EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

13 February 2020
EMA/PRAC/297855/2020
Inspections, Human Medicines Pharmacovigilance and Committees Division

Pharmacovigilance Risk Assessment Committee (PRAC)

Minutes of PRAC meeting on 13 – 16 January 2020

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 13 - 16 January 2020 meeting by welcoming all participants.

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

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

The PRAC welcomed the new Croatian presidency of the Council of the EU.

1.2. Agenda of the meeting on 13-16 January 2020

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

1.3. Minutes of the previous meeting on 25 – 28 November 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 25 – 28 November 2019 were published on the EMA website on 27 May 2020 (EMA/PRAC/287927/2020).

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

2.1. Newly triggered procedures

None

2.2. Ongoing procedures

None

2.3. Procedures for finalisation

None

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

3.1. Newly triggered procedures

None

3.2. Ongoing procedures

3.2.1. 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

A referral procedure under Article 20 of Regulation (EC) No 726/2004 is ongoing to review the possible risk of skin tumour in the treatment area in patients treated with Picato (ingenol mebutate). For further background, see PRAC minutes September 2019.

Discussion

The PRAC considered the ongoing procedure under Article 20 of Regulation (EC) No 726/2004 resulting from pharmacovigilance data, in particular regarding the need for provisional measures in accordance with Article 20(3) of Regulation (EC) No 726/2004 for Picato (ingenol mebutate) and taking into account the grounds set out in Article 116 of Directive 2001/83/EC.

The PRAC reviewed the information currently available to the Committee from clinical trials, post-marketing reports and non-clinical studies, on the risk of skin tumour in the treatment area in patients treated with Picato (ingenol mebutate). The PRAC also noted the MAH's request to withdraw the marketing authorisation(s) (MA).

The PRAC considered of concern the evidence on skin malignancies from all the available data with ingenol mebutate, including the statistically significant imbalance in skin malignancy with ingenol mebutate compared to imiquimod, observed in the interim results of study LP0041-63[1], and confirmed in the final study results.

The PRAC considered the remaining uncertainties regarding a mechanism for a tumour promoting effect of ingenol. The PRAC noted that recent study results further support that the efficacy of Picato (ingenol mebutate) is not maintained over time.

Therefore, given the growing concerns on the serious risk of skin tumour possibly associated with Picato (ingenol mebutate), the PRAC provisionally recommended, as a precaution while

[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

the review continues, that patients should no longer be treated with Picato (ingenol mebutate).

Finally, the PRAC discussed a list of outstanding issues (LoOI) to be addressed during the procedure together with a timetable for conducting the review.

Summary of recommendation(s)/conclusions

- The PRAC recommended provisional suspension of the marketing authorisation(s) for Picato (ingenol mebutate), without prejudice to the final conclusions of the ongoing procedure under Article 20 of Regulation (EC) 726/2004.
- The PRAC adopted a LoOI to be addressed by the MAH in accordance with a revised timetable (EMA/PRAC/484544/2019 Rev.1).
- The PRAC agreed on the content of a direct healthcare professional communication (DHPC) along with a communication plan for its distribution.

See EMA press release (EMA/32231/2020) entitled 'EMA suspends Picato as a precaution while review of skin cancer risk continues'.

Post-meeting note: On 17 January 2020, the European Commission (EC) issued a Commission Decision (CD) on the provisional measures (C(2020) 383 final). On 21 January 2020, the PRAC assessment report on provisional measures (EMA/30347/2020) and scientific conclusions were published on the EMA website. In addition, on 11 February 2020, the EC issued a CD withdrawing the marketing authorisation(s) for Picato (ingenol mebutate) at the MAH's request (C(2020) 856 final).

3.3. Procedures for finalisation

None

3.4. Re-examination procedures[2]

3.4.1. Estradiol[3] (NAP) - EMEA/H/A-31/1482

Applicant(s): various

PRAC Rapporteur: Jan Neuhauser; PRAC Co-rapporteur: Nikica Mirošević Skvrce

Scope: Re-examination under Article 32 of Directive 2001/83/EC for the review of the benefit-risk balance of medicinal product(s) containing estradiol 0.01% for topical use following notification by the European Commission (EC) of a referral under Article 31 of Directive 2001/83/EC, based on pharmacovigilance data

Background

Following the PRAC recommendation adopted at the October 2019 PRAC meeting[4], to vary the marketing authorisations of medicinal products containing estradiol 0.01% for topical use, a MAH concerned by this referral procedure requested a re-examination of the PRAC recommendation in line with Article 32 of Directive 2001/83/EC. For further background, see

[2] Re-examination of PRAC recommendation under Article 32 of Directive 2001/83/EC
[3] 0.01% w/w, topical use only
[4] Held 30 September – 03 October 2019

PRAC minutes April 2019, PRAC minutes July 2019, PRAC minutes October 2019 and PRAC minutes November 2019[5].

Discussion

The PRAC considered the re-examination of the procedure under Article 31 of Directive 2001/83/EC for medicinal products containing estradiol 0.01% for topical use.

The PRAC reviewed the totality of data submitted with regard to the risk of adverse drug reactions due to systemic absorption of estradiol. This includes the responses submitted by the MAHs, published literature, spontaneous reporting, as well as the outcome of an ad-hoc expert group of gynaecologists and patient representatives. The PRAC also considered the grounds submitted by one MAH as a basis for the request for re-examination of the PRAC recommendation.

The PRAC considered that the efficacy of estradiol-containing medicinal products (0.01% w/w) for topical use has been sufficiently demonstrated in comparison to placebo over a period of 4 weeks treatment in the treatment of the symptoms of vaginal atrophy due to oestrogen deficiency in postmenopausal women.

In view of the currently available data, the PRAC concluded that there is a systemic exposure above the normal post-menopausal range after topical use of estradiol-containing medicinal products (0.01% w/w) for topical use that warrants risk minimisation measures (RMMs).

In addition, the PRAC noted that safety and efficacy data on treatment longer than 4 weeks as well as repeated use of estradiol-containing medicinal products (0.01% w/w) for topical use is either lacking or extremely limited. Therefore, given limitations of the data, the systemic exposure to estradiol above normal postmenopausal range of these products and the risks associated with systemic exposure to oestrogen, these products should only be used for a single treatment period up to 4 weeks maximum.

The PRAC also concluded that the product information should be updated to take into account the current clinical knowledge on safety of oestrogen products for vaginal application of which the systemic exposure to the oestrogen is higher than the normal postmenopausal range, especially regarding risks of thromboembolism events, breast and endometrial cancer.

To minimise the risk of prolonged or repeated use and to ensure patients adherence to the recommended duration of use, the maximum package size of the medicinal product authorised should not exceed 25 g.

Finally, the PRAC concluded that the product information should be updated to increase awareness on the strength of these medicinal products and on the maximum treatment period.

The Committee considered that the benefit-risk balance of estradiol-containing medicinal products (0.01% w/w) for topical use remains favourable subject to the agreed amendments to the product information and RMMs.

Summary of recommendation(s)/conclusions

- In view of the available data including the detailed grounds submitted by the MAH during the re-examination procedure, the PRAC concluded that the benefit-risk balance

[5] Held 28 – 31 October 2019

of estradiol-containing (0.01% w/w) medicinal products for topical use remains favourable subject to the changes to the product information and other RMMs.

- The PRAC adopted a recommendation to vary[6] the terms of the marketing authorisations for estradiol-containing medicinal products (0.01% w/w) for topical use[7] to be considered by the CMDh for a position – see EMA Press Release (EMA/20248/2020) entitled 'PRAC confirms four-week limit for use of high-strength estradiol creams' published on 17 January 2020.
- The PRAC agreed on the content of a direct healthcare professional communication (DHPC) along with a communication plan for its distribution.

Post-meeting note 1: the press release entitled 'Four-week limit for use of high-strength estradiol creams confirmed' (EMA/48567/2020) representing the position adopted by the CMDh was published on the EMA website on 31 January 2020.

Post-meeting note 2: the PRAC assessment report (EMA/62697/2020) was published on 10 February 2020.

3.5. Others

None

4. Signals assessment and prioritisation[8]

4.1. New signals detected from EU spontaneous reporting systems

See Annex I 14.1.

4.2. New signals detected from other sources

4.2.1. Dabrafenib – TAFINLAR (CAP); trametinib – MEKINIST (CAP)

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Annika Folin

Scope: Signal of disseminated intravascular coagulation (DIC)

EPITT 19510 – New signal

Lead Member State(s): NO, SE

Background

Dabrafenib is a rapidly accelerated fibrosarcoma (RAF) kinase inhibitor indicated, as Tafinlar, in monotherapy or in combination with trametinib for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation and in combination with trametinib for the adjuvant treatment of adult patients with stage III melanoma with a BRAF

[6] Update of SmPC sections 4.2, 4.3, 4.4, 4.8, 5.1 and Annex II. The package leaflet is updated accordingly
[7] Cream and emulsion
[8] 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

V600 mutation following complete resection. Dabrafenib in combination with trametinib is also indicated for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with a BRAF V600 mutation.

The exposure for Tafinlar (dabrafenib) is estimated to have been more than 24,908 patient-years worldwide, in the period from first authorisation in 2013 to 2018. The exposure for Mekinist (trametinib) is estimated to have been more than 27,193 patient-years worldwide, in the period from first authorisation in 2014 to 2019.

During routine signal detection activities, a signal of disseminated intravascular coagulation (DIC) was identified by the EMA, based on 26 cases retrieved from EudraVigilance. Sweden confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

Having considered the available evidence from EudraVigilance, the PRAC agreed to request a cumulative review of clinical trial data and literature on DIC in relation to dabrafenib and trametinib. A discussion on the need for any potential amendments to the product information and/or the RMP should also be provided.

The PRAC appointed Annika Folin as Rapporteur for the signal.

Summary of recommendation(s)

- The MAH for Tafinlar (dabrafenib) and Mekinist (trametinib) should submit to the EMA, within 60 days, a cumulative review of clinical trial data and literature on DIC, and a proposal to amend the product information as appropriate.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.2.2. Fluoroquinolones: cinoxacin (NAP); ciprofloxacin (NAP); ciprofloxacin, dexamethasone (NAP); ciprofloxacin, fluocinolone (NAP); ciprofloxacin, hydrocortisone (NAP); delafloxacin – QUOFENIX (CAP); levofloxacin – QUINSAIR (CAP); lomefloxacin (NAP); moxifloxacin (NAP); nadifloxacin (NAP); norfloxacin (NAP); ofloxacin (NAP); ofloxacin, dexamethasone (NAP); ozenoxacin (NAP); pefloxacin (NAP); prulifloxacin (NAP); rufloxacin (NAP)

Applicant(s): A. Menarini Industrie Farmaceutiche Riunite (Quofenix), Chiesi Farmaceutici S.p.A. (Quinsair), various

PRAC Rapporteur: Martin Huber

Scope: Signal of heart valve regurgitation

EPITT 19522 – New signal

Lead Member State(s): DE, DK, ES, FR, IT, HR

Background

Fluoroquinolones are broad-spectrum antibiotics indicated for a variety of infections including serious bacterial infections, especially hospital-acquired infections and others caused by susceptible microorganisms. Some fluoroquinolones have restricted indications limited to situations where other commonly recommended antibacterials are not appropriate. Quofenix

and Quinsair are centrally authorised products containing delafloxacin and levofloxacin, respectively.

Following the publication by *Etminan et al*[9], a signal of heart valve regurgitation was identified by Germany, suggesting an association between exposure to fluoroquinolones and aortic valve and mitral valve regurgitation. Germany confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC considered the evidence provided in the publication by *Etminan et al* on the risk of heart valve regurgitation with fluoroquinolones and case reports in EudraVigilance. Taking also into consideration new data from the literature[10] regarding the risk of cervical artery dissection and the review of the PSUR single assessment (PSUSA) procedure for moxifloxacin systemic use (PSUSA/00009231/201905) finalised this month (see 6.3.6.) on the risk of aortic aneurysm and dissection, the PRAC agreed on the need to broaden the scope of this signal and perform a further literature review on cardiovascular events (carotid dissection, heart valve regurgitation and the aortic dissection) associated with fluoroquinolones, and supported the EMA to perform a review of EudraVigilance.

The PRAC appointed Martin Huber as Rapporteur for the signal.

Summary of recommendation(s)

- The PRAC Rapporteur will perform a literature review on cardiovascular events associated with fluoroquinolones and the EMA will perform an extended search in EudraVigilance.
- A 90-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. Abiraterone – ZYTIGA (CAP) - EMEA/H/C/002321/SDA/022; 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 – Follow-up to September 2019

Background

For background information, see PRAC minutes September 2019.

[9] Etminan et al. Oral fluoroquinolones and risk of mitral and aortic regurgitation. J Am Coll Cardiol. 2019;74(11):1444-1450
[10] Del Zotto et al. Use of fluoroquinolones and the risk of spontaneous cervical artery dissection; Eur J Neurol. 2019;26(7):1028-1031

The MAH for Zytiga (abiraterone) replied to the request for information on the signal of interaction with sulphonylureas leading to hypoglycaemia and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence in EudraVigilance and in the literature, together with the data from the cumulative review provided by the MAH of Zytiga (abiraterone), the PRAC agreed that there is sufficient evidence that the drug interaction may lead to hypoglycaemia and that the product information should be updated accordingly.

Summary of recommendation(s)

- The MAH of Zytiga (abiraterone) should submit to the EMA, within 60 days, a variation to amend the product information[11].

For the full PRAC recommendation, see EMA/PRAC/8637/2020 published on 10 February 2020 on the EMA website.

4.3.2. Adalimumab – AMGEVITA (CAP); HALIMATOZ (CAP); HEFIYA (CAP); HULIO (CAP); HUMIRA (CAP) - EMEA/H/C/000481/SDA/115; HYRIMOZ (CAP); IDACIO (CAP); IMRALDI (CAP)

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

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of pericarditis

EPITT 19457 – Follow-up to September 2019

Background

For background information, see PRAC minutes September 2019.

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

Discussion

Having considered the available evidence, including the responses from the MAH for Humira (adalimumab), the PRAC agreed that a causal relationship between adalimumab and pericarditis and/or pericardial effusion cannot be established at this stage and that no further regulatory actions are warranted.

Summary of recommendation(s)

- The MAHs for adalimumab-containing medicinal products should continue to monitor pericarditis and pericardial effusion as part of routine safety surveillance.

4.3.3. Anastrozole (NAP)

Applicant(s): various

[11] Update of SmPC sections 4.4 and 4.5. The package leaflet is to be updated accordingly

PRAC Rapporteur: Zane Neikena

Scope: Signal of hallucinations

EPITT 19449 – Follow-up to September 2019

Background

For background information, see PRAC minutes September 2019.

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

Discussion

Having considered the available evidence from the cumulative review of post-marketing reports, clinical trials and literature provided by the MAH, the PRAC agreed that a causal relationship between treatment with anastrozole and hallucinations is not sufficiently strong at this stage and that no further regulatory actions were warranted. The PRAC agreed that the MAH should closely monitor cases of hallucinations and present them in future PSURs.

Summary of recommendation(s)

- The MAHs for anastrozole-containing products should continue to monitor hallucinations as part of routine safety surveillance.

4.3.4. Dipeptidyl peptidase-4 (DPP4) inhibitors: alogliptin - VIPIDIA (CAP) - EMEA/H/C/002182/SDA/012; alogliptin, metformin hydrochloride - VIPDOMET (CAP) - EMEA/H/C/002654/SDA/009; alogliptin, pioglitazone - INCRESYNC (CAP) - EMEA/H/C/002178/SDA/009; linagliptin - TRAJENTA (CAP) - EMEA/H/C/002110/SDA/019; saxagliptin - ONGLYZA (CAP) - EMEA/H/C/001039/SDA/044; saxagliptin, dapagliflozin - QTERN (CAP) - EMEA/H/C/004057/SDA/007; sxagliptin, metformin hydrochloride - KOMBOGLYZE (CAP) - EMEA/H/C/002059/SDA/019; sitagliptin – JANUVIA (CAP) - EMEA/H/C/000722/SDA/039, RISTABEN (CAP) - EMEA/H/C/001234/SDA/017, TESAVEL (CAP) - EMEA/H/C/000910/SDA/033, XELEVIA (CAP) - EMEA/H/C/000762/SDA/038; NAP; sitagliptin, ertugliflozin – STEGLUJAN (CAP); sitagliptin, metformin – EFFICIB (CAP); JANUMET (CAP); VELMETIA (CAP);NAP; vildagliptin - GALVUS (CAP) - EMEA/H/C/000771/SDA/048, JALRA (CAP) - EMEA/H/C/001048/SDA/032, XILIARX (CAP) - EMEA/H/C/001051/SDA/032; vildagliptin, metformin hydrochloride - EUCREAS (CAP) - EMEA/H/C/000807/SDA/026, ICANDRA (CAP) - EMEA/H/C/001050/SDA/024, ZOMARIST (CAP) - EMEA/H/C/001049/SDA/024; NAP

Applicant(s): AstraZeneca AB (Kombogzyle, Onglyza, Qtern), Boehringer Ingelheim International GmbH (Trajenta), Merck Sharp & Dohme B.V. (Efficib, Janumet, Januvia, Ristaben, Steglujan, Tesavel, Velmetia, Xelevia), Takeda Pharma A/S (Incresync, Vipidia, Vipdomet), Novartis Europharm Limited (Eucreas, Galvus, Icandra, Jalra, Xiliarx, Zomarist), various

PRAC Rapporteur: Menno van der Elst

Scope: Signal of rhabdomyolysis

EPITT 19466 – Follow-up to September 2019

Background

For background information, see PRAC minutes September 2019.

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

Discussion

Based on the available evidence provided by the MAHs, the PRAC agreed that for saxagliptin, linagliptin and sitagliptin there is currently insufficient evidence for a causal relationship with rhabdomyolysis/myopathy, or an interaction between dipeptidyl peptidase-4 (DPP4)-inhibitors and statins. Nevertheless, the PRAC agreed that a further review was warranted for alogliptin and vildagliptin.

Summary of recommendation(s)

- The MAHs for alogliptin- and vildagliptin-containing products should submit to the EMA, within 60 days, responses to a request for supplementary information (RSI) agreed by the PRAC.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.3.5. Golimumab – SIMPONI (CAP) – EMEA/H/C/000992/SDA/035

Applicant(s): Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of inflammatory myopathy

EPITT 19460 – Follow-up to September 2019

Background

For background information, see PRAC minutes September 2019.

The MAH for Simponi (golimumab) replied to the request for information on the signal of inflammatory myopathy and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence from EudraVigilance and the literature, as well as the cumulative review submitted by the MAH, the PRAC agreed that there is sufficient evidence for a causal relationship between golimumab treatment and the worsening of symptoms of inflammatory myopathy (dermatomyositis). The PRAC agreed that the product information should be updated accordingly.

Summary of recommendation(s)

- The MAH for Simponi (golimumab) should submit to the EMA, within 60 days, a variation to update the product information[12].

For the full PRAC recommendation, see EMA/PRAC/8637/2020 published on 10 February 2020 on the EMA website.

4.3.6. Hormone replacement therapy (HRT): chlorotrianisene (NAP); conjugated estrogens (NAP); conjugated estrogens, bazedoxifene - DUAVIVE (CAP); dienestrol (NAP); diethylstilbestrol (NAP); estradiol

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

(NAP); estradiol, norethisterone (NAP); estriol (NAP); estrone (NAP); ethinylestradiol (NAP); methallenestril (NAP); moxestrol (NAP); promestriene (NAP); tibolone (NAP)

Applicant(s): Pfizer Europe MA EEIG (Duavive), various

PRAC Rapporteur: Menno van der Elst

Scope: New information on the known risk of breast cancer

EPITT 19482 – Follow-up to October 2019

Background

For background information, see PRAC minutes October 2019[13].

The Rapporteur assessed the new information on the signal of breast cancer as recommended by the PRAC in October 2019.

Discussion

Having considered the results from the meta-analysis[14] from the 'Collaborative Group on Hormonal Factors in Breast Cancer', the PRAC agreed that the results are sufficiently robust to justify a revision of the current product information of hormone replacement therapy (HRT) regarding the risk of breast cancer. Nevertheless, the PRAC agreed that further clarifications from the meta-analysis authors are necessary before drawing a final recommendation.

Summary of recommendation(s)

- The authors of the meta-analysis are invited to provide responses to the EMA within 60 days to a request for supplementary information (RSI) agreed by the PRAC.

4.3.7. Immune checkpoint inhibitors: atezolizumab – TECENTRIQ (CAP) - EMEA/H/C/004143/SDA/018; avelumab – BAVENCIO (CAP) - EMEA/H/C/004338/SDA/005; cemiplimab – LIBTAYO (CAP) EMEA/H/C/004844/SDA/004; durvalumab – IMFINZI (CAP) EMEA/H/C/004771/SDA/003; ipilimumab – YERVOY (CAP) EMEA/H/C/002213/SDA/039; nivolumab – OPDIVO (CAP) EMEA/H/C/003985/SDA/039; pembrolizumab - KEYTRUDA (CAP) EMEA/H/C/003820/SDA/024

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 – Follow-up to September 2019

Background

[13] Held 30 September – 03 October 2019
[14] Collaborative Group on Hormonal Factors in Breast Cancer. Type and timing of menopausal hormone therapy and breast cancer risk: individual participant meta-analysis of the worldwide epidemiological evidence. Lancet. 2019;394(10204):1159-1168

For background information, see PRAC minutes September 2019.

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

Discussion

Having considered the available evidence from the cumulative reviews provided by the MAHs, the PRAC agreed that the incidence of tuberculosis and reactivation of latent tuberculosis from clinical trials and postmarketing cases reported with immune checkpoint inhibitors was in the range of globally estimated incidence of tuberculosis. Nevertheless, the PRAC agreed that an update of the product information was warranted to highlight that infectious- and disease-related aetiologies should be ruled out in patients with signs and symptoms suggestive for immune-related pneumonitis, for medicinal products without such warnings already present.

Summary of recommendation(s)

- The MAHs for Imfinzi (durvalumab), Libtayo (cemiplimab) and Tecentriq (atezolizumab) should submit to the EMA, within 30 days, their comments on the PRAC agreed wording for updating the product information.
- A 30-day timetable was recommended for the assessment leading to a further PRAC recommendation.
- The MAHs of Keytruda (pembrolizumab), Opdivo (nivolumab), Yervoy (ipilimumab), Bavencio (avelumab), Imfinzi (durvalumab), Libtayo (cemiplimab) and Tecentriq (atezolizumab) should continue to monitor events of *Mycobacterium tuberculosis* infection and reactivation as well as systemic *Bacillus Calmette-Guérin* (BCG) infection in patients with urothelial cancer, previously treated with BCG for immunotherapy, as part of routine safety surveillance.

4.3.8. Prasugrel – EFIENT (CAP) - EMEA/H/C/000984/SDA/035, PRASUGREL MYLAN (CAP), NAP

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

PRAC Rapporteur: Anette Kirstine Stark

Scope: Signal of severe cutaneous adverse reactions (SCARs)

EPITT 19463 – Follow-up to September 2019

Background

For background information, see PRAC minutes September 2019.

The MAH for Efient (prasugrel) 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 available evidence from the cumulative review provided by the MAH, the PRAC agreed that there was insufficient evidence to conclude on causality, due to confounding by concomitant medications and lacking confirmatory diagnostic information. Nevertheless, the PRAC concurred that the role of prasugrel could not be fully excluded. Therefore, the Committee recommended that acute generalised exanthematous pustulosis

(AGEP) and drug reaction with eosinophilia and systemic symptoms (DRESS) are classified as important potential risks and be reviewed in future PSURs.

Summary of recommendation(s)

- The MAHs for prasugrel-containing products should review cases of AGEP and DRESS in future PSURs as important potential risks.

4.3.9. Sacubitril, valsartan – ENTRESTO (CAP) - EMEA/H/C/004062/SDA/009; NEPARVIS (CAP) - EMEA/H/C/004343/SDA/004

Applicant(s): Novartis Europharm Limited

PRAC Rapporteur: Anette Kirstine Stark

Scope: Signal of ventricular arrhythmia

EPITT 19448 – Follow-up to September 2019

Background

For background information, see PRAC minutes September 2019.

The MAH for Entresto and Neparvis (sacubitril/valsartan) replied to the request for information on the signal of ventricular arrhythmia and the responses were assessed by the Rapporteur.

Discussion

Based on the evaluation of all available data including the review provided by the MAH, the PRAC agreed that there is currently insufficient evidence to confirm a causal relationship between the use of sacubitril/valsartan in patients with heart failure with reduced ejection fraction (HFrEF) and the risk of ventricular arrhythmias, and that no further regulatory actions are warranted at present.

Summary of recommendation(s)

- The MAH for Entresto (sacubitril/valsartan) and Neparvis (sacubitril/valsartan) should continue to monitor ventricular arrhythmia as part of routine safety surveillance.

5. Risk management plans (RMPs)

5.1. Medicines in the pre-authorisation phase

See also Annex I 15.1.

Assessment Reports (EPARs) to be published at the end of the evaluation procedure.

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

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

5.1.1. Budesonide, glycopyrronium, formoterol fumarate dihydrate - EMEA/H/C/004983

Scope: Maintenance treatment in adult patients with moderate to very severe chronic obstructive pulmonary disease (COPD)

5.1.2. Bulevirtide - EMEA/H/C/004854, Orphan

Applicant: MYR GmbH

Scope (accelerated assessment): Treatment of chronic hepatitis delta virus (HDV) infection in adult patients with compensated liver disease

5.1.3. Elexacaftor, tezacaftor, ivacaftor - EMEA/H/C/005269, Orphan

Applicant: Vertex Pharmaceuticals (Ireland) Limited

Scope (accelerated assessment): Treatment of cystic fibrosis

5.1.4. Indacaterol, glycopyrronium, mometasone - EMEA/H/C/005061

Scope: Treatment of asthma and reduction of asthma exacerbations

5.1.5. Indacaterol, glycopyrronium, mometasone - EMEA/H/C/005518

Scope: Treatment of asthma and reduction of asthma exacerbations

5.1.6. Indacaterol, mometasone furoate - EMEA/H/C/005067

Scope: Treatment of asthma

5.1.7. Pretomanid - EMEA/H/C/005167, Orphan

Applicant: FGK Representative Service GmbH

Scope: Treatment of tuberculosis

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. Tacrolimus - PROTOPIC (CAP) - EMEA/H/C/000374/II/0083/G

Applicant: LEO Pharma A/S

PRAC Rapporteur: Rhea Fitzgerald

Scope: Update of sections 4.4, 4.8, 5.1, 5.2 and 5.3 of the SmPC following results from two non-interventional PASS, namely: 1) JOELLE study (listed as a category 3 study in the RMP): a joint European longitudinal lymphoma and skin cancer evaluation; 2) APPLES study

(listed as a category 3 study in the RMP): a prospective paediatric longitudinal evaluation to assess the long-term safety of tacrolimus ointment for the treatment of atopic dermatitis. The package leaflet and the RMP (version 15.1) are updated accordingly. In addition, the MAH took the opportunity to bring the product information in line with the latest quality review of documents (QRD) template (version 10.1)

Background

Tacrolimus inhibits calcium-dependent signal transduction pathways in T cells. It is indicated, as Protopic, for the treatment of moderate to severe atopic dermatitis in adults who are not adequately responsive to or are intolerant of conventional therapies such as topical corticosteroids and for the treatment of moderate to severe atopic dermatitis in children who failed to respond adequately to conventional therapies such as topical corticosteroids. It is also indicated for the treatment of moderate to severe atopic dermatitis for the prevention of flares and the prolongation of flare-free intervals in patients experiencing a high frequency of disease exacerbations (i.e. occurring 4 or more times per year) who have had an initial response to a maximum of 6 weeks treatment of twice daily tacrolimus ointment (lesions cleared, almost cleared or mildly affected).

The CHMP is evaluating a type II variation for Protopic, a centrally authorised product containing tacrolimus, consisting of an update the product information of Protopic with the results from two non-interventional PASS studies, a joint European longitudinal lymphoma and skin cancer evaluation (JOELLE study) and a prospective paediatric longitudinal evaluation to assess the long-term safety of tacrolimus ointment for the treatment of atopic dermatitis (APPLES study). 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 Protopic (tacrolimus) 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 is submitted.
- The PRAC agreed to remove ‘off-label use of Protopic 0.1% in children between 2 and 16 years’ as an important potential risk and ‘children below 2 years of age’ as missing information. In addition, ‘systemic absorption’ and the ‘risk of inappropriate use by non-specialists’ should be monitored in future PSURs. Finally, the PRAC agreed with the MAH’s proposal to retire targeted follow-up questionnaires (FUQ) for lymphoma and lymphadenopathy given the limitations of assessing causality from spontaneous reports in this context.

See also under 10.1.1.

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. Alectinib - ALECENSA (CAP) - PSUSA/00010581/201907

Applicant: Roche Registration GmbH

PRAC Rapporteur: Jana Lukacisinova

Scope: Evaluation of a PSUSA procedure

Background

Alectinib is a highly selective and potent anaplastic lymphoma kinase (ALK) and rearranged during transfection (RET) tyrosine kinase inhibitor. It is indicated, as Alecensa, for the treatment of adult patients with ALK-positive advanced non-small cell lung cancer (NSCLC) and adult patients with ALK-positive advanced NSCLC previously treated with crizotinib.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Alecensa, a centrally authorised medicine containing alectinib 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 Alecensa (alectinib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning on gastrointestinal perforation. Therefore, the current terms of the marketing authorisation(s) should be varied[15].
- In the next PSUR, the MAH should provide a cumulative review of cases of renal failure and renal impairment. In addition, the MAH should closely monitor and evaluate cases of gastrointestinal disorders and should propose to update the product information as warranted.

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

6.1.2. Belatacept - NULOJIX (CAP) - PSUSA/00000311/201906

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Background

Belatacept is an antibody that binds to CD[16]80 and CD86 on antigen presenting cells. It is indicated, as Nulojix, in combination with corticosteroids and a mycophenolic acid (MPA), for prophylaxis of graft rejection in adults receiving a renal transplant.

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

Summary of recommendation(s) and conclusions

[15] 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
[16] Cluster of differentiation

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Nulojix (belatacept) in the approved indication(s) remains unchanged.
- The PRAC considered that the patient alert card (PAC) is no longer needed, based on the results of a PASS evaluating the effectiveness of the patient alert card (PAC). This recommendation is also made taking into account that Nulojix (belatacept) has been on the market in the EU for nearly a decade, and the existing safety concerns have been adequately managed by routine risk minimisation measures (RMMs) so far and no new safety concerns that would warrant putting any additional RMMs in place have been identified. As a consequence, the product information should be updated to remove reference to the PAC. Therefore, the current terms of the marketing authorisation(s) should be varied[17].

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. Galsulfase - NAGLAZYME (CAP) - PSUSA/00001515/201905

Applicant: BioMarin International Limited

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

Background

Galsulfase is a recombinant form of human N-acetylgalactosamine 4-sulfatase indicated, as Naglazyme, for the long-term enzyme replacement therapy in patients with a confirmed diagnosis of mucopolysaccharidosis VI (MPS VI, Maroteaux-Lamy syndrome).

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Naglazyme, a centrally authorised medicine containing galsulfase 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 Naglazyme (galsulfase) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning on the risk of acute cardio-respiratory failure and a warning on immune-mediated reactions. Therefore, the current terms of the marketing authorisation(s) should be varied[18].

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

[17] Update of Annexes II, III-A and III-B. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion
[18] Update of SmPC section 4.4. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

6.1.4. Hydroxycarbamide[19] - SIKLOS (CAP) - PSUSA/00001692/201906

Applicant: Addmedica S.A.S.

PRAC Rapporteur: Laurence de Fays

Scope: Evaluation of a PSUSA procedure

Background

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

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Siklos, a centrally authorised medicine containing hydroxycarbamide 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 Siklos (hydroxycarbamide) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAH should provide cumulative reviews of cases of hepatotoxicity, neutropenic sepsis, interstitial pneumonitis, interstitial lung disease and infections.
- The MAH should discuss, in the framework of the upcoming variation (II/45), updating the RMP appropriate measures to reduce the risk of dispensing errors. This should also include a discussion whether/how the targeted population of the educational materials could be expanded to pharmacists dispensing Siklos (hydroxycarbamide) and whether separate educational material for pharmacists is needed.

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

6.1.5. Lutetium (^{177}Lu) oxodotreotide - LUTATHERA (CAP) - PSUSA/00010643/201906

Applicant: Advanced Accelerator Applications

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

Background

Lutetium (^{177}Lu) oxodotreotide is a β-emitting radionuclide indicated, as Lutathera, for the treatment of unresectable or metastatic, progressive, well differentiated (G1 and G2), somatostatin receptorutes now positive gastroenteropancreatic neuroendocrine tumours (GEP-NETs) in adults.

[19] Centrally authorised product(s) only

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Lutathera, a centrally authorised medicine containing lutetium (^{177}Lu) oxodotreotide 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 Lutathera (lutetium (^{177}Lu) oxodotreotide) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning on the risk of tumour lysis syndrome (TLS). Therefore, the current terms of the marketing authorisation(s) should be varied[20].

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. Pentosan polysulfate sodium[21] - ELMIRON (CAP) - PSUSA/00010614/201906 (with RMP)

Applicant: bene-Arzneimittel GmbH

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

Background

Pentosan polysulfate sodium is a semi-synthetic polysulfated xylan. It is indicated, as Elmiron, for the treatment of bladder pain syndrome characterised by either glomerulations or Hunner's lesions in adults with moderate to severe pain, urgency and frequency of micturition.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Elmiron, a centrally authorised medicine containing pentosan polysulfate sodium 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 Elmiron (pentosan polysulfate sodium) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include more details on pigmentary maculopathy in the existing warning, including the periodicity of the ophthalmological examination. Therefore, the current terms of the marketing authorisation(s) should be varied[22].
- In the next PSUR, the MAH should monitor and discuss all information on the important potential risk of pigmentary maculopathy that may arise.

[20] 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
[21] Centrally authorised product(s) only
[22] 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

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

6.1.7. Semaglutide - OZEMPIC (CAP) - PSUSA/00010671/201905

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

Background

Semaglutide is a glucagon-like peptide-1 (GLP-1) analogue. It is indicated as Ozempic, for the treatment of adults with insufficiently controlled type 2 diabetes mellitus (T2DM) as an adjunct to diet and exercise under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Ozempic, a centrally authorised medicine containing semaglutide 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 Ozempic (semaglutide) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning for 'diabetes ketoacidosis' when semaglutide is initiated and insulin is reduced. In addition, acute pancreatitis is added as an undesirable effect with a frequency 'uncommon'. Therefore, the current terms of the marketing authorisation(s) should be varied[23].
- In the next PSUR, the MAH should provide a detailed root cause analysis of medication errors related to inappropriate schedule of product administration and incorrect dose administered. The MAH should also provide a cumulative review of cases of angioedema.

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

6.1.8. Sofosbuvir, velpatasvir - EPCLUSA (CAP) - PSUSA/00010524/201906

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

Background

Sofosbuvir is a pan-genotypic inhibitor of the hepatitis C virus (HCV) non-structural protein 5B (NS5B) ribonucleic acid (RNA)-dependent RNA polymerase. Velpatasvir is an HCV inhibitor targeting the HCV non-structural protein 5A (NS5A) protein. In combination,

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

sofosbuvir/velpatasvir is indicated, as Epclusa, for the treatment of chronic HCV infection in adults.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Epclusa, a centrally authorised medicine containing sofosbuvir/velpatasvir 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 Epclusa (sofosbuvir/velpatasvir) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to strengthen the existing warning on bradyarrhythmia involving drug-drug interaction between sofosbuvir-containing products and amiodarone. Therefore, the current terms of the marketing authorisation(s) should be varied[24].
- In the next PSUR, the MAH should provide a further review of bradyarrhythmia (including cardiac arrest/syncope) limited to cases of co-administration with amiodarone. The MAH should propose an update of the product information as warranted. In addition, the MAH should include a review of cases of increased human immunodeficiency virus (HIV) ribonucleic acid (RNA) or deoxyribonucleic acid (DNA) in HIV-hepatitis C virus (HCV) co-infected patients reported with sofosbuvir-containing products.

The PRAC considered that the above recommendation is also relevant for the other medicinal products containing sofosbuvir, namely Sovaldi (sofosbuvir), Harvoni (ledipasvir/sofosbuvir), and Vosevi (sofosbuvir/velpatasvir/voxilaprevir) and should be implemented in their product information accordingly. Further consideration will be given at the level of CHMP.

The PRAC also considered that the information regarding bradyarrhythmia involving drug-drug interaction with sofosbuvir-containing products and amiodarone should be implemented in the product information of amiodarone-containing products. Further consideration should be given at the level of CMDh.

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

6.1.9. Venetoclax - VENCLYXTO (CAP) - PSUSA/00010556/201906

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

Background

Venetoclax is a potent, selective inhibitor of B-cell lymphoma (BCL)-2 indicated, as Venclyxto, alone or in combination with rituximab for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy.

[24] Update of SmPC sections 4.4 and 4.5. 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 Venclyxto, a centrally authorised medicine containing venetoclax 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 Venclyxto (venetoclax) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning on infections and an amendment of existing information for dose modifications for concomitant use with CYP3A[25] inhibitors. Therefore, the current terms of the marketing authorisation(s) should be varied[26].

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

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

See also Annex I 16.2.

6.2.1. Edotreotide - SOMAKIT TOC (CAP); NAP - PSUSA/00010552/201906

Applicants: Advanced Accelerator Applications (SomaKit TOC), various

PRAC Rapporteur: Ronan Grimes

Scope: Evaluation of a PSUSA procedure

Background

Edotreotide is a diagnostic radiopharmaceutical indicated, as SomaKit TOC and nationally approved product(s) after radiolabelling with gallium (^{68}Ga) chloride solution, for positron emission tomography (PET) imaging of somatostatin receptor overexpression in adult patients with confirmed or suspected well-differentiated gastro-enteropancreatic neuroendocrine tumours (GEP-NET) for localising primary tumours and their metastases.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of SomaKit TOC, a centrally authorised medicine containing edotreotide, and nationally authorised medicines containing edotreotide 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 edotreotide-containing medicinal products in the approved indications remains unchanged.

[25] Cytochrome P450 3A4
[26] Update of SmPC sections 4.2 and 4.4. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

- Nevertheless, the product information should be updated to include injection site pain as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisations should be varied[27].
- In the next PSUR, MAHs should provide a cumulative review of cases of hypersensitivity reactions.

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

6.2.2. Ulipristal[28] - ELLAONE (CAP); NAP - PSUSA/00003074/201905

Applicants: Laboratoire HRA Pharma (ellaOne), various

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

Background

Ulipristal is a selective progesterone receptor modulator indicated for emergency contraception within 120 hours (5 days) of unprotected sexual intercourse or contraceptive failure.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of ellaOne, a centrally authorised medicine containing ulipristal, and nationally authorised medicines containing ulipristal 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 ulipristal-containing medicinal products in the approved indications remains unchanged.
- The current terms of the marketing authorisations should be maintained.
- The MAH should continue to actively maintain the pregnancy registry as listed in the RMP as a category 3 study.

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

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

See also Annex I 16.3.

[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
[28] Indicated for female emergency contraception only

6.3.1. Cidofovir (NAP) - PSUSA/00010558/201906

Applicant(s): various

PRAC Lead: Rugilė Pilviniene

Scope: Evaluation of a PSUSA procedure

Background

Cidofovir is an antiviral indicated for the treatment of cytomegalovirus (CMV) retinitis in adults with acquired immunodeficiency syndrome (AIDS) and without renal dysfunction.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing cidofovir 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 cidofovir-containing medicinal product(s) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAH(s) should provide a detailed overview of the status of the imposed PASS study[29] entitled 'cidofovir exposure registry study: a non-interventional, prospective, exposure (safety outcome) registry study of cidofovir to further elucidate the characteristics of the different patient populations for cidofovir use'. In addition, the MAH(s) should include a status update on the dissemination of the educational material in each of the relevant Member States.

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. Iobitridol (NAP) - PSUSA/00001761/201904

Applicant(s): various

PRAC Lead: Ronan Grimes

Scope: Evaluation of a PSUSA procedure

Background

Iobitridol is an iodinated contrast agent indicated in adults and children for diagnostic use during venography, whole-body computed tomography (CT) or intra-arterial digital subtraction angiography.

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

Summary of recommendation(s) and conclusions

[29] Protocol (EMEA/H/N/PSP/S/0052.3) endorsed at the November 2018 PRAC meeting (held 29-31 October)

- Based on the review of the data on safety and efficacy, the benefit-risk balance of iobitridol-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning on severe cutaneous adverse reactions (SCARs). In addition, drug reaction with eosinophilia and systemic symptoms (DRESS) and bradycardia should be added as undesirable effects with a frequency 'not known' and 'rare' respectively. Therefore, the current terms of the marketing authorisation(s) should be varied[30].
- In the next PSUR, the MAH should provide a cumulative review of evidence from all data sources on SCARs. In addition, the MAH should closely monitor and provide reviews of cases of intestinal angioedema and hypertensive crisis.

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. Levomethadone (NAP) - PSUSA/00001855/201905

Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

Background

Levomethadone is a synthetic opioid analgesic with agonistic action on nociceptive opioid receptors indicated for the treatment of severe pain and substitution treatment in opioid-dependent adults.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing levomethadone 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 levomethadone-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include warnings on reversible adrenal insufficiency, decreased sex hormone levels and increased prolactin levels, as well as a warning on the need for monitoring infants while breastfeeding. In addition, hypoglycaemia is added as a warning to recommend blood glucose monitoring in cases of overdose or dose escalation and as an undesirable effect with a frequency 'not known'. Moreover, the product information is updated to reflect the interaction between methadone and other serotonergic drugs that can lead to serotonergic

[30] Update of SmPC sections 4.3, 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

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

The frequency of PSUR submission should be revised from five-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 Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC is updated accordingly.

6.3.4. Levonorgestrel (NAP) - PSUSA/00001856/201905

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Levonorgestrel is a second generation progestin (synthetic progesterone) indicated for oral contraception, heavy menstrual bleeding (hypermenorrhea, idiopathic menorrhagia) and emergency contraception. It is also indicated in some EU Member States for the protection from endometrial hyperplasia during oestrogen replacement therapy.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of levonorgestrel-containing medicinal product(s) remains unchanged in the approved indication(s).
- The current terms of the marketing authorisation(s) for levonorgestrel-containing medicinal product(s) authorised as sub-dermal implant, progestin-only pills and for emergency contraception should be maintained.
- Nevertheless, the product information of levonorgestrel-containing medicinal product(s) authorised as intra-uterine devices (IUDs) should be updated to include dizziness as an undesirable effect with a frequency 'common' for levonorgestrel-IUDs with 52 mg or 19.5 mg levonorgestrel and with a frequency 'uncommon' for levonorgestrel-IUDs with 13.5 mg levonorgestrel. Therefore, the current terms of the marketing authorisation(s) should be varied[32].
- In the next PSUR, all MAHs of levonorgestrel-containing medicinal product(s) authorised as IUDs should provide a cumulative review and causality assessment of cases of seizures/epilepsy. MAHs should also discuss the potential pathomechanism for cases of hypoaesthesia/paraesthesia and provide a causality assessment. In addition, MAHs should analyse cases of dry eye, vision blurred and vision impaired and discuss whether the existing warning regarding the increased expulsion rate following immediate insertion after medical termination of late first trimester pregnancy needs to be

[31] Update of SmPC sections 4.4, 4.5, 4.6, 4.8 and 4.9. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position
[32] 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

updated. All MAHs should also provide reviews of cases of loss of libido and toxic shock syndrome. The MAH Bayer should provide a review of cases of drug-induced liver injury. The MAHs Mithra and Exeltis should discuss whether angioedema should be added to the product information and the MAH Mithra should provide further information on the signals of foetal death, pyrexia, systemic inflammatory response syndrome and spontaneous abortion.

- In the next PSUR, the MAH Gedeon Richter for levonorgestrel-containing medicinal product(s) indicated for emergency contraception should analyse cases of product dose omission, and for cases of reduced efficacy/effectiveness the MAH should state whether the reduced efficacy resulted in patient's pregnancy. The MAH Mylan should provide an analysis of paediatric cases, cases with exposure during pregnancy and during lactation.

The PRAC considered that a review of all case reports of meningioma should be performed for IUDs-containing levonorgestrel. Further consideration should be given at the level of CMDh.

The PRAC also considered that for levonorgestrel-only pills a review of all data from clinical trials, literature and spontaneous reporting on the potential decreased contraceptive efficacy in overweight and obese women should be performed by the MAHs Bayer and Pfizer. Further consideration should be given at the level of CMDh.

The PRAC considered that specific levonorgestrel indications should be assessed in the future within separate PSUSA procedures. As a consequence, the PRAC recommended splitting the exiting entry of the EURD list into two entries: 'levonorgestrel – indication for emergency contraception only' and 'levonorgestrel – all indications except emergency contraception'. The frequency of PSUR submission should be revised from one-yearly to three-yearly for 'levonorgestrel – indication for emergency contraception only' and the next PSUR should be submitted to the EMA within 90 days of the data lock point. The frequency of PSUR submission should be revised from one-yearly to two-yearly for 'levonorgestrel – all indications except emergency contraception' and the next PSUR should be submitted to the EMA within 90 days of the data lock point.

6.3.5. Methadone (NAP) - PSUSA/00002004/201905

Applicant(s): various

PRAC Lead: Ronan Grimes

Scope: Evaluation of a PSUSA procedure

Background

Methadone is a synthetic opioid analgesic indicated for the treatment of severe pain and opioid addiction.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing methadone 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 methadone-containing medicinal product(s) in the approved indication(s) remains unchanged.

- Nevertheless, the product information should be updated to include warnings on reversible adrenal insufficiency, decreased sex hormone levels and increased prolactin levels as well as a warning on the need for monitoring infants while breastfeeding. In addition, hypoglycaemia should be added as a warning to recommend blood glucose monitoring in cases of overdose or dose escalation and as an undesirable effect with a frequency 'not known'. Moreover, the product information should be updated to reflect the interaction between methadone and other serotonergic drugs that can lead to serotonergic syndrome. Therefore, the current terms of the marketing authorisation(s) should be varied[33].
- In the next PSUR, all MAHs should consider abuse, misuse, overdose and dependence as important safety concerns. MAHs should also provide a cumulative review of cases of drug abuse, dependence and withdrawal. Comparable cumulative review should also be provided for overdose including accidental overdose and cases of accidental exposure in paediatric population.

The frequency of PSUR submission should be revised from five-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 Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC is updated accordingly.

6.3.6. Moxifloxacin[34] (NAP) - PSUSA/00009231/201905

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Moxifloxacin is a fluoroquinolone antibiotic indicated for the treatment of bacterial infections in line with official recommendations.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing moxifloxacin for systemic 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 moxifloxacin-containing medicinal product(s) for systemic use in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning on the risk of acute generalised exanthematous pustulosis (AGEP) and to include as undesirable effects, pancytopenia, syndrome of inappropriate antidiuretic hormone secretion (SIADH) and hypoglycaemic coma with a frequency 'very rare', delirium with a frequency 'rare',

[33] Update of SmPC sections 4.4, 4.5, 4.6, 4.8 and 4.9. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position
[34] Systemic use

AGEP and rhabdomyolysis with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[35].

- In the next PSUR, the MAHs should monitor and include reviews of cases of fixed drug eruption, lactic acidosis and metabolic acidosis, potential interaction of moxifloxacin with angiotensin converting enzyme (ACE) inhibitors, masking of active tuberculosis (TB) by systemic moxifloxacin, memory impairment, pancreatitis and DRESS.

The PRAC considered that in light of the risks of 'long-lasting and/or potentially irreversible severe adverse reactions' and 'aortic aneurysm and dissection', the MAH Bayer should be requested to submit an updated RMP in line with revision 2 of GVP module V on 'Risk management systems'. Further consideration should be given at the level of CMDh.

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

6.3.7. Nicardipine (NAP) - PSUSA/00002149/201905

Applicant(s): various

PRAC Lead: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

Background

Nicardipine is a calcium channel blocker (CCB) with vasodilatory activity, both on the coronary level and on systemic level, reducing afflux of calcium ion through cell membrane indicated, subject to certain conditions, for the treatment of essential hypertension, prophylaxis and treatment of angina pectoris, prophylaxis and treatment of ischemia caused by cerebral infarction and its sequels, prophylaxis of neurological impairment caused by cerebral vasospasm secondary to subarachnoid haemorrhage, treatment of chronic congestive heart failure for oral formulation and treatment of acute hypertension in which immediate control of the blood pressure is essential and for treatment of acute heart failure.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing nicardipine 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 nicardipine-containing medicinal product(s) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, all MAHs should submit detailed cumulative reviews of cases of angioedema, Stevens-Johnson syndrome, toxic skin eruption, maculopapular rash, acute pancreatitis, acute kidney injury, renal failure, renal impairment and hepatitis, as well as discuss the causal relationship of these events with the use of nicardipine. The MAHs should propose an update of the product information as warranted. In addition, the

[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 CMDh for adoption of a position

MAHs should monitor white blood cell disorders cases with particular focus on those that are not confounded by concomitant drugs and risk factors. They should also monitor cases of purpura, vascular purpura and petechiae, cases reporting white blood cell disorders without platelet abnormalities, and provide a cumulative review of cases resulting from the interaction between nicardipine and dantrolene. The MAH Cardixo should continue to monitor and provide a cumulative review of cases of bradycardia and monitor cases of renal disorders in patients exposed to nicardipine during pregnancy.

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. Pholcodine (NAP) - PSUSA/00002396/201905

Applicant(s): various

PRAC Lead: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

Background

Pholcodine is a centrally-acting cough suppressant indicated for the treatment of non-productive cough.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing pholcodine 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 pholcodine-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include acute generalised exanthematous pustulosis (AGEP) 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].
- In the next PSUR, all MAHs should closely monitor cases of drug abuse and dependence.

The PRAC considered that the risk of AGEP is also relevant to be included in the product information of other fixed dose combination products containing pholcodine. Further consideration should be given at the level of CMDh.

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.

[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 CMDh for adoption of a position

6.3.9. Tolperisone (NAP) - PSUSA/00002991/201906

Applicant(s): various

PRAC Lead: Julia Pallos

Scope: Evaluation of a PSUSA procedure

Background

Tolperisone is a centrally acting muscle relaxant indicated for the symptomatic treatment of post-stroke spasticity (PSS) in adults.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing tolperisone 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 tolperisone-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include additional information on tolperisone overdose. Therefore, the current terms of the marketing authorisation(s) should be varied[37].
- The PRAC agreed on key messages for communication in Member States (MSs) where off-label use of tolperisone-containing product(s) in revoked indications[38] is considered to be of high extent and of concern in order to prevent this off label use. Risk communication tools were recommended to be agreed at national level, should National Competent Authorities (NCAs) of the Member State(s) consider it necessary.
- In the next PSUR, all MAHs should summarise any formal and informal risk communication activities in association with the prevention of off-label use in revoked indications, together with an assessment of their effectiveness. All MAHs should monitor spontaneous reporting rates of both hypersensitivity reactions and all adverse drug reactions in which tolperisone is reported as suspect or interacting drug.

The frequency of PSUR submission should be revised from eight-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 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. Ibrutinib - IMBRUVICA (CAP) - EMEA/H/C/003791/LEG 030

Applicant: Janssen-Cilag International NV

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

[38] As per the conclusions of the referral procedure under Article 31 of Directive 2001/83/EC as amended for tolperisone-containing product(s) (EMEA/H/A-31/1311) finalised in 2012

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Cumulative analysis of cases of hepatic failure and hepatitis B virus (HBV) reactivation as requested in the conclusions of PSUSA/00010301/201811 adopted by PRAC in June 2019

Background

Ibrutinib is a potent, small-molecule inhibitor of Bruton's tyrosine kinase (BTK) indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL) as single agent, as a single agent or in combination with obinutuzumab for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL), as a single agent or in combination with bendamustine and rituximab (BR) for the treatment of adult patients with CLL who have received at least one prior therapy and as a single agent or in combination with rituximab for the treatment of adult patients with Waldenström's macroglobulinaemia (WM).

Following the evaluation of the most recently submitted PSURs for the above mentioned medicine(s), the PRAC requested the MAH to submit a cumulative analysis of all cases reporting hepatic failure with a special focus on cases with fatal outcome. For further background, see PRAC minutes June 2019. The responses were assessed by the Rapporteur for further PRAC advice.

Summary of advice/conclusion(s)

- The MAH should submit to the EMA, within 60 days, a variation to update the product information to add to the existing undesirable effects of hepatic failure and hepatitis B reactivation information about cases with fatal outcome.
- In the next PSUR, the MAH should provide an assessment for every fatal case of hepatic failure and hepatitis B virus reactivation. In the assessment, the MAH should analyse risk factors that led to hepatic failure/death and whether existing risk minimisation measures (RMMs) were followed and comment whether these are sufficient.

7. Post-authorisation safety studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)[39]

See also Annex I 17.1.

7.1.1. Methylphenidate hydrochloride (NAP) - EMEA/H/N/PSP/S/0064.3

Applicant: Medice Arzneimittel Pütter GmbH & Co. KG

PRAC Rapporteur: Martin Huber

Scope: MAH's response to PSP/S/0064.2 [protocol for a multicentre, observational, prospective PASS to evaluate the safety concerns of long-term cardiovascular and psychiatric risks within the adult attention deficit/hyperactivity disorder (ADHD) population taking Medikinet Retard (methylphenidate hydrochloride) according to normal standard clinical practice] as per the request for supplementary information (RSI) adopted in June

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

2019

Background

Methylphenidate is a centrally acting sympathomimetic indicated for the treatment of attention deficit hyperactivity disorder (ADHD) in children between the ages of 6 and 18 and adults.

Due to a disagreement between EU Member States in the context of a variation for Medikinet Retard (methylphenidate hydrochloride) to add a new therapeutic indication for use in adults (DE/H/0690/004-010/II/043/G), a CMDh referral procedure was triggered in 2017. Further to the conclusion of the referral procedure at CMDh in November 2017 (see CMDh minutes November 2017), the MAH was required to conduct an imposed non-interventional PASS in adult patients (aged ≥ 18 years) with ADHD to generate long-term safety data on cardiovascular and psychiatric adverse events.

In order to fulfil the obligation to conduct a PASS imposed in accordance with Article 107n(3) of Directive 2001/83/EC, Medice Arzneimittel Pütter GmbH & Co. KG submitted to the EMA in 2018 a PASS protocol for Medikinet retard (methylphenidate hydrochloride) and further responses to requests for supplementary for information (RSI) were assessed. For further background, see PRAC minutes July 2018, PRAC minutes January 2019 and PRAC minutes June 2019.

Endorsement/Refusal of the protocol

- The PRAC, having considered protocol version 3.0 in accordance with Article 107n of Directive 2001/83/EC, objected to the draft protocol as the Committee considered that the design of the study does not fulfil the study objectives at this stage.
- The PRAC considered that some clarifications and complementary information are needed before drawing final conclusions on the protocol. In particular, the MAH should provide clarification on the study milestones, the study time period and patients' follow-up.
- The MAH should submit a revised PASS protocol within 60 days to the EMA. A 60 days-assessment timetable will be followed.

7.1.2. Turoctocog alfa pegol - ESPEROCT (CAP) - EMEA/H/C/PSP/S/0085

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Protocol for a multinational, prospective, open labelled, non-controlled, non-interventional post-authorisation study of turoctocog alfa pegol (N8-GP) during long-term routine prophylaxis and treatment of bleeding episodes in patients with haemophilia A

Background

Turoctocog alfa pegol is a purified recombinant human factor VIII (rFVIII). Esperoct (turoctocog alfa pegol) is a centrally authorised medicine indicated for the treatment and prophylaxis of bleeding in patients 12 years and above with haemophilia A (congenital factor VIII deficiency).

In order to fulfil the obligation to conduct a PASS (Annex II-D) imposed in accordance with Article 107n(3) of Directive 2001/83/EC, the MAH Novo Nordisk A/S submitted a protocol for

a PASS entitled: 'a multinational, prospective, open labelled, non-controlled, non-interventional post-authorisation study during long-term routine prophylaxis and treatment of bleeding episodes in patients with haemophilia A' for review by the PRAC.

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, as the Committee considered that that the design of the study does not fulfil the study objectives at this stage.
- The PRAC considered that the MAH should clarify the use of diary by all patients. In addition, the MAH should provide further details on the reporting timelines regarding adverse event of special interest (AESIs).
- The MAH should submit a revised PASS protocol within 30 days to the EMA. A 60 days-assessment timetable will be followed.

7.2. Protocols of PASS non-imposed in the marketing authorisation(s)[40]

See Annex I 17.2.

7.3. Results of PASS imposed in the marketing authorisation(s)[41]

7.3.1. Brentuximab vedotin – ADCETRIS (CAP) - EMEA/H/C/PSR/S/0022

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Menno van der Elst

Scope: Results for study MA25101: an observational cohort study of the safety of brentuximab vedotin in the treatment of relapsed or refractory CD30+ Hodgkin lymphoma and relapsed or refractory systemic anaplastic large cell lymphoma (sALCL) evaluating the occurrence of serious adverse events (SAEs) and adverse events of special interest (AESIs) and identifying and describing potential risk factors for peripheral neuropathy

Background

Brentuximab vedotin is an antibody drug conjugate (ADC) that delivers an antineoplastic agent. Adcetris (brentuximab vedotin) is indicated for the treatment of adult patients with previously untreated CD30+ stage IV Hodgkin lymphoma (HL) in combination with doxorubicin, vinblastine and dacarbazine, treatment of adult patients with CD30+ HL at increased risk of relapse or progression following autologous stem cell transplant (ASCT), adult patients with relapsed or refractory CD30+ Hodgkin lymphoma (HL) following ASCT, or following at least two prior therapies when ASCT or multi -agent chemotherapy is not a treatment option. Adcetris is also indicated for the treatment of adult patients with relapsed or refractory systemic anaplastic large cell lymphoma (sALCL) and adult patients with CD30+ cutaneous T-cell lymphoma (CTCL) after at least 1 prior systemic therapy.

Adcetris, a centrally authorised medicine containing brentuximab vedotin, was authorised in 2012. As a specific obligation of the conditional marketing authorisation (Annex II-E), the MAH was required to conduct a PASS to demonstrate the safety of brentuximab vedotin in

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

patients with relapsed or refractory CD30+ HL or sALCL treated with brentuximab vedotin as part of routine clinical care.

The final study report was submitted to EMA by the MAH Takeda Pharma A/S on 28 October 2019. The PRAC discussed the final study results.

Summary of recommendation(s) and conclusions

- Based on the review of the final report of the non-interventional PASS entitled 'an observational cohort study of the safety of brentuximab vedotin in the treatment of relapsed or refractory CD30+ Hodgkin lymphoma and relapsed or refractory systemic anaplastic large cell lymphoma (ARROVEN)', the PRAC considered that a request for supplementary for information (RSI) was necessary before a recommendation could be made on the benefit-risk balance of Adcetris (brentuximab vedotin) concerned by the PASS final report. In particular, the MAH should discuss the need to update the product information to reflect the differences observed in the incidences of several adverse drug reactions (ADRs) of patients ≥65 years compared to patients <65 years.
- The MAH should submit responses to the request for supplementary information within 60 days to the EMA. A 60 days-assessment timetable will be followed.

7.4. Results of PASS non-imposed in the marketing authorisation(s)[42]

See also Annex I 17.4.

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

Applicant: Genzyme Europe BV

PRAC Rapporteur: Liana Gross-Martirosyan

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

Background

Fabrazyme is a centrally authorised medicine containing agalsidase beta, a recombinant human α-galactosidase. Fabrazyme (agalsidase beta) is indicated for long-term enzyme replacement therapy in patients with a confirmed diagnosis of Fabry disease.

As stated in the RMP of Fabrazyme (agalsidase beta), the MAH conducted a non-imposed non-interventional PASS entitled: 'study on Fabrazyme (agalsidase beta) home infusion educational materials effectiveness evaluation: a survey of healthcare providers and patients/caregivers'. The Rapporteur assessed the final study report. For further background on the protocol, see PRAC minutes October 2018.

[42] 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

Summary of advice

- Based on the available data and the Rapporteur's review, the PRAC considered that a request for supplementary information (RSI) was necessary before a conclusion could be drawn on the assessment of the final study report. In particular, the PRAC considered that the current key elements need to be adjusted to better focus on the risks for which additional risk minimisation measures (aRMM) are required.

7.4.2. 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

Background

Aerius, Azomyr and Neoclarityn are centrally authorised medicines containing desloratadine, an antihistamine. Aerius, Azomyr and Neoclarityn (desloratadine) are indicated for the relief of symptoms associated with allergic rhinitis and urticaria.

As stated in the RMP of Aerius, Azomyr and Neoclarityn (desloratadine), the MAH conducted a non-imposed non-interventional PASS (EUPAS15038) to assess the potential risk of desloratadine exposure on seizures, supraventricular tachycardia, and atrial fibrillation or flutter of Aerius, Azomyr and Neoclarityn (desloratadine). The Rapporteur assessed the MAH's final study report in addition to the MAH's answers to the request for supplementary information (RSI). For further background, see PRAC minutes September 2019.

Summary of advice

- Based on the available data, the MAH's responses to the RSI and the Rapporteur's review, the PRAC considered that the variation assessing the final study report can be advised for approval. It includes amendments to the product information on seizures to reflect the results of the study.

7.4.3. 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 educational materials. As part of the submission, the MAH proposes a revised patient card

Background

Aubagio is a centrally authorised medicine containing teriflunomide, a selective immunosuppressant. Aubagio (teriflunomide) is indicated for the treatment of adult patients with relapsing remitting multiple sclerosis (RRMS).

As stated in the RMP of Aubagio (teriflunomide), the MAH conducted a non-imposed non-interventional PASS to assess the effectiveness of risk minimisation measures (RMMs) of Aubagio (teriflunomide). The Rapporteur assessed the MAH's final study report in addition to the MAH's answers to the request for supplementary information (RSI). For further background, see PRAC minutes September 2019 and PRAC minutes November 2019[43].

Summary of advice

- Based on the available data, the MAH's responses to the RSI and the Rapporteur's review, the PRAC considered that the ongoing variation assessing the final study report can be advised for approval. It includes amendments to Annex II-D on 'Conditions or restrictions with regard to the safe and effective use of the medicinal product' of the product information to adjust the key elements of the healthcare professionals (HCPs) guide in line with the results of the study. The results of HCPs knowledge and understanding survey confirm that educational materials are effective in supporting HCP knowledge relating to the safe use of Aubagio (teriflunomide).

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

See also Annex I 17.5.

7.5.1. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/MEA 022.18

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Rhea Fitzgerald

Scope: MAH's response to MEA 022.17 [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 September 2019

Background

Stelara is a centrally authorised medicine containing ustekinumab, an interleukin (IL) inhibitor of IL-12 and IL-23. Stelara (ustekinumab) is indicated, subject to certain conditions, for the treatment of adult patients with moderately to severely active Crohn's disease or ulcerative colitis, treatment of moderate to severe plaque psoriasis in adults, children and adolescent patients from the age of 6 years and older, as well as alone or in combination with methotrexate (MTX) for the treatment of active psoriatic arthritis in adult patients.

The MAH had committed to perform an international prospective cohort study to collect data on psoriasis (PSO) patients that are eligible to receive systemic therapies according to the RMP of Stelara (ustekinumab). For further background, see PRAC minutes September 2019. Interim results of the study which aims to monitor the long-term safety of Stelara (ustekinumab) in routine practice were assessed by the Rapporteur for PRAC review.

Summary of advice

[43] Held 28 – 31 October 2019

- The PRAC discussed the Rapporteur's assessment and agreed that further data was necessary before a final advice could be made.
- The MAH should provide, in the next submission of the annual interim safety report, updated Kaplan-Meier curves with different scales to allow a closer inspection of the timing of the events as well as the complete list of MEdDRA[44] preferred terms (PTs) included in the original search strategy used in the registry. The MAH should also provide, in the next PSUR, clarification on the search strategy used to define major adverse cardiovascular events (MACE) and provide a further cumulative review of cardiovascular events (including MACE), using both search strategies to define MACE.

7.6. Others

See Annex I 17.6.

7.7. New Scientific Advice

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

7.8. Ongoing Scientific Advice

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

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

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

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

8.1. Annual reassessments of the marketing authorisation

See Annex I 18.1.

8.2. Conditional renewals of the marketing authorisation

See Annex I 18.2.

8.3. Renewals of the marketing authorisation

See Annex I 18.3.

[44] Medical Dictionary for Regulatory Activities

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. Tacrolimus - PROTOPIC (CAP) - EMEA/H/C/000374/II/0083/G

Applicant: LEO Pharma A/S

PRAC Rapporteur: Rhea Fitzgerald

Scope: PRAC consultation on a variation updating sections 4.4, 4.8, 5.1, 5.2 and 5.3 of the SmPC following results from two non-interventional PASS, namely: 1) JOELLE study (listed as a category 3 study in the RMP): a joint European longitudinal lymphoma and skin cancer evaluation; 2) APPLES study (listed as a category 3 study in the RMP): a prospective paediatric longitudinal evaluation to assess the long-term safety of tacrolimus ointment for the treatment of atopic dermatitis. The package leaflet and the RMP (version 15.1) are updated accordingly. In addition, the MAH took the opportunity to bring the product information in line with the latest quality review of documents (QRD) template (version 10.1)

Background

Tacrolimus inhibits calcium-dependent signal transduction pathways in T cells. It is indicated, as Protopic, for the treatment of moderate to severe atopic dermatitis in adults who are not adequately responsive to or are intolerant of conventional therapies such as topical corticosteroids and for the treatment of moderate to severe atopic dermatitis in children who failed to respond adequately to conventional therapies such as topical corticosteroids. It is also indicated for the treatment of moderate to severe atopic dermatitis for the prevention of flares and the prolongation of flare-free intervals in patients experiencing a high frequency of disease exacerbations (i.e. occurring 4 or more times per year) who have had an initial response to a maximum of 6 weeks treatment of twice daily tacrolimus ointment (lesions cleared, almost cleared or mildly affected).

A type II variation proposing to update the product information of Protopic (tacrolimus) with the results from two non-interventional PASS studies, a joint European longitudinal lymphoma and skin cancer evaluation and a prospective paediatric longitudinal evaluation to assess the long-term safety of tacrolimus ointment for the treatment of atopic dermatitis 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 supported the available assessment and agreed on the updates of the product information[45] to amend the existing warnings on the development of malignancies and remove information on these reactions as undesirable effects. In addition, the PRAC advised not to update the product information section on 'pharmacodynamic properties' with the information from these two studies in line with the Rapporteur's proposal.

See also under 5.3.1.

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

None

10.3. Other requests

None

10.4. Scientific Advice

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

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

11.1. Safety related variations of the marketing authorisation

11.1.1. Dexamethasone (NAP) - MT/H/0348/II/002

Applicant(s): Panpharma (Dexamethasone Panpharma)

PRAC Lead: John Joseph Borg

Scope: PRAC consultation on a type II variation assessing a proposal to update the product information with pheochromocytoma crisis following a signal detected by the MAH, on request of Malta

Background

Dexamethasone is a synthetic corticosteroid with predominant glucocorticoid activity indicated for use in certain endocrine and non-endocrine disorders responsive to corticosteroid therapy.

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

In the context of the evaluation of a national type II variation procedure (MT/H/0348/II/002) proposing to update the product information with pheochromocytoma crisis following a signal detected by an MAH, Malta requested PRAC advice on its assessment.

Summary of advice

- Based on the review of the available information and evidence, the PRAC supported the PRAC lead's assessment and supported that the product information is updated to include a warning[46] on the risk of pheochromocytoma crisis.

11.1.2. Valproate (NAP) and related substances: sodium valproate (NAP), valproate semi-sodium (NAP), valproic acid (NAP), magnesium valproate (NAP), valpromide (NAP)- NL/H/xxxx/WS/0354

Applicant(s): Sanofi (Depakine) on behalf of a consortium

PRAC Lead: Liana Gross-Martirosyan

Scope: PRAC follow-up consultation on a national worksharing variation on existing registries relating to the condition requesting 'MAHs to conduct a PASS preferably based on existing registries to further characterise the foetal anticonvulsant syndrome in children with valproate in utero exposure as compared to other anti-epileptic drugs' imposed in the outcome of the referral procedure for valproate-containing products under Article 31 of Directive 2001/83/EC (EMEA/H/A-31/1454) completed in 2018, on request of the Netherlands

Background

Valproate and related substances sodium valproate, valproate semi-sodium, valproic acid, magnesium valproate and valpromide are antiepileptics indicated for the treatment of generalized, partial or other epilepsy and the treatment of manic episode in bipolar disorder.

In the context of the evaluation of a national worksharing variation on existing registries relating to the condition requesting MAHs to conduct a PASS imposed as an outcome of the referral procedure for valproate-containing products under Article 31 of Directive 2001/83/EC (EMEA/H/A-31/1454) completed in 2018, the Netherlands requested PRAC advice on its assessment.

Summary of advice

- Based on the review of the available information and evidence, the PRAC supported the PRAC lead's assessment and agreed that the incidence and characteristics of minor congenital malformations related to foetal anticonvulsant syndrome (FACS) should be better characterised. The PRAC advised that the consortium of MAHs should pay special attention to neurodevelopmental disorders (NDD) including autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD) with an adequate follow up (at least 10 years from birth) to estimate the absolute and relative risk and describe the characteristics of children exposed to valproate in utero and diagnosed with NDD. The study should assess the course of NDD including ASD and ADHD over time and in comparison with other anti-epileptic drugs (AEDs), including outcomes related to medical, psycho-social, health care utilisation and educational attainment. The study should also assess the incidence and characteristics of minor congenital malformations

[46] Update of SmPC section 4.4. The package leaflet is to be updated accordingly

related to FACS in children with in utero exposure to valproate. The consortium of MAHs should provide further clarification at the time of preparing the full study protocol.

11.2. Other requests

11.2.1. Valaciclovir (NAP) - CZ/H/PSUFU/00003086/201812

Applicant(s): GlaxoSmithKline (Valtrex, Zelitrex)

PRAC Lead: Jana Lukačišinová

Scope: PRAC consultation on a worksharing PSUR follow-up (PSU FU) procedure on reviews of cases of severe cutaneous reactions, including blister, skin exfoliation and skin erosion, on drug reaction with eosinophilia and systemic symptoms (DRESS) as well as a review of cases of acute kidney injury (AKI) as discussed at PRAC and agreed by CMDh following the conclusion of the PSUSA procedure on valaciclovir (PSUSA/00003086/201812) concluded in July 2019

Background

Valaciclovir is the L-valine ester of acyclovir, an antiviral drug indicated for the treatment of herpes zoster (shingles) and ophthalmic zoster, for the treatment and suppression of *Herpes simplex* virus (HSV) infections and ocular HSV infections, and for the prophylaxis of cytomegalovirus (CMV) infection and disease following solid organ transplantation.

Based on the assessment of the recent PSUR single assessment (PSUSA) procedure for valaciclovir (PSUSA/00003086/201812) concluded in July 2019, the PRAC considered that reviews of cases of severe cutaneous reaction and the risk of acute kidney injury (AKI) should be further assessed. For further background, see PRAC minutes July 2019.

On request of the CMDh, the originator MAH for valaciclovir-containing product(s) submitted the requested safety reviews for evaluation within a worksharing periodic safety update (PSU) follow-up procedure. In the context of the ongoing evaluation of the PSU FU procedure (CZ/H/PSUFU/00003086/201812), Czech Republic, as lead Member State (LMS), requested PRAC advice on its assessment.

Summary of advice

- Based on the review of the available information, the PRAC supported the conclusions by the LMS to update[47] the product information with drug reaction with eosinophilia and systemic symptoms (DRESS) as a warning and as an undesirable effect with a frequency 'not known'.

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,

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

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 EMA secretariat informed the PRAC via written procedure about the quantitative measures collected for the third and fourth quarter of 2019 of PRAC meetings. For previous update, see PRAC minutes September 2019.

12.2. Coordination with EMA Scientific Committees or CMDh-v

None

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

None

12.4. Cooperation within the EU regulatory network

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

PRAC lead: Kirsti Villikka, Kimmo Jaakkola

The Finnish delegation presented the report with the conclusions of the PRAC strategic review and learning meeting (SRLM) held under the Finnish presidency of the European Union (EU) Council in Helsinki, Finland on 22-23 October 2019. The PRAC also noted the information about the upcoming meeting under the Croatian presidency of the EU Council.

12.5. Cooperation with International Regulators

None

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

None

12.7. PRAC work plan

12.7.1. PRAC work plan 2020

PRAC lead: Sabine Straus, Martin Huber

The EMA secretariat presented to the PRAC the draft final PRAC work plan 2020, further to previous discussion and comments received (see PRAC minutes December 2019[48]).

[48] Held 25-28 November 2019

Post-meeting note: On 31 January 2020, the PRAC adopted the work plan 2020 via written procedure. It was published on the EMA website (EMA/PRAC/131664/2020) on 11 March 2020.

12.8. Planning and reporting

12.8.1. PRAC workload statistics – Q3 & Q4 2019

The EMA secretariat informed the PRAC via written procedure of the quarterly and cumulative figures to estimate the evolution of the workload of the PRAC for Q3 and Q4 2019, by reflecting on the number of procedures and agenda items covered at each PRAC plenary meeting. For previous update, see PRAC minutes September 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 Granularity and Periodicity Advisory Group (GPAG) focussing on harmonising and streamlining the EURD list, and noted the GPAG progress highlights. The PRAC noted the progress towards optimising PSUR cycles for PSURs which are due to be submitted in 2025.

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 January 2020, reflecting the PRAC's comments impacting on the data lock point (DLP) and PSUR submission frequencies of the

substances/combinations. The PRAC endorsed the newly allocated Rapporteurs for upcoming PSUSAs in accordance with the principles previously endorsed by the PRAC (see PRAC minutes April 2013).

Post-meeting note: following the PRAC meeting of January 2020, the updated EURD list was adopted by the CHMP and CMDh at their January 2020 meetings and published on the EMA website on 05/02/2020, see:

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

12.11. Signal management

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

None

12.12. Adverse drug reactions reporting and additional monitoring

12.12.1. Management and reporting of adverse reactions to medicinal products

None

12.12.2. Additional monitoring

None

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

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

Post-meeting note: The updated additional monitoring list was published on the EMA website on 29/01/2020, see: Home>Human Regulatory>Post-authorisation>Pharmacovigilance>Medicines under additional monitoring>List of medicines under additional monitoring

12.13. EudraVigilance database

12.13.1. Activities related to the confirmation of full functionality

None

12.14. Risk management plans and effectiveness of risk minimisations

12.14.1. Risk management systems

None

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

None

12.15. Post-authorisation safety studies (PASS)

12.15.1. Post-authorisation Safety Studies – imposed PASS

None

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

None

12.16. Community procedures

12.16.1. Referral procedures for safety reasons

None

12.17. Renewals, conditional renewals, annual reassessments

None

12.18. Risk communication and transparency

12.18.1. Public participation in pharmacovigilance

None

12.18.2. Safety communication

None

12.19. Continuous pharmacovigilance

12.19.1. Incident management

None

12.20. Others

None

13. Any other business

None

14. Annex I – Signals assessment and prioritisation[49]

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[50].

14.1.1. Baricitinib – OLUMIANT (CAP)

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Signal of diverticulitis

EPITT 19496 – New signal

Lead Member State(s): PL

14.1.2. Desogestrel (NAP)

Applicant(s): various

PRAC Rapporteur: Annika Folin

Scope: Signal of suppressed lactation

EPITT 19504 – New signal

Lead Member State(s): SE

14.1.3. Dupilumab – DUPIXENT (CAP)

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Kimmo Jaakkola

Scope: Signal of corneal disorders

EPITT 19509 – New signal

Lead Member State(s): FI

14.1.4. Mirtazapine (NAP)

Applicant(s): various

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Signal of amnesia

[49] 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

[50] 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

EPITT 19506 – New signal

Lead Member State(s): NL

14.1.5. Nivolumab – OPDIVO (CAP)

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Signal of lichen sclerosus

EPITT 19505 – New signal

Lead Member State(s): DE

14.1.6. Sertraline (NAP)

Applicant(s): various

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Signal of microscopic colitis

EPITT 19513 – New signal

Lead Member State(s): NL

14.2. New signals detected from other sources

None

15. Annex I – Risk management plans

15.1. Medicines in the pre-authorisation phase

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

15.1.1. Budesonide, formoterol fumarate dihydrate – EMEA/H/C/004882

Scope: Treatment of asthma and chronic obstructive pulmonary disease (COPD)

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. Abacavir - ZIAGEN (CAP) - EMEA/H/C/000252/WS1713/0109; abacavir, lamivudine - KIVEXA (CAP) - EMEA/H/C/000581/WS1713/0083; dolutegravir, abacavir,

lamivudine - TRIUMEQ (CAP) - EMEA/H/C/002754/WS1713/0075; lamivudine, abacavir, zidovudine - TRIZIVIR (CAP) - EMEA/H/C/000338/WS1713/0115

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Adrien Inoubli

Scope: Submission of updated RMPs (version 2.0 for Kivexa, Trizivir and Ziagen; version 17.0 for Triumeq) in order to remove the additional risk minimisation measure (aRMM) on the education materials for healthcare professionals on abacavir hypersensitivity. Annex II is updated accordingly

15.2.2. Alirocumab - PRALUENT (CAP) - EMEA/H/C/003882/II/0050/G

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Submission of an updated RMP (version 5.0) in order to amend the list of safety concerns to remove ‘cataract (in the context of very low ‘low-density lipoprotein cholesterol’ (LDL-C))’ as an important potential risk; ‘long-term use (>5years)’ and ‘clinical impact of very low LDL-C for extended period of time’ as missing information. As a consequence, the following additional pharmacovigilance activities (listed as category 3 studies in the RMP) are removed from the RMP: 1) study R727-CL-1609: a long term safety study of Praluent (alirocumab) in patients with heterozygous familial hypercholesterolemia or with non-familial hypercholesterolemia at high and very high cardiovascular risk and previously enrolled in the neurocognitive function trial (MEA 016); 2) study OBS14697: a drug utilisation study (DUS) of alirocumab in Europe to assess the effectiveness of the dosing recommendation to avoid very low low-density lipoprotein (LDL)-C levels (MEA 019); 3) study ALIROC07997: a PASS using healthcare databases, in order to monitor the safety of Praluent (alirocumab) in patients affected with the human immunodeficiency virus (HIV) (MEA 017) based on a review of data since the marketing authorisation (MA) was granted including the first interim report for study OBS14697 (in fulfilment of MEA 019.4)

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

Applicant: Allergan Pharmaceuticals Ireland

PRAC Rapporteur: Eva Segovia

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

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

Applicant: Zentiva, k.s.

PRAC Rapporteur: Ghania Chamouni

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

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

Applicant: Aventis Pharma S.A.

PRAC Rapporteur: Ghania Chamouni

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

15.2.6. Follitropin alfa - GONAL-F (CAP) - EMEA/H/C/000071/II/0147

Applicant: Merck Europe B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Submission of an updated RMP (version 2.1) in order to bring it in line with revision 2.0.1 of the guidance on the format of RMP in the EU (template), to remove the important identified risks of 'ovarian hyperstimulation syndrome (OHSS)', 'thromboembolic events usually with OHSS', 'hypersensitivity reactions, including anaphylactic reactions', 'asthma aggravated/exacerbation', 'multiple pregnancies' and 'gynecomastia in males'. In addition, the RMP is updated to remove the important potential risks of 'breast cancer', 'other reproductive system cancers', 'ectopic pregnancy' and 'congenital abnormalities'. Finally, the RMP is updated to increase the age from 40 to 42 years for the missing information of 'women older than 40 years'

15.2.7. Follitropin alfa, lutropin alfa - PERGOVERIS (CAP) - EMEA/H/C/000714/II/0066

Applicant: Merck Europe B.V.

PRAC Rapporteur: Hans Christian Siersted

Scope: Submission of an updated RMP (version 5.3) in order to bring it in line with revision 2.0.1 of the guidance on the format of RMP in the EU (template), to remove the important identified risks of 'ovarian hyperstimulation syndrome (OHSS)', 'thromboembolic events usually with OHSS' and 'hypersensitivity reactions', to remove the important potential risks of 'breast cancer', 'ovarian cancer', 'endometrial cancer', 'congenital anomalies' and 'malignant melanoma'

15.2.8. Imatinib - GLIVEC (CAP) - EMEA/H/C/000406/II/0115

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Eva Segovia

Scope: Submission of an updated RMP (version 12) in order to revise the lists of safety concerns and to bring it in line with revision 2 of GVP module V on 'Risk management systems'

15.2.9. Lacosamide - LACOSAMIDE UCB (CAP) - EMEA/H/C/005243/WS1748/0003; Lacosamide - VIMPAT (CAP) - EMEA/H/C/000863/WS1748/0085

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of an updated RMP in order to change due dates for three studies (listed as a category 3 studies in the RMP): 1) study SP848: an open-label study to determine safety, tolerability and efficacy of long -term oral lacosamide (LCM) as adjunctive therapy in children with epilepsy - from November 2021 to December 2021; 2) study EP0012: an open-label, multicentre extension study to evaluate the long-term safety and efficacy of LCM as adjunctive therapy for uncontrolled primary generalised tonic clonic seizures in subjects with idiopathic generalised epilepsy - from November 2022 to December 2022; 3) study EP0034: a multicentre, open-label, long-term extension study to investigate the efficacy and safety of LCM as adjunctive therapy in paediatric subjects with epilepsy with partial-onset seizures - from May 2024 to August 2024. In addition, the submission includes amendments to the agreed protocols for studies SP848 and EP0034

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

Applicant: Eisai GmbH

PRAC Rapporteur: David Olsen

Scope: Submission of an updated RMP (version 11.3) as a result of interim analysis and updated final report submission dates for study E7080-G000-307: a multicentre, open-label, randomized, phase 3 trial to compare the efficacy and safety of lenvatinib in combination with everolimus or pembrolizumab versus sunitinib alone in first-line treatment of subjects with advanced renal cell carcinoma (CLEAR). The protocol is also updated to include an interim analysis for profession-free survival and overall survival

15.2.11. Teduglutide - REVESTIVE (CAP) - EMEA/H/C/002345/II/0050, Orphan

Applicant: Shire Pharmaceuticals Ireland Limited

PRAC Rapporteur: Hans Christian Siersted

Scope: Submission of an updated RMP (version 9) in order to update the list of safety concerns, consisting of: 1) deletion of the important identified risk ‘occurrence of anti-teduglutide antibodies, cross reactivity with glucagon-like peptide-2 (GLP-2) and occurrence of anti-eosinophil cationic protein (ECP) antibodies’; 2) deletion of the important potential risk ‘increased C-reactive protein (CRP)’; 3) renaming of important identified risks for clarity to ‘biliary events’, ‘pancreatic events’ and ‘intestinal polyps’. In addition, the submission includes a minor amendment to a protocol for study TED-R-13-002: an international short bowel syndrome registry: a prospective, long-term observational cohort study of patients with short bowel syndrome, as requested by PRAC in procedure PSA/S/0040 adopted in July 2019

15.2.12. Temsirolimus - TORISEL (CAP) - EMEA/H/C/000799/II/0078

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Martin Huber

Scope: Submission of an updated RMP (version 4.0) in order to remove the following safety concerns: ‘risk of cardiovascular events in patients with coexisting cardiovascular conditions’ and ‘reproductive toxicity’ as missing information and to bring it in line with revision 2 of GVP module V on ‘Risk management systems’

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

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

15.3.1. Adalimumab - HALIMATOZ (CAP) - EMEA/H/C/004866/X/0013

Applicant: Sandoz GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension application to add a new strength of 20 mg (20 mg/0.4 mL) for Halimatoz (adalimumab) solution for injection in pre-filled syringe. The RMP (version 2.0) is updated accordingly. The MAH took also the opportunity to consolidate the RMP with changes approved in two other procedures (WS1565 and IA/11 finalised in March 2019 and June 2019 respectively) and to align the product information with the latest quality review of documents (QRD) template (version 10.1)

15.3.2. Adalimumab - HEFIYA (CAP) - EMEA/H/C/004865/X/0013

Applicant: Sandoz GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension application to add a new strength of 20 mg (20 mg/0.4 mL) for Hefiya (adalimumab) solution for injection in pre-filled syringe. The RMP (version 2.0) is updated accordingly. The MAH took also the opportunity to consolidate the RMP with changes approved in two other procedures (WS1565 and IA/11 finalised in March 2019 and June 2019 respectively) and to align the product information with the latest quality review of documents (QRD) template (version 10.1)

15.3.3. Adalimumab - HYRIMOZ (CAP) - EMEA/H/C/004320/X/0013

Applicant: Sandoz GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension application to add a new strength of 20 mg (20 mg/0.4 mL) for Hyrimoz (adalimumab) solution for injection in pre-filled syringe. The RMP (version 2.0) is updated accordingly. The MAH took also the opportunity to consolidate the RMP with changes approved in two other procedures (WS1565 and IA/11 finalised in March 2019 and June 2019 respectively) and to align the product information with the latest quality review of documents (QRD) template (version 10.1)

15.3.4. Albutrepenonacog alfa - IDELVION (CAP) - EMEA/H/C/003955/X/0035, Orphan

Applicant: CSL Behring GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Extension application to add a new strength of 3,500 IU (700 IU/mL) for albutrepenonacog alfa powder and solvent for solution for injection. The RMP (version 3.1) is updated accordingly

15.3.5. Anakinra - KINERET (CAP) - EMEA/H/C/000363/II/0070

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Hans Christian Siersted

Scope: Extension of indication to include the treatment of familial Mediterranean fever (FMF) to be given in combination with colchicine, if appropriate. As a consequence, sections 4.1, 4.2, 4.8, 5.1 of the SmPC are updated. The package leaflet and the RMP (version 5.0) are updated accordingly

15.3.6. 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'

15.3.7. 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, randomized, 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'

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

Applicant: Pierre Fabre Medicament

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

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

brought in line with the latest quality review of documents (QRD) template (version 10.1)

15.3.9. Burosumab - CRYSVITA (CAP) - EMEA/H/C/004275/II/0010/G, Orphan

Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include the treatment of adults with X-linked hypophosphataemia (XLH), and modification of the currently approved indication in children and adolescents, by removing the qualification 'with growing skeletons', in order to include the treatment in all children with radiographic evidence of bone disease. The application provides new week-48 data from study UX023-CL304; a randomized, double-blind, placebo-controlled, phase 3 study with open-label extension to assess the efficacy and safety of KRN23 in adults with XLH. 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 2.0) are updated in accordance. Furthermore, the product information is brought in line with the latest quality review of documents (QRD) template (version 10.1)

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

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Ulla Wändel Liminga

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

15.3.11. Conestat alfa - RUCONEST (CAP) - EMEA/H/C/001223/II/0053/G

Applicant: Pharming Group N.V

PRAC Rapporteur: Jan Neuhauser

Scope: Grouped variations consisting of an extension of indication to include children in the treatment of acute angioedema attacks with hereditary angioedema (HAE) due to C1 esterase inhibitor deficiency, based on the results from study C1 1209: an open-label, phase 2, single arm study to evaluate the safety, immunogenicity, pharmacokinetics and efficacy of recombinant human C1 inhibitor for the treatment of acute attacks in paediatric patients with hereditary angioedema, from 2 up to and including 13 years of age. In

addition, final efficacy and safety data from the open label extension (OLE) phases of 1) study C1 1304: a randomised, placebo-controlled, double-blind, multicentre study performed in order to demonstrate the efficacy of recombinant human C1 inhibitor (rhC1INH) at 100 U/kg in patients with HAE with attacks of angioedema; 2) study C1 1205: a randomised, placebo-controlled, double-blind phase 2 study on the safety and efficacy of rhC1INH at doses of 50 and 100U/kg in relieving eligible attacks of angioedema with involvement of sub-mucosal tissues in patients with HAE; and completed study C1 1310: a phase 3, randomized, placebo-controlled trial on rhC1INH relieved symptoms of hereditary angioedema attacks; together with the final results of studies C1 1207 and 3201 concerning prophylactic treatment of HAE patients. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.7, 4.8, 5.1, 5.2 and 5.3 are updated. The package leaflet and the RMP (version 19.0) are updated accordingly. The RMP is also brought in line with revision 2.0.1 of the guidance on the format of RMP in the EU (template). Furthermore, the MAH requested an extension for the completion of registry study C1 1412: C1 inhibitor treatment registry to assess the safety and immunological profile of Ruconest (conestat alfa) in the treatment of HAE attacks, from March 2020 to June 2022. Finally, the product information is brought in line with the latest quality review of documents (QRD) template (version 10.1)

15.3.12. Darunavir,cobicistat - REZOLSTA (CAP) - EMEA/H/C/002819/II/0033

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Ilaria Baldelli

Scope: Extension of indication to extend the approved therapeutic indication of Rezolsta (darunavir/cobicistat) to include a new population, namely the adolescent population aged 12 years old and older with a body weight at least 40 kg. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 6.0) are updated accordingly. The RMP is also brought in line with revision 2 of GVP module V on 'Risk management systems' and in line with revision 2 of the guidance on the format of RMP in the EU (template). In addition, the MAH took the opportunity to update section 4.2 of the SmPC in line with recommendations for other human immunodeficiency virus (HIV) products with regards to administration Rezolsta (darunavir/cobicistat) in case of vomiting

15.3.13. Dimethyl fumarate - TECFIDERA (CAP) - EMEA/H/C/002601/II/0058

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Martin Huber

Scope: Submission of the final clinical study report (CSR) of study 109MS310 (listed as category 3 study in the RMP): an open-label study to assess the effects of Tecfidera (dimethyl fumarate) on lymphocyte subsets in subjects with relapsing remitting multiple sclerosis (RRMS). The RMP (version 10.1) is updated accordingly, includes updates to reflect safety information available until the data lock point (DLP) of 24 January 2019 and in line with revision 2.01 of the guidance on the format of the risk management plan (RMP) accompanying GVP module V on 'Risk management systems'

15.3.14. Edoxaban - LIXIANA (CAP) - EMEA/H/C/002629/WS1756/0025; ROTEAS (CAP) - EMEA/H/C/004339/WS1756/0012

Applicant: Daiichi Sankyo Europe GmbH

PRAC Rapporteur: Adrien Inoubli

Scope: Update of sections 4.2, 4.4 and 5.1 of the SmPC in order to update the safety information based on final results from the post-authorisation efficacy study DU176b-C-E314: evaluation of edoxaban in anticoagulant naive patients with non-valvular atrial fibrillation (NVAF) and high creatinine clearance [protocol MEA004]. This is a study to compare the exposure of edoxaban 75 mg once daily dose to edoxaban 60 mg once daily dose in NVAF anticoagulant-naive patients with $CHADS_2$ score of ≥2 and creatinine clearance (CrCL) >100 mL/min treated for up to 12 months. The RMP (version 9.0) is updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet and to bring the product information in line with the latest quality review of documents (QRD) template (version 10.1)

15.3.15. Etravirine - INTELENCE (CAP) - EMEA/H/C/000900/II/0058

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Adrien Inoubli

Scope: Extension of indication in order to include patient population from 2 to 6 years of age based on the 48 week study results from study TMC125-C234/P1090: a phase 1/2, open-label trial to evaluate the safety, tolerability, pharmacokinetics and antiviral activity of etravirine (ETR) in antiretroviral (ARV) treatment-experienced human immunodeficiency virus-1 (HIV-1) infected infants and children, aged ≥2 months to <6 years. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 13.1) are updated accordingly. The RMP is also brought in line with revision 2 of GVP module V on 'Risk management systems' and revision 2.0.1 of the guidance on the format of RMP in the EU (template) leading to a reclassification of safety concerns. Finally, the MAH took the opportunity to introduce minor updates to the product information

15.3.16. Flutemetamol (^{18}F) - VIZAMYL (CAP) - EMEA/H/C/002557/II/0021

Applicant: GE Healthcare AS

PRAC Rapporteur: Martin Huber

Scope: Update of sections 4.4 and 5.1 of the SmPC in order to include information on the possibility of quantitative methodology assessment based on published studies. The RMP (version 2.1) is updated accordingly to introduce a new educational programme and to bring it in line with revision 2.0.1 of the guidance on the format of RMP in the EU (template)

15.3.17. Galcanezumab - EMGALITY (CAP) - EMEA/H/C/004648/X/0004

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Kirsti Villikka

Scope: Extension application to add a new strength of 100 mg/mL solution for injection in

pre-filled syringe for Emgality (galcanezumab) associated with a new indication to include treatment of episodic cluster headache. The RMP (version 1.1) is updated accordingly

15.3.18. Guselkumab - TREMFYA (CAP) - EMEA/H/C/004271/II/0017

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication for the treatment of active psoriatic arthritis in adult patients who have had an inadequate response or who have been intolerant to a prior disease-modifying antirheumatic drug (DMARD) therapy. As a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 5.1) are updated accordingly. Furthermore, the product information is brought in line with the latest quality review of documents (QRD) template (version 10.1)

15.3.19. Insulin aspart - FIASP (CAP) - EMEA/H/C/004046/II/0018/G

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Ilaria Baldelli

Scope: Grouped variations consisting of: 1) introduction of a new container closure system: Pumpcart cartridge to be used with insulin infusion pump systems (EU/1/16/1160/012); 2) introduction of a new multipack presentation of Fiasp (insulin aspart) 100 units/mL PumpCart solution for injection in cartridge (EU/1/16/1160/013). The RMP (version 4.0) is updated accordingly

15.3.20. Iron - VELPHORO (CAP) - EMEA/H/C/002705/X/0020/G

Applicant: Vifor Fresenius Medical Care Renal Pharma France

PRAC Rapporteur: Kimmo Jaakkola

Scope: Grouped application consisting of: 1) extension application to add a new pharmaceutical form with a new strength - powder for oral suspension 125 mg, 2) extension of indication to add the use of Velphoro (iron) for the control of serum phosphorus levels in paediatric patients 2 years of age and older with chronic kidney disease (CKD) stages 4-5 (defined by a glomerular filtration rate (GFR) <30 mL/min/1.73 m^2) or with CKD on dialysis, based on the results from study PA-CL-PED-01: an open-label, randomised, active-controlled, parallel group, multicentre, phase 3 study investigating the safety and efficacy of Velphoro (iron) and calcium acetate in paediatric and adolescent CKD patients with hyperphosphataemia. As a consequence, sections 4.1, 4.2, 4.8, and 5.1 of the SmPC are updated. The package leaflet, labelling and the RMP (version 7.0) are updated in accordance. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet. Furthermore, the product information is brought in line with the latest quality review of documents (QRD) template (version 10.1)

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

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Maria del Pilar Rayon

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

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

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

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

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

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Rugile Pilviniene

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

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

Applicant: AstraZeneca AB

PRAC Rapporteur: Amelia Cupelli

Scope: Extension of indication to support the use of Lynparza (olaparib) tablets (100 mg and 150 mg) for the maintenance treatment of germline breast cancer gene (BRCA) mutation (gBRCAm) metastatic pancreatic cancer based on the results from the pivotal phase 3 study POLO: a phase 3, randomised, double blind, placebo controlled, multicentre study of maintenance olaparib monotherapy in patients with gBRCA mutated metastatic

pancreatic cancer whose disease has not progressed on first line platinum based chemotherapy. As a consequence, sections 4.1, 4.2, 4.8, 5.1 of the SmPC are updated. The package leaflet and the RMP (version 18) are updated in accordance. In addition, the MAH took the opportunity to update section 4.8 for Lynparza (olaparib) hard capsules (50 mg) to revise the list of adverse drug reactions (ADR) based on a pooled safety data analysis. Furthermore, the product information is brought in line with the latest Annex to the European Commission (EC) guideline on 'excipients in the labelling and package leaflet of medicinal products for human use' on sodium content. The MAH also took the opportunity to include some minor editorial changes in the product information

15.3.25. Pemetrexed - PEMETREXED ACCORD (CAP) - EMEA/H/C/004072/X/0010

Applicant: Accord Healthcare S.L.U.

PRAC Rapporteur: Ghania Chamouni

Scope: Extension application to introduce a new pharmaceutical form associated with a new strength (25 mg/mL solution for infusion). The RMP (version 1.0) is updated accordingly

15.3.26. Plasmodium falciparum and hepatitis B vaccine (recombinant, adjuvanted) - MOSQUIRIX (Art 58[51]) - EMEA/H/W/002300/II/0043

Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Jean-Michel Dogné

Scope: Update of section 4.5 of the SmPC in order to add immunogenicity data following the interim results from study Malaria-073 (listed as a category 3 study in the RMP): a phase 3 randomized, open, controlled study to evaluate the immunogenicity and safety of Mosquirix when administered as a primary vaccination schedule at 6, 7.5 and 9 months-of-age, with or without co-administration of measles and rubella and yellow fever vaccines, to children living in sub-Saharan Africa. The RMP (version 5.1) is updated accordingly. In addition, the Scientific Opinion Holder (SOH) took the opportunity to bring the product information in line with the latest quality review of documents (QRD) template (version 10.1)

15.3.27. 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

15.3.28. Rituximab - BLITZIMA (CAP) - EMEA/H/C/004723/WS1724/0029; RITEMVIA (CAP) - EMEA/H/C/004725/WS1724/0029; TRUXIMA (CAP) - EMEA/H/C/004112/WS1724/0032

Applicant: Celltrion Healthcare Hungary Kft.

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

PRAC Rapporteur: Hans Christian Siersted

Scope: Submission of the final report from study CT-P10 3.3 (listed as a category 3 study in the RMP): a phase 3, randomised, parallel-group, active-controlled, double-blind study to demonstrate equivalence of pharmacokinetics and non-inferiority of efficacy for CT-P10 (biosimilar rituximab) in comparison with Rituxan (rituximab), each administered in combination with cyclophosphamide, vincristine, and prednisone (CVP) in patients with advanced follicular lymphoma. The RMP (version 9.1) is updated accordingly and aligned with the safety concerns of MabThera (rituximab)

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

Applicant: AstraZeneca AB

PRAC Rapporteur: Maria del Pilar Rayon

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

15.3.30. Saxagliptin, dapagliflozin - QTERN (CAP) - EMEA/H/C/004057/II/0024

Applicant: AstraZeneca AB

PRAC Rapporteur: Ilaria Baldelli

Scope: Update of sections 4.2, 4.4 and 5.1 of the SmPC with information on the glycaemic efficacy and renal safety of dapagliflozin in patients with type 2 diabetes mellitus (T2DM) and moderate renal impairment (chronic kidney disease (CKD) 3A) based on final results from study D1690C00024 (DERIVE) (dapagliflozin): a multicentre, double-blind, placebo-controlled, parallel group, randomised, phase 3 study to evaluate the glycaemic efficacy and renal safety of dapagliflozin in patients with T2DM and CKD 3A who have inadequate glycaemic control, and to reflect a change in renal cut-off value for saxagliptin. The package leaflet and the RMP (version 4.1) are updated accordingly. In addition, the MAH took the opportunity to update sections 2, 4.8, 5.2 of the SmPC and Annex II to include the required excipient information in relation to sodium levels and lactose following the update to the Annex to the European Commission (EC) guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use', as well as to bring the product information in line with the EMA guidance on 'Compilation of quality review of documents (QRD) decisions on stylistic matters in product information' (EMA/25090/2002 Rev.18)

15.3.31. Sonidegib - ODOMZO (CAP) - EMEA/H/C/002839/II/0024

Applicant: Sun Pharmaceutical Industries Europe B.V.

PRAC Rapporteur: Željana Margan Koletić

Scope: Submission of the final report of study CLDE225X2116 (listed as a category 3 study

in the RMP): an interventional phase 1b/2, open-label, multicentre, dose-finding study to assess the safety and efficacy of the oral combination of LDE225 (sonidegib) and INC424 (ruxolitinib) in subjects with myelofibrosis. The RMP (version 7.1) is updated accordingly

15.3.32. Trastuzumab - OGIVRI (CAP) - EMEA/H/C/004916/II/0009

Applicant: Mylan S.A.S

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Submission of the final clinical study report for study MYL-Her-3001: a multicentre, double-blind, randomized, parallel-group, phase 3 study of the efficacy and safety of Hercules (trastuzumab Mylan S.A.S) plus taxane versus Herceptin (trastuzumab) plus taxane as first line therapy in patients with epidermal growth factor receptor 2+ (HER2+) metastatic breast cancer) with the final overall survival (OS). The RMP (version 3) is updated accordingly

15.3.33. Venetoclax - VENCLYXTO (CAP) - EMEA/H/C/004106/II/0023/G

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Eva Jirsová

Scope: Extension of indication to include Venclyxto (venetoclax) in combination with an anti - CD20[52] antibody (obinutuzumab) for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL) based on the results of pivotal study CLL14/BO25323:a prospective, open-label, multicentre randomized phase 3 trial to compare the efficacy and safety of a combined regimen of obinutuzumab and venetoclax (GDC-0199/ABT-199) versus obinutuzumab and chlorambucil in previously untreated patients with CLL and coexisting medical conditions. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 of the SmPC are updated. The package leaflet and the RMP (version 5.1) are updated accordingly. Furthermore, section 5.3 of the SmPC is updated based on the 6 month-carcinogenicity mouse study report, supported by the 4 week dose ranging study in mice and embryo-foetal development (EFD) data. The MAH took the opportunity to introduce minor editorial changes throughout the product information (PI)

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

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Anette Kirstine Stark

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

[52] B cell differentiation antigen

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. Afamelanotide - SCENESSE (CAP) - PSUSA/00010314/201906

Applicant: Clinuvel Europe Limited

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.2. Allopurinol, lesinurad - DUZALLO (CAP) - PSUSA/00010704/201906

Applicant: Grunenthal GmbH

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

16.1.3. Asfotase alfa - STRENSIQ (CAP) - PSUSA/00010421/201907

Applicant: Alexion Europe SAS

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

16.1.4. Binimetinib - MEKTOVI (CAP) - PSUSA/00010717/201906

Applicant: Pierre Fabre Medicament

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Evaluation of a PSUSA procedure

16.1.5. Blinatumomab - BLINCYTO (CAP) - PSUSA/00010460/201906

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

16.1.6. Brexpiprazole - RXULTI (CAP) - PSUSA/00010698/201907

Applicant: Otsuka Pharmaceutical Netherlands B.V.

PRAC Rapporteur: Tatiana Magalova

Scope: Evaluation of a PSUSA procedure

16.1.7. Bromfenac - YELLOX (CAP) - PSUSA/00000436/201905 (with RMP)

Applicant: PharmaSwiss Ceska Republika s.r.o

PRAC Rapporteur: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

16.1.8. Budesonide[53] - JORVEZA (CAP) - PSUSA/00010664/201907

Applicant: Dr. Falk Pharma GmbH

PRAC Rapporteur: Zane Neikena

Scope: Evaluation of a PSUSA procedure

16.1.9. Cenegermin - OXERVATE (CAP) - PSUSA/00010624/201907

Applicant: Dompe farmaceutici S.p.A.

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.1.10. Cladribine[54] - MAVENCLAD (CAP) - PSUSA/00010634/201907

Applicant: Merck Europe B.V.

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Evaluation of a PSUSA procedure

16.1.11. Dasatinib - SPRYCEL (CAP) - PSUSA/00000935/201906

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Hans Christian Siersted

Scope: Evaluation of a PSUSA procedure

16.1.12. Dengue tetravalent vaccine (live, attenuated) - DENGVAXIA (CAP) - PSUSA/00010740/201906

Applicant: Sanofi Pasteur

PRAC Rapporteur: Sonja Hrabcik

[53] Centrally authorised product(s) only
[54] Indicated for the treatment of multiple sclerosis

Scope: Evaluation of a PSUSA procedure

16.1.13. Dimethyl fumarate[55] - SKILARENCE (CAP) - PSUSA/00010647/201906

Applicant: Almirall S.A

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

16.1.14. Efmoroctocog alfa - ELOCTA (CAP) - PSUSA/00010451/201906

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Sonja Hrabcik

Scope: Evaluation of a PSUSA procedure

16.1.15. Elotuzumab - EMPLICITI (CAP) - PSUSA/00010500/201905

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.16. Encorafenib - BRAFTOVI (CAP) - PSUSA/00010719/201906

Applicant: Pierre Fabre Medicament

PRAC Rapporteur: Rugile Pilviniene

Scope: Evaluation of a PSUSA procedure

16.1.17. Ertugliflozin - STEGLATRO (CAP) - PSUSA/00010682/201906

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.18. Ertugliflozin, metformin - SEGLUROMET (CAP) - PSUSA/00010680/201906

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.19. Ertugliflozin, sitagliptin - STEGLUJAN (CAP) - PSUSA/00010681/201906

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

[55] Indicated for the treatment of psoriasis

Scope: Evaluation of a PSUSA procedure

16.1.20. Fluciclovine (^{18}F) - AXUMIN (CAP) - PSUSA/00010594/201905

Applicant: Blue Earth Diagnostics Ireland Limited

PRAC Rapporteur: Rugile Pilviniene

Scope: Evaluation of a PSUSA procedure

16.1.21. Glibenclamide[56] - AMGLIDIA (CAP) - PSUSA/00010690/201905

Applicant: Ammtek

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

16.1.22. Human fibrinogen, human thrombin - EVICEL (CAP); TACHOSIL (CAP); VERASEAL (CAP) - PSUSA/00010297/201906

Applicant(s): Omrix Biopharmaceuticals N. V. (Evicel), Takeda Austria GmbH (TachoSil), Instituto Grifols, S.A. (VeraSeal)

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.23. Human papillomavirus 9-valent vaccine (recombinant, adsorbed) - GARDASIL 9 (CAP) - PSUSA/00010389/201906

Applicant: MSD Vaccins

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

16.1.24. Human papillomavirus vaccine (rDNA) - 4-valent - GARDASIL (CAP) - PSUSA/00001634/201905

Applicant: MSD Vaccins

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.25. Human plasma protease C1 inhibitor - CINRYZE (CAP) - PSUSA/00010104/201906

Applicant: Shire Services BVBA

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

[56] Centrally authorised product(s) only

16.1.26. Inotersen - TEGSEDI (CAP) - PSUSA/00010697/201907

Applicant: Akcea Therapeutics Ireland Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

16.1.27. Inotuzumab ozogamicin - BESPONSA (CAP) - PSUSA/00010659/201906

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.28. Levofloxacin[57] - QUINSAIR (CAP) - PSUSA/00010429/201905

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

16.1.29. Lonoctocog alfa - AFSTYLA (CAP) - PSUSA/00010559/201907

Applicant: CSL Behring GmbH

PRAC Rapporteur: Sonja Hrabcik

Scope: Evaluation of a PSUSA procedure

16.1.30. Macimorelin - MACIMORELIN AETERNA ZENTARIS (CAP) - PSUSA/00010746/201907

Applicant: Aeterna Zentaris GmbH

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.31. Mexiletine[58] - NAMUSCLA (CAP) - PSUSA/00010738/201906

Applicant: Lupin Europe GmbH

PRAC Rapporteur: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

16.1.32. Migalastat - GALAFOLD (CAP) - PSUSA/00010507/201905

Applicant: Amicus Therapeutics Europe Limited

PRAC Rapporteur: Ulla Wändel Liminga

[57] For inhalation use only
[58] Centrally authorised product(s) only

Scope: Evaluation of a PSUSA procedure

16.1.33. Nepafenac - NEVANAC (CAP) - PSUSA/00002143/201905

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

16.1.34. Nivolumab - OPDIVO (CAP) - PSUSA/00010379/201907 (with RMP)

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.35. Nonacog beta pegol - REFIXIA (CAP) - PSUSA/00010608/201905

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.36. Nonacog gamma - RIXUBIS (CAP) - PSUSA/00010320/201906

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.37. Nusinersen - SPINRAZA (CAP) - PSUSA/00010595/201905

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.38. Obeticholic acid - OCALIVA (CAP) - PSUSA/00010555/201905

Applicant: Intercept Pharma International Limited

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.39. Opicapone - ONGENTYS (CAP) - PSUSA/00010516/201906

Applicant: Bial - Portela & Cª, S.A.

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

16.1.40. Pegvaliase - PALYNZIQ (CAP) - PSUSA/00010761/201905

Applicant: BioMarin International Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

16.1.41. Peramivir - ALPIVAB (CAP) - PSUSA/00010687/201906

Applicant: BioCryst Ireland Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.42. Pertuzumab - PERJETA (CAP) - PSUSA/00010125/201906

Applicant: Roche Registration GmbH

PRAC Rapporteur: Hans Christian Siersted

Scope: Evaluation of a PSUSA procedure

16.1.43. Rucaparib - RUBRACA (CAP) - PSUSA/00010694/201906

Applicant: Clovis Oncology Ireland Limited

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

16.1.44. Selexipag - UPTRAVI (CAP) - PSUSA/00010503/201906

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

16.1.45. Sonidegib - ODOMZO (CAP) - PSUSA/00010408/201906

Applicant: Sun Pharmaceutical Industries Europe B.V.

PRAC Rapporteur: Željana Margan Koletić

Scope: Evaluation of a PSUSA procedure

16.1.46. Spheroids of human autologous matrix-associated chondrocytes - SPHEROX (CAP) - PSUSA/00010630/201907

Applicant: CO.DON AG, ATMP[59]

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

[59] Advanced therapy medicinal product

16.1.47. Tasimelteon - HETLIOZ (CAP) - PSUSA/00010394/201907

Applicant: Vanda Pharmaceuticals Germany GmbH

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.48. Tedizolid phosphate - SIVEXTRO (CAP) - PSUSA/00010369/201906

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

16.1.49. Trametinib - MEKINIST (CAP) - PSUSA/00010262/201905

Applicant: Novartis Europharm Limited

PRAC Rapporteur: David Olsen

Scope: Evaluation of a PSUSA procedure

16.1.50. Vonicog alfa - VEYVONDI (CAP) - PSUSA/00010714/201906

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Ulla Wändel Liminga

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. Naloxone[60] - NYXOID (CAP); NAP - PSUSA/00010657/201905

Applicants: Mundipharma Corporation (Ireland) Limited (Nyxoid), various

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

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

16.3.1. Amsacrine (NAP) - PSUSA/00000199/201906

Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

[60] For use in non-medical setting(s) only

16.3.2. Bemiparin (NAP) - PSUSA/00000312/201904

Applicant(s): various

PRAC Lead: Eva Segovia

Scope: Evaluation of a PSUSA procedure

16.3.3. Bupivacaine (NAP); bupivacaine hydrochloride, epinephrine (NAP) - PSUSA/00010335/201904

Applicant(s): various

PRAC Lead: Zane Neikena

Scope: Evaluation of a PSUSA procedure

16.3.4. Clevidipine (NAP)- PSUSA/00010288/201905

Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.3.5. Fusidic acid[61] (NAP) - PSUSA/00010226/201905

Applicant(s): various

PRAC Lead: Julia Pallos

Scope: Evaluation of a PSUSA procedure

16.3.6. Human hemin (NAP) - PSUSA/00001629/201905

Applicant(s): various

PRAC Lead: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

16.3.7. Isoniazide, rifampicin (NAP) - PSUSA/00001792/201905

Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.3.8. Macrogol 3350 (NAP) - PSUSA/00001924/201905

Applicant(s): various

PRAC Lead: Ilaria Baldelli

Scope: Evaluation of a PSUSA procedure

[61] Systemic use only

16.3.9. Macrogol 4000 (NAP); macrogol 4000 combinations[62] (NAP) - PSUSA/00010392/201905

Applicant(s): various

PRAC Lead: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

16.3.10. Measles vaccine (live attenuated) (NAP) - PSUSA/00001938/201905

Applicant(s): various

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.3.11. Methoxyflurane (NAP) - PSUSA/00010484/201905

Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.3.12. Misoprostol[63] (NAP) - PSUSA/00010353/201905

Applicant(s): various

PRAC Lead: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

16.3.13. Ozenoxacin (NAP) - PSUSA/00010651/201905

Applicant(s): various

PRAC Lead: Eva Segovia

Scope: Evaluation of a PSUSA procedure

16.3.14. Sulprostone (NAP) - PSUSA/00002828/201904

Applicant(s): various

PRAC Lead: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

16.3.15. Tirofiban (NAP) - PSUSA/00002974/201905

Applicant(s): various

PRAC Lead: Martin Huber

[62] Oral use only
[63] Gynaecological indication - labour induction

Scope: Evaluation of a PSUSA procedure

16.3.16. Treprostinil (NAP) - PSUSA/00003013/201905

Applicant(s): various

PRAC Lead: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

16.3.17. Yohimbine (NAP) - PSUSA/00003136/201905

Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.4. Follow-up to PSUR/PSUSA procedures

16.4.1. Dolutegravir - TIVICAY (CAP) - EMEA/H/C/002753/LEG 012

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Martin Huber

Scope: Detailed review on weight gain as requested in the conclusions of PSUSA/00010075/201901 adopted by PRAC in September 2019

16.4.2. Dolutegravir, abacavir, lamivudine - TRIUMEQ (CAP) - EMEA/H/C/002754/LEG 009

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Martin Huber

Scope: Detailed review on weight gain as requested in the conclusions of PSUSA/00010075/201901 adopted by PRAC in September 2019

16.4.3. Dolutegravir, lamivudine - DOVATO (CAP) - EMEA/H/C/004909/LEG 004

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: David Olsen

Scope: Detailed review on weight gain as requested in the conclusions of PSUSA/00010075/201901 adopted by PRAC in September 2019

16.4.4. Pegfilgrastim - NEULASTA (CAP) - EMEA/H/C/000420/LEG 062

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Cumulative review of severe cutaneous skin reactions (SCARs) following the conclusions of periodic safety update single assessment procedure PSUSA/00002326/201901 adopted in September 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)[64]

17.1.1. Dapagliflozin – EDISTRIDE (CAP), FORXIGA (CAP) - EMEA/H/C/PSP/S/0083.1

Applicant: AstraZeneca

PRAC Rapporteur: Annika Folin

Scope: MAH's response to PSP/S/0083 [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] as per the request for supplementary information (RSI) adopted in September 2019

17.1.2. Ingenol mebutate - PICATO (CAP) - EMEA/H/C/PSP/S/0081.1

Applicant: LEO Laboratories Ltd

PRAC Rapporteur: Adam Przybylkowski

Scope: MAH's response to PSP/S/0081 [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] as per the request for supplementary information (RSI) adopted in June 2019

17.1.3. Rurioctocog alfa pegol – ADYNOVI (CAP) - EMEA/H/C/PSA/S/0045

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Substantial amendment to a protocol previously agreed in July 2019 (PSP/S/0077.1) for a study evaluating the long-term safety of Adynovi/Adynovate (rurioctocog alfa pegol) in adults and adolescents ≥12 years of age with haemophilia A

17.1.4. Volanesorsen – WAYLIVRA (CAP) - EMEA/H/C/PSP/S/0080.1

Applicant: Akcea Therapeutics Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: MAH's response to PSP/S/0080 [protocol for a multinational observational registry (WAY4001) of patients treated with volanesorsen to evaluate the safety on severe

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

thrombocytopenia and bleeding in patients with familial chylomicronemia syndrome (FCS)] as per the request for supplementary information (RSI) adopted in September 2019

17.2. Protocols of PASS non-imposed in the marketing authorisation(s)[65]

17.2.1. Ciclosporin - VERKAZIA (CAP) - EMEA/H/C/004411/MEA 001.2

Applicant: Santen Oy

PRAC Rapporteur: Jan Neuhauser

Scope: MAH's response to MEA 001.1 [protocol and feasibility study for a case-control study linked to existing cancer registries to understand the data sources and analytic methods available to quantify the risk of periocular skin cancer, conjunctival or corneal neoplasia in children treated with Verkazia (ciclosporin)] as per the request for supplementary information (RSI) adopted in July 2019

17.2.2. Erenumab - AIMOVIG (CAP) - EMEA/H/C/004447/MEA 001.1

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Kirsti Villikka

Scope: MAH's response to MEA 001 [protocol for study CAMG334A2023: a non-interventional study to examine patient characteristics and drug utilisation patterns in migraine patients treated with prophylactic drugs in the Nordic registries [final clinical study report (CSR) expected end of data collection + 1 year]] as per the request for supplementary information (RSI) adopted in July 2019

17.2.3. Exenatide - BYDUREON (CAP) - EMEA/H/C/002020/MEA 027

Applicant: AstraZeneca AB

PRAC Rapporteur: Annika Folin

Scope: Protocol for study EXCEED (listed as a category 3 study in the RMP): a pan-European PASS to assess the risk of pancreatic cancer among type 2 diabetes mellitus (T2DM) patients who initiated exenatide as compared with those who initiated other non-glucagon-like peptide 1 receptor agonists based glucose lowering drugs

17.2.4. Exenatide - BYETTA (CAP) - EMEA/H/C/000698/MEA 047

Applicant: AstraZeneca AB

PRAC Rapporteur: Annika Folin

Scope: Protocol for study EXCEED (listed as a category 3 study in the RMP): a pan-European PASS to assess the risk of pancreatic cancer among type 2 diabetes mellitus (T2DM) patients who initiated exenatide as compared with those who initiated other non-glucagon-like peptide 1 receptor agonists based glucose lowering drugs

[65] 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. Human papillomavirus vaccine [types 6, 11, 16, 18] (recombinant, adsorbed) - GARDASIL (CAP) - EMEA/H/C/000703/MEA 086.1

Applicant: MSD Vaccins

PRAC Rapporteur: Ulla Wändel Liminga

Scope: MAH's response to MEA 086 [yearly interim results for study P070 (listed as category 3 study in the RMP): a post-licensure safety study in males to monitor safety signals through a systematic evaluation in a research database] as per the request for supplementary information (RSI) adopted in October 2019

17.2.6. Insulin glargine, lixisenatide - SULIQUA (CAP) - EMEA/H/C/004243/MEA 002.4

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Menno van der Elst

Scope: Amendment to protocol previously agreed in January 2019 for study INSLIC08571 (listed as a category 3 study in the RMP): a cross-sectional multinational, multichannel survey conducted among healthcare professionals and patients to measure the effectiveness of Suliqua (insulin glargine/lixisenatide) educational materials set up to evaluate the knowledge and understanding of the key safety messages in the healthcare professional guide and the patient guide

17.2.7. Lenvatinib - LENVIMA (CAP) - EMEA/H/C/003727/MEA 014.2

Applicant: Eisai GmbH

PRAC Rapporteur: Annika Folin

Scope: MAH's response to MEA 014.1 [protocol for study E7080-G000-508: an observational study to characterise hepatic related toxicity and overall safety profile in real-life conditions in the EU (Western population) in hepatocellular carcinoma (HCC) patients, including patients with Child-Pugh B] as per the request for supplementary information (RSI) adopted in July 2019

17.2.8. Mogamulizumab - POTELIGEO (CAP) - EMEA/H/C/004232/MEA 001.1

Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Hans Christian Siersted

Scope: MAH's response to MEA 001 [protocol for a PASS to characterise the safety of allogeneic haematopoietic stem cell transplantation (HSCT) in patients with cutaneous t-cell lymphoma (CTCL) treated with mogamulizumab [final clinical study report expected in July 2024]] as per the request for supplementary information (RSI) adopted in July 2019

17.3. Results of PASS imposed in the marketing authorisation(s)[66]

None

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

17.4. Results of PASS non-imposed in the marketing authorisation(s)[67]

17.4.1. Belatacept - NULOJIX (CAP) - EMEA/H/C/002098/II/0063/G

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of the final report from studies IM103075 and IM103076 (listed as category 3 studies in the RMP). Study IM103075 is a prospective cohort study to assess the association between belatacept use and risk of post-transplant lymphoproliferative disorder (PTLD) in renal transplant recipients in the United States (US). Study IM103076 is a prospective patient registry study to estimate the incidence rates of confirmed PTLD, central nervous system (CNS) PTLD and progressive multifocal leukoencephalopathy (PML) in adult renal transplant recipients treated with belatacept in the US. The RMP (version 17.0) is updated accordingly and includes some administrative updates

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

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Eva Jirsová

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

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

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ghania Chamouni

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

17.4.4. Duloxetine - CYMBALTA (CAP) - EMEA/H/C/000572/WS1755/0083; DULOXETINE LILLY (CAP) - EMEA/H/C/004000/WS1755/0020; XERISTAR (CAP) - EMEA/H/C/000573/WS1755/0086; YENTREVE (CAP) - EMEA/H/C/000545/WS1755/0068

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Submission of the final report from study FIJ-MC-B059: an observational study to assess foetal outcomes following maternal exposure to duloxetine and the revised final report from study F1J-MC-B057: an observational study to assess maternal and foetal

[67] 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

outcomes following exposure to duloxetine

17.4.5. Edoxaban - LIXIANA (CAP) - EMEA/H/C/002629/WS1760/0024; ROTEAS (CAP) - EMEA/H/C/004339/WS1760/0011

Applicant: Daiichi Sankyo Europe GmbH

PRAC Rapporteur: Adrien Inoubli

Scope: Submission of the final study report from study ETNA-DUS (listed as a category 3 study in the RMP): the edoxaban treatment in routine clinical practice drug utilisation study, a retrospective drug utilisation chart review study to gain insight on how edoxaban is used in real practice, to identify prescription patterns and to measure the effectiveness of the educational programmes

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

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Eva Segovia

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

17.4.7. Rilpivirine - EDURANT (CAP) - EMEA/H/C/002264/II/0037

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Submission of the final report from study EUPAS5766 in the EuroSIDA cohort (listed as a category 3 study in the RMP) - a drug utilisation study (DUS): an observational cohort study to assess rilpivirine (RPV) utilisation according to the European SmPC. The RMP (version 9.0) is updated accordingly

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 001.7

Applicant: AstraZeneca AB

PRAC Rapporteur: Adam Przybylkowski

Scope: MAH's response to ANX 001.6 [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] as per the request for supplementary information (RSI) adopted in

September 2019

17.5.2. Aclidinium - EKLIRA GENUAIR (CAP) - EMEA/H/C/002211/ANX 001.7

Applicant: AstraZeneca AB

PRAC Rapporteur: Adam Przybylkowski

Scope: MAH's response to ANX 001.6 [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] as per the request for supplementary information (RSI) adopted in September 2019

17.5.3. Aclidinium, formoterol fumarate dihydrate - BRIMICA GENUAIR (CAP) - EMEA/H/C/003969/ANX 003.4

Applicant: AstraZeneca AB

PRAC Rapporteur: Adam Przybylkowski

Scope: MAH's response to ANX 003.3 [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] as per the request for supplementary information (RSI) adopted in September 2019

17.5.4. Aclidinium, formoterol fumarate dihydrate - DUAKLIR GENUAIR (CAP) - EMEA/H/C/003745/ANX 003.4

Applicant: AstraZeneca AB

PRAC Rapporteur: Adam Przybylkowski

Scope: MAH's response to ANX 003.3 [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] as per the request for supplementary information (RSI) adopted in September 2019

17.5.5. Adalimumab - HUMIRA (CAP) - EMEA/H/C/000481/MEA 080.7

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Fifth annual interim report for P11-292 registry: a long-term non-interventional registry to assess safety and effectiveness of Humira (adalimumab) in paediatric patients with moderately to severely active Crohn's disease (CD) – CAPE

17.5.6. Ataluren - TRANSLARNA (CAP) - EMEA/H/C/002720/MEA 002.6

Applicant: PTC Therapeutics International Limited

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: MAH's response to MEA 002.5 [four-year interim report for study PTC124-GD-025o-DMD (listed as a category 3 study in the RMP): a post-approval registry observational study exploring the long-term of ataluren safety and effectiveness in usual care setting [final clinical study report (CSR) expected in April 2023]] as per the request for supplementary information (RSI) adopted in July 2019

17.5.7. Bedaquiline - SIRTURO (CAP) - EMEA/H/C/002614/MEA 010.5

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Sixth interim report for study TMC207TBC4002 (listed as a category 3 study in the RMP): a multi-country prospective multidrug resistant tuberculosis (MDR-TB) patient registry to monitor bedaquiline safety, utilisation, and emergence of resistance

17.5.8. Belimumab - BENLYSTA (CAP) - EMEA/H/C/002015/MEA 013.4

Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Interim report for study BEL114256/ HGS1006-C1101: a pregnancy register collecting information on pregnancy and live birth outcomes, and following infants for serious infections during the first year of life [final report submission extended from April 2019 to April 2022]

17.5.9. Cabozantinib - CABOMETYX (CAP) - EMEA/H/C/004163/MEA 001.2

Applicant: Ipsen Pharma

PRAC Rapporteur: Menno van der Elst

Scope: Interim report for study F-FR-60000-001 (CASSIOPE): a prospective non-interventional study of the utilisation of cabozantinib tablets in adults with advanced renal cell carcinoma (RCC) following prior vascular endothelial growth factor (VEGF)-targeted therapy in real life settings in terms of dose modifications due to adverse events (AEs) when used as a second line therapy or third and later line therapy

17.5.10. Estrogens conjugated, bazedoxifene - DUAVIVE (CAP) - EMEA/H/C/002314/MEA 003.7

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Martin Huber

Scope: MAH's response to MEA 003.6 [MAH's response to MEA 003.5 [second interim report for drug utilisation study (DUS) B2311061 on conjugated oestrogens/bazedoxifene (CE/BZA) in the European Union (EU) to describe baseline characteristics and utilisation patterns of EU patients initiating Duavive (CE/BZA) or oestrogen + progestin (E+P) combination hormone replacement therapy (HRT)]] as per the request for supplementary information (RSI) adopted in July 2019

17.5.11. Infliximab - REMICADE (CAP) - EMEA/H/C/000240/MEA 089.14

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Interim study report from the Swedish biologics register: Anti-Rheumatic Therapy In Sweden (ARTIS) [final report for ARTIS registry expected in October 2021]

17.5.12. Ketoconazole - KETOCONAZOLE HRA (CAP) - EMEA/H/C/003906/ANX 002.6

Applicant: HRA Pharma Rare Diseases

PRAC Rapporteur: Željana Margan Koletić

Scope: Second interim annual report for a prospective, multi-country, observational registry study to collect clinical information on patients with endogenous Cushing's syndrome exposed to ketoconazole using the existing European registry on Cushing's syndrome (ERCUSYN) to assess drug utilisation pattern and to document the safety (e.g. hepatotoxicity, QT prolongation) and effectiveness of ketoconazole

17.5.13. Neratinib - NERLYNX (CAP) - EMEA/H/C/004030/MEA 001

Applicant: Pierre Fabre Medicament

PRAC Rapporteur: Menno van der Elst

Scope: Interim report for study PUMA-NER-6201: an open-label study to characterize the incidence and severity of diarrhoea in patients with early stage human epidermal growth factor receptor 2 positive (HER2+) breast cancer treated with neratinib and intensive loperamide prophylaxis, with/without anti-inflammatory treatment (budesonide) and with/without a bile acid sequestrant (colestipol) [final study results expected in March 2021]

17.5.14. Ospemifene - SENSHIO (CAP) - EMEA/H/C/002780/ANX 001.8

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]

17.5.15. Rotavirus vaccine (live, oral) - ROTARIX (CAP) - EMEA/H/C/000639/MEA 094.1

Applicant: GlaxoSmithKline Biologicals S.A.

PRAC Rapporteur: Jean-Michel Dogné

Scope: Annual report for study EPI-ROTA-052 BOD EU SUPP (201433) (EuroRotaNet): an observational community-based strain surveillance study to monitor the potential emergence and spread of novel rotavirus strains throughout Europe [study extended until December 2020]

17.5.16. Sebelipase alfa - KANUMA (CAP) - EMEA/H/C/004004/ANX 001.3

Applicant: Alexion Europe SAS

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Fourth interim report for study ALX-LALD-501: a non-interventional, multicentre, prospective disease and clinical outcome registry of patients with lysosomal acid lipase deficiency (LAL-D) to further understand the disease, its progression and any associated complication, and to evaluate the long-term efficacy and safety of Kanuma (sebelipase alfa)

17.6. Others

17.6.1. Avatrombopag - DOPTELET (CAP) - EMEA/H/C/004722/MEA 002

Applicant: Dova Pharmaceuticals Ireland Limited

PRAC Rapporteur: Eva Segovia

Scope: Feasibility assessment for study AVA-CLD-402: evaluation of the feasibility of conducting a PASS of Doptelet (avatrombopag) in patients with severe chronic liver disease (CLD) and potential utilisation of data from TARGET PharmaSolutions' ongoing observational studies in patients with severe CLD

17.6.2. Fentanyl - INSTANYL (CAP) - EMEA/H/C/000959/LEG 028

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Ghania Chamouni

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

17.6.3. Lopinavir, ritonavir - KALETRA (CAP) - EMEA/H/C/000368/LEG 121.2

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Adrien Inoubli

Scope: Annual safety review in children aged from 14 days to 2 years as regards to chronic exposure to propylene glycol and ethanol and toxicity, medication errors and lack of efficacy/resistance in relation to potentially suboptimal pharmacokinetic (PK) parameters

17.7. New Scientific Advice

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

17.8. Ongoing Scientific Advice

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

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

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

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

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

18.1. Annual reassessments of the marketing authorisation

18.1.1. Idebenone - RAXONE (CAP) - EMEA/H/C/003834/S/0019 (without RMP)

Applicant: Santhera Pharmaceuticals (Deutschland) GmbH

PRAC Rapporteur: Amelia Cupelli

Scope: Annual reassessment of the marketing authorisation

18.1.2. Lomitapide - LOJUXTA (CAP) - EMEA/H/C/002578/S/0036 (without RMP)

Applicant: Amryt Pharmaceuticals DAC

PRAC Rapporteur: Menno van der Elst

Scope: Annual reassessment of the marketing authorisation

18.1.3. Mecasermin - INCRELEX (CAP) - EMEA/H/C/000704/S/0061 (without RMP)

Applicant: Ipsen Pharma

PRAC Rapporteur: Kirsti Villikka

Scope: Annual reassessment of the marketing authorisation

18.1.4. Metreleptin - MYALEPTA (CAP) - EMEA/H/C/004218/S/0009 (with RMP)

Applicant: Aegerion Pharmaceuticals B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Annual reassessment of the marketing authorisation

18.2. Conditional renewals of the marketing authorisation

18.2.1. Andexanet alfa - ONDEXXYA (CAP) - EMEA/H/C/004108/R/0004 (with RMP)

Applicant: Portola Netherlands B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Conditional renewal of the marketing authorisation

18.2.2. Autologous CD34⁺ cell enriched population that contains hematopoietic stem cells transduced with lentiglobin BB305 lentiviral vector encoding the beta-A-T87Q-globin gene - ZYNTEGLO (CAP) - EMEA/H/C/003691/R/0005 (without RMP)

Applicant: bluebird bio (Netherlands) B.V, ATMP[68]

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Conditional renewal of the marketing authorisation

18.2.3. Delamanid - DELTYBA (CAP) - EMEA/H/C/002552/R/0041 (without RMP)

Applicant: Otsuka Novel Products GmbH

PRAC Rapporteur: Jean-Michel Dogné

Scope: Conditional renewal of the marketing authorisation

18.2.4. Pandemic influenza vaccine (H5N1) (live attenuated, nasal) - PANDEMIC INFLUENZA VACCINE H5N1 ASTRAZENECA (CAP) - EMEA/H/C/003963/R/0031 (without RMP)

Applicant: AstraZeneca AB

PRAC Rapporteur: Sonja Hrabcik

Scope: Conditional renewal of the marketing authorisation

18.2.5. Rucaparib - RUBRACA (CAP) - EMEA/H/C/004272/R/0016 (without RMP)

Applicant: Clovis Oncology Ireland Limited

PRAC Rapporteur: Annika Folin

Scope: Conditional renewal of the marketing authorisation

[68] Advanced therapy medicinal product

18.2.6. Volanesorsen - WAYLIVRA (CAP) - EMEA/H/C/004538/R/0003 (without RMP)

Applicant: Akcea Therapeutics Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: Conditional renewal of the marketing authorisation

18.3. Renewals of the marketing authorisation

18.3.1. Aripiprazole - ARIPIPRAZOLE ZENTIVA (CAP) - EMEA/H/C/003899/R/0012 (with RMP)

Applicant: Zentiva, k.s.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: 5-year renewal of the marketing authorisation

18.3.2. Asfotase alfa - STRENSIQ (CAP) - EMEA/H/C/003794/R/0044 (without RMP)

Applicant: Alexion Europe SAS

PRAC Rapporteur: Rhea Fitzgerald

Scope: 5-year renewal of the marketing authorisation

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

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Adrien Inoubli

Scope: 5-year renewal of the marketing authorisation

18.3.4. Bortezomib - BORTEZOMIB ACCORD (CAP) - EMEA/H/C/003984/R/0022 (without RMP)

Applicant: Accord Healthcare S.L.U.

PRAC Rapporteur: Amelia Cupelli

Scope: 5-year renewal of the marketing authorisation

18.3.5. Empagliflozin, metformin - SYNJARDY (CAP) - EMEA/H/C/003770/R/0044 (with RMP)

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Eva Segovia

Scope: 5-year renewal of the marketing authorisation

18.3.6. Evolocumab - REPATHA (CAP) - EMEA/H/C/003766/R/0040 (without RMP)

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Kimmo Jaakkola

Scope: 5-year renewal of the marketing authorisation

18.3.7. Ivabradine - IVABRADINE ANPHARM (CAP) - EMEA/H/C/004187/R/0014 (with RMP)

Applicant: ANPHARM Przedsiebiorstwo Farmaceutyczne S.A.

PRAC Rapporteur: Menno van der Elst

Scope: 5-year renewal of the marketing authorisation

18.3.8. Lorlatinib - LORVIQUA (CAP) - EMEA/H/C/004646/R/0004 (without RMP)

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: 5-year renewal of the marketing authorisation

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

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: 5-year renewal of the marketing authorisation

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

Applicant: Mylan S.A.S

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: 5-year renewal of the marketing authorisation

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

Applicant: Mylan S.A.S

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: 5-year renewal of the marketing authorisation

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

Applicant: Sandoz GmbH

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: 5-year renewal of the marketing authorisation

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

Applicant: Sandoz GmbH

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: 5-year renewal of the marketing authorisation

18.3.14. Pregabalin - PREGABALIN ZENTIVA (CAP) - EMEA/H/C/003900/R/0021 (with RMP)

Applicant: Zentiva k.s.

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: 5-year renewal of the marketing authorisation

18.3.15. Roflumilast - DAXAS (CAP) - EMEA/H/C/001179/R/0039 (without RMP)

Applicant: AstraZeneca AB

PRAC Rapporteur: Maria del Pilar Rayon

Scope: 5-year renewal of the marketing authorisation

18.3.16. Sonidegib - ODOMZO (CAP) - EMEA/H/C/002839/R/0028 (without RMP)

Applicant: Sun Pharmaceutical Industries Europe B.V.

PRAC Rapporteur: Željana Margan Koletić

Scope: 5-year renewal of the marketing authorisation

18.3.17. Tolvaptan - JINARC (CAP) - EMEA/H/C/002788/R/0027 (without RMP)

Applicant: Otsuka Pharmaceutical Netherlands B.V.

PRAC Rapporteur: Amelia Cupelli

Scope: 5-year renewal of the marketing authorisation

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

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

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: 5-year renewal of the marketing authorisation

19. Annex II – List of participants

including any restrictions with respect to involvement of members / alternates / experts following evaluation of declared interests for the 13-16 January 2020 meeting.

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Sabine Straus	Chair	The Netherlands	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Jan Neuhauser	Member	Austria	No interests declared	Full involvement
Jean-Michel Dogné	Member	Belgium	No interests declared	Full involvement
Laurence de Fays	Alternate	Belgium	No participation in final deliberations and voting on:	4.3.8. Prasugrel – EFIENT (CAP) 17.5.9. Cabozantinib - CABOMETYX (CAP) 18.1.3. Mecasermin - INCRELEX (CAP)
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
Panagiotis Psaras	Alternate	Cyprus	No interests declared	Full involvement
Jana Lukacisinova	Alternate	Czech Republic	No interests declared	Full involvement
Anette Stark	Member	Denmark	No interests declared	Full involvement
Hans Christian Siersted	Alternate	Denmark	No restrictions applicable to this meeting	Full involvement
Maia Uusküla	Member	Estonia	No interests declared	Full involvement
Kirsti Villikka	Member	Finland	No interests declared	Full involvement
Kimmo Jaakkola	Alternate	Finland	No interests declared	Full involvement
Ghania Chamouni	Member	France	No participation in discussion, final deliberations and voting on:	4.2.2. Fluoroquinolones for systemic and inhalation use 16.1.28. Levofloxacin - QUINSAIR (CAP)

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Adrien Inoubli	Alternate	France	No interests declared	Full involvement
Martin Huber	Member (Vice-Chair)	Germany	No interests declared	Full involvement
Brigitte Keller-Stanislawski	Alternate	Germany	No interests declared	Full involvement
Sophia Trantza	Alternate	Greece	No participation in discussion, final deliberations and voting on:	4.3.8. Prasugrel – EFIENT (CAP), PRASUGREL MYLAN (CAP), NAP
Julia Pallos	Member	Hungary	No interests declared	Full involvement
Melinda Palfi	Alternate - via telephone*	Hungary	No interests declared	Full involvement
Rhea Fitzgerald	Member	Ireland	No restrictions applicable to this meeting	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
John Joseph Borg	Member	Malta	No interests declared	Full involvement
Benjamin Micallef	Alternate	Malta	No interests declared	Full involvement
Menno van der Elst	Member	Netherlands	No interests declared	Full involvement
Liana Gross-Martirosyan	Alternate	Netherlands	No interests declared	Full involvement
David Olsen	Member	Norway	No participation in final	3.4.1. Estradiol (NAP) 4.2.2.

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			deliberations and voting on:	Fluoroquinolones 4.3.6. Hormone replacement therapy (HRT) 6.3.6. Moxifloxacin (NAP)
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
Michal Radik	Member	Slovakia	No participation in discussion, final deliberations and voting on:	4.3.8. Prasugrel – EFIENT (CAP), PRASUGREL MYLAN (CAP), NAP
Jasmina Klopcic	Alternate	Slovenia	No interests declared	Full involvement
Eva Segovia	Member	Spain	No interests declared	Full involvement
Maria del Pilar Rayon	Alternate	Spain	No interests declared	Full involvement
Ulla Wändel Liminga	Member	Sweden	No interests declared	Full involvement
Annika Folin	Alternate	Sweden	No interests declared	Full involvement
Julie Williams	Member	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 final deliberations and voting on:	4.3.8. Prasugrel – EFIENT (CAP), PRASUGREL MYLAN (CAP), NAP 16.1.38.

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				Obeticholic acid - OCALIVA (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:	4.3.8. Prasugrel – EFIENT (CAP), PRASUGREL MYLAN (CAP), NAP
Cathalijne van Doorne	Member	Patients' Organisation Representative	No interests declared	Full involvement
Virginie Hivert	Alternate	Patients' Organisation Representative	No restrictions applicable to this meeting	Full involvement
Mirjam Hinterleitner	Expert - via telephone*	Austria	No interests declared	Full involvement
Margareta Bego	Expert - via telephone*	Croatia	No interests declared	Full involvement
Ivona Bahnik Bišević	Expert - via telephone*	Croatia	No restrictions applicable to this meeting	Full involvement
Ivana Ljubičić	Expert - via telephone*	Croatia	No restrictions applicable to this meeting	Full involvement
Magdalena Fabianova	Expert - in person*	Czech Republic	No interests declared	Full involvement
Helle Esbjørn Kristensen	Expert - via telephone*	Denmark	No interests declared	Full involvement
Krõõt Aab	Expert - in person*	Estonia	No interests declared	Full involvement
Benjamin Burrus	Expert - via telephone*	France	No interests declared	Full involvement
Samuel Crommelynck	Expert - via telephone*	France	No restrictions applicable to this meeting	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Nathalie Dumarcet	Expert - in person*	France	No interests declared	Full involvement
Bilal Majed	Expert - via telephone*	France	No restrictions applicable to this meeting	Full involvement
Nicole Bick	Expert - via telephone*	Germany	No interests declared	Full involvement
Dennis Lex	Expert - in person*	Germany	No participation in final deliberations and voting on:	Full involvement
Wiebke Seemann	Expert - via telephone*	Germany	No interests declared	Full involvement
Grainne Kirwan	Expert - in person*	Ireland	No interests declared	Full involvement
Aine McKenna	Expert - via telephone*	Ireland	No interests declared	Full involvement
Robert Nistico	Expert - via telephone*	Malta	No restrictions applicable to this meeting	Full involvement
Ineke (HJMJ) Crijns	Expert - in person*	Netherlands	No interests declared	Full involvement
Lies van Vlijmen (Liesbeth Van Vlijmen)	Expert - in person*	Netherlands	No interests declared	Full involvement
Eva Cantarero de la Barrera	Expert - in person*	Spain	No interests declared	Full involvement
Charlotte Backman	Expert - in person*	Sweden	No interests declared	Full involvement
Robert Hägerkvist	Expert - via telephone*	Sweden	No interests declared	Full involvement
Helena Möllby	Expert - via telephone*	Sweden	No interests declared	Full involvement
A representative from the European Commission attended the meeting				
Meeting run with support from relevant EMA staff				

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

20. Annex III - List of acronyms and abbreviations

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

21. Explanatory notes

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

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

(Items 2 and 3 of the PRAC minutes)

A referral is a procedure used to resolve issues such as concerns over the safety or benefit-risk balance of a medicine or a class of medicines. In a referral, the EMA is requested to conduct a scientific assessment of a particular medicine or class of medicines on behalf of the European Union (EU). For further detailed information on safety related referrals please see:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000150.jsp&mid=WC0b01ac05800240d0

Signals assessment and prioritisation

(Item 4 of the PRAC minutes)

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

Risk Management Plans (RMPs)

(Item 5 of the PRAC minutes)

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

Assessment of Periodic Safety Update Reports (PSURs)

(Item 6 of the PRAC minutes)

A PSUR is a report providing an evaluation of the benefit-risk balance of a medicine, which is submitted by marketing authorisation holders at defined time points following a medicine's authorisation.

PSURs summarises data on the benefits and risks of a medicine and includes the results of all studies carried out with this medicine (in the authorised and unauthorised indications).

Post-authorisation Safety Studies (PASS)

(Item 7 of the PRAC minutes)

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

Product related pharmacovigilance inspections

(Item 9 of the PRAC minutes)

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

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