non-interventional study A1501103: an active safety surveillance programme to monitor selected events in patients with long-term voriconazole use] as per the request for supplementary information (RSI) adopted in March 2019

17.6. Others

17.6.1. Naltrexone hydrochloride, bupropion hydrochloride - MYSIMBA (CAP) - EMEA/H/C/003687/MEA 003.7

Applicant: Orexigen Therapeutics Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: First feasibility assessment report for study NB-451: an observational retrospective study based on secondary data analysis using existing databases, in order to evaluate the potential population of patients or prescriptions in each database and confirm the ability to use each database for the drug utilisation study (DUS) of Mysimba (naltrexone hydrochloride/bupropion hydrochloride) in selected European countries to describe the demographic and baseline characteristics of users of Mysimba (naltrexone hydrochloride/bupropion hydrochloride)

17.6.2. Prucalopride - RESOLOR (CAP) - EMEA/H/C/001012/REC 022.1

Applicant: Shire Pharmaceuticals Ireland Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: MAH's response to REC 022 [report from the FDA[87] on study SPD555-802: a retrospective cohort (observational) study measuring the incidence of major adverse cardiovascular events (MACE; non-fatal acute myocardial infarction, non-fatal stroke, or in-hospital cardiovascular death) in five European data sources, as requested in the conclusions of variation II/42 concluded in September 2018] as per the request for supplementary information (RSI) adopted in May 2019

17.6.3. Teriflunomide - AUBAGIO (CAP) - EMEA/H/C/002514/MEA 005.1

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Martin Huber

Scope: Proposal for amendment to previously agreed protocols in September 2014 for: 1) pregnancy registry OBS12751 (international): an international pregnancy exposure registry of women with multiple sclerosis (MS) exposed to Aubagio (teriflunomide) and; 2) pregnancy registry OBS13499 (US/CA): teriflunomide pregnancy outcome exposure registry: a 'teratology information specialists (OTIS)' autoimmune diseases in pregnancy project. The purpose of this position paper is to describe the challenges in achieving enrolment targets, to outline the actions implemented to date to increase enrolment, to provide statistical considerations

17.7. New Scientific Advice

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

[87] US Food & Drug Administration

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. Cholic acid - KOLBAM (CAP) - EMEA/H/C/002081/S/0029 (without RMP)

Applicant: Retrophin Europe Ltd

PRAC Rapporteur: Agni Kapou

Scope: Annual reassessment of the marketing authorisation

18.2. Conditional renewals of the marketing authorisation

18.2.1. Obeticholic acid - OCALIVA (CAP) - EMEA/H/C/004093/R/0018 (without RMP)

Applicant: Intercept Pharma International Limited

PRAC Rapporteur: Menno van der Elst

Scope: Conditional renewal of the marketing authorisation

18.3. Renewals of the marketing authorisation

18.3.1. Afamelanotide - SCENESSE (CAP) - EMEA/H/C/002548/R/0026 (without RMP)

Applicant: Clinuvel Europe Limited

PRAC Rapporteur: Martin Huber

Scope: 5-year renewal of the marketing authorisation

18.3.2. Ciclosporin - IKERVIS (CAP) - EMEA/H/C/002066/R/0017 (without RMP)

Applicant: Santen Oy

PRAC Rapporteur: Jan Neuhauser

Scope: 5-year renewal of the marketing authorisation

18.3.3. Clopidogrel - CLOPIDOGREL RATIOPHARM (CAP) - EMEA/H/C/004006/R/0014 (with RMP)

Applicant: Teva B.V.

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: 5-year renewal of the marketing authorisation

18.3.4. Dalbavancin - XYDALBA (CAP) - EMEA/H/C/002840/R/0028 (without RMP)

Applicant: Allergan Pharmaceuticals International Limited

PRAC Rapporteur: Rugile Pilviniene

Scope: 5-year renewal of the marketing authorisation

18.3.5. Estrogens conjugated, bazedoxifene - DUAVIVE (CAP) - EMEA/H/C/002314/R/0021 (without RMP)

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Martin Huber

Scope: 5-year renewal of the marketing authorisation

18.3.6. Nonacog gamma - RIXUBIS (CAP) - EMEA/H/C/003771/R/0029 (with RMP)

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: 5-year renewal of the marketing authorisation

18.3.7. Oritavancin - ORBACTIV (CAP) - EMEA/H/C/003785/R/0027 (without RMP)

Applicant: Menarini International Operations Luxembourg S.A.

PRAC Rapporteur: Adam Przybylkowski

Scope: 5-year renewal of the marketing authorisation

18.3.8. Paliperidone - TREVICTA (CAP) - EMEA/H/C/004066/R/0022 (with RMP)

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Ulla Wändel Liminga

Scope: 5-year renewal of the marketing authorisation

18.3.9. Sevelamer carbonate - SEVELAMER CARBONATE WINTHROP (CAP) - EMEA/H/C/003971/R/0022 (with RMP)

Applicant: Genzyme Europe BV

PRAC Rapporteur: Laurence de Fays

Scope: 5-year renewal of the marketing authorisation

18.3.10. Tedizolid phosphate - SIVEXTRO (CAP) - EMEA/H/C/002846/R/0031 (without RMP)

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Maria del Pilar Rayon

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 02 – 05 September 2019 meeting.

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Sabine Straus	Chair	The Netherlands	No interests declared	Full involvement
Jan Neuhauser	Member	Austria	No interests declared	Full involvement
Jean-Michel Dogné	Member	Belgium	No interests declared	Full involvement
Maria Popova-Kiradjieva	Member	Bulgaria	No interests declared	Full involvement
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
Eva Jirsova	Member	Czech Republic	No interests declared	Full involvement
Anette Kirstine Stark	Member	Denmark	No interests declared	Full involvement
Hans Christian Siersted	Alternate	Denmark	No restrictions applicable to this meeting	Full involvement
Maia Uusküla	Member	Estonia	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Kirsti Villikka	Member	Finland	No interests declared	Full involvement
Kimmo Jaakkola	Alternate	Finland	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 interests declared	Full involvement
Guðrún Stefánsdóttir	Member	Iceland	No restrictions applicable to this meeting	Full involvement
Rhea Fitzgerald	Member	Ireland	No restrictions applicable to this meeting	Full involvement
Ronan Grimes	Alternate	Ireland	No interests declared	Full involvement
Amelia Cupelli	Member	Italy	No interests declared	Full involvement
Ilaria Baldelli	Alternate	Italy	No interests declared	Full involvement
Zane Neikena	Member	Latvia	No interests declared	Full involvement
Rugile Pilviniene	Member	Lithuania	No interests declared	Full involvement
Marcel Bruch	Member	Luxembourg	No interests declared	Full involvement
Benjamin Micallef	Alternate	Malta	No interests declared	Full involvement
Menno van der Elst	Member	Netherlands	No interests declared	Full involvement
Liana Gross-Martirosyan	Alternate	Netherlands	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
David Olsen	Member	Norway	No participation in discussion, final deliberations and voting on:	4.3.2. Ibuprofen (NAP) and fixed-dose combinations 10.1.1. Interferon beta-1a – AVONEX (CAP) - REBIF (CAP); Interferon beta-1b - BETAFERON (CAP); EXTAVIA (CAP); peginterferon beta-1a - PLEGRIDY (CAP) 15.3.17. Interferon beta-1b - BETAFERON (CAP) 17.5.17. Octocog alfa - KOVALTRY (CAP)
Karen Pernille Harg	Alternate	Norway	No interests declared	Full involvement
Adam Przybylkowski	Member	Poland	No interests declared	Full involvement
Ana Diniz Martins	Member	Portugal	No interests declared	Full involvement
Roxana Stefania Stroe	Member	Romania	No interests declared	Full involvement
Michal Radik	Member	Slovakia	No restrictions applicable to this meeting	Full involvement
Gabriela Jazbec	Member	Slovenia	No interests declared	Full involvement
Eva Segovia	Member	Spain	No interests declared	Full involvement
Maria del Pilar Rayon	Alternate	Spain	No interests	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			declared	
Ulla Wändel Liminga	Member	Sweden	No interests declared	Full involvement
Annika Folin	Alternate	Sweden	No interests declared	Full involvement
Patrick Batty	Alternate	United Kingdom	No interests declared	Full involvement
Birgitta Grundmark	Member	Independent scientific expert	No interests declared	Full involvement
Daniel Morales	Member	Independent scientific expert	No interests declared	Full involvement
Antoine Pariente	Member	Independent scientific expert	No participation in discussion, final deliberations and voting on:	18.2.1. Obeticholic acid - OCALIVA (CAP)
Livia Puljak	Member	Independent scientific expert	No interests declared	Full involvement
Stefan Weiler	Member	Independent scientific expert	No participation in discussion, final deliberations and voting on:	16.1.54. Ulipristal acetate - ESMYA (CAP); ULIPRISTAL ACETATE GEDEON RICHTER (CAP)
Raymond Anderson	Member	Healthcare Professionals' Representative	No interests declared	Full involvement
Roberto Frontini	Alternate	Healthcare Professionals' Representative	No participation in final deliberations and voting on:	16.1.47. Simoctocog alfa - NUWIQ (CAP); VIHUMA (CAP)
Cathalijne van Doorne	Member	Patients' Organisation Representative	No interests declared	Full involvement
Virginie Hivert	Alternate	Patients' Organisation Representative	No restrictions applicable to	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			this meeting	
Ivana Ljubicic	Expert - via telephone*	Croatia	No restrictions applicable to this meeting	Full involvement
Marian Hjortlund Allon	Expert - in person*	Denmark	No interests declared	Full involvement
Marie-Caroline Pesquidous	Expert - in person*	France	No restrictions applicable to this meeting	Full involvement
Dennis Lex	Expert - in person*	Germany	No participation in discussion, final deliberations and voting on:	Full involvement
Martina Schuessler Lenz	Expert - via telephone*	Germany	No interests declared	Full involvement
Wiebke Seemann	Expert - via telephone*	Germany	No interests declared	Full involvement
Sophie Sommerer	Expert - in person*	Health Canada	No interests declared	Full involvement
Eleanor Carey	Expert - via telephone*	Ireland	No interests declared	Full involvement
Ruchika Sharma	Expert - via telephone*	Ireland	No restrictions applicable to this meeting	Full involvement
Peter Mol	Expert - via telephone*	Netherlands	No interests declared	Full involvement
Evelyn Olthof	Expert - in person*	Netherlands	No interests declared	Full involvement
Joost Romme (Jacobus Johannes Christianus Maria Romme)	Expert - in person*	Netherlands	No interests declared	Full involvement
Elisabeth Johanne Rook	Expert - via telephone*	Netherlands	No interests declared	Full involvement
Priscilla Schoondermark	Expert - in person*	Netherlands	No interests declared	Full involvement
Virginie Seelen	Expert - in	Netherlands	No interests	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
	person*		declared	
Rune Kjeken	Expert - in person*	Norway	No interests declared	Full involvement
Charlotte Backman	Expert - in person*	Sweden	No interests declared	Full involvement
Hong Wang	Expert - in person*	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/