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Pharmacovigilance Risk Assessment Committee (PRAC) Minutes of the meeting on 11 – 14 May 2020

Chair: Sabine Straus – Vice-Chair: Martin Huber

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

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1. Introduction

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

The Chairperson opened the 11–14 May 2020 meeting by welcoming all participants. In light of the current crisis (COVID-19 outbreak), the EMA Business Continuity Plan (BCP) and exceptional measures taken to protect the staff members and all delegates, experts and members of the Committee are maintained. This entails that the participation and the voting from remote are allowed, based on the current exceptional circumstances. In light of the unanimous agreement of all members to hold the meeting in a virtual mode, the Chair confirmed the validity of the notice of the meeting and proceeded to welcome the new members and alternates.

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

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

The PRAC Chairperson announced that Livia Puljak resigned as an independent scientific expert member nominated by the European Commission (EC) after the last plenary meeting. The position is vacant until a new nomination is granted from the EC. In addition, the Chair announced that Ghania Chamouni, the member for France, was to step down after the current plenary meeting. The PRAC thanked her for her valuable contribution to the work of the Committee.

1.2. Agenda of the meeting on 11 – 14 May 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 14 - 17 April 2020

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

Post-meeting note: the PRAC minutes of the meeting held on 14-17 April 2020 were published on the EMA website on 14 October 2020 ([EMA/PRAC/546361/2020](#)).

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

2.1. Newly triggered procedures

None

2.2. Ongoing procedures

None

2.3. Procedures for finalisation

None

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

3.1. Newly triggered procedures

None

3.2. Ongoing procedures

None

3.3. Procedures for finalisation

3.3.1. Leuprorelin¹ (NAP) – EMEA/H/A-31/1486

Applicant(s): various

PRAC Rapporteur: Željana Margan Koletić; PRAC Co-rapporteur: Eva Segovia

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

Background

A referral procedure under Article 31 of Directive 2001/83/EC for leuprorelin-containing products is to be concluded. The procedure reviewed handling errors during preparation and administration of the products in order to further characterise and mitigate the risk of handling errors and associated risk of lack of efficacy for leuprorelin-containing depot products. A final assessment of the data submitted was produced by the Rapporteurs according to the agreed timetable. For further background, see [PRAC minutes June 2019](#), [PRAC minutes November 2019](#)² and [PRAC minutes March 2020](#).

Discussion

¹ Depot formulation(s)

² Held 28 – 31 October 2019

The PRAC discussed the conclusions reached by the Rapporteurs.

The PRAC considered the totality of the data submitted for leuprorelin-containing depot medicinal products with regards to medication errors, the discussion on the steps of the reconstitution process and the effectiveness of the risk minimisation measures in place. This included the responses submitted by the MAHs in writing as well as data obtained by a EudraVigilance analysis.

The PRAC noted the established efficacy of leuprorelin-containing medicinal products in their approved indications, if they are used in accordance with the terms of the marketing authorisations and administered correctly. The PRAC confirmed the risk of medication errors associated with incorrect reconstitution and administration process of these medicinal products. The PRAC noted that these medication errors might lead in some cases to underdosing and consequently a lack of efficacy. In addition, the data indicated that medicinal products which require a higher number of reconstitution steps in their preparation and administration have a higher risk of medication errors. With regard to Eligard (leuprorelin) specifically, the medicinal product with the highest number of reconstitution steps, medication errors continued to be reported despite several risk minimisation activities in place over the years. Therefore, the PRAC considered that the most effective measure to minimise medication errors associated with Eligard (leuprorelin) is to replace the administration device with a new one, requiring fewer reconstitution steps. Until the new administration device for Eligard (leuprorelin) becomes available, the PRAC considered that emphasis should be put on the careful following of the instructions for reconstitution and administration, by updating the product information. As for Lutrate Depot (leuprorelin) and associated names, the PRAC noted that most of the medication errors reported for the products concern a specific step of the preparation process, and concluded that the product information should be revised to clarify the instructions for this step and the packaging of the medicinal products should be modified in order to facilitate the access to instructions to healthcare professionals (HCPs).

In view of the number of reported medication errors performed by patients, given the complexity of the reconstitution process of leuprorelin-containing depot medicinal products, the PRAC was of the view that these medicinal products should not be self-administered and be prepared and administered only by HCPs who are familiar with these procedures.

The PRAC agreed that medication errors resulting in lack of efficacy should be monitored as a safety issue of special concern through future PSURs and should be added as an important identified risk in existing RMPs. In addition, the frequency of PSUR submission should be revised from five-yearly to two-yearly and the next PSUR should be submitted to EMA within 90 days of the data lock point. The list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC has been updated accordingly.

The Committee considered that the benefit-risk balance of leuprorelin-containing depot medicinal products remains favourable subject to the agreed conditions³ to the marketing authorisations and taking into account the agreed amendments to the product information and other risk minimisation measures.

Summary of recommendation(s)/conclusions

³ MAH Astellas should replace the current Eligard (leuprorelin) drug device combination product with a new one with the objective of reducing the risk of medication errors

- The PRAC adopted a recommendation to vary⁴ the terms of the marketing authorisations of leuprorelin-containing depot medicinal products to be considered by CMDh for a position – see EMA Press Release ([EMA/250923/2020](#)) entitled 'Leuprorelin depot medicines: PRAC recommends new measures to avoid handling errors' published on 15 June 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 'New measures to avoid handling errors with leuprorelin depot medicines' ([EMA/330921/2020](#)) representing the position adopted by the CMDh was published on the EMA website on 26 June 2020.

Post-meeting note 2: the PRAC assessment report ([EMA/397961/2020](#)) was published on 29 July 2020.

3.4. Re-examination procedures⁵

None

3.5. Others

None

4. Signals assessment and prioritisation⁶

4.1. New signals detected from EU spontaneous reporting systems

See also Annex I 14.1.

4.1.1. Mirtazapine (NAP)

Applicant(s): various

PRAC Rapporteur: Liana Gross-Martirosyan

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

EPITT 19565 – New signal

Lead Member State(s): NL

Background

Mirtazapine is an antidepressant indicated for the treatment of episodes of major depression.

The exposure for mirtazapine is estimated to have been more than 21.8 million patient-years worldwide, in the period from first authorisation in 1994 to 2018.

⁴ Update of SmPC section 4.2 for all leuprorelin-containing depot medicinal products. Update of SmPC sections 4.2 and 4.4 for Eligard (leuprorelin). Update of SmPC section 6.6 for Lutrate Depot (leuprorelin) and associated names. The package leaflets are updated accordingly

⁵ Re-examination of PRAC recommendation under Article 32 of Directive 2001/83/EC

⁶ Each signal refers to a substance or therapeutic class. The route of marketing authorisation is indicated in brackets (CAP for Centrally Authorised Products; NAP for Nationally Authorised Products including products authorised via Mutual Recognition Procedures and Decentralised Procedure). Product names are listed for reference Centrally Authorised Products (CAP) only. PRAC recommendations will specify the products concerned in case of any regulatory action required

During routine signal detection activities, a signal of drug reaction with eosinophilia and systemic symptoms (DRESS) was identified by the Netherlands, based on 18 cases retrieved from EudraVigilance data. The Netherlands as the lead Member State (LMS) for mirtazapine confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the available evidence from the EudraVigilance cases of DRESS and agreed that there is sufficient evidence for a causal association between mirtazapine treatment and the occurrence of DRESS. The PRAC agreed that the product information should be updated accordingly.

The PRAC appointed Liana Gross-Martirosyan as Rapporteur for the signal.

Summary of recommendation(s)

- The MAHs for mirtazapine-containing products should submit to the relevant National Competent Authorities (NCAs) of the Member States, within 60 days, a variation for amending the product information⁷.

For the full PRAC recommendation, see [EMA/PRAC/257435/2020](#) published on 23/06/2020 on the EMA website.

4.2. New signals detected from other sources

None

4.3. Signals follow-up and prioritisation

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

Applicant(s): Portola Netherlands B.V.

PRAC Rapporteur: Menno van der Elst

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

EPITT 19493 – Follow-up to April 2020

Background

For background information, see [PRAC minutes December 2019](#)⁸ and [PRAC minutes April 2020](#).

Based on data from EudraVigilance, literature and data from the MAH of Ondexxya (andexanet alfa), the PRAC agreed in April 2020 that the product information should be updated to reflect the risk of erroneous assay results obtained with commercial anti-factor Xa (anti-FXa) activity assays for levels of anti-FXa activity. In addition, the PRAC requested the MAH to submit a proposal for direct healthcare professional communication (DHPC) along with a communication plan.

Discussion

⁷ Update of SmPC sections 4.4 and 4.8. The package leaflet is to be updated accordingly

⁸ Held 25-28 November 2019

At the current meeting, the PRAC reviewed and agreed on the content of the DHPC and a communication plan in order to highlight to prescribers that commercial anti-FXa activity assays are unsuitable for measuring anti-FXa activity following administration of andexanet alfa.

Summary of recommendation(s)

- The MAH for Ondexxya (andexanet alfa) should distribute a [DHPC](#) in line with the agreed communication plan for its distribution.

For the full PRAC recommendation, see [EMA/PRAC/257435/2020](#) published on 23/06/2020 on the EMA website.

4.3.2. Baricitinib - OLUMIANT (CAP) - EMEA/H/C/004085/SDA/010

Applicant(s): Eli Lilly Nederland B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Signal of diverticulitis

EPITT 19496 – Follow-up to January 2020

Background

For background information, see [PRAC minutes January 2020](#).

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

Discussion

Having considered the available evidence, including the review provided by the MAH, the PRAC agreed that there is sufficient evidence to establish an association between treatment with baricitinib and the occurrence of diverticulitis. Therefore, the PRAC agreed that the product information should be updated accordingly.

Summary of recommendation(s)

- The MAH for Olumiant (baricitinib) should submit to EMA, within 60 days, a variation for amending the product information⁹.

For the full PRAC recommendation, see [EMA/PRAC/257435/2020](#) published on 23/06/2020 on the EMA website.

- 4.3.3. Buprenorphine – BUVIDAL (CAP) - EMEA/H/C/004651/SDA 002, SIXMO (CAP) - EMEA/H/C/004743/SDA 003, NAP; buprenorphine, naloxone – SUBOXONE (CAP) - EMEA/H/C/000697/SDA 028, ZUBSOLV (CAP), NAP;**
Selective serotonin reuptake inhibitors (SSRIs): citalopram (NAP); escitalopram (NAP); fluvoxamine (NAP); fluoxetine (NAP); paroxetine (NAP); sertraline (NAP); Serotonin norepinephrine reuptake inhibitors (SNRIs): desvenlafaxine (NAP); duloxetine – CYMBALTA (CAP), DULOXETINE LILLY (CAP), DULOXETINE MYLAN (CAP), DULOXETINE ZENTIVA (CAP), XERISTAR (CAP), YENTREVE (CAP), NAP; milnacipran (NAP); venlafaxine (NAP); Tricyclic antidepressants (TCAs): amitriptyline (NAP); clomipramine (NAP); doxepin (NAP); imipramine (NAP); nortriptyline (NAP); trimipramine (NAP);

⁹ Update of SmPC sections 4.4 and 4.8. The package leaflet is to be updated accordingly

Monoamine oxidase inhibitors (MAOIs): isocarboxazid (NAP); phenelzine (NAP); selegiline (NAP); tranylcypramine (NAP);
Other psychiatric medicines: amoxapine (NAP); buspirone (NAP); lithium (NAP); maprotiline (NAP); mirtazapine (NAP); trazodone (NAP);
Serotonin receptor agonists: almotriptan (NAP); frovatriptan (NAP); naratriptan (NAP); rizatriptan (NAP); sumatriptan (NAP); zolmitriptan (NAP);
Antiemetics: granisetron - SANCUSO (CAP), NAP; ondansetron (NAP); palonosetron – ALOXI (CAP), PALONOSETRON ACCORD (CAP), NAP; netupitant, palonosetron – AKYNZEO (CAP); tropisetron (NAP);
Other serotonergic drugs: cyclobenzaprine (NAP); dextromethorphan (NAP); hypericum perforatum (NAP); linezolid (NAP); methylene blue (NAP); tryptophan (NAP)

Applicant(s): Accord Healthcare S.L.U. (Palonosetron Accord), Camurus AB (Buvidal), Eli Lilly Nederland B.V. (Cymbalta, Duloxetine Lilly, Xeristar, Yentreve), Helsinn Birex Pharmaceuticals (Aloxi, Akynzeo), Indivior Europe Limited (Suboxone), Kyowa Kirin Holdings B.V. (Sancuso), L. Molteni & C. dei Fratelli Alitti (Sixmo), Mundipharma Corporation (Nyxoid), Mylan S.A.S (Duloxetine Mylan), Orexo AB (Zubsolv), Zentiva k.s. (Duloxetine Zentiva), various

PRAC Rapporteur: Martin Huber

Scope: Signal of drug-drug interaction between buprenorphine and serotonergic drugs leading to serotonin syndrome

EPITT 19475 – Follow-up to March 2020

Background

For background information, see [PRAC minutes November 2019](#)¹⁰ and [PRAC minutes March 2020](#).

The MAHs for Sixmo (buprenorphine), Buvidal (buprenorphine) and Suboxone (buprenorphine/naloxone) replied to the request for information on the signal of drug-drug interaction between buprenorphine and serotonergic drugs leading to serotonin syndrome and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence, including the responses from the MAHs on the risk of serotonin syndrome following interaction between buprenorphine and other serotonergic drugs, the PRAC agreed that an association is possible and agreed that the product information of buprenorphine-containing products should be updated accordingly.

Summary of recommendation(s)

- The MAHs for buprenorphine- and buprenorphine/naloxone-containing products should submit to EMA or to the relevant National Competent Authorities (NCAs) of the Member States, within 60 days, a variation for amending the product information¹¹.

For the full PRAC recommendation, see [EMA/PRAC/257435/2020](#) published on 23/06/2020 on the EMA website.

¹⁰ Held 28-31 October 2019

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

4.3.4. Dabrafenib – TAFINLAR (CAP) - EMEA/H/C/002604/SDA/016; trametinib – MEKINIST (CAP) - EMEA/H/C/002643/SDA/011

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Annika Folin

Scope: Signal of disseminated intravascular coagulation (DIC)

EPITT 19510 – Follow-up to January 2020

Background

For background information, see [PRAC minutes January 2020](#).

The MAH for Tafinlar (dabrafenib) and Mekinist (trametinib) replied to the request for information on the signal of disseminated intravascular coagulation (DIC) and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence from clinical trials and the literature provided by the MAH for Tafinlar (dabrafenib) and Mekinist (trametinib), the PRAC agreed that the number of cases without possible confounding factors is low and that a causal relationship between treatment with dabrafenib and trametinib and disseminated intravascular coagulation cannot be established at the moment. Therefore, the PRAC agreed that no further regulatory action was warranted at this stage.

Summary of recommendation(s)

- The MAH for Tafinlar (dabrafenib) and Mekinist (trametinib) should continue to monitor cases of DIC as part of routine safety surveillance.

4.3.5. Dipeptidyl peptidase-4 (DPP4) inhibitors: alogliptin - VIPIDIA (CAP) - EMEA/H/C/002182/SDA/012.1; alogliptin, metformin hydrochloride - VIPDOMET (CAP) - EMEA/H/C/002654/SDA/009.1; alogliptin, pioglitazone - INCRESYNC (CAP) - EMEA/H/C/002178/SDA/009.1; linagliptin - TRAJENTA (CAP) - EMEA/H/C/002110/SDA/019.1; saxagliptin - ONGLYZA (CAP) - EMEA/H/C/001039/SDA/044.1; saxagliptin, dapagliflozin - QTERN (CAP) - EMEA/H/C/004057/SDA/007.1; saxagliptin, metformin hydrochloride - KOMBOGLYZE (CAP) - EMEA/H/C/002059/SDA/019.1; sitagliptin - JANUVIA (CAP) - EMEA/H/C/000722/SDA/039.1, RISTABEN (CAP) - EMEA/H/C/001234/SDA/017.1, TESAVEL (CAP) - EMEA/H/C/000910/SDA/033.1, XELEVIA (CAP) - EMEA/H/C/000762/SDA/038.1; NAP; sitagliptin, ertugliflozin – STEGLUJAN (CAP); sitagliptin, metformin – EFFICIB (CAP); JANUMET (CAP); VELMETIA (CAP); NAP; vildagliptin - GALVUS (CAP) - EMEA/H/C/000771/SDA/048.1, JALRA (CAP) - EMEA/H/C/001048/SDA/032.1, XILIXARX (CAP) - EMEA/H/C/001051/SDA/032.1; vildagliptin, metformin hydrochloride - EUCREAS (CAP) - EMEA/H/C/000807/SDA/026.1, ICANDRA (CAP) - EMEA/H/C/001050/SDA/024.1, ZOMARIST (CAP) - EMEA/H/C/001049/SDA/024.1; 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 (Incesync, 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 January 2020

Background

For background information, see [PRAC minutes September 2019](#) and [PRAC minutes January 2020](#).

The MAH for alogliptin-containing products (Incesync (alogliptin/pioglitazone), Vipidia (alogliptin) and Vipdomet (alogliptin/metformin)) and the MAH for vildagliptin-containing products (Eucreas/Icandra/Zomarist (vildagliptin/metformin) and Galvus/Jalra/Xiliarx (vildagliptin)) replied to the request for information on the signal of rhabdomyolysis and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence, the PRAC agreed that for alogliptin and vildagliptin a causal relationship with the development of rhabdomyolysis cannot be excluded but the evidence is insufficient at present. With regard to saxagliptin, linagliptin and sitagliptin, the PRAC confirmed its conclusion dated January 2020 that there is at present insufficient evidence to support a causal relationship with rhabdomyolysis/myopathy, or an interaction between these dipeptidyl peptidase-4 (DPP4)-inhibitors and statins.

Summary of recommendation(s)

- The MAH for vildagliptin-containing products (including fixed dose combinations) should further monitor cases of rhabdomyolysis in the next PSUR¹² and include rhabdomyolysis as part of the important potential risk of ‘muscle events/myopathy with and without concurrent statin use’ of the list of safety concerns. The MAHs for all other DPP4-inhibitors: saxagliptin-, linagliptin-, sitagliptin- and alogliptin-containing products (including fixed dose combinations) should continue monitoring this issue in the next PSURs and review any new cases.

For the full PRAC recommendation, see [EMA/PRAC/257435/2020](#) published on 23/06/2020 on the EMA website.

4.3.6. Fluoroquinolones: ciprofloxacin (NAP); delafloxacin – QUOFENIX (CAP); levofloxacin – QUINSAIR (CAP), NAP; lomefloxacin (NAP); moxifloxacin (NAP); norfloxacin (NAP); ofloxacin (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, cervical artery dissection, and aortic aneurysm and dissection

EPITT 19522 – Follow-up to January 2020

Background

¹² Data lock point (DLP): 28/02/2021

For background information, see [PRAC minutes January 2020](#).

The Rapporteur conducted a thorough literature review and EMA performed a search in EudraVigilance and the reviews were assessed by the Rapporteur.

Discussion

Having considered the evidence from case reports in EudraVigilance and from the literature review regarding the risk of heart valve regurgitation/incompetence and of aortic aneurysm and dissection associated with the use of fluoroquinolones (systemic and inhalation formulations), the PRAC agreed that further regulatory action and communication are warranted to inform patients and healthcare professionals on these risks.

Summary of recommendation(s)

- The MAHs for originator fluoroquinolone-containing products for systemic and inhalation use, namely Bayer (ciprofloxacin, moxifloxacin), Sanofi (levofloxacin, ofloxacin), Neuraxpharm (norfloxacin), Meda Pharma (lomefloxacin), Sandoz (pefloxacin); Angelini (prulifloxacin), Lanova Farmaceutici (rufloxacin), A. Menarini (delafloxacin), Horizon Pharma Europe (levofloxacin) should submit to EMA, within 30 days, comments on a proposed update of the product information and on a key elements for a direct healthcare professional communication (DHPC) and a communication plan.
- The PRAC will assess the responses from MAHs within a 30-days timetable, leading to a further PRAC recommendation.
- The MAHs of fluoroquinolone-containing products for systemic and inhalation use should closely monitor in future PSURs cases of fluoroquinolones-induced disorders of arteries other than the aorta.

For the full PRAC recommendation, see [EMA/PRAC/257435/2020](#) published on 23/06/2020 on the EMA website.

4.3.7. Hormone replacement therapy (HRT): chlorotrianisene (NAP); conjugated estrogens (NAP); conjugated estrogens, bazedoxifene - DUAVIVE (CAP) - EMEA/H/C002314/SDA 005; dienestrol (NAP); diethylstilbestrol (NAP); estradiol (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 March 2020

Background

For background information, see [PRAC minutes October 2019](#)¹³, [PRAC minutes January 2020](#) and [PRAC minutes March 2020](#).

The MAHs IBSA Farmaceutici Italia s.r.l., Mylan, Pierre Fabre Medicament, Pfizer Limited, Pharmachemie B.V./Teva, Aurobindo Pharma Ltd., Abiogen Pharma S.p.A., Biose France, Orifarm Generics A/S, Norgine, Laboratorio Aldo-Unión, S.L., Mithra Pharmaceuticals, Novo

¹³ Held 30 September – 03 October 2019

Nordisk A/S, Bayer AG, Theramex, Gedeon Richter Plc., ITF Hellas Pharmaceuticals, PharmaSwiss Česká republika s.r.o./Bausch Health Poland Sp. z o.o., Effik, Orion Pharma, Merck Sharp & Dohme (Europe) Inc., Laboratoire CCD, and Pfizer Europe MA EEIG for Duavive (conjugated oestrogens/bazedoxifene) replied to the request for comments on the proposed update of the product information regarding the signal of new information on the known risk of breast cancer and the responses were assessed by the Rapporteur.

Discussion

Having considered the results from the large meta-analysis¹⁴, as well as the MAHs' comments, the PRAC agreed that the study provides relevant new information regarding the known risk of breast cancer that justifies a revision of the current product information of hormone replacement therapy (HRT) products.

Summary of recommendation(s)

- The MAHs for oestrogen only and combined oestrogen-progestagen HRT-products, MAHs for HRT-products which are vaginally applied oestrogens of which the systemic exposure remains within postmenopausal range, the MAH for Duavive (conjugated oestrogens/bazedoxifene) and the MAHs of tibolone-containing products should submit to EMA or to the relevant National Competent Authorities (NCAs) of the Member States, within 90 days, a variation to amend the product information¹⁵.

For the full PRAC recommendation, see [EMA/PRAC/257435/2020](#) published on 23/06/2020 on the EMA website.

Post-meeting note: the revised core SmPC for hormone replacement therapy products ([CMDh/131/2003 Rev. 7](#)) and revised core package leaflet for hormonal replacement therapy products ([CMDh/240/2011, Rev.5](#)) agreed by the CMDh on 07 June 2020 were published on the HMA/CMDh webpage on 05 August 2020.

4.3.8. Mirtazapine (NAP)

Applicant(s): various

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Signal of amnesia

EPITT 19506 – Follow-up to January 2020

Background

For background information, see [PRAC minutes January 2020](#).

The MAH Merck Sharp & Dohme B.V. for the originator mirtazapine-containing product replied to the request for information on the signal of amnesia and the responses were assessed by the Rapporteur.

Discussion

Having considered the available data, including the review provided by the MAH, the PRAC agreed that there is sufficient evidence to establish a causal association between the use of

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 Sep 28;394(10204):1159-1168

¹⁵ Update of SmPC sections 4.4 and 4.8. The package leaflets are to be updated accordingly

mirtazapine-containing products and the risk of amnesia. Therefore, the PRAC agreed that the product information should be updated accordingly.

Summary of recommendation(s)

- The MAHs for mirtazapine-containing products should submit to the relevant National Competent Authorities (NCAs) of the Member States, within 60 days, a variation to amend the product information¹⁶.

For the full PRAC recommendation, see [EMA/PRAC/257435/2020](#) published on 23/06/2020 on the EMA website.

4.3.9. Sertraline (NAP)

Applicant(s): various

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Signal of microscopic colitis

EPITT 19513 – Follow-up to January 2020

Background

For background information, see [PRAC minutes January 2020](#).

The MAH Pfizer for the originator sertraline-containing product replied to the request for information on the signal of microscopic colitis and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence from EudraVigilance and the literature, including the review provided by the MAH, the PRAC agreed that there is sufficient evidence for an association between the use of sertraline and the occurrence of microscopic colitis. The PRAC agreed that the product information should be updated accordingly.

Summary of recommendation(s)

- The MAH for sertraline-containing products should submit to the relevant National Competent Authorities (NCAs) of the Member States, within 60 days, a variation to amend¹⁷ the product information.

For the full PRAC recommendation, see [EMA/PRAC/257435/2020](#) published on 23/06/2020 on the EMA website.

4.4. Variation procedure(s) resulting from signal evaluation

4.4.1. Cobicistat - TYBOST (CAP) - EMEA/H/C/002572/II/0054

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Update of sections 4.4 and 4.5 of the SmPC in order to add a new contraindication regarding drug-drug interactions between cobicistat-containing products and

¹⁶ Update of SmPC section 4.8. The package leaflet is to be updated accordingly

¹⁷ Update of SmPC section 4.8. The package leaflet is to be updated accordingly

thienopyridines, based on a cumulative safety review conducted by the MAH and related to the final signal recommendation adopted in May 2019 (EPITT 19325) regarding the interaction of clopidogrel with boosted antiviral human immunodeficiency virus (HIV)-therapy leading to insufficient inhibition of platelet aggregation. In addition, the MAH took the opportunity to amend section 2 of the SmPC regarding the amount of sunset yellow FCF aluminium lake (E110) per tablet. Moreover, the MAH took the opportunity to update the product information in accordance with the European Commission (EC) guideline on 'excipients in the labelling and package leaflet of medicinal products for human use' and to introduce minor linguistic amendments in the product information. The package leaflet is updated accordingly

Background

Cobicistat is a selective, mechanism-based inhibitor of cytochrome P450 (CYP) enzymes of the CYP3A subfamily. It is indicated, as Tybost, as a pharmacokinetic enhancer of atazanavir 300 mg once daily or darunavir 800 mg once daily as part of antiretroviral combination therapy in human immunodeficiency virus-1 (HIV-1) infected adults and adolescents aged 12 years and older, subject to certain conditions.

Based on the evaluation of a signal procedure concluded in May 2019 on the interaction of clopidogrel with boosted antiviral human immunodeficiency virus (HIV)-therapy leading to insufficient inhibition of platelet aggregation (EPITT 19325), the MAH for Tybost (cobicistat) submitted to EMA a variation to update the product information to add information on drug-drug interactions between cobicistat and thienopyridines. For background information, see [PRAC minutes May 2019](#). The PRAC is responsible for adopting an outcome based on the assessment report from the PRAC Rapporteur, to be further considered at the level of the CHMP, responsible for adopting an opinion on this variation.

Summary of outcome(s)

- Based on the available data and the Rapporteur's assessment, the PRAC supported to update the product information¹⁸ in order to highlight the interaction between cobicistat and thienopyridines and the potential for lower exposures of active metabolites of drugs that rely on CYP3A for transformation of prodrug to active metabolite.

5. Risk management plans (RMPs)

5.1. Medicines in the pre-authorisation phase

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

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

See also Annex I 15.1.

¹⁸ Update of SmPC sections 4.4 and 4.5. The package leaflet is updated accordingly

5.1.1. Abicipar pegol – EMEA/H/C/005103

Scope: Treatment of neovascular (wet) age-related macular degeneration (AMD)

5.1.2. Acalabrutinib - EMEA/H/C/005299, Orphan

Applicant: AstraZeneca AB

Scope: Treatment of adult patients with chronic lymphocytic leukaemia (CLL), small lymphocytic lymphoma (SLL)

5.1.3. Arsenic trioxide - EMEA/H/C/005218

Scope: Treatment of relapsed acute promyelocytic leukaemia (APL)

5.1.4. Autologous peripheral blood T cells CD¹⁹⁴ and CD8 selected and CD3 and CD28 activated transduced with retroviral vector expressing anti-CD19, CD28/CD3-zeta chimeric antigen receptor and cultured - EMEA/H/C/005102, Orphan

Applicant: Kite Pharma EU B.V, ATMP²⁰

Scope (accelerated assessment): Treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL)

5.1.5. Deferiprone - EMEA/H/C/005004, Orphan

Applicant: Apotex B.V

Scope: Treatment of neurodegeneration with brain iron accumulation

5.1.6. Eladocagene exuparvovec - EMEA/H/C/005352, Orphan

Applicant: PTC Therapeutics International Limited, ATMP²¹

Scope: Treatment of aromatic L-amino acid decarboxylase (AADC) deficiency

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

Applicant: Vertex Pharmaceuticals (Ireland) Limited

Scope (accelerated assessment): Treatment of cystic fibrosis (CF) in patients aged 12 years and older who have at least one F508del²² mutation in the CF transmembrane conductance regulator (CFTR) gene

For further background, see [PRAC minutes January 2020](#).

5.1.8. Filgotinib – EMEA/H/C/005113

Scope: Treatment of adult patients with moderately to severely active rheumatoid arthritis

¹⁹ Cluster of differentiation

²⁰ Advanced therapy medicinal product

²¹ Advanced therapy medicinal product

²² Deletion of a phenylalanine at residue 508

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 Annex I 15.3.

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. Axicabtagene ciloleucel - YESCARTA (CAP) - PSUSA/00010703/201910

Applicant: Kite Pharma EU B.V., ATMP²³

PRAC Rapporteur: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

Background

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

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Yescarta, a centrally authorised medicine containing axicabtagene ciloleucel 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 Yescarta (axicabtagene ciloleucel) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAH should include CD19²⁴ negative relapse as an important potential risk and present any new information on this safety issue. This should include a cumulative rate review of antigen-negative relapses and a discussion on the feasibility of monitoring and further characterising the risk of CD19-relapses. In addition, the MAH should include 'failure to produce a viable chimeric antigen receptor T (CAR-T) cell product' as an important potential risk together with a medical assessment of new cases and review of the published literature.

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.

²³ Advanced therapy medicinal product

²⁴ Cluster of differentiation 19

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

Background

Deferasirox is an orally active iron chelating agent highly selective for iron (III) indicated, as Exjade, a centrally authorised product, for the treatment of chronic iron overload due to frequent blood transfusions (≥ 7 mL/kg/month of packed red blood cells) in patients with beta thalassaemia major aged 6 years and older. It is also indicated for the treatment of chronic iron overload due to blood transfusions when deferoxamine therapy is contraindicated or inadequate in paediatric patients with beta thalassaemia major with iron overload due to frequent blood transfusions (≥ 7 mL/kg/month of packed red blood cells) aged 2 to 5 years, in adult and paediatric patients with beta thalassaemia major with iron overload due to infrequent blood transfusions (< 7 mL/kg/month of packed red blood cells) aged 2 years and older as well as in adult and paediatric patients with other anaemias aged 2 years and older. Finally, it is indicated for the treatment of chronic iron overload requiring chelation therapy when deferoxamine therapy is contraindicated or inadequate in patients with non-transfusion-dependent thalassaemia syndromes aged 10 years and older.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Exjade, a centrally authorised medicine containing deferasirox, 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 Exjade (deferasirox) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the existing information on factors contributing to hepatic failure and to revise the recommendation on treatment discontinuation in case of gastrointestinal ulceration or haemorrhage. Additionally, the undesirable effects section should be updated to remove the reference to dispersible tablets and pre-existing liver cirrhosis. Therefore, the current terms of the marketing authorisation(s) should be varied²⁵.
- In the next PSUR, the MAH should provide a detailed cumulative review of all cases of hyperammonaemia associated with hepatic and/or renal impairment in context of overchelation, especially in paediatric cases. The MAH should also provide a cumulative review to determine whether the frequency of hearing loss is higher in patients receiving doses greater than 30 mg/kg/day with decreased serum ferritin rates, with a proposal for updating the product information, as appropriate. In addition, the MAH should provide a cumulative review to determine whether the frequency of lens opacities, retinal changes and optic neuritis is higher in patients receiving doses greater than 30 mg/kg/day with decreased serum ferritin rates, with a proposal to update the product information, as appropriate.

²⁵ Update of SmPC sections 4.4 and 4.8. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

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

6.1.3. Durvalumab - IMFINZI (CAP) - PSUSA/00010723/201910 (with RMP)

Applicant: AstraZeneca AB

PRAC Rapporteur: David Olsen

Scope: Evaluation of a PSUSA procedure

Background

Durvalumab is a fully human immunoglobulin G1 kappa (IgG1 κ) monoclonal antibody indicated, as Imfinzi, for the treatment of locally advanced, unresectable non-small cell lung cancer (NSCLC) in adults whose tumours express programmed death-ligand 1 (PD-L1) on \geq 1% of tumour cells and whose disease has not progressed following platinum-based chemoradiation therapy.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Imfinzi (durvalumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the existing warning on immune-mediated adverse reactions to include meningitis, encephalitis and Guillain-Barre syndrome (GBS). In addition, the product information should be updated to include meningitis as an undesirable effect with a frequency 'rare', as well as encephalitis and GBS with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied²⁶.

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

6.1.4. Irinotecan²⁷ - ONIVYDE PEGYLATED LIPOSOMAL (CAP) - PSUSA/00010534/201910

Applicant: Les Laboratoires Servier

PRAC Rapporteur: David Olsen

Scope: Evaluation of a PSUSA procedure

Background

Irinotecan is an inhibitor of the topoisomerase I enzyme encapsulated in a lipid bilayer vesicle or liposome indicated, as Onivyde pegylated liposomal, for the treatment of

²⁶ Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

²⁷ Liposomal formulation(s)

metastatic adenocarcinoma of the pancreas, in combination with 5-fluorouracil (5-FU) and leucovorin (LV), in adult patients who have progressed following gemcitabine based therapy.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Onivyde pegylated liposomal, a centrally authorised medicine containing irinotecan 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 Onivyde pegylated liposomal (irinotecan) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include regorafenib in the list of examples of uridine diphosphate (UDP) glucuronosyltransferase family 1 member A1 (UGT1A1) inhibitors as interacting substances. Therefore, the current terms of the marketing authorisation(s) should be varied²⁸.

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. Nintedanib²⁹ - VARGATEF (CAP) - PSUSA/00010318/201910

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Agni Kapou

Scope: Evaluation of a PSUSA procedure

Background

Nintedanib is a triple angiokinase inhibitor indicated, as Vargatef, for the treatment of adult patients with locally advanced, metastatic or locally recurrent non-small cell lung cancer (NSCLC) of adenocarcinoma tumour histology after first-line chemotherapy.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Vargatef (nintedanib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the existing warning on sepsis to reflect that fatal cases have been reported. Therefore, the current terms of the marketing authorisation(s) should be varied³⁰.
- In the next PSUR, the MAH should further monitor cases of venous thromboembolism (VTE), pulmonary embolism (PE) and sepsis.

²⁸ Update of SmPC section 4.5. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

²⁹ Oncology indication(s)

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

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

6.1.6. Pazopanib - VOTRIENT (CAP) - PSUSA/00002321/201910

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Hans Christian Siersted

Scope: Evaluation of a PSUSA procedure

Background

Pazopanib is a multi-target tyrosine kinase inhibitor (TKI) indicated, as Votrient, for the first-line treatment of advanced renal cell carcinoma (RCC) and for patients who have received prior cytokine therapy for advanced disease, in adults. It is also indicated for the treatment of adult patients with selective subtypes of advanced soft-tissue sarcoma (STS) who have received prior chemotherapy for metastatic disease or who have progressed within 12 months after (neo) adjuvant therapy.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Votrient, a centrally authorised medicine containing pazopanib 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 Votrient (pazopanib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning on tumour lysis syndrome (TLS). In addition, TLS should be added as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied³¹.

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

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

See also Annex I 6.2.

6.2.1. Methotrexate - JYLAMVO (CAP); NORDIMET (CAP); NAP - PSUSA/00002014/201910

Applicants: Nordic Group B.V. (Nordimet), Therakind (Europe) Limited (Jylamvo), various

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

³¹ Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

Background

Methotrexate is an antineoplastic and immunomodulating agent and folic acid analogue indicated for use in rheumatological and dermatological diseases (active rheumatoid arthritis, polyarthritic forms of active, severe juvenile idiopathic arthritis (JIA), and severe, treatment-refractory, disabling psoriasis under certain conditions) as well as in oncology for the maintenance treatment of acute lymphoblastic leukaemia (ALL) under certain conditions.

Based on the assessment of the periodic safety update reports (PSURs), the PRAC reviewed the benefit-risk balance of Jylamvo and Nordimet, centrally authorised medicines containing methotrexate, together with nationally authorised medicine(s) containing methotrexate, 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 methotrexate-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include information on medication errors due to handling issues resulting from a lack of training for self-administration³². In addition, the product information should be updated to improve the wording regarding the interaction between methotrexate and nitrous oxide³³. Furthermore, the product information of all methotrexate-containing products should be updated to include skin exfoliation/dermatitis exfoliative as an undesirable effect with a frequency 'not known' and the product information of low-dose methotrexate-containing products should be updated to include or amend the information on paraesthesia/hypoaesthesia not restricted to the extremities with a frequency 'very rare' and oedema with a frequency 'not known'. Therefore, the current terms of the marketing authorisations should be varied³⁴.
- In the next PSUR, all MAHs should continue close monitoring of concomitant use of methotrexate and nitrous oxide leading to increased toxicity and discuss the need for a contraindication of concomitant use of methotrexate and nitrous oxide in the overall population or in the oncologic population. All MAHs with indications requiring once weekly dosing in the treatment of inflammatory diseases should include the important identified risk of 'medication error, including overdose from inadvertent daily instead of weekly dosing' in their PSUR list of safety concerns and should summarise the implementation of the additional risk minimisation measures (aRMMs) resulting from the referral procedure under Article 31 of Directive 2001/83/EC (EMA/H/A-31/1463) finalised in 2019 and comment on the effectiveness of the risk minimisation measures resulting from the referral procedure, including the effectiveness of the targeted questionnaires. The MAHs that have not included the risk of 'reproductive toxicity (including teratogenicity)' in their PSUR summary of safety concerns of the PSUR yet, should include this risk and discuss relevant information in upcoming PSURs. Finally, all MAHs should further review their list of PSUR safety concerns and include the identified risk of drug-drug interactions with a focus on interactions resulting in drug clearance of

³² Medicinal products containing methotrexate suitable for parenteral self-administration by patients (i.e. prefilled syringes and prefilled pens)

³³ Medicinal products without any indication in oncology or extra-uterine pregnancy

³⁴ Update of SmPC sections 4.2, 4.5 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

methotrexate being decreased and interactions which lead to documented adverse events with grade 3 and higher.

- The MAHs for Jylamvo and Nordimet (methotrexate) should submit to EMA, within 60 days, a comprehensive review of the value of performing liver biopsies as a diagnostic tool to monitor hepatotoxicity of methotrexate in non-oncologic indications. Additionally, the PRAC considered that this review should be also requested from MAHs of nationally approved products containing methotrexate. 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 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.

6.2.2. [Midazolam^{35 36} - BUCCOLAM \(CAP\); NAP - PSUSA/00010118/201909](#)

Applicants: Shire Services BVBA (Buccolam), various

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

Background

Midazolam is a benzodiazepine indicated for the treatment of prolonged, acute, convulsive seizures in infants, toddlers, children and adolescents (from 3 months to < 18 years).

Based on the assessment of the periodic safety update reports (PSURs), the PRAC reviewed the benefit-risk balance of Buccolam, a centrally authorised medicine containing midazolam^{37 38}, and nationally authorised medicines containing midazolam 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 midazolam^{39 40}-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include angioedema as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisations should be varied⁴¹.
- In the next PSUR, MAHs should provide a cumulative analysis of anaphylactic reaction/shock and anaphylactoid reaction/shock reported for oromucosal midazolam identified in the published literature and safety databases, as well as a proposal for updating the product information as appropriate. The MAH Shire should additionally

³⁵ Oromucosal solution

³⁶ Indicated for the treatment of prolonged, acute, convulsive seizures

³⁷ Oromucosal solution

³⁸ Indicated for the treatment of prolonged, acute, convulsive seizures

³⁹ Oromucosal solution

⁴⁰ Indicated for the treatment of prolonged, acute, convulsive seizures

⁴¹ 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

provide an analysis of all cases reported in relation to oromucosal midazolam reported in EudraVigilance.

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.

6.3.1. Artemether, lumefantrine⁴² (NAP) - PSUSA/00000236/201910

Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Background

Artemether/lumefantrine are antimalarials indicated for stand-by emergency treatment of adults, children and infants (weighing 5 kg or more) with acute, uncomplicated infections due to *Plasmodium falciparum* or mixed infections including *P. falciparum*.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing artemether/lumefantrine⁴³ 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 artemether/lumefantrine-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include delayed haemolytic anaemia as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied⁴⁴.

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. Carbidopa, levodopa (NAP) - PSUSA/00000548/201910

Applicant(s): various

PRAC Lead: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

⁴² All except dispersible tablet(s)

⁴³ All except dispersible tablet(s)

⁴⁴ 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

Background

Carbidopa is an immediate precursor of dopamine and levodopa a peripheral dopa-decarboxylase inhibitor. In combination, it is indicated for the treatment of Parkinson's disease.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing carbidopa/levodopa 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 carbidopa/levodopa-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning on polyneuropathy and the need for monitoring, which is already listed as an undesirable effect. Therefore, the current terms of the marketing authorisation(s) should be varied⁴⁵.
- In the next PSUR, all MAHs (except AbbVie) should provide a cumulative review of cases of neuropathy with a proposal to update the product information, as appropriate. The MAH AbbVie should provide a review on cases of cholecystitis and analyse its occurrence after percutaneous endoscopic gastro-jejunostomy (PEG-J placement) procedure in patients with gallstones.

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. Dinoprostone (NAP) - PSUSA/00001104/201909

Applicant(s): various

PRAC Lead: Annika Folin

Scope: Evaluation of a PSUSA procedure

Background

Dinoprostone is a prostaglandin of the E series (PGE₂) indicated for the induction of labour, as an oral formulation. As endocervical and intravaginal formulations, it is indicated for the ripening of an unfavourable cervix when there is a medical or obstetrical need for labour induction, and for induction of labour, for the termination of pregnancy from the twelfth through the twentieth gestational week and evaluation of the uterine contents in the management of missed abortion or intrauterine foetal death up to 28 weeks of gestational age as well as for management of non-metastatic gestational trophoblastic disease. Finally, as a sterile solution for intravenous (IV) or for extra-amniotic use, it is indicated for the induction of labour and for therapeutic termination of pregnancy, missed abortion and hydatidiform mole.

⁴⁵ Update of SmPC section 4.4. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing dinoprostone 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 dinoprostone-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 Pfizer should provide a detailed review of cases of medication errors and confusion regarding similarly named or packaged medicinal products. The MAHs Pfizer and Ferring should provide a detailed review of cases of new onset of hypertension/increased blood pressure or worsening of hypertension. The MAHs should also discuss a plausible mechanism as well as causality for the occurrence of the cases with a proposal for updating the product information, as appropriate.

Additionally, the PRAC considered that the risk of uterine hyperstimulation, including serious complications such as uterine rupture, foetal and neonatal death and uterine haemorrhage should be further minimised. 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.

6.3.4. Levosimendan (NAP) - PSUSA/00001858/201909

Applicant(s): various

PRAC Lead: Annika Folin

Scope: Evaluation of a PSUSA procedure

Background

Levosimendan is a pyridazinone derivative indicated for the short-term treatment of acutely decompensated severe chronic heart failure in situations where conventional therapy is not sufficient, and in cases where inotropic support is considered appropriate.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing levosimendan 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 levosimendan-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to revise the existing information regarding lactation and recommendation for use during breastfeeding in order to specify that women who receive levosimendan should not breastfeed to avoid potential cardiovascular adverse events in the infant. In addition, information on the occurrence of opalescence and precipitation in high concentration should be included in

the product information. Therefore, the current terms of the marketing authorisation(s) should be varied⁴⁶.

Additionally, the PRAC considered that the perioperative use of levosimendan in the cardiac surgery setting needs to be further assessed. Further consideration should be given at the level of CHMP and CMDh.

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

6.3.5. Methylphenidate (NAP) - PSUSA/00002024/201910

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Methylphenidate is a mild central nervous system (CNS) stimulant with more prominent effects on mental activities indicated for the treatment of attention deficit hyperactivity disorder (ADHD) in children between the ages of 6 and 18 years and adults.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing methylphenidate 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 methylphenidate-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include dysphemia as an undesirable effect with a frequency 'not known' and to add a footnote to the already known undesirable effects bruxism and trismus to clarify how the frequency is calculated. Therefore, the current terms of the marketing authorisation(s) should be varied⁴⁷.
- In the next PSUR, the MAHs should provide a detailed cumulative review on precocious puberty with a proposal for updating the product information, as appropriate. All MAHs should describe activities undertaken to evaluate the effectiveness and usefulness of the educational materials and comment whether these additional risk minimisation measures (aRMMs) are warranted.

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

⁴⁶ Update of SmPC sections 4.6 and 6.6. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

⁴⁷ 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

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

6.3.6. Opium (NAP) - PSUSA/00010670/201909

Applicant(s): various

PRAC Lead: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

Background

Opium is an herbal narcotic with morphine content indicated for the treatment of diarrhoea.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing opium 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 opium-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning on the interaction between P2Y12⁴⁸ inhibitors and morphine in order to minimise the risk of delayed and reduced effect of and/or decreased exposure of P2Y12 inhibitors. Therefore, the current terms of the marketing authorisation(s) should be varied⁴⁹.
- In the next PSUR, the MAH(s) should provide a cumulative review on use during pregnancy of opium and morphine, with a proposal for updating the product information, as appropriate.

Additionally, the PRAC considered that the risk of interaction between morphine and P2Y12 inhibitors is also relevant for medicinal products containing morphine or morphine/cyclizine. 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. 1-Propanol, 2-propanol, lactic acid (NAP) - PSUSA/00010414/201909

Applicant(s): various

PRAC Lead: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

Background

1-propanol, 2-propanol and lactic acid are disinfectants and antiseptics indicated for surgical and hygienic hand disinfection.

⁴⁸ Type of adenosine diphosphate (ADP) chemoreceptor

⁴⁹ 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 CMDh for adoption of a position

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing 1-propranolol/2-propranolol/lactic acid and issued a recommendation on their marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of 1-propranolol/2-propranolol/lactic acid-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include erythema and burning sensation as undesirable effects with a frequency 'very rare'. Therefore, the current terms of the marketing authorisation(s) should be varied⁵⁰.

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

6.3.8. Sumatriptan (NAP) - PSUSA/00002832/201909

Applicant(s): various

PRAC Lead: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

Background

Sumatriptan is a selective vascular 5-hydroxytryptamine 1B/D (5-HT_{1B/D}) receptor agonist indicated for the acute treatment of migraine attacks, with or without aura. The injection formulation is also indicated for the acute treatment of cluster headache.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing sumatriptan 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 sumatriptan-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include dysphagia, pain trauma activated and pain inflammation activated as undesirable effects with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied⁵¹.
- In the next PSUR, the MAHs should discuss the following safety concerns: cardiovascular events, cardiac arrhythmias (including QT prolongation, Torsade de pointes and ventricular arrhythmias), as well as the risk on embryo-foetal development and use in

⁵⁰ 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

⁵¹ 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

elderly population. In addition, all MAHs should provide a detailed cumulative review of cases of spontaneous abortion and stillbirth, including any relevant published literature.

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.

6.4. Follow-up to PSUR/PSUSA procedures

See also Annex I 16.4.

6.4.1. Dexmedetomidine - DEXDOR (CAP) - EMEA/H/C/002268/LEG 016

Applicant: Orion Corporation

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Analysis of available mortality data from controlled clinical trials in the dexmedetomidine development programme as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00000998/201903) adopted in November 2019

Background

Dexmedetomidine is a selective alpha-2 receptor agonist indicated, as Dexdor, for the sedation of adult intensive care unit (ICU) patients requiring a sedation level not deeper than arousal in response to verbal stimulation (corresponding to Richmond agitation-sedation scale (RASS) 0 to -3) and for the sedation of non-intubated adult patients prior to and/or during diagnostic or surgical procedures requiring sedation, i.e. procedural/awake sedation.

Following the evaluation of the most recently submitted PSURs for the above mentioned medicine(s), the PRAC requested the MAH to submit further analysis of mortality data from controlled clinical trials. For background, see [PRAC minutes November 2019](#)⁵². The responses were assessed by the Rapporteur for further PRAC advice.

Summary of advice/conclusion(s)

- Based on the available data and the Rapporteur's assessment, the PRAC agreed that the observed imbalance in mortality in the younger age group remains of concern and further information is required.
- The MAH should submit to EMA, within 30 days, responses to a request for supplementary information.

6.4.2. Dolutegravir - TIVICAY (CAP) - EMEA/H/C/002753/LEG 012.1

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Martin Huber

Scope: MAH's response to LEG 012 [detailed review on weight gain as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00010075/201901) adopted by PRAC in September 2019] as per the request for supplementary information

⁵² Held 28-31 October 2019

(RSI) adopted in January 2020

Background

Dolutegravir is an inhibitor of human immunodeficiency virus (HIV) integrase. It is indicated as Tivicay in combination with other anti-retroviral medicinal products for the treatment of HIV infected adults, adolescents and children above 6 years of age.

Following the evaluation of the most recently submitted PSUR(s) for the above mentioned medicine(s), the PRAC requested the MAH to submit further data on weight gain. For background information, see [PRAC minutes September 2019](#) and [PRAC minutes January 2020](#). The responses were assessed by the Rapporteur for further PRAC advice.

Summary of advice/conclusion(s)

- Based on the available data and the Rapporteur's assessment, the PRAC agreed that the product information should be updated to reflect that an increase in weight and in levels of blood lipids and glucose may occur during antiretroviral therapy with dolutegravir, similar to other integrase inhibitors.
- The MAH should submit to EMA, within 60 days, a variation to reflect these amendments in the product information⁵³.
- The MAH should submit to EMA, as an addendum to the ongoing PSUSA procedure (PSUSA/00010075/202001⁵⁴), further data on weight gain from the ADVANCE study⁵⁵, as well as a discussion on the study by *Gorwood et al*⁵⁶.

6.4.3. Dolutegravir, abacavir, lamivudine - TRIUMEQ (CAP) - EMEA/H/C/002754/LEG 009.1

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Martin Huber

Scope: MAH's response to LEG 009 [detailed review on weight gain as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00010075/201901) adopted by PRAC in September 2019] as per the request for supplementary information (RSI) adopted in January 2020

Background

Dolutegravir is an inhibitor of human immunodeficiency virus (HIV) integrase and abacavir and lamivudine are potent selective inhibitors of HIV-1 and HIV-2. In combination dolutegravir/abacavir/lamivudine is indicated, as Triumeq, for the treatment of HIV infected adults and adolescents above 12 years of age weighing at least 40 kg.

Following the evaluation of the most recently submitted PSUR(s) for the above mentioned medicine(s), the PRAC requested the MAH to submit further data on weight gain. For

⁵³ Update of SmPC sections 4.4 and 4.8. The package leaflet is to be updated accordingly

⁵⁴ Recommendation due in September 2020

⁵⁵ WRHI 060 (ADVANCE): a randomised, phase 3 non-inferiority study of dolutegravir (DTG) + tenofovir alafenamide fumarate (TAF) + emtricitabine (FTC) compared with DTG + TDF + FTC and efavirenz (EFV) + TDF + FTC in patients infected with HIV-1 starting first-line antiretroviral therapy - extension to 192 weeks

⁵⁶ Gorwood J et al. The integrase inhibitors dolutegravir and raltegravir exert pro-adipogenic and profibrotic effects and induce insulin resistance in human/simian adipose tissue and human adipocytes. *Clin Infect Dis.* 2020 Mar 13;ciaa259. doi: 10.1093/cid/ciaa259

background information, see [PRAC minutes September 2019](#) and [PRAC minutes January 2020](#). The responses were assessed by the Rapporteur for further PRAC advice.

Summary of advice/conclusion(s)

- Based on the available data and the Rapporteur's assessment, the PRAC agreed that the product information should be updated to reflect that an increase in weight and in levels of blood lipids and glucose may occur during antiretroviral therapy with dolutegravir, similar to other integrase inhibitors.
- The MAH should submit to EMA, within 60 days, a variation to reflect these amendments in the product information⁵⁷.
- The MAH should submit to EMA, as an addendum to the ongoing PSUSA procedure (PSUSA/00010075/202001⁵⁸), further data on weight gain from the ADVANCE⁵⁹ study, as well as a discussion on the study by *Gorwood et al*⁶⁰.

6.4.4. Dolutegravir, lamivudine - DOVATO (CAP) - EMEA/H/C/004909/LEG 004.1

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: David Olsen

Scope: MAH's response to LEG 004 [detailed review on weight gain as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00010075/201901) adopted by PRAC in September 2019] as per the request for supplementary information (RSI) adopted in January 2020

Background

Dolutegravir is an inhibitor of human immunodeficiency virus (HIV) integrase and lamivudine inhibits reverse transcriptase of HIV-1 and HIV-2. In combination, dolutegravir/lamivudine is indicated, as Dovato, for the treatment of HIV-1 infection in adults and adolescents above 12 years of age weighing at least 40 kg, with no known or suspected resistance to the integrase inhibitor class, or lamivudine.

Following the evaluation of the most recently submitted PSUR(s) for the above mentioned medicine(s), the PRAC requested the MAH to submit further data on weight gain. For background information, see [PRAC minutes September 2019](#) and [PRAC minutes January 2020](#). The responses were assessed by the Rapporteur for further PRAC advice.

Summary of advice/conclusion(s)

- Based on the available data and the Rapporteur's assessment, the PRAC agreed that the product information should be updated to reflect that an increase in weight and in levels of blood lipids and glucose may occur during antiretroviral therapy with dolutegravir, similar to other integrase inhibitors.

⁵⁷ Update of SmPC sections 4.4 and 4.8. The package leaflet is to be updated accordingly

⁵⁸ Recommendation due in September 2020

⁵⁹ WRHI 060 (ADVANCE): a randomised, phase 3 non-inferiority study of dolutegravir (DTG) + tenofovir alafenamide fumarate (TAF) + emtricitabine (FTC) compared with DTG + TDF + FTC and efavirenz (EFV) + TDF + FTC in patients infected with HIV-1 starting first-line antiretroviral therapy - extension to 192 weeks

⁶⁰ Gorwood J et al. The integrase inhibitors dolutegravir and raltegravir exert pro-adipogenic and profibrotic effects and induce insulin resistance in human/simian adipose tissue and human adipocytes. *Clin Infect Dis.* 2020 Mar 13;ciaa259. doi: 10.1093/cid/ciaa259

- The MAH should submit to EMA, within 60 days, a variation to reflect these amendments in the product information⁶¹.
- The MAH should submit to EMA, as an addendum to the ongoing PSUSA procedure (PSUSA/00010075/202001⁶²), further data on weight gain from the ADVANCE study⁶³, as well as a discussion on the study by *Gorwood et al*⁶⁴.

6.5. Variation procedure(s) resulting from PSUSA evaluation

6.5.1. Dupilumab - DUPIXENT (CAP) – EMEA/H/C/004390/II/0030

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Kimmo Jaakkola

Scope: Update of section 4.8 of the SmPC to include arthralgia as a new adverse drug reaction (ADR) with a frequency not known, based on a safety review of post marketing data and as per the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00010645/201909) adopted in April 2020

Background

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

Following the evaluation of the most recently submitted PSUR for the above mentioned medicine(s), the PRAC requested the MAH to submit a variation to update the product information to include arthralgia as a new adverse drug reaction. For background information, see [PRAC minutes April 2020](#). The PRAC is responsible for adopting an outcome based on the assessment report from the PRAC Rapporteur, to be further considered at the level of the CHMP, responsible for adopting an opinion on this variation.

Summary of outcome(s)

- Based on the available data and the Rapporteur's assessment, the PRAC supported to include arthralgia in the product information⁶⁵ as an undesirable effect with a frequency 'not known'.

⁶¹ Update of SmPC sections 4.4 and 4.8. The package leaflet is to be updated accordingly

⁶² Recommendation due in September 2020

⁶³ WRHI 060 (ADVANCE): a randomised, phase 3 non-inferiority study of dolutegravir (DTG) + tenofovir alafenamide fumarate (TAF) + emtricitabine (FTC) compared with DTG + TDF + FTC and efavirenz (EFV) + TDF + FTC in patients infected with HIV-1 starting first-line antiretroviral therapy - extension to 192 weeks

⁶⁴ Gorwood J et al. The integrase inhibitors dolutegravir and raltegravir exert pro-adipogenic and profibrotic effects and induce insulin resistance in human/simian adipose tissue and human adipocytes. *Clin Infect Dis.* 2020 Mar 13;ciaa259. doi: 10.1093/cid/ciaa259

⁶⁵ Update of SmPC section 4.8. The package leaflet is updated accordingly

7. Post-authorisation safety studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)⁶⁶

See also Annex I 17.1.

7.1.1. Deferasirox – EXJADE (CAP) - EMEA/H/C/PSA/S/0052

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ghania Chamouni

Scope: Amendment to a protocol previously agreed in March 2016 (PSP/0010.4.A.2) for study CICAL670E2422: an observational, multicentre study to evaluate the safety of deferasirox in the treatment of paediatric patients with non-transfusion dependent iron overload

Background

Deferasirox is an orally active iron chelating agent highly selective for iron (III) indicated, as Exjade, for the treatment of chronic iron overload due to frequent blood transfusions (≥ 7 mL/kg/month of packed red blood cells) in patients with beta thalassaemia major aged 6 years and older. It is also indicated for the treatment of chronic iron overload due to blood transfusions when deferoxamine therapy is contraindicated or inadequate in paediatric patients with beta thalassaemia major with iron overload due to frequent blood transfusions (≥ 7 mL/kg/month of packed red blood cells) aged 2 to 5 years, in adult and paediatric patients with beta thalassaemia major with iron overload due to infrequent blood transfusions (< 7 mL/kg/month of packed red blood cells) aged 2 years and older as well as in adult and paediatric patients with other anaemias aged 2 years and older. Finally, it is indicated for the treatment of chronic iron overload requiring chelation therapy when deferoxamine therapy is contraindicated or inadequate in patients with non-transfusion-dependent thalassaemia syndromes aged 10 years and older.

Exjade, a centrally authorised medicine containing brentuximab vedotin, was authorised in 2006. In line with the obligation to conduct a PASS ([Annex II-D](#)), the MAH Novo Nordisk A/S submitted a substantial amendment to the previously agreed protocol in 2016 for study [CICAL670E2422](#): an observational, multicentre study to evaluate the safety of deferasirox in the treatment of paediatric patients with non-transfusion dependent iron overload to be performed with deferasirox, for review by the PRAC. For further background, see [PRAC minutes March 2016](#).

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.

⁶⁶ In accordance with Article 107n of Directive 2001/83/EC

7.2. Protocols of PASS non-imposed in the marketing authorisation(s)⁶⁷

See Annex I 17.2.

7.3. Results of PASS imposed in the marketing authorisation(s)⁶⁸

See also Annex I 17.3.

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: MAH's response to PSR/S/002 [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] as per the request for supplementary information (RSI) adopted January 2020

Background

Brentuximab vedotin is an antibody drug conjugate (ADC) that delivers an antineoplastic agent. It is indicated, as Adcetris, for the treatment of adult patients with previously untreated CD30+ stage IV Hodgkin lymphoma (HL) in combination with doxorubicin, vinblastine and dacarbazine, for the 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. It 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 patients with relapsed or refractory CD30+ HL or sALCL treated with brentuximab vedotin as part of routine clinical care.

The PRAC discussed the final study results in addition to the MAH's responses to the request for supplementary information (RSI) adopted in January 2020. The PRAC is responsible for evaluating the PASS final results. For further background, see [PRAC minutes January 2020](#).

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 (sALCL) evaluating the occurrence of serious adverse events (SAEs) and adverse events of special interest (AESIs) and identifying and

⁶⁷ 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

⁶⁸ In accordance with Article 107p-q of Directive 2001/83/EC

describing potential risk factors for peripheral neuropathy', the PRAC considered that the benefit-risk balance of Adcetris (brentuximab vedotin) remains unchanged.

- Nevertheless, the product information should be updated to reflect that, while the safety profile in elderly patients is generally in line with that of adult patients, elderly patients may be more susceptible to events such as pneumonia, neutropenia and febrile neutropenia. In addition, the PASS MA25101 as an 'obligation to perform a PASS' should be removed from the 'conditions or restrictions with regard to the safe and effective use of the medicinal product'. Therefore, the current terms of the marketing authorisation(s) should be varied⁶⁹.

7.4. Results of PASS non-imposed in the marketing authorisation(s)⁷⁰

See Annex I 17.4.

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

See Annex I 17.5.

7.6. Others

See Annex I 17.6.

7.7. New Scientific Advice

None

7.8. Ongoing Scientific Advice

None

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.

⁶⁹ Update of SmPC section 4.8 And Annex II-E. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

⁷⁰ In accordance with Article 61a (6) of Regulation (EC) No 726/2004, in line with the revised variations regulation for any submission as of 4 August 2013

8.3. Renewals of the marketing authorisation

See also Annex I 18.3.

8.3.1. Elvitegravir, cobicistat, emtricitabine, tenofovir alafenamide - GENVOYA (CAP) - EMEA/H/C/004042/R/0069 (with RMP)

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ilaria Baldelli

Scope: 5-year renewal of the marketing authorisation

Background

Elvitegravir is a human immunodeficiency virus-1 (HIV-1) integrase strand transfer inhibitor (INSTI); cobicistat a selective, mechanism-based inhibitor of cytochrome P450 (CYP) enzymes of the CYP3A subfamily; emtricitabine is a nucleoside reverse transcriptase inhibitor (NRTI) and nucleoside analogue of 2'-deoxycytidine while tenofovir alafenamide is a nucleotide reverse transcriptase inhibitor (NtRTI) and phosphoramidate prodrug of tenofovir (2'-deoxyadenosine monophosphate analogue). In combination, elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide is indicated, as Genvoya, for the treatment of HIV-1 infection without any known mutations associated with resistance to the integrase inhibitor class, emtricitabine or tenofovir under certain conditions.

Genvoya, a centrally authorised medicine containing elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide, was authorised in 2015.

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

Summary of advice

- Based on the review of the available pharmacovigilance data for Genvoya (elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide) and the CHMP Rapporteur's assessment report, the PRAC considered that the renewal of the marketing authorisation(s) can be granted with unlimited validity.
- The PRAC supported the proposed update of the product information to reflect that the use of Genvoya (elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide) and lomitapide are contraindicated following the request made in the conclusions of the PSUR single assessment (PSUSA) (PSUSA/00010449/201811) adopted in May 2019.

9. Product related pharmacovigilance inspections

9.1. List of planned pharmacovigilance inspections

None

9.2. Ongoing or concluded pharmacovigilance inspections

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

9.3. Others

None

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

10.1. Safety related variations of the marketing authorisation

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

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Martin Huber

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

Background

Dimethyl fumarate is an antineoplastic and immuno-modulating agent indicated, as Tecfidera, for the treatment of adult patients with relapsing remitting multiple sclerosis (RRMS).

A type II variation proposing to update the product information of Tecfidera (dimethyl fumarate) on the risk of progressive multifocal leukoencephalopathy (PML) is under evaluation at the CHMP. The PRAC was requested to provide advice on this variation. For further background, see [PRAC minutes September 2019](#) and [PRAC minutes November 2019](#)⁷¹.

Summary of advice

- Based on the review of the available information and assessment, the PRAC considered that the proposed risk minimisation measures (RMMs) are currently insufficient to address the risk of PML across the variable range of lymphopenia in patients treated with Tecfidera (dimethyl fumarate). In addition, the PRAC advised to update the product information to reflect the occurrence of PML in the context of mild to moderate lymphopenia and to provide clear guidance for treatment discontinuation during prolonged severe lymphocytopenia. Additionally, PRAC supported to enhance in the product information patient's vigilance towards PML symptoms and to encourage

⁷¹ Held 28-31 October 2019

partners/caregivers to monitor symptoms. Lastly, the PRAC supported communicating these changes via a direct healthcare professional communication (DHPC).

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. Paracetamol⁷², tramadol (NAP) - HU/H/0190/003/II/035

Applicant: Krka, d.d., Novo mesto (Doreta SR)

PRAC Lead: Julia Pallos

Scope: PRAC consultation on a type II variation procedure in the decentralised procedure (DCP) to update the RMP (version 3.0) for tramadol/paracetamol 75 mg/650 mg prolonged-release tablet to provide evidence in support of proportionate, feasible and effective measures to prevent the risk of overdose and minimise the risk of hepatic injury following intentional or accidental overdoses with the medicinal product to lift the suspension concluded in the referral procedure under Article 31 of Directive 2001/83/EC (EMEA/H/A-31/1445) finalised in December 2017, on request of Hungary

Background

Paracetamol is an antipyretic and analgesic drug indicated for the treatment of fever and pain.

In the context of the evaluation of a type II variation to update the RMP for Doreta SR (tramadol/paracetamol 75 mg/650 mg prolonged-release tablet) to lift the suspension concluded in the referral procedure under Article 31 of Directive 2001/83/EC ([EMEA/H/A-31/1445](#)) in 2017, Hungary requested PRAC advice on its assessment.

Summary of advice

- Based on the review of the available information and assessment, the PRAC discussed the set of risk minimisation measures (RMMs) proposed by the MAH to further minimise the risk of overdose and the risk of hepatic injury. The PRAC noted the key concerns

⁷² modified release

related to the modified release paracetamol containing products, including its complex pharmacokinetic (PK) profile after an overdose, which makes the standard treatment protocol for paracetamol poisoning inadequate and which would not be addressed by the proposed measures. The PRAC advised that the implementation of risk minimisation depends on national healthcare systems and local guidance, such as paracetamol overdose treatment protocols or warnings on the outer packaging. Therefore, the feasibility of these measures to minimise the risks needs to be further addressed at national level.

11.2. Other requests

None

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 -Q1 2020

PRAC lead: Ulla Wändel Liminga, Martin Huber, Menno van der Elst, 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 about the quantitative measures collected for the Q1 2020 of PRAC meetings. For previous update, see [PRAC minutes January 2020](#).

12.2. Coordination with EMA Scientific Committees or CMDh-v

None

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

None

12.4. Cooperation within the EU regulatory network

12.4.1. Coronavirus (COVID-19) pandemic – update

The EMA secretariat updated the PRAC on the activities of the [COVID-19 EMA pandemic Task Force](#) (ETF), including an overview of ongoing clinical trials and epidemiological studies, as well as a summary of medicines in development and medicines authorised for other indications, as potential treatments for COVID-19, and their safety surveillance.

Further to the start on 30 April 2020 of the [rolling review of remdesivir](#) as an investigational COVID-19 treatment, the PRAC provided comments on the PRAC Rapporteur's assessment

of the data provided by the company developing remdesivir in this round of the rolling review.

12.4.2. [PRAC strategic review and learning meeting \(SRLM\) under the Croatian presidency of the European Union \(EU\) Council - Split, Croatia, 02-04 June 2020 - cancellation](#)

PRAC lead: Nikica Mirošević Skvrce, Željana Margan Koletić

The Croatian delegation informed the PRAC that the PRAC strategic review and learning meeting (SRLM) under the Croatian presidency of the EU Council due to be held 02-04 June 2020 was cancelled due to the COVID-19 pandemic. Instead, a teleconference will be held on 03 June 2020 to discuss a number of topics originally scheduled for the meeting.

12.5. **Cooperation with International Regulators**

None

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

None

12.7. **PRAC work plan**

None

12.8. **Planning and reporting**

12.8.1. [EU Pharmacovigilance system – quarterly workload measures and performance indicators - Q1 2020 and predictions](#)

The EMA Secretariat presented to the PRAC an overview of the quarterly figures on the EMA pharmacovigilance system-related workload and performance indicators. For previous update see [PRAC minutes February 2020](#).

12.8.2. [PRAC workload statistics – Q1 2020](#)

The EMA secretariat informed the PRAC of the quarterly and cumulative figures to estimate the evolution of the workload of the PRAC for Q1 2020, by reflecting on the number of procedures and agenda items covered at each PRAC plenary meeting. For previous update see [PRAC minutes January 2020](#).

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

12.10.1. Granularity and Periodicity Advisory Group (GPAG)

PRAC lead: Menno van der Elst, Maia Uusküla

None

12.10.2. PSURs repository

None

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

The PRAC endorsed the draft revised EURD list, version May 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 May 2020, the updated EURD list was adopted by the CHMP and CMDh at their May 2020 meetings and published on the EMA website on 05/06/2020, see:

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

12.11. Signal management

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

PRAC lead: Menno van der Elst

The SMART WG updated the PRAC on their discussions on the best practices for sharing information on monitoring of COVID-19 treatments between the Member States (MSs) as well as on the practicalities of the guidance provided by the EC-HMA-EMA [Questions and answers on regulatory expectations for medicinal products for human use during the COVID-19 pandemic](#), as regards the prioritisation of signal detection activities by the MAHs.

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 26/05/2020, 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

12.15.3. Good pharmacovigilance practices (GVP) module VIII on 'Post-authorisation safety studies (PASS)' – Addendum I - revision 3

The EMA secretariat presented to the PRAC revision 3 of Addendum I on 'Requirements and recommendations for the submission of information on non-interventional post-

authorisation safety studies' to the good pharmacovigilance practices (GVP) module VIII on 'Post-authorisation safety studies (PASS)'. The revision consists of two changes, to delete the notification procedure and an update to one of the Member States lists for national requirements. The PRAC adopted the revised Addendum I.

Post-meeting note: the final document ([EMA/395730/2012 Rev 3*](#)) was published on 23/06/2020 on the EMA website.

12.16. Community procedures

12.16.1. Referral procedures for safety reasons

None

12.17. Renewals, conditional renewals, annual reassessments

None

12.18. Risk communication and transparency

12.18.1. Public participation in pharmacovigilance

None

12.18.2. Safety communication

None

12.19. Continuous pharmacovigilance

12.19.1. Incident management

None

12.20. Others

12.20.1. Drug-induced hepatotoxicity - PRAC assessors' guide - draft

PRAC lead: Menno van der Elst, Martin Huber

In line with the [PRAC work plan 2020](#), and as a follow-up to the last discussion (for further background, see [PRAC minutes March 2020](#)), the EMA secretariat, presented to the PRAC on behalf of the drafting group progress on the update of the assessors' guide regarding drug-induced hepatotoxicity after implementation of comments. Further discussion is planned in June 2020.

12.20.2. Good Pharmacovigilance Practice (GVP) - update on GVP status overview

The PRAC was provided with an overview of the GVP module status, including an update on the ongoing or planned work on new or revised GVP modules together with their scope, proposed timelines for PRAC discussion and adoption.

12.20.3. Serious cutaneous adverse reactions (SCARs) - PRAC assessors' guide - update

PRAC lead: Sabine Straus, Zane Neikena

As a follow-up to March 2020 discussion (for further background see [PRAC minutes March 2020](#)), the EMA secretariat presented to the PRAC on behalf of the drafting group progress on the update of the assessors' guide regarding severe cutaneous adverse reactions (SCARs), and a further draft revised PRAC assessors' guide after implementation of comments. Further discussion is planned in June 2020.

13. Any other business

None

14. Annex I – Signals assessment and prioritisation⁷³

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 timetables⁷⁴.

14.1.1. Olaparib - LYNPARZA (CAP)

Applicant(s): AstraZeneca AB

PRAC Rapporteur: Amelia Cupelli

Scope: Signal of angioedema

EPITT 19558 – New signal

Lead Member State(s): IT

14.1.2. Pembrolizumab – KEYTRUDA (CAP)

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

PRAC Rapporteur: Menno van der Elst

Scope: Signal of Sjogren's syndrome

EPITT 19564 – New signal

Lead Member State(s): NL

⁷³ 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

⁷⁴ 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

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. Bevacizumab - EMEA/H/C/005181

Scope: Treatment of metastatic carcinoma of the colon or rectum, metastatic breast cancer and recurrence of platinum-sensitive epithelial ovarian, fallopian tube or primary peritoneal cancer, for the first-line treatment of patients with unresectable advanced, metastatic or recurrent non-small cell lung cancer (NSCLC) as well as the first line treatment of patients with advanced and/or metastatic renal cell cancer

15.1.2. Caffeine citrate - EMEA/H/C/005435

Scope: Treatment of primary apnoea

15.1.3. Fampridine - EMEA/H/C/005359

Scope: Treatment of multiple sclerosis

15.1.4. Rivaroxaban - EMEA/H/C/005279

Scope: Prevention of atherothrombotic events

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

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

Applicant: Roche Registration GmbH

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

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

Applicant: medac Gesellschaft für klinische Spezialpräparate mbH

PRAC Rapporteur: Jan Neuhauser

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

15.2.2. Autologous CD34⁺ enriched cell fraction that contains CD34⁺ cells transduced with retroviral vector that encodes for the human adenosine deaminase (ADA) complementary deoxyribonucleic acid (cDNA) sequence - STRIMVELIS (CAP) - EMEA/H/C/003854/II/0026, Orphan

Applicant: Orchard Therapeutics (Netherlands) BV, ATMP⁷⁵

PRAC Rapporteur: Menno van der Elst

Scope: Submission of an updated RMP (version 4.1) to introduce changes to the design of post-authorisation study STRIM-002: a methodology study to investigate the utility of retroviral insertion site analysis in samples from subjects treated with Strimvelis gene therapy, in order to reflect a change in the analysis methodology and shifting the timelines

15.2.3. Epoetin zeta - RETACRIT (CAP) - EMEA/H/C/000872/II/0094

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Martin Huber

Scope: Submission of an updated RMP (version 11.1) in order to align the safety concerns of Retacrit (epoetin zeta – biosimilar) to the medicinal product of reference containing epoetin alfa (Eprex). The RMP (version 15.0) is updated accordingly

15.2.4. Estrogens conjugated, bazedoxifene - DUAVIVE (CAP) - EMEA/H/C/002314/II/0024

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Martin Huber

Scope: Submission of an updated RMP (version 3.0) in order to include amended study milestones and to bring the RMP 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)

15.2.5. Galsulfase - NAGLAZYME (CAP) - EMEA/H/C/000640/II/0081

Applicant: BioMarin International Limited

⁷⁵ Advanced therapy medicinal product

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Submission of an updated RMP (version 6.0) in order to update the safety specifications based on a review of the preclinical, clinical, post-marketing and literature data. In addition, the MAH took the opportunity to update the RMP in line with revision 2.0.1 of the guidance on the format of RMP in the EU (template)

15.2.6. Infliximab - FLIXABI (CAP) - EMEA/H/C/004020/II/0052

Applicant: Samsung Bioepis NL B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of an updated RMP (version 11.0) to replace the prospective observational cohort study of Flixabi (infliximab) in patients with Crohn's disease (CD) (SB2-G42-CD), with real-world data from the following studies: 1) PERFUSE: a French cohort study with the primary aim to evaluate the persistence of Flixabi (infliximab) treatment over one year; 2) CREDIT: a nationwide German inflammatory bowel disease (IBD) registry: a long term observation of IBD patients; 3) CEDUR: Czech register of IBD patients on biological therapy

15.2.7. Naloxegol - MOVENTIG (CAP) - EMEA/H/C/002810/II/0029/G

Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Grouped variations consisting of the submission of an updated RMP (version 6.0) in order to: 1) update the list of safety concerns in line with revision 2 of GVP module V on 'Risk management systems'; 2) reclassify the risk of gastrointestinal (GI) perforation as requested in the conclusions of the PSUR single assessment (PSUSA) (PSUSA/00010317/201809) concluded in April 2019

15.2.8. Spheroids of human autologous matrix-associated chondrocytes - SPHEROX (CAP) - EMEA/H/C/002736/II/0016

Applicant: CO.DON AG, ATMP⁷⁶

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Submission of an updated RMP (version 6.0) in order to bring it in line with revision 2.0.1 of the guidance on the format of RMP in the EU (template). The educational materials described in Annex II-D on 'Conditions or restrictions with regard to the safe and effective use of the medicinal product' is updated accordingly

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).

⁷⁶ Advanced therapy medicinal product

15.3.1. Afamelanotide - SCENESSE (CAP) - EMEA/H/C/002548/II/0033, Orphan

Applicant: Clinuvel Europe Limited

PRAC Rapporteur: Martin Huber

Scope: Update of section 4.8 of the SmPC to revise the frequencies of adverse drug reactions (ADRs) based on safety reports and to add new ADRs based on post-marketing spontaneous reports as requested in the conclusions of the renewal procedure (R/0026) finalised in September 2019. The package leaflet and the RMP (version 9.0) 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). In addition, the MAH took the opportunity to introduce minor editorial changes in section 2 of the SmPC and Annex III-A on labelling

15.3.2. Atezolizumab - TECENTRIQ (CAP) - EMEA/H/C/004143/II/0039

Applicant: Roche Registration GmbH

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Extension of indication to include in combination with bevacizumab the treatment of patients with unresectable hepatocellular carcinoma (HCC) who have not received prior systemic therapy, based on the results of pivotal study YO40245 (IMbrave150): a phase 3, open-label, randomised study of atezolizumab in combination with bevacizumab compared with sorafenib in patients with untreated locally advanced or metastatic hepatocellular carcinoma, as well as data from arms A and F of the supportive phase Ib study GO30140: an open-label, multicentre phase 1b study of the safety and efficacy of atezolizumab administered in combination with bevacizumab and/or other treatments in patients with solid tumours. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the Tecentriq (atezolizumab) 1200 mg concentrate for solution for infusion SmPC are updated. The package leaflet and the RMP (version 13.0) are updated in accordance

15.3.3. Avatrombopag - DOPTLET (CAP) - EMEA/H/C/004722/II/0004/G

Applicant: Dova Pharmaceuticals Ireland Limited

PRAC Rapporteur: Eva Segovia

Scope: Grouped variations consisting of: 1) extension of indication to include the treatment of chronic immune thrombocytopenia (ITP) in adult patients who are refractory to other treatments. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. In addition, section 5.3 of the SmPC is updated with data from juvenile toxicity studies; 2) addition of a pack size of 30 tablets with subsequent updates of sections 6.5 and 8 of the SmPC. The package leaflet, labelling and the RMP (version 2.1) are updated in accordance. Furthermore, the product information is brought in line with the latest quality review of documents (QRD) template (version 10.1)

15.3.4. Avelumab - BAVENCIO (CAP) - EMEA/H/C/004338/II/0013

Applicant: Merck Europe B.V.

PRAC Rapporteur: Hans Christian Siersted

Scope: Update of section 5.1 of the SmPC in order to update efficacy information following

results from study EMR100070-003 Part B (listed as a specific obligation in Annex II): a phase 2, open-label, multicentre trial to investigate the clinical activity and safety of avelumab (MSB0010718C) in subjects with Merkel cell carcinoma. The MAH took the opportunity to update Annex II proposing the deletion of the specific obligation and proposing the switch from conditional to full marketing authorisation. The package leaflet and the RMP (version 2.1) are updated accordingly

15.3.5. Axicabtagene ciloleucel - YESCARTA (CAP) - EMEA/H/C/004480/II/0021, Orphan

Applicant: Kite Pharma EU B.V., ATMP⁷⁷

PRAC Rapporteur: Anette Kirstine Stark

Scope: Update of sections 4.2, 4.4 and 6.6 of the SmPC to allow clinicians to administer Yescarta (axicabtagene ciloleucel) to seriously ill patients with relapsed/refractory non-Hodgkin lymphoma while having on site an adequate supply of tocilizumab (i.e. to ensure that one dose of tocilizumab per patient is available at the treating centres to manage cytokine release syndrome (CRS), in addition, treatment centres should have access to an additional dose within 8 hours of each previous dose). Annex II-D on 'Conditions or restrictions with regard to the safe and effective use of the medicinal product', the package leaflet and the RMP (version 2.4) are updated accordingly

15.3.6. Baricitinib - OLUMIANT (CAP) - EMEA/H/C/004085/II/0016

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Extension of indication to include a new indication in the treatment of moderate to severe atopic dermatitis in adult patients who are candidates for systemic therapy. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 of the SmPC are updated. The package leaflet and the RMP (version 8.1) are updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet and to introduce minor editorial changes to the labelling. Furthermore, Annex II is brought in line with the latest quality review of documents (QRD) template (version 10.1)

15.3.7. Bortezomib - BORTEZOMIB FRESENIUS KABI (CAP) - EMEA/H/C/005074/II/0001/G

Applicant: Fresenius Kabi Deutschland GmbH

PRAC Rapporteur: Amelia Cupelli

Scope: Grouped variations consisting of: 1) addition of a new pack size (EU number- EU/1/19/1397/002) for the sterile parenteral biological medicinal product Bortezomib Fresenius Kabi (bortezomib) powder for solution for injection with a fill volume for a single dose vial of 1 mg per vial in addition to the authorised 3.5 mg per vial; 2) addition of a new pack size within a range (EU number- EU/1/19/1397/003) for the sterile parenteral biological medicinal product Bortezomib Fresenius Kabi (bortezomib) powder for solution for injection with a fill volume for a single dose vial of 2.5 mg per vial in addition to the authorised 3.5 mg per vial. The RMP (version 2.0) is updated accordingly

⁷⁷ Advanced therapy medicinal product

15.3.8. Botulinum toxin type A - NUCEIVA (CAP) - EMEA/H/C/004587/X/0005

Applicant: Evolus Pharma Limited

PRAC Rapporteur: Adam Przybylkowski

Scope: Extension application to add a new strength of 50 U for botulinum toxin type A for powder for solution for injection in vial (glass) for intramuscular administration. The RMP (version 3.0) is updated accordingly

15.3.9. Dolutegravir - TIVICAY (CAP) - EMEA/H/C/002753/X/0058/G

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Martin Huber

Scope: Grouped application consisting of: 1) extension application to add a new pharmaceutical form associated with new strength (5mg dispersible tablet). The new presentation is indicated for the treatment of human immunodeficiency virus (HIV) infected children from 4 weeks of life and weighing at least 3 kg; 2) update of the currently approved SmPC, labelling and package leaflet for the existing film-coated tablets (10mg, 25mg and 50mg) for children of 6 years and older and weighing at least 15 kg, based on pharmacokinetic (PK), safety, and efficacy data from study P1093: a phase 1/2, multicentre, open-label pharmacokinetic, safety, tolerability and antiviral activity of dolutegravir, a novel integrase inhibitor, in combination regimens in HIV-1 infected infants, children and adolescents and PK and safety data from relevant sub-studies nested within study ODYSSEY (PENTA 20): a phase 2/3 randomised trial of dolutegravir (DTG)-based antiretroviral therapy vs. standard of care (SOC) in children with HIV infection starting first-line or switching to second-line antiretroviral therapy (ART). In addition, the MAH took the opportunity to amend section 4.1 of SmPC to clarify that children should be 'aged at least 6 years' as the current approved indication is inclusive of those aged 6 years. The RMP (version 16) is updated in accordance

15.3.10. Durvalumab - IMFINZI (CAP) - EMEA/H/C/004771/II/0014/G

Applicant: AstraZeneca AB

PRAC Rapporteur: David Olsen

Scope: Grouped variations consisting of: 1) extension of indication to include the use of Imfinzi (durvalumab) in combination with etoposide and either carboplatin or cisplatin for the first-line treatment of adults with extensive-stage small cell lung cancer (ES-SCLC). The proposed indication is supported by study D419QC00001 (CASPIAN): an ongoing phase 3 randomised, multicentre, open-label, comparative study designed to determine the efficacy and safety of durvalumab, or durvalumab and tremelimumab, in combination with etoposide and platinum-based chemotherapy (EP) for the first-line treatment of patients with ES-SCLC; 2) update of sections 4.4 and 4.8 of the SmPC to update the safety information based on the durvalumab pan-tumour pool: a safety dataset comprising of 9 clinical studies building on the existing safety database and summarising the safety information for durvalumab monotherapy characterised across tumour types in the durvalumab clinical programme to date, The package leaflet and the RMP (version 2.1) are updated in accordance

15.3.11. Enzalutamide - XTANDI (CAP) - EMEA/H/C/002639/II/0047/G

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Eva Segovia

Scope: Grouped variations consisting of: 1) extension of indication to include the treatment of adult men with metastatic hormone-sensitive prostate cancer (mHSPC) for Xtandi (enzalutamide) in combination with androgen deprivation therapy (ADT). As a consequence, sections 4.1, 4.7, 4.8, 5.1, 5.3 and 6.6 of the SmPC are updated. Furthermore the MAH took the opportunity to introduce minor corrections to section 4.7 of the SmPC. The package leaflet and the RMP (version 13.0) are updated accordingly; 2) update of section 5.1 of the SmPC based on the 5-year overall survival (OS) results obtained from study MDV310003 (PREVAIL), a phase 3 study of enzalutamide in chemotherapy naïve patients with metastatic prostate cancer that progressed on ADT

15.3.12. Guselkumab - TREMFYA (CAP) - EMEA/H/C/004271/II/0020

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of sections 4.4 and 4.8 of the SmPC to include anaphylactic reactions as an adverse drug reaction. The package leaflet and the RMP (version 5.2) are updated accordingly

15.3.13. Human normal immunoglobulin - HYQVIA (CAP) - EMEA/H/C/002491/II/0056

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to replace the therapeutic indications of replacement therapy in hypogammaglobulinaemia and recurrent bacterial infections in patients with chronic lymphocytic leukaemia and multiple myeloma and hypogammaglobulinaemia in patients with hematopoietic stem cell transplantation (HSCT), by the therapeutic indication of replacement therapy in secondary immunodeficiencies (SID) in patients who suffer from severe or recurrent infections, ineffective antimicrobial treatment and either proven specific antibody failure (PSAF) or serum immunoglobulin G (IgG) level of <4 g/L. As a consequence, sections 4.1 and 4.2 of the SmPC are updated. The package leaflet and the RMP (version 10.0) are updated in accordance

15.3.14. Human papillomavirus vaccine [types 16, 18] (recombinant, adjuvanted, adsorbed) - CERVARIX (CAP) - EMEA/H/C/000721/II/0106

Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Jean-Michel Dogné

Scope: Update of section 4.4 and 5.1 of the SmPC based on final results from study HPV-019 (listed as a category 3 study in the RMP) (in fulfilment of MEA 080): a safety and immunogenicity study of Cervarix (human papillomavirus vaccine) in human immunodeficiency virus (HIV)-positive female subjects aged 15-25 years as compared to human papillomavirus 4 (HPV-4). In addition, the MAH took the opportunity to reflect an

update in section 4.2 of the SmPC to indicate that limited clinical data is now available in 4-6 years old children based on study HPV-073: a safety and immunogenicity study of Cervarix (human papillomavirus vaccine) in girls aged 4-6 years, as an alternative to the current adolescent HPV vaccination schedule. The RMP (version 21.0) is updated accordingly and also reflect the removal of the use of Cervarix (human papillomavirus vaccine) in HIV-infected subjects or subjects with known immune deficiencies as missing information. Furthermore, the MAH took the opportunity to bring the product information in line with the latest quality review of documents (QRD) template (version 10.1)

15.3.15. Iron - VELPHORO (CAP) - EMEA/H/C/002705/II/0021

Applicant: Vifor Fresenius Medical Care Renal Pharma France

PRAC Rapporteur: Kimmo Jaakkola

Scope: Update of section 5.1 of the SmPC in order to add information related to the results of the VERIFIE study (listed as a category 3 study in the RMP): a non-interventional voluntary PASS trial to investigate the short and long-term real-life safety, effectiveness, and adherence of Velphoro (iron) in patients with hyperphosphataemia undergoing haemodialysis or peritoneal dialysis. Furthermore, minor editorial changes in section 4.2 of the SmPC were introduced to provide consistent information between the SmPC, the labelling and the package leaflet. The RMP (version 8.0) 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)

15.3.16. Liraglutide - SAXENDA (CAP) - EMEA/H/C/003780/II/0026

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to include treatment as an adjunct to a healthy nutrition and physical activity counselling for weight management in adolescent patients from the age of 12 years and above with body weight above 60 kg and obesity (body mass index (BMI) corresponding to ≥ 30 kg/m² for adults) based on study NN8022-4180: effect of liraglutide for weight management in pubertal adolescent subjects with obesity, 56-week, double-blind, randomised, parallel-group, placebo-controlled multi-national trial followed by a 26-week period off study-drug. 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 32.0) are updated in accordance. The application relates to paediatric studies submitted according to Article 46 of the paediatric regulation

15.3.17. Measles, mumps, rubella and varicella vaccine (live) - PROQUAD (CAP) - EMEA/H/C/000622/II/0139

Applicant: MSD Vaccins

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of sections 4.4 and 4.8 of the SmPC to amend the safety information and further characterise the risk of secondary transmission following MAH's evaluation of new significant pharmacovigilance data. The package leaflet and the RMP (version 7.1) are updated accordingly. The MAH took the opportunity to implement some changes in section

6.5 of the SmPC with information on the glass type for the immediate container in accordance with the European Commission (EC) guideline on 'excipients in the labelling and package leaflet of medicinal products for human use' and the guideline on 'quality aspects included in the product information for vaccines for human use'. Annex A is updated accordingly. Furthermore, the product information is brought in line with the latest quality review of documents (QRD) template (version 10.1) taking into account the 'compilation of QRD decisions on stylistic matters in product information'. Finally, the MAH took the opportunity to align some wordings with other MAH's measles, mumps, rubella, and varicella (MMRV) vaccines, in particular section 6.6 of the SmPC

15.3.18. [Meningococcal group B vaccine \(recombinant, adsorbed\) - TRUMENBA \(CAP\) - EMEA/H/C/004051/II/0023](#)

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Jean-Michel Dogné

Scope: Update of sections 4.8 and 5.1 of the SmPC in order to update the safety and immunogenicity information based on final results from study B1971033 (listed as a category 3 study in the RMP) (in fulfilment of MEA 007): a duration of immunity study to assess persistence of hSBA (serum bactericidal activity using human complement) response for up to 48 months after completion of vaccination with Trumenba (meningococcal group B vaccine) and the immunogenicity, safety, and tolerability of a booster dose of Trumenba (meningococcal group B vaccine). The RMP (version 3) is updated accordingly and includes changes agreed in variation II/13 as well as editorial changes. In addition, the MAH took the opportunity to introduce editorial changes in Annex II, in the labelling and in the package leaflet

15.3.19. [Nintedanib - OFEV \(CAP\) - EMEA/H/C/003821/II/0027, Orphan](#)

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Extension of indication to include the treatment of other chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype based on the results of pharmacology studies and the double-blind, randomised, placebo-controlled phase 3 trial (INBUILD). As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 9.0) are updated accordingly. In addition, the MAH took the opportunity to introduce minor formatting changes in the product information. Furthermore, the product information is brought in line with the latest quality review of documents (QRD) template (version 10.1)

15.3.20. [Niraparib - ZEJULA \(CAP\) - EMEA/H/C/004249/II/0019, Orphan](#)

Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Jan Neuhauser

Scope: Extension of indication to include the maintenance treatment of adult patients with advanced high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy. As a consequence, sections 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated.

The package leaflet and the RMP (version 4.0) are updated in accordance. The RMP is also brought in line with revision 2.0.1 of the guidance on the format of RMP in the EU (template) and includes updated due dates for category 3 studies. Finally, the MAH took the opportunity to introduce minor corrections throughout the product information

15.3.21. Nitisinone - ORFADIN (CAP) - EMEA/H/C/000555/II/0071

Applicant: Swedish Orphan Biovitrum International AB

PRAC Rapporteur: Amelia Cupelli

Scope: Extension of indication to include treatment of adult patients with alkaptonuria (AKU). As a consequence, sections 4.1, 4.2, 4.4, 4.6, 4.8, 5.1 and 10 of the SmPC are updated. The package leaflet and the RMP (version 5.2) are updated in accordance. The RMP is also brought in line with revision 2 of GVP module V on 'Risk management systems'

15.3.22. Prucalopride - RESOLOR (CAP) - EMEA/H/C/001012/II/0051

Applicant: Shire Pharmaceuticals Ireland Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of Section 4.4 of the SmPC with suicidal ideation and behaviour and to add 'suicidal ideation and behaviour' to the list of safety concerns as an important potential risk in the RMP based on post-marketing reports. The package leaflet and the RMP (version 16.0) are updated accordingly. The MAH took to opportunity to introduce editorial changes to the RMP and SmPC

15.3.23. Ribociclib - KISQALI (CAP) - EMEA/H/C/004213/II/0021

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Hans Christian Siersted

Scope: Update of sections 4.2 and 4.4 of the SmPC in order to add a warning on interstitial lung disease (ILD)/pneumonitis and related dose modification recommendations. The package leaflet and the RMP (version 4.0) are updated accordingly

15.3.24. Secukinumab - COSENTYX (CAP) - EMEA/H/C/003729/II/0057

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Eva Segovia

Scope: Extension of indication to include the treatment of moderate to severe plaque psoriasis in children and adolescents from the age of 6 years who are candidates for systemic therapy for Cosentyx (secukinumab). As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 of the SmPC are updated. Section 6.6 of the SmPC for the solution for injection is also updated. The package leaflet and the RMP (version 6.0) are updated in accordance. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet. Furthermore, Annex II is brought in line with the latest quality review of documents (QRD) template (version 10.1)

15.3.25. Secukinumab - COSENTYX (CAP) - EMEA/H/C/003729/X/0059

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Eva Segovia

Scope: Extension application to add a new strength of 300mg (in 2mL) solution for injection in pre-filled syringe and pre-filled pen. The RMP (version 7.0) is updated in accordance

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

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Ana Sofia Diniz Martins

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

15.3.27. Tezacaftor, ivacaftor - SYMKEVI (CAP) - EMEA/H/C/004682/II/0016, Orphan

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Update of sections 4.8 and 5.1 of the SmPC in order to update the information based on final results from study VX14-661-110 (listed as a category 3 study in the RMP): a phase 3, multicentre, open label, rollover study for studies 103, 106, 107, 108, 109, 111, 112 and 114 designed to evaluate the long-term safety and tolerability of tezacaftor/ivacaftor (TEZ/IVA) treatment for 96 weeks in cystic fibrosis (CF) subjects 12 years and older, homozygous or heterozygous for the phenylalanine in position 508 of the cystic fibrosis transmembrane conductance regulator (F508del CFTR) mutation. 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). The RMP (version 2.2) is updated accordingly

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

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

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

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

16.1.1. Alglucosidase alfa - MYOZYME (CAP) - PSUSA/00000086/201909

Applicant: Genzyme Europe BV
PRAC Rapporteur: Adrien Inoubli
Scope: Evaluation of a PSUSA procedure

16.1.2. Andexanet alfa - ONDEXXYA (CAP) - PSUSA/00010764/201910

Applicant: Portola Netherlands B.V.
PRAC Rapporteur: Menno van der Elst
Scope: Evaluation of a PSUSA procedure

16.1.3. Bezlotoxumab - ZINPLAVA (CAP) - PSUSA/00010576/201910

Applicant: Merck Sharp & Dohme B.V.
PRAC Rapporteur: Adam Przybylkowski
Scope: Evaluation of a PSUSA procedure

16.1.4. Brigatinib - ALUNBRIG (CAP) - PSUSA/00010728/201910

Applicant: Takeda Pharma A/S
PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva
Scope: Evaluation of a PSUSA procedure

16.1.5. Ceftaroline fosamil - ZINFORO (CAP) - PSUSA/00010013/201910

Applicant: Pfizer Ireland Pharmaceuticals
PRAC Rapporteur: Maia Uusküla
Scope: Evaluation of a PSUSA procedure

16.1.6. Ceritinib - ZYKADIA (CAP) - PSUSA/00010372/201910

Applicant: Novartis Europharm Limited
PRAC Rapporteur: Annika Folin
Scope: Evaluation of a PSUSA procedure

16.1.7. Cerliponase alfa - BRINEURA (CAP) - PSUSA/00010596/201910

Applicant: BioMarin International Limited
PRAC Rapporteur: Ulla Wändel Liminga
Scope: Evaluation of a PSUSA procedure

16.1.8. Conestat alfa - RUCONEST (CAP) - PSUSA/00000873/201910

Applicant: Pharming Group N.V

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.1.9. Defibrotide - DEFITELIO (CAP) - PSUSA/00010086/201910 (with RMP)

Applicant: Gentium S.r.l.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.10. Delamanid - DELTYBA (CAP) - PSUSA/00010213/201910

Applicant: Otsuka Novel Products GmbH

PRAC Rapporteur: Laurence de Fays

Scope: Evaluation of a PSUSA procedure

16.1.11. Eculizumab - SOLIRIS (CAP) - PSUSA/00001198/201910

Applicant: Alexion Europe SAS

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

16.1.12. Edoxaban - LIXIANA (CAP); ROTEAS (CAP) - PSUSA/00010387/201910

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

PRAC Rapporteur: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

16.1.13. Glycopyrronium bromide⁷⁸ - ENUREV BREEZHALER (CAP); SEEBRI BREEZHALER (CAP); TOVANOR BREEZHALER (CAP) - PSUSA/00010047/201909

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Hans Christian Siersted

Scope: Evaluation of a PSUSA procedure

16.1.14. Glycopyrronium bromide, formoterol - BEVESPI AEROSPHERE (CAP) - PSUSA/00010739/201910

Applicant: AstraZeneca AB

PRAC Rapporteur: Jan Neuhauser

⁷⁸ Centrally authorised product(s) indicated for chronic obstructive pulmonary disease

Scope: Evaluation of a PSUSA procedure

16.1.15. Granisetron⁷⁹ - SANCUSO (CAP) - PSUSA/00010101/201910

Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Rugile Pilviniene

Scope: Evaluation of a PSUSA procedure

16.1.16. Herpes zoster vaccine (recombinant, adjuvanted) - SHINGRIX (CAP) - PSUSA/00010678/201910

Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Sonja Hrabcik

Scope: Evaluation of a PSUSA procedure

16.1.17. Idarucizumab - PRAXBIND (CAP) - PSUSA/00010435/201910

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.18. Meningococcal group B vaccine (recombinant, adsorbed) - TRUMENBA (CAP) - PSUSA/00010607/201910

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

16.1.19. Midostaurin - RYDAPT (CAP) - PSUSA/00010638/201910

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Evaluation of a PSUSA procedure

16.1.20. Nintedanib⁸⁰ - OFEV (CAP) - PSUSA/00010319/201910

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

⁷⁹ Transdermal patch

⁸⁰ Respiratory indication(s)

16.1.21. Obinutuzumab - GAZYVARO (CAP) - PSUSA/00010279/201910

Applicant: Roche Registration GmbH

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

16.1.22. Ocriplasmin - JETREA (CAP) - PSUSA/00010122/201910

Applicant: Oxurion NV

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.23. Pandemic influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) – FOCLIVIA (CAP); prepandemic influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) - AFLUNOV (CAP) - PSUSA/00010008/201910

Applicant: Seqirus S.r.l

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.1.24. Parathyroid hormone - NATPAR (CAP) - PSUSA/00010591/201910

Applicant: Shire Pharmaceuticals Ireland Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

16.1.25. Pasireotide - SIGNIFOR (CAP) - PSUSA/00009253/201910

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

16.1.26. Patiromer - VELTASSA (CAP) - PSUSA/00010618/201910

Applicant: Vifor Fresenius Medical Care Renal Pharma France

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

16.1.27. Ranibizumab - LUCENTIS (CAP) - PSUSA/00002609/201910

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.28. Sotagliflozin - ZYNQUISTA (CAP) - PSUSA/00010766/201910

Applicant: Navigant Germany GmbH

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.29. Talazoparib - TALZENNA (CAP) - PSUSA/00010781/201910

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Evaluation of a PSUSA procedure

16.1.30. Talimogene laherparepvec - IMLYGIC (CAP) - PSUSA/00010459/201910

Applicant: Amgen Europe B.V., ATMP⁸¹

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.31. Turoctocog alfa - NOVOEIGHT (CAP) - PSUSA/00010138/201910

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

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

16.2.1. Buprenorphine, naloxone - SUBOXONE (CAP); ZUBSOLV (CAP); NAP - PSUSA/00002113/201909

Applicants: Indivior Europe Limited (Suboxone), Orexo AB (Zubsolv), various

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.2.2. Sodium oxybate⁸² - XYREM (CAP); NAP - PSUSA/00010612/201910

Applicants: UCB Pharma S.A. (Xyrem), various

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

⁸¹ Advanced therapy medicinal product

⁸² Oral use

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

16.3.1. Acitretin (NAP) - PSUSA/00000051/201910

Applicant(s): various

PRAC Lead: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

16.3.2. Ambrosia artemisiifolia^{83 84 85 86} (NAP) - PSUSA/00010693/201910

Applicant(s): various

PRAC Lead: Brigitte Keller-Stanislowski

Scope: Evaluation of a PSUSA procedure

16.3.3. Ambroxol (NAP) - PSUSA/00000130/201909

Applicant(s): various

PRAC Lead: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.3.4. Ambroxol, clenbuterol (NAP) - PSUSA/00000131/201909

Applicant(s): various

PRAC Lead: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.3.5. Aminosalicylate sodium (NAP) - PSUSA/00000165/201910

Applicant(s): various

PRAC Lead: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

16.3.6. Atenolol, chlortalidone (NAP) - PSUSA/00000260/201909

Applicant(s): various

PRAC Lead: Marek Juračka

Scope: Evaluation of a PSUSA procedure

⁸³ Allergen for therapy

⁸⁴ (302)

⁸⁵ Sublingual use

⁸⁶ Medicinal product(s) authorised via decentralised procedure

16.3.7. Betamethasone, tetryzoline (NAP) - PSUSA/00010072/201909

Applicant(s): various

PRAC Lead: Željana Margan Koletić

Scope: Evaluation of a PSUSA procedure

16.3.8. Bromhexine (NAP) - PSUSA/00000437/201909

Applicant(s): various

PRAC Lead: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.3.9. Chlorquinaldol⁸⁷, promestriene (NAP) - PSUSA/00009272/201909

Applicant(s): various

PRAC Lead: Roxana Stefania Stroe

Scope: Evaluation of a PSUSA procedure

16.3.10. Clenbuterol (NAP) - PSUSA/00000794/201909

Applicant(s): various

PRAC Lead: Melinda Palfi

Scope: Evaluation of a PSUSA procedure

16.3.11. Drospirenone, ethinylestradiol (NAP) - PSUSA/00010217/201909

Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.3.12. Felbamate (NAP) - PSUSA/00010155/201909

Applicant(s): various

PRAC Lead: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

16.3.13. Hexaminolevulinate hydrochloride (NAP) - PSUSA/00001606/201909

Applicant(s): various

PRAC Lead: Annika Folin

Scope: Evaluation of a PSUSA procedure

⁸⁷ Vaginal tablet(s)

16.3.14. Pramiracetam (NAP) - PSUSA/00002492/201909

Applicant(s): various

PRAC Lead: Zane Neikena

Scope: Evaluation of a PSUSA procedure

16.3.15. Technetium (^{99m}Tc) bismate (NAP) - PSUSA/00002856/201910

Applicant(s): various

PRAC Lead: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

16.3.16. Valsartan, rosuvastatin (NAP) - PSUSA/00010735/201910

Applicant(s): various

PRAC Lead: Gabriela Jazbec

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

16.4. Follow-up to PSUR/PSUSA procedures

16.4.1. Aflibercept - EYLEA (CAP) - EMEA/H/C/002392/LEG 018

Applicant: Bayer AG

PRAC Rapporteur: Ghania Chamouni

Scope: Detailed review of available epidemiological and clinical data to estimate background incidence of retinal artery occlusion (RAO) in the population with similar risk profile as that treated with Eylea (aflibercept) together with a discussion on potential pathophysiological mechanisms for development of RAO, an overview of pharmacokinetic (PK) and pharmacodynamic (PD) data on systemic exposure including the potential for occurrence of systemic adverse reactions as well as an updated causality assessment of all RAO events as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00010020/201811) adopted by PRAC in June 2019

16.4.2. Levetiracetam - KEPPRA (CAP) - EMEA/H/C/000277/LEG 088.1

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Laurence de Fays

Scope: MAH's response to LEG 088 [cumulative review of cases of cardiac arrhythmia and cases of torsades de pointes/QT prolongation as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00001846/201811) adopted in July 2019] as per the request for supplementary information (RSI) adopted in February 2020

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)⁸⁸

17.1.1. Cholic acid – ORPHACOL (CAP) - EMEA/H/C/PSA/S/0051

Applicant: Laboratoires CTRS

PRAC Rapporteur: Sofia Trantza

Scope: Amendment to a protocol previously agreed in the initial marketing authorisation procedure for a patient surveillance database to monitor accumulating data on efficacy and safety in the treatment of inborn errors in primary bile acid synthesis due to 3 β -hydroxy- Δ 5-C27-steroid oxidoreductase deficiency or Δ 4-3-oxosteroid-5 β -reductase deficiency with Orphacol (cholic acid) in infants, children, adolescents and adults

17.2. Protocols of PASS non-imposed in the marketing authorisation(s)⁸⁹

17.2.1. Darbepoetin alfa - ARANESP (CAP) - EMEA/H/C/000332/MEA 092

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Martin Huber

Scope: Protocol for study 20190404: a retrospective cohort study to assess the use of erythropoiesis stimulating agents (ESAs) in subjects receiving myelosuppressive chemotherapy in Europe

17.2.2. Dulaglutide - TRULICITY (CAP) - EMEA/H/C/002825/MEA 006.1

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Ilaria Baldelli

Scope: MAH's response to MEA 006 [protocol for study H9X-MC-B013 (listed as a category 3 study in the RMP): a non-interventional retrospective study to estimate the incidence rates of events of interest among type 2 diabetes mellitus (T2DM) patients treated with dulaglutide compared to other glucagon-like peptide 1 (GLP-1) receptor agonists in order to better characterise the safety profile of dulaglutide in terms of acute pancreatitis, pancreatic and thyroid malignancies] as per the request for supplementary information (RSI) adopted in October 2019

⁸⁸ In accordance with Article 107n of Directive 2001/83/EC

⁸⁹ 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

17.2.3. Estrogens conjugated, bazedoxifene - DUAVIVE (CAP) - EMEA/H/C/002314/MEA 002.14

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Martin Huber

Scope: MAH's response to MEA 002.13 [substantial amendment to a protocol previously agreed in May 2015 for ongoing US study B2311060 (listed as a category 3 study in the RMP): a study to estimate the incidence and to compare the risks of endometrial hyperplasia and endometrial cancer in postmenopausal women initiating either Duavive (estrogens conjugated/bazedoxifene) or estrogen + progestin (E+P) combination hormone replacement therapy (HRT)] as per the request for supplementary information (RSI) adopted in December 2019

17.2.4. Insulin glargine, lixisenatide - SULIQUA (CAP) - EMEA/H/C/004243/MEA 002.5

Applicant: sanofi-aventis groupe

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to MEA 002.4 [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] as per the request for supplementary information (RSI) adopted in January 2020

17.2.5. Lenalidomide - REVLIMID (CAP) - EMEA/H/C/000717/MEA 046.4

Applicant: Celgene Europe BV

PRAC Rapporteur: Ghania Chamouni

Scope: MAH's response to MEA 046.3 [substantial amendment (version 4.0) to a protocol previously endorsed in November 2017 for study CC-5013-MCL-005 to further investigate and characterise the association of lenalidomide and tumour flare reaction (TFR)/high tumour burden following the extension of indication for the treatment of adult patients with relapsed and/or refractory mantle cell lymphoma (RRMCL) [final clinical study report (CSR) expected in December 2022] as per the request for supplementary information (RSI) adopted in December 2019

17.2.6. Micafungin - MYCAMINE (CAP) - EMEA/H/C/000734/MEA 015.11

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Martin Huber

Scope: Protocol for study 9463-PV-0002 (listed as a category 3 study in the RMP): a non-interventional PASS on the effectiveness of the updated prescriber checklist for Mycamine (micafungin)

17.2.7. Naldemedine - RIZMOIC (CAP) - EMEA/H/C/004256/MEA 001.1

Applicant: Shionogi B.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: MAH's response to MEA 001 [protocol for an observational PASS of patients with chronic opioid use for non-cancer and cancer pain who have opioid-induced constipation (OIC) [final clinical study report (CSR) expected in January 2026]] as per the request for supplementary information (RSI) adopted in December 2019

17.2.8. Neratinib - NERLYNX (CAP) - EMEA/H/C/004030/MEA 003.1

Applicant: Pierre Fabre Medicament

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to MEA 003 [protocol for study PUMA-NER-7402: a non-interventional study exploring the safety of neratinib among breast cancer patients to characterise the incidence and duration of diarrhoea in a real world setting, to describe patient characteristics, incidence rates and duration of diarrhoea, to describe use of loperamide and other concomitant anti-diarrhoeal medication, describe adherence to neratinib therapy, assess the impact of neratinib therapy on patient self-reported, health related quality of life and their ability to perform their activities of daily living and to further assess and characterise adverse events hepatic, cardiac, pulmonary, reproductive and developmental toxicity] as per the request for supplementary information (RSI) adopted in July 2019

17.2.9. Neratinib - NERLYNX (CAP) - EMEA/H/C/004030/MEA 004.1

Applicant: Pierre Fabre Medicament

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to MEA 004 [protocol for study PUMA-NER-7403: a study to evaluate the availability, interpretability, and impact of Nerlynx (neratinib) educational materials] as per the request for supplementary information (RSI) adopted in July 2019

17.2.10. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/MEA 013

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Protocol for study A3921344 (listed as a category 3 study in the RMP): an active surveillance, post-authorisation study to characterise the safety of tofacitinib in patients with moderately to severely active ulcerative colitis (UC) in the real-world setting using data from the Swedish Quality Register for Inflammatory Bowel Disease (SWIBREG) registry as requested in the conclusions of procedure X/0005/G finalised in May 2018 and in the conclusions of the referral procedure under Article 20 of Regulation (EC) No 726/2004 (EMEA/H/A-20/1485) finalised in November 2019

17.3. Results of PASS imposed in the marketing authorisation(s)⁹⁰

17.3.1. Teicoplanin (NAP) - EMEA/H/N/PSR/S/0025

Applicant: Sanofi (Targocid)

PRAC Rapporteur: Martin Huber

Scope: Results for a PASS study: a prospective, observational cohort, evaluating the incidence of nephrotoxicity and other adverse events of interest in patients treated with the higher recommended teicoplanin loading dose (12mg/kg twice a day), and comparison with external historical comparator data

17.4. Results of PASS non-imposed in the marketing authorisation(s)⁹¹

17.4.1. Anakinra - KINERET (CAP) - EMEA/H/C/000363/II/0073

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Hans Christian Siersted

Scope: Submission of the final report from study Sobi.ANAKIN-302 (listed as a category 3 study in the RMP): a non-interventional PASS to evaluate the long-term safety of Kineret (anakinra) in patients with systemic juvenile idiopathic arthritis. The RMP (version 5.1) is updated accordingly

17.4.2. Concentrate of proteolytic enzymes enriched in bromelain - NEXOBRID (CAP) - EMEA/H/C/002246/II/0047, Orphan

Applicant: MediWound Germany GmbH

PRAC Rapporteur: Martin Huber

Scope: Submission of the final report from study MW2013-06-01 (listed as a category 3 study in the RMP): an international, observational retrospective, data-collection study assessing efficacy of applied risk-minimisation measures in burn patients treated with NexoBrid (concentrate of proteolytic enzymes enriched in bromelain). The RMP (version 7.0) is updated accordingly. In addition, the MAH took the opportunity to bring the RMP in line with revision 2 of GVP module V on 'Risk management systems' and to change the due dates for: 1) study MW2013-06-01 (listed as a category 3 study in the RMP): a drug utilisation study (DUS) for further evaluation of the effectiveness of the risk minimisation activities; 2) study MW2010-03-02 (DETECT) (listed as a category 3 study in the RMP): a multicentre, multinational, randomized, controlled, open-label study, performed in subjects with thermal burns, to evaluate the efficacy and safety of NexoBrid (concentrate of proteolytic enzymes enriched in bromelain) as compared to standard of care (SOC) treatment

17.4.3. Dapagliflozin - EDISTRIDE (CAP) - EMEA/H/C/004161/WS1742/0037; FORXIGA (CAP) - EMEA/H/C/002322/WS1742/0056; dapagliflozin, metformin - EBYMECT

⁹⁰ In accordance with Article 107p-q of Directive 2001/83/EC

⁹¹ 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

Applicant: AstraZeneca AB

PRAC Rapporteur: Annika Folin

Scope: Update of section 4.4 of the SmPC based on the final results of a PASS (listed as a category 3 study in the RMPs): a meta-analysis across the following studies: 1) study D1690C00018: a 24-week, multicentre, randomised, double-blind, age-stratified, placebo controlled, phase 3 study with a 80-week extension period to evaluate the efficacy and safety of dapagliflozin 10 mg once daily in patients with type 2 diabetes mellitus (T2DM), cardiovascular disease (CVD) and hypertension who exhibit inadequate glycaemic control on usual care; 2) study D1690C00019: A 24-week, multicentre, randomised, double-blind, age-stratified, placebo controlled phase 3 study with an 80-week extension period to evaluate the efficacy and safety of dapagliflozin 10 mg once daily in patients with T2DM and CVD, who exhibit inadequate glycaemic control on usual care; 3) study D1693C00001 (DECLARE): a multicentre, randomized, double-blind, placebo-controlled trial to evaluate the effect of dapagliflozin 10 mg once daily on the incidence of cardiovascular death, myocardial infarction or ischemic stroke in patients with T2DM, for analysis of lower limb amputation and relevant preceding adverse events. The package leaflets are updated accordingly. In addition, the MAH took the opportunity to implement a minor editorial change in the product information of Edistride (dapagliflozin). The RMPs (version 19 for Edistride/Forxiga (dapagliflozin) and version 12 for Ebymect/Xigduo (dapagliflozin/metformin) are updated accordingly

17.4.4. Degarelix - FIRMAGON (CAP) - EMEA/H/C/000986/II/0037

Applicant: Ferring Pharmaceuticals A/S

PRAC Rapporteur: Ghania Chamouni

Scope: Update of Annex II-D on 'Conditions or restrictions with regard to the safe and effective use of the medicinal product' in order to revise the additional risk minimisation measures (educational programme) based on previous assessment and results from study FE 200486 CS39: a prospective observational safety study in patients with advanced prostate cancer treated with Firmagon (degarelix) or a gonadotropin-releasing hormone (GnRH) agonist conducted in multiple countries in the European Economic Area (EEA). As a consequence, the RMP (version 16.0) is updated accordingly. The MAH took the opportunity to bring the RMP in line with revision 2 of GVP module V on 'Risk management systems', to bring the product information in line with the latest quality review of documents (QRD) template (version 10.1) and to propose a combination of different strengths in the product information

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

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

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. Safinamide - XADAGO (CAP) - EMEA/H/C/002396/II/0035

Applicant: Zambon S.p.A.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Submission of the final clinical study report (CSR) for study Z7219N02 (listed as a category 3 study in the RMP): a European multicentre retrospective-prospective cohort study to observe safinamide safety profile and pattern of use in clinical practice during the first post-commercialisation phase (SYNAPSES). The RMP (version 6.2) 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 001.8

Applicant: AstraZeneca AB

PRAC Rapporteur: Adam Przybylkowski

Scope: MAH's response to ANX 001.7 [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 January 2020

17.5.2. Aclidinium - EKLIRA GENUAIR (CAP) - EMEA/H/C/002211/ANX 001.8

Applicant: AstraZeneca AB

PRAC Rapporteur: Adam Przybylkowski

Scope: MAH's response to ANX 001.7 [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 January 2020

17.5.3. Aclidinium, formoterol fumarate dihydrate - BRIMICA GENUAIR (CAP) - EMEA/H/C/003969/ANX 003.5

Applicant: AstraZeneca AB

PRAC Rapporteur: Adam Przybylkowski

Scope: MAH's response to ANX 003.4 [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 January 2020

17.5.4. [Aclidinium, formoterol fumarate dihydrate - DUAKLIR GENUAIR \(CAP\) - EMEA/H/C/003745/ANX 003.5](#)

Applicant: AstraZeneca AB

PRAC Rapporteur: Adam Przybylkowski

Scope: MAH's response to ANX 003.4 [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 January 2020

17.5.5. [Adalimumab - HUMIRA \(CAP\) - EMEA/H/C/000481/MEA 065.10](#)

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Eleventh interim annual report for study P10-023, a psoriasis patient registry: a 10-year, post-marketing observational study to assess the long term safety of Humira (adalimumab) in adult patients with chronic plaque psoriasis (PS) [final registry report expected in February 2023] together with MAH's response to MEA 065.9 adopted in May 2019

17.5.6. [Abatacept - ORENCIA \(CAP\) - EMEA/H/C/000701/MEA 048.8](#)

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Kimmo Jaakkola

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

17.5.7. [Avelumab - BAVENCIO \(CAP\) - EMEA/H/C/004338/MEA 002.2](#)

Applicant: Merck Europe B.V.

PRAC Rapporteur: Hans Christian Siersted

Scope: First yearly interim progress update report for study MS100070-0031 (listed as a category 3 study in the RMP): a non-interventional cohort study to assess characteristics and management of patients with Merkel cell carcinoma (MCC) in Germany [final study report expected in Q1/2024]

17.5.8. Cabozantinib - CABOMETYX (CAP) - EMEA/H/C/004163/MEA 001.3

Applicant: Ipsen Pharma

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to MEA 001.2 [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] as per the request for supplementary information (RSI) adopted in January 2020

17.5.9. Damoctocog alfa pegol - JIVI (CAP) - EMEA/H/C/004054/MEA 003

Applicant: Bayer AG

PRAC Rapporteur: Menno van der Elst

Scope: Tenth annual European Haemophilia Safety Surveillance (EUHASS) report for study 14149 (listed as a category 3 study in the RMP): evaluation of cases with adverse events (AEs) of special interest in the EUHASS registry [final clinical study report (CSR) expected in 2024]

17.5.10. Lesinurad - ZURAMPIC (CAP) - EMEA/H/C/003932/ANX 002.3

Applicant: Grunenthal GmbH

PRAC Rapporteur: Eva Segovia

Scope: Annual progress report for study D5310R00016: an observational PASS of lesinurad patients (SATURATES) to further assess cardiovascular (CV) safety with a focus on major adverse cardiovascular events (MACE) in gout patients treated with Zurampic (lesinurad) in combination with a xanthine oxidase inhibitor (XOI)

17.5.11. Levofloxacin - QUINSAIR (CAP) - EMEA/H/C/002789/ANX 004.4

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Second annual interim report for a post-marketing, open-label, observational safety study of Quinsair (nebulised levofloxacin hemihydrate) in patients with cystic fibrosis and chronic *Pseudomonas aeruginosa* infection, using data collected through European cystic fibrosis registries [final clinical study report (CSR) expected in June 2022]

17.5.12. Nomegestrol acetate, estradiol - ZOELY (CAP) - EMEA/H/C/001213/ANX 011.5

Applicant: Theramex Ireland Limited

PRAC Rapporteur: Adrien Inoubli

Scope: Fourth interim report for a prospective observational study to assess the risk of venous thromboembolic events (VTE) and arterial thromboembolic events (ATE) in nomegestrel/estradiol users compared with the VTE risk in users of combined oral contraceptives containing levonorgestrel (as imposed in accordance with Article 10(a) of Regulation (EC) No 726/2004)

17.5.13. Octocog alfa - KOGENATE BAYER (CAP) - EMEA/H/C/000275/MEA 086.8

Applicant: Bayer AG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Tenth annual European Haemophilia Safety Surveillance (EUHASS) report for study 14149 (listed as a category 3 study in the RMP): evaluation of cases with adverse events (AEs) of special interest in the EUHASS registry [final clinical study report (CSR) expected in December 2021]

17.5.14. Octocog alfa - KOVALTRY (CAP) - EMEA/H/C/003825/MEA 004.2

Applicant: Bayer AG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Tenth annual European Haemophilia Safety Surveillance (EUHASS) report for study 14149 (listed as a category 3 study in the RMP): evaluation of cases with adverse events (AEs) of special interest in the EUHASS registry [final clinical study report (CSR) expected in December 2021]

17.5.15. Venetoclax - VENCLYXTO (CAP) - EMEA/H/C/004106/MEA 006.2

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Eva Jirsová

Scope: Third interim clinical study report (CSR) for study M12-175 (listed as a category 3 study in the RMP): a phase 1 study evaluating the safety and pharmacokinetics of venetoclax (ABT-199) in subjects with relapsed or refractory chronic lymphocytic leukaemia and non-Hodgkin lymphoma; together with MAH's response to MEA 006.1 adopted in December 2019

17.6. Others

17.6.1. Belimumab - BENLYSTA (CAP) - EMEA/H/C/002015/MEA 031

Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Feasibility report for study D2019-6798: review of the possibility to undertake a

PASS within established registries, to further characterise the safety of Benlysta (belimumab) in children with systemic lupus erythematosus (SLE) with particular focus on infections (from the conclusions of variation II/0062 on the extension of the indication to include patients with systemic lupus erythematosus (SLE) aged 5 years and older adopted in September 2019)

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

Applicant: Laboratoires CTRS

PRAC Rapporteur: Sofia Trantz

Scope: Annual reassessment of the marketing authorisation

18.2. Conditional renewals of the marketing authorisation

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

Applicant: PTC Therapeutics International Limited

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Conditional renewal of the marketing authorisation

18.2.2. Avelumab - BAVENCIO (CAP) - EMEA/H/C/004338/R/0017 (without RMP)

Applicant: Merck Europe B.V.

PRAC Rapporteur: Hans Christian Siersted

Scope: Conditional renewal of the marketing authorisation

18.2.3. Larotrectinib - VITRAKVI (CAP) - EMEA/H/C/004919/R/0006 (without RMP)

Applicant: Bayer AG

PRAC Rapporteur: Rugile Pilviniene

Scope: Conditional renewal of the marketing authorisation

18.3. Renewals of the marketing authorisation

18.3.1. Aripiprazole - ARIPIPRAZOLE ACCORD (CAP) - EMEA/H/C/004021/R/0019 (without RMP)

Applicant: Accord Healthcare S.L.U.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: 5-year renewal of the marketing authorisation

18.3.2. Brivaracetam - BRIVIACT (CAP) - EMEA/H/C/003898/R/0025 (without RMP)

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Adam Przybylkowski

Scope: 5-year renewal of the marketing authorisation

18.3.3. Cinacalcet - CINACALCET MYLAN (CAP) - EMEA/H/C/004014/R/0011 (without RMP)

Applicant: Mylan S.A.S

PRAC Rapporteur: Ulla Wändel Liminga

Scope: 5-year renewal of the marketing authorisation

18.3.4. Dapagliflozin - EDISTRIDE (CAP) - EMEA/H/C/004161/R/0038 (without RMP)

Applicant: AstraZeneca AB

PRAC Rapporteur: Annika Folin

Scope: 5-year renewal of the marketing authorisation

18.3.5. Dapagliflozin, metformin - EBYMECT (CAP) - EMEA/H/C/004162/R/0046 (without RMP)

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: 5-year renewal of the marketing authorisation

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

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Martin Huber

Scope: 5-year renewal of the marketing authorisation

18.3.7. Guanfacine - INTUNIV (CAP) - EMEA/H/C/003759/R/0022 (without RMP)

Applicant: Shire Pharmaceuticals Ireland Limited

PRAC Rapporteur: Maria del Pilar Rayon

Scope: 5-year renewal of the marketing authorisation

18.3.8. Idarucizumab - PRAXBIND (CAP) - EMEA/H/C/003986/R/0019 (with RMP)

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Menno van der Elst

Scope: 5-year renewal of the marketing authorisation

18.3.9. Idebenone - RAXONE (CAP) - EMEA/H/C/003834/R/0020 (without RMP)

Applicant: Santhera Pharmaceuticals (Deutschland) GmbH

PRAC Rapporteur: Amelia Cupelli

Scope: 5-year renewal of the marketing authorisation

18.3.10. Isavuconazole - CRESEMBA (CAP) - EMEA/H/C/002734/R/0027 (without RMP)

Applicant: Basilea Pharmaceutica Deutschland GmbH

PRAC Rapporteur: Adam Przybylkowski

Scope: 5-year renewal of the marketing authorisation

18.3.11. Lumacaftor, ivacaftor - ORKAMBI (CAP) - EMEA/H/C/003954/R/0056 (with RMP)

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: 5-year renewal of the marketing authorisation

18.3.12. Pemetrexed - CIAMBRA (CAP) - EMEA/H/C/003788/R/0006 (without RMP)

Applicant: Menarini International Operations Luxembourg S.A.

PRAC Rapporteur: Ghania Chamouni

Scope: 5-year renewal of the marketing authorisation

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

Applicant: Omeros Ireland Limited

PRAC Rapporteur: Jan Neuhauser

Scope: 5-year renewal of the marketing authorisation

18.3.14. Susoctocog alfa - OBIZUR (CAP) - EMEA/H/C/002792/R/0033 (with RMP)

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: 5-year renewal of the marketing authorisation

18.3.15. Talimogene laherparepvec - IMLYGIC (CAP) - EMEA/H/C/002771/R/0039 (without RMP)

Applicant: Amgen Europe B.V., ATMP⁹²

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: 5-year renewal of the marketing authorisation

18.3.16. Velaglucerase alfa - VPRIV (CAP) - EMEA/H/C/001249/R/0045 (without RMP)

Applicant: Shire Pharmaceuticals Ireland Limited

PRAC Rapporteur: Martin Huber

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 11-14 May 2020 meeting.

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Sabine Straus	Chair	The Netherlands	No interests declared	Full involvement
Jan Neuhauser	Member	Austria	No interests declared	Full involvement
Sonja Hrabcik	Alternate	Austria	No interests declared	Full involvement
Jean-Michel Dogné	Member	Belgium	No interests declared	Full involvement

⁹² Advanced therapy medicinal product

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Laurence de Fays	Alternate	Belgium	No restrictions applicable to this meeting	Full involvement
Maria Popova-Kiradjieva	Member	Bulgaria	No interests declared	Full involvement
Nikica Mirošević Skvrce	Member	Croatia	No interests declared	Full involvement
Željana Margan Koletić	Alternate	Croatia	No interests declared	Full involvement
Helena Panayiotopoulou	Member	Cyprus	No interests declared	Full involvement
Panagiotis Psaras	Alternate	Cyprus	No interests declared	Full involvement
Eva Jirsová	Member	Czech Republic	No interests declared	Full involvement
Jana Lukacisinova	Alternate	Czech Republic	No interests declared	Full involvement
Anette Stark	Member	Denmark	No interests declared	Full involvement
Hans Christian Siersted	Alternate	Denmark	No 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 interests declared	Full involvement
Adrien Inoubli	Alternate	France	No interests declared	Full involvement
Martin Huber	Member (Vice-Chair)	Germany	No interests declared	Full involvement
Brigitte Keller-Stanislawski	Alternate	Germany	No interests declared	Full involvement
Agni Kapou	Member	Greece	No interests declared	Full involvement
Sophia Trantza	Alternate	Greece	No restrictions	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			applicable to this meeting	
Julia Pallos	Member	Hungary	No restrictions applicable to this meeting	Full involvement
Guðrún Stefánsdóttir	Member	Iceland	No restrictions applicable to this meeting	Full involvement
Rhea Fitzgerald	Member	Ireland	No restrictions applicable to this meeting	Full involvement
Ronan Grimes	Alternate	Ireland	No interests declared	Full involvement
Amelia Cupelli	Member	Italy	No interests declared	Full involvement
Ilaria Baldelli	Alternate	Italy	No interests declared	Full involvement
Zane Neikena	Member	Latvia	No interests declared	Full involvement
Rugile Pilviniene	Member	Lithuania	No interests declared	Full involvement
Marcel Bruch	Member	Luxembourg	No interests declared	Full involvement
Benjamin Micallef	Alternate	Malta	No interests declared	Full involvement
Menno van der Elst	Member	Netherlands	No interests declared	Full involvement
Liana Gross-Martirosyan	Alternate	Netherlands	No interests declared	Full involvement
David Olsen	Member	Norway	No restrictions applicable to this meeting	Full involvement
Karen Pernille Harg	Alternate	Norway	No interests declared	Full involvement
Adam Przybylkowski	Member	Poland	No interests declared	Full involvement
Katarzyna Ziolkowska	Alternate	Poland	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Ana Diniz Martins	Member	Portugal	No interests declared	Full involvement
Marcia Silva	Alternate	Portugal	No interests declared	Full involvement
Alexandra - Maria Spurni	Alternate	Romania	No interests declared	Full involvement
Michal Radik	Member	Slovakia	No restrictions applicable to this meeting	Full involvement
Marek Juracka	Alternate	Slovakia	No interests declared	Full involvement
Jasmina Klopčič	Alternate	Slovenia	No interests declared	Full involvement
Eva Segovia	Member	Spain	No interests declared	Full involvement
Maria del Pilar Rayon	Alternate	Spain	No interests declared	Full involvement
Ulla Wändel Liminga	Member	Sweden	No interests declared	Full involvement
Annika Folin	Alternate	Sweden	No interests declared	Full involvement
Birgitta Grundmark	Member	Independent scientific expert	No interests declared	Full involvement
Daniel Morales	Member	Independent scientific expert	No interests declared	Full involvement
Hedvig Nordeng	Member	Independent scientific expert	No interests declared	Full involvement
Antoine Pariente	Member	Independent scientific expert	No restrictions applicable to this meeting	Full involvement
Stefan Weiler	Member	Independent scientific expert	No restrictions applicable to this meeting	Full involvement
Raymond Anderson	Member	Healthcare Professionals' Representative	No interests declared	Full involvement
Roberto Frontini	Alternate	Healthcare Professionals' Representative	No restrictions	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			applicable to this meeting	
Cathalijne van Doorne	Member	Patients' Organisation Representative	No interests declared	Full involvement
Ivana Bahnik	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
Livia Puljak	Expert - via telephone*	Croatia	No interests declared	Full involvement
Karin Susanne Erneholt	Expert - via telephone*	Denmark	No restrictions applicable to this meeting	Full involvement
Astrid Munch Hestbæk	Expert - via telephone*	Denmark	No restrictions applicable to this meeting	Full involvement
Caroline Marie Voss	Expert - via telephone*	Denmark	No interests declared	Full involvement
Sandra Wallerek	Expert - via telephone*	Denmark	No interests declared	Full involvement
Päivi Susanna Worsøe	Expert - via telephone*	Denmark	No restrictions applicable to this meeting	Full involvement
Martin Zahle Larsen	Expert - via telephone*	Denmark	No interests declared	Full involvement
Krõõt Aab	Expert - via telephone*	Estonia	No interests declared	Full involvement
Caroline Auriche	Expert - via telephone*	France	No interests declared	Full involvement
Anissa Benlazar	Expert - via telephone*	France	No interests declared	Full involvement
Henning Brohmann	Expert - via telephone*	Germany	No interests declared	Full involvement
Christine Greiner	Expert - via telephone*	Germany	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
Marion Haberkamp	Expert – via telephone*	Germany	No interests declared	Full involvement
Dennis Lex	Expert – via telephone*	Germany	No restrictions applicable to this meeting	Full involvement
Kerstin Loeschcke	Expert – via telephone*	Germany	No interests declared	Full involvement
Vivien Molitor	Expert – via telephone*	Germany	No interests declared	Full involvement
Jan Müller-Berghaus	Expert – via telephone*	Germany	No interests declared	Full involvement
Karin Seifert	Expert – via telephone*	Germany	No restrictions applicable to this meeting	Full involvement
Martina Schuessler-Lenz	Expert – via telephone*	Germany	No interests declared	Full involvement
Maura O'Donovan	Expert - via telephone*	Ireland	No restrictions applicable to this meeting	Full involvement
Ida Bergva Aas	Expert - via telephone*	Norway	No interests declared	Full involvement
Fernando de Andres-Trelles	Expert - via telephone*	Spain	No restrictions applicable to this meeting	Full involvement
Charlotte Backman	Expert – via telephone*	Sweden	No interests declared	Full involvement
Lisbeth Barkholt	Expert – via telephone*	Sweden	No interests declared	Full involvement
Karin Nylén	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, 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/>