27 October 2022
EMA/PRAC/822311/2022
Human Medicines Division

Pharmacovigilance Risk Assessment Committee (PRAC)

Minutes of the meeting of the meeting on 07-10 February 2022

Chair: Sabine Straus – Vice-Chair: Martin Huber

Disclaimers

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

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

Note on access to documents

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

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1. Introduction

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

The Chairperson opened the meeting by welcoming all participants. Due to the coronavirus (COVID-19) outbreak, and the associated EMA Business Continuity Plan (BCP), the meeting was held remotely.

In accordance with the Agency's policy on handling of declarations of interests of scientific Committees' members and experts, based on the declarations of interest submitted by the Committee members, alternates and experts and on the topics in the agenda of the meeting, the Committee Secretariat announced the restricted involvement of some Committee members, alternates and experts for concerned agenda topics.

Discussions, deliberations and voting took place in full respect of the restricted involvement of Committee members and experts in line with the relevant provisions of the Rules of Procedure. All decisions, recommendations and advice were agreed by consensus, unless otherwise specified.

The Chair welcomed the new member(s) and alternate(s) and thanked the departing members/alternates for their contributions to the Committee.

1.2. Agenda of the meeting on 07-10 February 2022

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

1.3. Minutes of the previous meeting on 10-13 January 2022

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 10-13 January 2022 were published on the EMA website on 07 October 2022.

1.4. Procedures for finalisation

None

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

2.1. Newly triggered procedures

None

2.2. Ongoing procedures

None

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

3.1. Newly triggered procedures

3.1.1. Janus kinase (JAK) inhibitors[1]: abrocitinib - CIBINQO (CAP); baricitinib - OLUMIANT (CAP); filgotinib - JYSELECA (CAP); tofacitinib - XELJANZ (CAP); upadacitinib - RINVOQ (CAP) – EMEA/H/A-20/1517

Applicant(s): AbbVie Deutschland GmbH & Co. KG (Rinvoq), Eli Lilly Nederland B.V. (Olumiant), Galapagos N.V. (Jyseleca), Pfizer Europe MA EEIG (Cibinqo, Xeljanz)

PRAC Rapporteur: Ulla Wändel Liminga; PRAC Co-rapporteurs: Liana Gross-Martirosyan (Xeljanz (tofacitinib), Olumiant (baricitinib)); Nikica Mirošević Skvrce (Rinvoq (upadacitinib), Jyseleca (filgotinib), Cibinqo (abrocitinib))

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

Background

The European Commission (EC) sent a letter of notification dated 28 January 2022 of a referral under Article 20 of Regulation (EC) No 726/2004 for the review of Janus kinase inhibitors (JAKi), a group of oral immunomodulatory disease-modifying antirheumatic drugs (DMARDs) indicated in the treatment of several chronic inflammatory disorders such as rheumatoid arthritis, atopic dermatitis, psoriatic arthritis, juvenile idiopathic arthritis, ankylosing spondylitis and ulcerative colitis. These are namely Xeljanz (tofacitinib), Cibinqo (abrocitinib), Olumiant (baricitinib), Jyseleca (filgotinib) and Rinvoq (upadacitinib).

The review was initiated after evaluation of the preliminary analysis of the final results from study A3921133[2] (ORAL surveillance) for Xeljanz (tofacitinib) showing an increase incidence of major adverse cardiovascular events (MACE) including myocardial infarction, stroke and cardiovascular death and a higher risk of malignancy with tofacitinib compared to tumour necrosis fibrosis (TNF)-inhibitors in patients with rheumatoid arthritis. These results were assessed in a signal procedure (EPITT 19382) finalised at PRAC in June 2021 and further evaluated in an ongoing variation procedure (II/0044) to implement the recommended changes. For further background, see PRAC minutes June 2021 and PRAC minutes December 2021[3]. Final results of study A3921133 have become available and indicate that in addition to the higher incidence of MACE and malignancies reported in the preliminary analysis, a higher incidence of venous thromboembolism (VTE), all-cause of mortality and serious infections in patients treated with tofacitinib compares to TNF-inhibitors. In addition, preliminary results from study I4V-MC-B023[4] for Olumiant (baricitinib) reviewed in the context of an ongoing variation procedure (II/0031) suggest also an increased risk of MACE and VTE in patients with rheumatoid arthritis treated with Olumiant (baricitinib) compared to those treated with TNF-inhibitors. For further background, see PRAC minutes January 2022.

[1] Indicated for the treatment of inflammatory disorders
[2] A phase 3b/4 randomised safety endpoint study of 2 doses of tofacitinib in comparison to a tumour necrosis fibrosis (TNF) inhibitor in subjects with rheumatoid arthritis
[3] Held 29 November – 02 December 2021
[4] A retrospective observational study to compare baricitinib relative to the standard of care

Considering the seriousness of the emerging data and the comparable mechanism of actions of all JAKi indicated in inflammatory disorders, the EC requested EMA to assess the above concerns and their impact on the benefit-risk balance of JAKi used in the treatment of chronic inflammatory disorders and to give its opinion by 30 September 2022 whether the marketing authorisations for Xeljanz (tofacitinib), Cibinqo (abrocitinib), Olumiant (baricitinib), Jyseleca (filgotinib) and Rinvoq (upadacitinib) should be maintained, varied, suspended or revoked. In addition, the EC requested EMA to give its opinion as to whether provisional measures were necessary to ensure the safe and effective use of the medicinal products.

Discussion

PRAC noted the notification letter from the EC.

PRAC appointed Ulla Wändel Liminga as Rapporteur along with Liana Gross-Martirosyan (Xeljanz (tofacitinib), Olumiant (baricitinib)) and Nikica Mirošević Skvrce (Cibinqo (abrocitinib), Jyseleca (filgotinib), Rinvoq (upadacitinib)) as Co-rapporteurs for the procedure.

PRAC discussed a list of questions (LoQ) to be addressed during the procedure together with a timetable for conducting the review. PRAC also discussed the need for a public hearing.

Summary of recommendation(s)/conclusions

- PRAC adopted a LoQ (EMA/PRAC/68283/2022) to the MAHs and a timetable for the procedure (EMA/PRAC/68282/2022).
- PRAC discussed the option to conduct a public hearing in the context of the current procedure according to the pre-defined criteria set out in the rules of procedure[5] (EMA/363479/2015). It was agreed by the Committee that at this stage in the assessment, in light of the currently available data and the need to determine the appropriate approach to stakeholder engagement, a public hearing would not be appropriate. PRAC can reconsider this at a later stage of the procedure, as needed.

See EMA press release (EMA/71746/2022) entitled 'EMA starts safety review of Janus kinase inhibitors for inflammatory disorders'.

3.2. Ongoing procedures

3.2.1. Chlormadinone (NAP); chlormadinone, ethinylestradiol (NAP); nomegestrol (NAP); nomegestrol, estradiol – ZOELY (CAP), NAP - EMEA/H/A-31/1510

Applicant(s): Theramex Ireland Limited (Zoely), various

PRAC Rapporteur: Martin Huber; PRAC Co-rapporteur: Željana Margan Koletić

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

Background

A referral procedure under Article 31 of Directive 2001/83/EC is ongoing for the review of nomegestrol- and chlormadinone-containing product(s) following new data from two epidemiological studies conducted in France in women taking these medicines. The results

[5] Rules of procedure on the organisation and conduct of public hearings at PRAC

showed an increase of reported cases of meningioma depending on the dose and duration of treatment and suggested that the risk may be greater in women taking nomegestrol or chlormadinone for several years. The studies also showed that after women had stopped taking nomegestrol or chlormadinone for one year or more, the risk of developing these tumours was reduced and comparable to the risk in people who never used these medicines. For further background, see PRAC minutes October 2021[6].

Summary of recommendation(s)/conclusions

- PRAC discussed the assessment reports issued by the Rapporteurs.
- PRAC adopted a list of outstanding issues (LoOI) to be addressed by the MAHs in accordance with a revised timetable (EMA/PRAC/522598/2021 – Rev. 1).
- PRAC agreed on a list of questions (LoQ) inviting the study authors of the EPI-PHARE[7] retrospective cohort studies[8] [9] on the risk of intracranial meningioma after prolonged exposure to either nomegestrol acetate or chlormadinone acetate, to address questions on the studies.

3.3. Procedures for finalisation

None

3.4. Re-examination procedures[10]

None

3.5. Others

None

4. Signals assessment and prioritisation[11]

4.1. New signals detected from EU spontaneous reporting systems

None

[6] Held 27-30 September 2021
[7] Epidemiologie des produits de Santé (EPI-PHARE)
[8] Nguyen P, Hoisnard L, Neumann A, Zureik M, Weill A. Utilisation prolongée de l'acétate de nomégestrol et risque de méningiome intracrânien: une étude de cohorte à partir des données du SNDS. EPI-PHARE, 2021. https://www.epi-phare.fr/app/uploads/2021/04/epi-phare_rapport_acetate_nomegetrol_avril-2021.pdf
[9] Nguyen P, Hoisnard L, Neumann A, Zureik M, Weill A. Utilisation prolongée de l'acétate de chlormadinone et risque de méningiome intracrânien: une étude de cohorte à partir des données du SND. EPI-PHARE, 2021. https://www.epi-phare.fr/app/uploads/2021/04/epi-phare_rapport_acetate_chlormadinone_avril-2021-1.pdf
[10] Re-examination of PRAC recommendation under Article 32 of Directive 2001/83/EC
[11] 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

4.2. New signals detected from other sources

4.2.1. Coronavirus (COVID-19) mRNA[12] vaccine (nucleoside-modified) - SPIKEVAX (CAP)

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Signal of amenorrhea

EPITT 19781 – New signal

Lead Member State(s): DE, DK

Background

Coronavirus (COVID-19) nucleoside-modified messenger ribonucleic acid (mRNA) vaccine is indicated, as Spikevax, for active immunisation to prevent COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 12 years of age and older.

A signal of amenorrhea was identified by Norway based on spontaneous case reports as well as the initial findings from a survey from a population-based Norwegian young adult cohort suggesting an increase in the incidence of menstrual changes among young women after vaccination against coronavirus. Denmark confirmed that the signal needed initial analysis and prioritisation by PRAC.

Discussion

Having considered the available evidence, including post-marketing cases and published literature, PRAC agreed that additional investigation is necessary to evaluate the occurrence of amenorrhea following vaccination with Spikevax (COVID-19 mRNA vaccine (nucleoside-modified)). Therefore, PRAC agreed that further assessment of the signal is warranted.

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

Summary of recommendation(s)

- The MAH for Spikevax (COVID-19 messenger ribonucleic acid (mRNA) vaccine (nucleoside-modified)) should submit to EMA, within 60 days, a detailed review of cases of amenorrhoea from all sources, including clinical trials, the literature and post-marketing data. The MAH should perform a literature review on the possible association between amenorrhoea and the vaccine, including the publications from *Lill Trogstad et al*[13], *Nguyen et al*[14] and *Edelman et al*[15]. In addition, the MAH should provide a discussion on pathophysiology of amenorrhea and whether any biological plausibility/mechanism of action can be identified. The MAH should also provide data on exposure of females of childbearing potential. Based on these reviews, the MAH should discuss the need for risk minimisation measures, including a proposal to update the product information and/or the RMP as warranted.

[12] Messenger ribonucleic acid
[13] Trogstad, Lill, Increased occurrence of menstrual disturbances in 18- to 30-year-old women after COVID-19 vaccination (January 1, 2022)
[14] Nguyen BT, Pang RD, Nelson AL, Pearson JT, Benhar Noccioli E, Reissner HR, et al. (2021) Detecting variations in ovulation and menstruation during the COVID-19 pandemic, using real-world mobile app data. PLoS ONE 16(10): e0258314. https://doi.org/10.1371/journal.pone.0258314
[15] Edelman A, Boniface ER, Benhar E, Han L, Matteson KA, Favaro C, Pearson JT, Darney BG. Association Between Menstrual Cycle Length and Coronavirus Disease 2019 (COVID-19) Vaccination: A U.S. Cohort. Obstet Gynecol. 2022 Jan 5. doi: 10.1097/AOG.0000000000004695. Epub ahead of print. PMID: 34991109

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

4.2.2. Coronavirus (COVID-19) mRNA[16] vaccine (nucleoside-modified) - SPIKEVAX (CAP)

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Signal of heavy menstrual bleeding

EPITT 19780 – New signal

Lead Member State(s): DE, DK

Background

Coronavirus (COVID-19) nucleoside-modified messenger ribonucleic acid (mRNA) vaccine is indicated, as Spikevax, for active immunisation to prevent COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 12 years of age and older.

A signal of heavy menstrual bleeding was identified by Norway based on spontaneous case reports and published studies as well as the initial findings from a survey from a population-based Norwegian young adult cohort suggesting an increase in the incidence of menstrual changes among young women after vaccination against coronavirus. Denmark confirmed that the signal needed initial analysis and prioritisation by PRAC.

Discussion

Having considered the available evidence, including post-marketing cases and the published literature, PRAC agreed that additional investigation is necessary to evaluate the occurrence of heavy menstrual bleeding following vaccination with Spikevax (COVID-19 mRNA vaccine (nucleoside-modified)). Therefore, PRAC agreed that further assessment of the signal is warranted.

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

Summary of recommendation(s)

- The MAH for Spikevax (COVID-19 messenger ribonucleic acid (mRNA) vaccine (nucleoside-modified)) should submit to EMA, within 60 days, a detailed review of cases of heavy menstrual bleeding from all sources, including clinical trials, the literature and post-marketing data. The MAH should perform a literature review on the possible association between amenorrhoea and the vaccine, including the publications from *Lill Trogstad et al*[17], *Nguyen et al*[18] and *Edelman et al*[19]. In addition, the MAH should provide a discussion on pathophysiology of heavy menstrual bleeding and whether any biological plausibility/mechanism of action can be identified. The MAH should also provide data on exposure of females of childbearing potential. Based on these reviews,

[16] Messenger ribonucleic acid
[17] Trogstad, Lill, Increased occurrence of menstrual disturbances in 18- to 30-year-old women after COVID-19 vaccination (January 1, 2022)
[18] Nguyen BT, Pang RD, Nelson AL, Pearson JT, Benhar Noccioli E, Reissner HR, et al. (2021) Detecting variations in ovulation and menstruation during the COVID-19 pandemic, using real-world mobile app data. PLoS ONE 16(10): e0258314. https://doi.org/10.1371/journal.pone.0258314
[19] Edelman A, Boniface ER, Benhar E, Han L, Matteson KA, Favaro C, Pearson JT, Darney BG. Association Between Menstrual Cycle Length and Coronavirus Disease 2019 (COVID-19) Vaccination: A U.S. Cohort. Obstet Gynecol. 2022 Jan 5. doi: 10.1097/AOG.0000000000004695. Epub ahead of print. PMID: 34991109

the MAH should discuss the need for risk minimisation measures, including a proposal to update the product information and/or the RMP as warranted.

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

4.2.3. Tozinameran - COMIRNATY (CAP)

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: David Olsen

Scope: Signal of amenorrhea

EPITT 19784 – New signal

Lead Member State(s): NL, NO

Background

Tozinameran is a nucleoside-modified messenger ribonucleic acid (mRNA) vaccine indicated, as Comirnaty, for the active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 12 years of age and older.

A signal of amenorrhea was identified by Norway based on spontaneous case reports as well as the initial findings from a population-based Norwegian young adult cohort suggesting an increase in the incidence of menstrual changes among young women after vaccination against coronavirus. The Netherlands confirmed that the signal needed initial analysis and prioritisation by PRAC.

Discussion

Having considered the available evidence, including post-marketing cases and published literature, PRAC agreed that additional investigation is necessary to evaluate the occurrence of amenorrhea following vaccination with Comirnaty (tozinameran). Therefore, PRAC agreed that further assessment of the signal is warranted.

PRAC appointed David Olsen as Rapporteur for the signal.

Summary of recommendation(s)

- The MAH for Comirnaty (tozinameran) should submit to EMA, within 60 days, a detailed review of cases of amenorrhoea from all sources, including clinical trials, the literature and post-marketing data. The MAH should perform a literature review on the possible association between amenorrhoea and the vaccine, including the publications from *Lill Trogstad et al*[20], *Nguyen et al*[21] and *Edelman et al*[22]. In addition, the MAH should provide a discussion on pathophysiology of amenorrhea and whether any biological plausibility/mechanism of action can be identified. The MAH should also provide data on exposure of females of childbearing potential. Based on these reviews, the MAH should

[20] Trogstad, Lill, Increased occurrence of menstrual disturbances in 18- to 30-year-old women after COVID-19 vaccination (January 1, 2022)
[21] Nguyen BT, Pang RD, Nelson AL, Pearson JT, Benhar Noccioli E, Reissner HR, et al. (2021) Detecting variations in ovulation and menstruation during the COVID-19 pandemic, using real-world mobile app data. PLoS ONE 16(10): e0258314. https://doi.org/10.1371/journal.pone.0258314
[22] Edelman A, Boniface ER, Benhar E, Han L, Matteson KA, Favaro C, Pearson JT, Darney BG. Association Between Menstrual Cycle Length and Coronavirus Disease 2019 (COVID-19) Vaccination: A U.S. Cohort. Obstet Gynecol. 2022 Jan 5. doi: 10.1097/AOG.0000000000004695. Epub ahead of print. PMID: 34991109

discuss the need for risk minimisation measures, including a proposal to update the product information and/or the RMP as warranted.

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

4.2.4. Tozinameran - COMIRNATY (CAP)

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: David Olsen

Scope: Signal of heavy menstrual bleeding

EPITT 19783 – New signal

Lead Member State(s): NL, NO

Background

Tozinameran is a nucleoside-modified messenger ribonucleic acid (mRNA) vaccine indicated, as Comirnaty, for the active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 12 years of age and older.

A signal of heavy menstrual bleeding was identified by Norway based on spontaneous case reports and published studies as well as the initial findings from a population-based Norwegian young adult cohort suggesting an increase in the incidence of menstrual changes among young women after vaccination against coronavirus. The Netherlands confirmed that the signal needed initial analysis and prioritisation by PRAC.

Discussion

Having considered the available evidence, including post-marketing cases and the published literature, PRAC agreed that additional investigation is necessary to evaluate the occurrence of heavy menstrual bleeding following vaccination with Comirnaty (tozinameran). Therefore, PRAC agreed that further assessment of the signal is warranted.

PRAC appointed David Olsen as Rapporteur for the signal.

Summary of recommendation(s)

- The MAH for Comirnaty (tozinameran) should submit to EMA, within 60 days, a detailed review of cases of heavy menstrual bleeding from all sources, including clinical trials, the literature and post-marketing data. The MAH should perform a literature review on the possible association between amenorrhoea and the vaccine, including the publications from *Lill Trogstad et al*[23], *Nguyen et al*[24] and *Edelman et al*[25]. In addition, the MAH should provide a discussion on pathophysiology of heavy menstrual bleeding and whether any biological plausibility/mechanism of action can be identified. The MAH should also provide data on exposure of females of childbearing potential. Based on

[23] Trogstad, Lill, Increased occurrence of menstrual disturbances in 18- to 30-year-old women after COVID-19 vaccination (January 1, 2022)
[24] Nguyen BT, Pang RD, Nelson AL, Pearson JT, Benhar Noccioli E, Reissner HR, et al. (2021) Detecting variations in ovulation and menstruation during the COVID-19 pandemic, using real-world mobile app data. PLoS ONE 16(10): e0258314. https://doi.org/10.1371/journal.pone.0258314
[25] Edelman A, Boniface ER, Benhar E, Han L, Matteson KA, Favaro C, Pearson JT, Darney BG. Association Between Menstrual Cycle Length and Coronavirus Disease 2019 (COVID-19) Vaccination: A U.S. Cohort. Obstet Gynecol. 2022 Jan 5. doi: 10.1097/AOG.0000000000004695. Epub ahead of print. PMID: 34991109

these reviews, the MAH should discuss the need for risk minimisation measures, including a proposal to update the product information and/or the RMP as warranted.

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

4.3. Signals follow-up and prioritisation

4.3.1. Enzalutamide - XTANDI (CAP) - EMEA/H/C/002639/SDA/015

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Eva Segovia

Scope: Signal of erythema multiforme

EPITT 19734 – Follow-up to October 2021

Background

For background information, see PRAC minutes October 2021[26].

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

Discussion

Having considered the available evidence from EudraVigilance, the data provided by the MAH together with the Rapporteur's assessment, PRAC considered that there is a reasonable possibility for a causal relationship between enzalutamide and erythema multiforme. Therefore, PRAC agreed that an update of the product information is warranted to add erythema multiforme as an undesirable effect with a frequency 'not known'.

Summary of recommendation(s)

- The MAH for Xtandi (enzalutamide) should submit to EMA, within 60 days, a variation to amend[27] the product information.

For the full PRAC recommendation, see EMA/PRAC/75386/2022 published on 07 March 2022 on the EMA website.

4.3.2. Obinutuzumab - GAZYVARO (CAP) - EMEA/H/C/002799/SDA/012

Applicant: Roche Registration GmbH

PRAC Rapporteur: Annika Folin

Scope: Signal of non-overt disseminated intravascular coagulation (DIC)

EPITT 19711 – Follow-up to September 2021

Background

For background information, see PRAC minutes September 2021[28].

[26] Held 27-30 September 2021
[27] Update of SmPC section 4.8. The package leaflet is to be updated accordingly
[28] Held 30 August – 02 September 2021

The MAH replied to the request for information on the signal of non-overt disseminated intravascular coagulation (DIC) and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence from EudraVigilance, the literature, the data provided by the MAH together with the Rapporteur's assessment, PRAC considered that there is a reasonable possibility for a causal relationship between obinutuzumab and non-overt DIC. Therefore, PRAC agreed that an update of the product information is warranted to add DIC as a warning and as an undesirable effect with a frequency 'uncommon'.

Summary of recommendation(s)

- The MAH for Gazyvaro (obinutuzumab) should submit to EMA, within 60 days, a variation to amend[29] the product information.

For the full PRAC recommendation, see EMA/PRAC/75386/2022 published on 07 March 2022 on the EMA website.

4.3.3. Sorafenib - NEXAVAR (CAP) - EMEA/H/C/000690/SDA/041

Applicant: Bayer AG

PRAC Rapporteur: Annika Folin

Scope: Signal of tumour lysis syndrome (TLS)

EPITT 19733 – Follow-up to October 2021

Background

For background information, see PRAC minutes October 2021[30].

The MAH replied to the request for information on the signal of tumour lysis syndrome (TLS) and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence from EudraVigilance, the literature and the data provided by the MAH together with the Rapporteur's assessment, PRAC considered that there is a reasonable possibility for a causal relationship between sorafenib and TLS. Therefore, PRAC agreed that an update of the product information is warranted to add TLS as a warning and as an undesirable effect with a frequency 'not known'.

Summary of recommendation(s)

- The MAH for Nexavar (sorafenib) should submit to EMA, within 60 days, a variation to amend[31] the product information.

For the full PRAC recommendation, see EMA/PRAC/75386/2022 published on 07 March 2022 on the EMA website.

[29] Update of SmPC sections 4.4 and 4.8. The package leaflet is to be updated accordingly
[30] Held 27-30 September 2021
[31] Update of SmPC sections 4.4 and 4.8. The package leaflet is to be updated accordingly

4.3.4. Tocilizumab – ROACTEMRA (CAP)

Applicant: Roche Registration GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

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

EPITT 19360 – Related to September 2019

Background

A signal of drug reaction with eosinophilia and systemic symptoms (DRESS) and tocilizumab was confirmed following new evidence emerged from two recent publications from *Saper VE et al*[32] and a conference abstract as well as two cases retrieved from EudraVigilance for which causality could not be excluded. In 2019, this signal was previously assessed at PRAC which had concluded to closely monitor cases of DRESS as part of routine safety surveillance. For background information, see PRAC minutes September 2019.

Discussion

Having considered the available evidence from EudraVigilance and the literature, PRAC considered that further evidence is necessary before concluding on the signal, and hence further assessment is warranted. Therefore, PRAC agreed to request additional information from the MAH of RoActemra (tocilizumab).

Summary of recommendation(s)

- The MAH for RoActemra (tocilizumab) should submit to EMA, within 60 days, a cumulative review of cases of DRESS including data from the literature, clinical trials and from post-marketing setting together with a discussion on the plausible pathophysiological mechanism. In addition, the MAH should provide a detailed review of the publication by *Saper VE et al.* (2021) and discuss the potential impact of tocilizumab treatment in patients with COVID-19 on DRESS based on the publication by *Ramirez G et al*[33]. Based on these reviews, the MAH should discuss the need for risk minimisation measures and should propose to update the product information and/or RMP as warranted.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation

4.4. Variation procedure(s) resulting from signal evaluation

See Annex I 14.4.

[32] Saper, Vivian E.; Chen, Guangbo; Deutsch, Gail H.; Guillerman, R. Paul; Birgmeier, Johannes; Jagadeesh, Karthik et al. (2019): Emergent high fatality lung disease in systemic juvenile arthritis. Annals of the rheumatic diseases 78 (12), S. 1722–1731. DOI: 10.1136/annrheumdis-2019-216040
Saper VE, Ombrello MJ, Tremoulet AH, et al. (2021): Severe delayed hypersensitivity reactions to IL-1 and IL-6 inhibitors link to common HLA-DRB1*15 alleles. Annals of the rheumatic diseases Epub ahead of print. DOI:10.1136/annrheumdis-2021-220578
Saper V. et al (2021): Effect of drug withdrawal on interleukin-1 or interleukin-6 inhibitor associated diffuse lung disease. In: Arthritis Rheumatol 73 (suppl 10). Available from: https: //acrabstracts.org/abstract/effect-of-drug-withdrawal-on-interleukin-1-or-interleukin-6-inhibitorassociated- diffuse-lung-disease/
[33] Ramirez G, Della-Torre E, Tresoldi M, Scarpellini P, Ciceri F, Dagna L et al. (2021): Drug reaction with eosinophilia and systemic symptoms (DRESS) in patients with COVID-19. In: Clinical Microbiology and Infection 27(8):1190-1192. DOI: 10.1016/j.cmi.2021.05.023

5. Risk management plans (RMPs)

5.1. Medicines in the pre-authorisation phase

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

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

See also Annex I 15.1.

5.1.1. Coronavirus (COVID-19) vaccine (inactivated, adjuvanted, adsorbed) - EMEA/H/C/006019

Scope: Active immunisation for prevention of coronavirus disease-2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 18 years of age and older

5.1.2. Fosdenopterin - EMEA/H/C/005378, Orphan

Applicant: Comharsa Life Sciences Ltd

Scope (accelerated assessment): Treatment of molybdenum cofactor deficiency type A

5.1.3. Molnupiravir – EMEA/H/C/005789

Scope: Treatment of coronavirus disease 2019 (COVID-19)

5.1.4. Olipudase alfa - EMEA/H/C/004850, PRIME, Orphan

Applicant: Genzyme Europe BV

Scope (accelerated assessment): Treatment of non-central nervous system (CNS) manifestations of acid sphingomyelinase deficiency (ASMD) in paediatric and adult patients with type A/B or type B

5.1.5. Ranibizumab - EMEA/H/C/005610

Scope: Treatment of neovascular age-related macular degeneration in adults

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

See Annex I 15.2.

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

See also Annex I 15.3.

5.3.1. Tenofovir disoproxil - VIREAD (CAP) - EMEA/H/C/000419/II/0204

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Nathalie Gault

Scope: Submission of the final study report for study GS-US-174-0144 (listed as category 3 study in the RMP): a randomised, double-blind evaluation of the antiviral efficacy, safety and tolerability of tenofovir disporoxil fumarate. This application fulfils the Article 46 commitment to provide the final week 192 study results for clinical measure 'study 5' (study GS_US_174-0144) listed in the paediatric investigation plan (PIP). As a consequence, section 5.1 of the SmPC is updated accordingly. Additionally, the risk minimisation measures for paediatrics are removed from the RMP and Annex II of the product information. The package leaflet and the RMP (version 25.1) are updated accordingly. In addition, the MAH took the opportunity to implement minor linguistic amendments throughout the product information. Furthermore, the expression of lactose content in Annex I for the tablets was changed to refer to lactose base (not as monohydrate) in line with current practice

Background

For background information on substance(s) and indication(s) of centrally authorised product(s) identified as 'CAP', see Human medicine European public assessment report (EPAR) on the EMA website.

The CHMP is evaluating a type II variation for Viread, a centrally authorised product containing tenofovir disoproxil, to assess the results of study GS-US-174-0144 exploring the antiviral efficacy, safety and tolerability of tenofovir disporoxil fumarate, in particular the 'long term safety in hepatitis B virus (HBV)-infected children aged 2 to < 12 years' as missing information. PRAC is responsible for providing advice to CHMP on the necessary updates to the RMP to support this variation. For further background, see PRAC minutes July 2021 and PRAC minutes November 2021[34].

Summary of advice

- The RMP version 25.3 for Viread (tenofovir disoproxil) in the context of the variation procedure under evaluation by PRAC and CHMP is considered acceptable.
- Based on the study results and the Rapporteur's assessment, PRAC agreed with the removal of the paediatric educational brochures in light of the better characterisation of the risks of HBV and hepatitis C virus pertaining to the renal and bone safety issues, the existing risk minimisation measures in the product information and the current therapeutic guidelines. The MAH should continue to closely monitor the risks of renal and bone toxicity associated with tenofovir disoproxil in future PSURs.

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.

[34] Held 25-28 October 2021

6.1.1. Alectinib - ALECENSA (CAP) - PSUSA/00010581/202107

Applicant: Roche Registration GmbH

PRAC Rapporteur: Jana Lukacisinova

Scope: Evaluation of a PSUSA procedure

Background

For background information on substance(s) and indication(s) of centrally authorised product(s) identified as 'CAP', see Human medicine European public assessment report (EPAR) on the EMA website.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Alecensa (alectinib) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- The MAH should submit to EMA, within 30 days, a cumulative review of cases of QT prolongation, including post-marketing, clinical trials and literature data. The MAH should propose to update the product information as warranted.

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

6.1.2. Ibandronic acid - BONDRONAT (CAP); BONVIVA (CAP) - PSUSA/00001702/202106

Applicant(s): Atnahs Pharma Netherlands B.V.

PRAC Rapporteur: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

Background

For background information on substance(s) and indication(s) of centrally authorised product(s) identified as 'CAP', see Human medicine European public assessment report (EPAR) on the EMA website.

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Bondronat and Bonviva, centrally authorised medicines containing ibandronic 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 Bondronat and Bonviva (ibandronic acid) in the approved indication(s) remains unchanged.

- Nevertheless, the product information should be updated to add hypocalcaemia as an undesirable effect with a frequency 'uncommon'. Therefore, the current terms of the marketing authorisation(s) should be varied[35].
- In the next PSUR, the MAH(s) should continue to follow-up on the effectiveness of risk minimisation measures (RMM) in place on osteonecrosis of the jaw (ONJ).

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

6.1.3. Icosapent ethyl - VAZKEPA (CAP) - PSUSA/00010922/202107

Applicant: Amarin Pharmaceuticals Ireland Limited

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

Background

For background information on substance(s) and indication(s) of centrally authorised product(s) identified as 'CAP', see Human medicine European public assessment report (EPAR) on the EMA website.

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Vazkepa, a centrally authorised medicine containing icosapent ethyl 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 Vazkepa (icosapent ethyl) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add pharyngeal swelling as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[36].

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. Nivolumab - OPDIVO (CAP) - PSUSA/00010379/202107

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

Background

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

For background information on substance(s) and indication(s) of centrally authorised product(s) identified as 'CAP', see Human medicine European public assessment report (EPAR) on the EMA website.

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Opdivo, a centrally authorised medicine containing nivolumab 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 Opdivo (nivolumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated in order to move the existing undesirable effects of lymphopenia, leukopenia, neutropenia, thrombocytopenia and anaemia under the system organ class (SOC) of 'blood and lymphatic system disorders'. Also, the following existing undesirable effects of hyperglycaemia, hypoglycaemia and weight decreased should be moved to the SOC of 'metabolism and nutrition disorders'. In addition, relevant symptoms of diabetic ketoacidosis (DKA) should be further detailed in the package leaflet in order to ensure that patients are fully informed of this risk. Therefore, the current terms of the marketing authorisation(s) should be varied[37].
- In the next PSUR, the MAH should provide cumulative reviews of cases of cholangitis sclerosing and optic neuritis, including post-marketing, clinical trials and literature data and discuss the need to update the product information as warranted.

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.

6.1.5. Perampanel - FYCOMPA (CAP) - PSUSA/00009255/202107

Applicant: Eisai GmbH

PRAC Rapporteur: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

Background

For background information on substance(s) and indication(s) of centrally authorised product(s) identified as 'CAP', see Human medicine European public assessment report (EPAR) on the EMA website.

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Fycompa, a centrally authorised medicine containing perampanel 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 Fycompa (perampanel) in the approved indication(s) remains unchanged.

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

- Nevertheless, the product information should be updated to add hallucination as an undesirable effect with a frequency 'uncommon'. Therefore, the current terms of the marketing authorisation(s) should be varied[38].
- In the next PSUR, the MAH should provide a review on contraceptive failure associated with the use of perampanel. In addition, the MAH should include a detailed review of cases of hyponatremia and discuss the need to update the product information as warranted. Moreover, the MAH should provide a detailed review of cases of 'psychosis and psychotic disorders', including a discussion on the plausible biological mechanism and possible risk factors, time to onset, outcomes and doses. The MAH should also discuss the need to update the product information as warranted.

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

6.1.6. Remimazolam - BYFAVO (CAP) - PSUSA/00010924/202107

Applicant: PAION Netherlands B.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

Background

For background information on substance(s) and indication(s) of centrally authorised product(s) identified as 'CAP', see Human medicine European public assessment report (EPAR) on the EMA website.

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Byfavo, a centrally authorised medicine containing remimazolam 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 Byfavo (remimazolam) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add anaphylactic reaction as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[39].

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.

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

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

See also Annex I 16.2.

6.2.1. Cabazitaxel - CABAZITAXEL ACCORD (CAP); JEVTANA (CAP); NAP - PSUSA/00000476/202106

Applicants: Accord Healthcare S.L.U. (Cabazitaxel Accord), Sanofi-aventis groupe (Jevtana), various

PRAC Rapporteur: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

Background

Cabazitaxel is an antineoplastic agent indicated in combination with prednisone or prednisolone, for the treatment of adult patients with metastatic castration resistant prostate cancer previously treated with a docetaxel-containing regimen.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of Cabazitaxel Accord and Jevtana, centrally authorised medicines containing cabazitaxel, and nationally authorised medicine(s) containing cabazitaxel 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 cabazitaxel-containing products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add gastrointestinal haemorrhage, ileus, gastritis, colitis and gastrointestinal perforation as undesirable effects with a frequency 'uncommon'. In addition, the frequency of the existing undesirable effect of nail disorder should be changed from 'uncommon' to 'common'. Therefore, the current terms of the marketing authorisations should be varied[40].

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. Acenocoumarol (NAP) - PSUSA/00000027/202107

Applicant(s): various

PRAC Lead: Maria Popova-Kiradjieva

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

Scope: Evaluation of a PSUSA procedure

Background

Acenocoumarol is a vitamin K antagonist (VKA) indicated for the treatment and prevention of thromboembolic events.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing acenocoumarol 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 acenocoumarol-containing product(s) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, all MAHs should provide a cumulative review of cases of anticoagulant related nephropathy together with a proposal to update the product information and/or RMP as warranted.

The frequency of PSUR submission should be revised from nine-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.

6.3.2. Calcifediol (NAP) - PSUSA/00000491/202106

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Calcifediol is a vitamin D3 analogue indicated in adults for the treatment of secondary hyperparathyroidism (SHPT) with chronic kidney disease (CKD) stage 3 or 4 and vitamin D insufficiency (VDI) or deficiency, renal osteodystrophy and prolonged haemodialysis, idiopathic or postoperative hypoparathyroidism prevention of vitamin D deficiency in patients with malabsorption syndrome, CKD-mineral and bone disorder (CKD-MBD) or other identified risks, spasmophilia due to lack of vitamin D, as well as in osteoporosis under certain conditions. It is also indicated in children in prevention and treatment of neonatal hypocalcaemia, vitamin-D-deficiency rickets with hypocalcaemia, vitamin-D-resistant rickets, rickets due to liver cirrhosis, renal osteodystrophy and prolonged haemodialysis, hypocalcaemia following corticotherapy, idiopathic hypoparathyroidism and treatment with anticonvulsants, osteomalacia due to long term treatment with antiepileptics, idiopathic or postoperative hypoparathyroidism, subject to certain conditions.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing calcifediol 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 calcifediol-containing product(s) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAHs should submit a cumulative review of cases of hypercalcaemia, including data from spontaneous case report and literature, and discuss the effectiveness of the current risk minimisation measures and the need to update the product information as warranted. In addition, the MAHs should provide a cumulative review of cases of off-label use in COVID-19 patients, including data from spontaneous case reports and literature. Moreover, the MAH Faes Farma S.A and Desma Pharma SARL should closely monitor the risk of medication errors, in particular cases related to overdose and wrong route of administration. Finally, the MAH Desma Pharma SARL should discuss the results of their pharmacovigilance survey on cases reporting hypercalcaemia in the paediatric population.

The frequency of PSUR submission should be revised from nine-yearly to 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.

6.3.3. Nimesulide[41] (NAP) - PSUSA/00009236/202106

Applicant(s): various

PRAC Lead: Ilaria Baldelli

Scope: Evaluation of a PSUSA procedure

Background

Nimesulide is a selective cyclooxygenase-2 (COX-2) inhibitor non-steroidal anti-inflammatory drug (NSAID) indicated for the treatment of acute pain and primary dysmenorrhoea in adults under certain conditions.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of nimesulide-containing product(s) for systemic use in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add fixed drug eruption as a warning and as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[42].
- In the next PSUR, the MAHs should provide cumulative reviews of cases of cutaneous lupus erythematosus, acute generalised exanthematous pustulosis (AGEP) and hepatic disorders.

[41] Systemic formulation(s) only
[42] Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position.

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. Tiagabine (NAP) - PSUSA/00002942/202106

Applicant(s): various

PRAC Lead: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

Background

Tiagabine is a nipecotic acid derivative indicated in adults and children over 12 years for the treatment of partial seizures as adjunctive therapy, for the treatment of refractory partial seizures with or without secondarily generalised seizures where control is not achieved by optimal doses of at least one other antiepileptic drug.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing tiagabine 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 tiagabine-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add amnesia as an undesirable effect with a frequency 'not known' with information on time-to-onset and reversibility of the undesirable effect. In addition, dyskinesia should be added as an undesirable effect in the context of overdose as well as amnesia in the same context. Therefore, the current terms of the marketing authorisation(s) should be varied[43].
- In the next PSUR, the MAH(s) should provide a cumulative review of cases of overdose together with a discussion on the need to update the product information as warranted.

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

6.4. Follow-up to PSUR/PSUSA procedures

See also Annex I 16.4.

6.4.1. Dolutegravir - TIVICAY (CAP) - EMEA/H/C/002753/LEG 015

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Martin Huber

Scope: Submission of all available data/results for the RESPOND study (International Cohort Consortium of Infectious Disease): a prospective, multi-cohort collaboration study of people living with human immunodeficiency virus (HIV) across Europe and Australia as

[43] Update of SmPC sections 4.8 and 4.9. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position.

requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00010075/202101) adopted in September 2021

Background

For background information on substance(s) and indication(s) of centrally authorised product(s) identified as 'CAP', see Human medicine European public assessment report (EPAR) on the EMA website.

Following the evaluation of the most recently submitted PSUR(s) for the above-mentioned medicine(s), PRAC requested the MAH to submit all available data from study 207709 (RESPOND) and to propose to update the product information as warranted. For background, see PRAC minutes September 2021[44]. 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, PRAC agreed that 'weight increased' should be added to the product information as an undesirable effect.
- The MAH should submit to EMA, within 60 days, a variation to amend[45] the product information. The MAH should propose a frequency for 'weight increased'.

6.4.2. Dolutegravir, abacavir, lamivudine - TRIUMEQ (CAP) - EMEA/H/C/002754/LEG 010

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Martin Huber

Scope: Submission of all available data/results for the RESPOND study (International Cohort Consortium of Infectious Disease): a prospective, multi-cohort collaboration study of people living with human immunodeficiency virus (HIV) across Europe and Australia as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00010075/202101) adopted in September 2021

Background

For background information on substance(s) and indication(s) of centrally authorised product(s) identified as 'CAP', see Human medicine European public assessment report (EPAR) on the EMA website.

Following the evaluation of the most recently submitted PSUR(s) for the above-mentioned medicine(s), PRAC requested the MAH to submit all available data from study 207709 (RESPOND) and to propose to update the product information as warranted. For background, see PRAC minutes September 2021[46]. 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, PRAC agreed that 'weight increased' should be added to the product information as an undesirable effect.

[44] Held 30 August – 02 September 2021
[45] Update of SmPC section 4.8. The package leaflet is to be updated accordingly
[46] Held 30 August – 02 September 2021

- The MAH should submit to EMA, within 60 days, a variation to amend[47] the product information. The MAH should propose a frequency for 'weight increased'.

6.4.3. Dolutegravir, lamivudine - DOVATO (CAP) - EMEA/H/C/004909/LEG 005

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: David Olsen

Scope: Submission of all available data/results for the RESPOND study (International Cohort Consortium of Infectious Disease): a prospective, multi-cohort collaboration study of people living with human immunodeficiency virus (HIV) across Europe and Australia as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00010075/202101) adopted in September 2021

Background

For background information on substance(s) and indication(s) of centrally authorised product(s) identified as 'CAP', see Human medicine European public assessment report (EPAR) on the EMA website.

Following the evaluation of the most recently submitted PSUR(s) for the above-mentioned medicine(s), PRAC requested the MAH to submit all available data from study 207709 (RESPOND) and to propose to update the product information as warranted. For background, see PRAC minutes September 2021[48]. 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, PRAC agreed that 'weight increased' should be added to the product information as an undesirable effect.
- The MAH should submit to EMA, within 60 days, a variation to amend[49] the product information. The MAH should propose a frequency for 'weight increased'.

6.5. Variation procedure(s) resulting from PSUSA evaluation

See also Annex I 16.5.

6.5.1. Dolutegravir - TIVICAY (CAP) - EMEA/H/C/002753/WS2192/0075; dolutegravir, abacavir, lamivudine - TRIUMEQ (CAP) - EMEA/H/C/002754/WS2192/0099; dolutegravir, lamivudine - DOVATO (CAP) - EMEA/H/C/004909/WS2192/0026; dolutegravir, rilpivirine - JULUCA (CAP) - EMEA/H/C/004427/WS2192/0040

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Martin Huber

Scope: Update of section 4.8 of the SmPC to add completed suicide to the list of adverse drug reactions (ADRs) with a frequency rare to Tivicay (dolutegravir), Dovato (dolutegravir/lamivudine) and Triumeq (dolutegravir/ abacavir/lamivudine) following the finalisation of the PSUR single assessment (PSUSA) procedure (PSUSA/00010075/202101) in September 2021. As the changes impact all dolutegravir-containing products, Juluca

[47] Update of SmPC section 4.8. The package leaflet is to be updated accordingly
[48] Held 30 August – 02 September 2021
[49] Update of SmPC section 4.8. The package leaflet is to be updated accordingly

(dolutegravir/rilpivirine) is also updated in accordance. The package leaflets are updated accordingly

Background

For background information on substance(s) and indication(s) of centrally authorised product(s) identified as 'CAP', see Human medicine European public assessment report (EPAR) on the EMA website.

Following the evaluation of the most recently submitted PSUR(s) for the above-mentioned medicine(s), the MAH submitted a variation to update the product information with information on suicide/self-injury in line with the conclusions of the PSUR single assessment (PSUSA) procedure. For background, see PRAC minutes September 2021[50]. PRAC is responsible for adopting an outcome based on the assessment report from the PRAC Rapporteur, to be further considered at the level of CHMP, responsible for adopting an opinion on this variation.

Summary of recommendation(s)

- Based on the available data and the Rapporteur's assessment, PRAC supported the proposed update of the product information to add 'completed suicide' as an undesirable effect[51] with a frequency 'rare'.

6.6. Expedited summary safety reviews[52]

See Annex I 16.6.

7. Post-authorisation safety studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)[53]

See Annex I 17.1.

7.2. Protocols of PASS non-imposed in the marketing authorisation(s)[54]

See Annex I 17.2.

7.3. Results of PASS imposed in the marketing authorisation(s)[55]

7.3.1. Aprotinin (NAP) - EMEA/H/N/PSR/S/0030

Applicant: Nordic Group BV (Trasylol)

PRAC Rapporteur: Laurence de Fays

Scope: MAH's response to PSR/S/0030 [results for a Nordic aprotinin patient registry to

[50] Held 30 August – 02 September 2021
[51] Update of SmPC section 4.8. The package leaflet is updated accordingly
[52] Submission of expedited summary safety reports for review in addition to the requirements for submission of PSUR(s) falling within the pandemic period and requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC
[53] In accordance with Article 107n of Directive 2001/83/EC
[54] 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
[55] In accordance with Article 107p-q of Directive 2001/83/EC

record utilisation information on patients at cardiac surgery centres] as per the request for supplementary information (RSI) adopted in September 2021

Background

Aprotinin is an antifibrinolytic indicated for the prevention of excessive blood loss under certain conditions.

In line with the conclusions reached in 2013 of the referral procedure under Article 31 of Directive 2001/83/EC (EMEA/H/A-1267) conducted by CHMP for antifibrinolytics containing aprotinin, aminocaproic acid and tranexamic acid, the MAH for Trasylol (aprotinin) was required to conduct a registry in order to monitor the pattern of use of aprotinin.

The MAH for Trasylol (aprotinin) submitted to EMA the final results of the study entitled: 'Nordic Aprotinin Patient Registry (NAPaR): a multicentre, non-interventional PASS with active surveillance via patient exposure registry' enrolling patients undergoing cardiac surgery on cardiopulmonary bypass and exposed to aprotinin at all centres in EU. PRAC is responsible for issuing a recommendation on the final study results including the assessment of the MAH's responses to requests for supplementary information (RSI). For background, see PRAC minutes April 2021 and PRAC minutes September 2021[56].

Summary of recommendation(s) and conclusions

- Based on the review of the final report of the registry study, the MAH's responses to the RSI and the Rapporteur's assessment, PRAC considered that a further RSI is necessary before a final recommendation can be issued.
- In view of the extensive off-label use that may be intentional in nature, PRAC considered that an additional direct healthcare professional communication (DHPC) and instruction video for healthcare professionals (HCP) are unlikely to be effective measures to ensure adherence to the restricted indication. In addition, PRAC did not support the video format as educational material due to promotional aspects. The MAH should propose and discuss more robust and effective additional risk minimisation measures (aRMMs) to improve the adherence to the restricted indication. The MAH should also discuss measures that could improve effectiveness of the current routine/additional RMMs in place.
- The MAH should submit responses to the RSI within 60 days to EMA. A 60 day-assessment timetable will be followed.

7.3.2. Human normal immunoglobulin - HYQVIA (CAP) - EMEA/H/C/PSR/S/0037

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Results of study 161302 (listed as a category 1 study in Annex II and the RMP): a non-interventional PASS on the long-term safety of Hyqvia in subjects treated with Hyqvia (human normal immunoglobulin)

Background

[56] Held 30 August – 02 September 2021

For background information on substance(s) and indication(s) of centrally authorised product(s) identified as 'CAP', see Human medicine European public assessment report (EPAR) on the EMA website.

In order to fulfil the obligation to conduct a PASS (Annex II-D) imposed in the marketing authorisation(s) of Hyqvia (human normal immunoglobulin), the MAH Baxalta Innovations GmbH submitted to EMA the results version 1.0 of study 161302: a non-interventional, prospective, uncontrolled, open-label, multicentre PASS to evaluate the long-term safety, treatment regimens and product administration of Hyqvia (human normal immunoglobulin) under clinical routine conditions. PRAC discussed the final study results of the PASS. PRAC is responsible for evaluating the PASS final results.

Summary of recommendation(s) and conclusions

- Based on the review of the final report of the PASS and the Rapporteur's assessment, PRAC considered that the obligation to perform the PASS is fulfilled.
- PRAC recommended to vary the terms of the marketing authorisation(s)[57] by removing the study requirement from the conditions with regard to the safe and effective use of the medicinal product.
- The MAH should submit to EMA, within 430 days, a variation to update the RMP accordingly.

7.3.3. Hydroxyethyl starch (HES) (NAP) - EMEA/H/N/PSR/J/0031

Applicant(s): B. Braun Melsungen AG (Tetraspan, Venofundin), Fresenius Kabi Deutschland GmbH (Volulyte, Voluven)

PRAC Rapporteur: Nathalie Gault

Scope: MAH's response to PSR/J/0031 [results for a joint retrospective, multinational, drug utilisation study (DUS) to assess the non-adherence of physicians in hydroxyethyl starch (HES) accredited hospitals to the approved European product information [regarding indication for use, contraindications and posology (dosage)] for HES 130-containing medicinal products in clinical routine after implementation of a set of risk minimisation measures as required in the outcome of the referral procedure under Article 107i of Directive 2001/83/EC for HES completed in 2018 (EMEA/H/A-107i/1457)] as per the request for supplementary information (RSI) adopted in January 2022

Background

Hydroxyethyl starch (HES) is a synthetic colloid indicated for intravenous use for infusion for the treatment of hypovolemia due to acute blood loss when crystalloids alone are not considered sufficient.

In line with the conclusions of the referral procedure under Article 107i of Directive 2001/83/EC (EMEA/H/A-107i/1457) concluded in 2018, MAHs were required as a condition of the marketing authorisations (Annex IV) to implement additional risk minimisation measures (aRMMs) and to demonstrate their effectiveness by means of a drug utilisation study (DUS).

The MAHs Fresenius Kabi Deutschland GmbH and B. Braun Melsungen AG submitted to EMA the results of the required DUS entitled 'a retrospective, multinational, DUS to investigate

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

the routine use of HES-containing infusion solutions in HES-accredited European (EU) hospitals after implementation of a set of risk minimisation measures' conducted as a joint study. For further background, see PRAC minutes January 2019, PRAC minutes June 2019, PRAC minutes September 2020[58] and PRAC minutes December 2020[59].

PRAC discussed the final study report of the DUS. PRAC is responsible for evaluating the final results together with the responses from the MAH(s) to requests for supplementary information (RSI). For further background, see PRAC minutes May 2021, PRAC minutes October 2021[60] and PRAC minutes January 2022.

Discussion

PRAC discussed the conclusions reached by the Rapporteur.

PRAC reviewed the DUS final report, including data and responses provided by the MAHs both in writing and in a joint oral explanation at the present meeting (B. Braun Melsungen AG and Fresenius Kabi Deutschland GmbH).

PRAC considered that non-adherence to the product information remains despite the extensive additional RMMs, which were implemented as an outcome of the referral procedure in 2018. PRAC considered that adherence to the RMMs imposed in referrals under Article 107i of Directive 2001/83/EC (EMEA/H/A-107i/1376) in 2013 for HES-containing medicines and Article 107i of Directive 2001/83/EC (EMEA/H/A-107i/1457) concluded in 2018 is critical to ensure a positive benefit-risk balance of the HES solutions for infusion.

In particular, PRAC was concerned about the continued high non-adherence to contraindications as reported in the current DUS, which constituted 6.6% of all non-adherent prescriptions. Moreover, PRAC was concerned with the high overall non-adherence to the product information observed in four Member States (Belgium, France, Italy and the Netherlands).

PRAC noted the general adherence to the recommended dose and duration of treatment. However, PRAC concluded that it is not possible to identify a cut-off level below which harm is avoided in vulnerable populations, and that evidence demonstrating harm is seen in patient groups treated at doses consistent with the current recommendations. Therefore, it cannot be concluded that the use in contraindicated patients seen in the DUS is safe because of the dose regimens used.

PRAC concluded that HES is still used in contraindicated populations including patients being critically ill, with renal impairment or patients with sepsis, and that the estimated level of continued usage in these populations where serious harm has been demonstrated, including an increased risk for mortality, raises important public health concerns.

PRAC also considered further RMMs to reduce the non-adherence to the product information in place for HES solutions for infusion. These included changes to the product information, and to the controlled access programme such as further restrictions in supply, an engagement letter, revision of training material, mandatory annual recertification and post-training testing of health care professionals, annual re-certification of hospitals, mandatory entry of some patient information into a database in a few selected Member States where the highest non-adherence was observed in the DUS, as well as further communication via a direct healthcare professional communication (DHPC). However, information provided within

[58] Held 31 August - 03 September 2020
[59] Held 23-26 November 2020
[60] Held 27-30 September 2021

this procedure shows that the non-adherence is not only due to a lack of awareness of the restrictions among prescribers, rendering further communication, education and the other proposed measures unlikely to be sufficiently effective. Based on information from the MAHs of an expected further reduction of accredited sites and limited interest of sites to participate in a DUS, PRAC also noted that an additional study to measure adherence to the proposed revised additional RMMs may not yield meaningful results, thereby rendering it impossible to measure if future patients would be treated according to the product information. PRAC concluded that no further RMM, or combination of RMMs, could be identified to sufficiently ensure safe use of HES solutions for infusion.

As a consequence, PRAC concluded that the risks related to the use of HES outweigh their benefits and thus the benefit-risk balance of HES solutions for infusion is no longer favourable.

Summary of recommendation(s) and conclusions

- PRAC adopted by majority a recommendation to suspend the marketing authorisation(s) for HES-containing products - to be considered by CMDh for a position – see EMA Press Release entitled 'PRAC recommends suspending hydroxyethyl-starch solutions for infusion from the market'. Twenty-two members voted in favour of the recommendation whilst nine members[61] had divergent views. The Icelandic and Norwegian PRAC members agreed with the recommendation.
- PRAC agreed on the content of a direct healthcare professional communication (DHPC) for HES-containing products along with a communication plan for its distribution.
- To lift the suspension, the MAH(s) shall provide robust scientific evidence showing a positive benefit-risk balance in (a) clinically relevant patient population(s), together with a set of RMMs that can sufficiently protect patients at an increased risk of serious harm from being exposed to HES solutions for infusions.

Post-meeting note 1: the CMDh scientific conclusions and conditions for lifting the suspension of the marketing authorisations (Annex I) were published on the EMA website on 24 June 2022.

Post-meeting note 2: the PRAC assessment report (EMA/596511/2022) was published on 24 June 2022.

7.4. Results of PASS non-imposed in the marketing authorisation(s)[62]

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.

[61] John Joseph Borg, Roxana Dondera, Eva Jirsová, Marek Juracka, Melinda Palfi, Milena Radoha-Bergoc, Eva Segovia, Sophia Trantza, Tiphaine Vaillant

[62] 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

7.6. Others

See Annex I 17.6.

7.7. New Scientific Advice

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

7.8. Ongoing Scientific Advice

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

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

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

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

8.1. Annual reassessments of the marketing authorisation

See Annex I 18.1.

8.2. Conditional renewals of the marketing authorisation

See Annex I 18.2.

8.3. Renewals of the marketing authorisation

See Annex I 18.3.

9. Product related pharmacovigilance inspections

9.1. List of planned pharmacovigilance inspections

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 CHMP or EMA

10.1. Safety related variations of the marketing authorisation

10.1.1. Infliximab – REMICADE (CAP) - EMEA/H/C/000240/IB/0233

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: PRAC consultation on a variation updating sections 4.4, 4.5 and 4.6 of the SmPC, the patient reminder card in Annex II with regards to the administration of live vaccines to infants following in utero exposure to Remicade (infliximab) as per the outcome of post-authorisation measure (LEG 159.2) adopted in November 2021. The package leaflet is updated accordingly

Background

For background information on substance(s) and indication(s) of centrally authorised product(s) identified as 'CAP', see Human medicine European public assessment report (EPAR) on the EMA website.

A type IB variation proposing to update the product information of Remicade (infliximab) with information on administration of live vaccines to infants following in utero exposure to Remicade (infliximab) is under evaluation at CHMP. The variation was submitted in line with the outcome of a post-authorisation procedure (LEG 159.2) adopted at PRAC in November 2021. PRAC was requested to provide advice on this variation. For further background, see PRAC minutes November 2021[63].

Summary of advice

- Based on the review of the available information and assessment, PRAC agreed on the content of a direct healthcare professional communication (DHPC)[64] along with a communication plan for its distribution. PRAC supported to keep the use of BCG[65] vaccination as a relevant example of a live attenuated vaccine in the DHPC and to maintain the information that the patient card should be given to patients treated with infliximab.

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

[63] Held 25-28 October 2021
[64] For all infliximab-containing products
[65] Bacillus Calmette–Guérin

contain commercially confidential information.

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

11.1. Safety related variations of the marketing authorisation

None

11.2. Other requests

None

12. Organisational, regulatory and methodological matters

12.1. Mandate and organisation of PRAC

12.1.1. PRAC membership

The Chair announced that Hans-Christian Siersted was to step down from PRAC after the current meeting as an alternate for Denmark. The Chair also announced that it was the last meeting in the 3-year mandates of Cathalijne Van Doorne (member) and Virginie Hivert (alternate) representing patients' organisations, along with Raymond Anderson (member) and Roberto Frontini (alternate) representing healthcare professionals. The European Commission (EC) decision on nominations of new/existing members to PRAC to represent patients' organisations and healthcare professionals are awaited. The Chair thanked them for their contribution to PRAC.

12.1.2. PRAC working group - Best practice guide on using PRAC plenary time efficiently and effectively – update on the implementation of quantitative goals – Q4 2021

In line with the adopted PRAC best practice guidance (BPG) on Committee efficiency (see 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 updated PRAC on the quantitative measures collected for Q4 2021 of PRAC meetings. For previous update, see PRAC minutes November 2021[66].

12.1.3. Vote by proxy

None

12.2. Coordination with EMA Scientific Committees or CMDh-v

None

[66] Held 25-28 October 2021

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

12.3.1. Classification of post-authorisation studies group (CPAS) - activities overview

The EMA secretariat updated PRAC on the activities on classification of post-authorisation studies (CPAS) together with the established advisory group at EMA, together with its mandate, composition and operations. PRAC noted the information. Further update will be given in due course, as needed.

12.4. Cooperation within the EU regulatory network

12.4.1. Coronavirus (COVID-19) pandemic - update

The EMA Secretariat updated PRAC on the activities of the COVID-19 EMA pandemic Task Force (ETF), including an overview of ongoing clinical trials and epidemiological studies and initiatives, 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.

12.5. Cooperation with International Regulators

None

12.6. Contacts of 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 – Q4 2021 and predictions

The EMA Secretariat presented to PRAC an overview of the quarterly figures on the EMA pharmacovigilance system-related workload and performance indicators. For previous update, see PRAC minutes October 2021[67].

12.8.2. PRAC workload statistics – Q4 2021

The EMA secretariat presented to PRAC the quarterly and cumulative figures to estimate the evolution of the workload of PRAC for Q4 2021, by reflecting on the number of procedures and agenda items covered at each PRAC plenary meeting. For previous update, see PRAC minutes October 2021[68].

[67] Held 27-30 September 2021
[68] Held 27-30 September 2021

12.9. Pharmacovigilance audits and inspections

12.9.1. Pharmacovigilance systems and their quality systems

None

12.9.2. Pharmacovigilance inspections

None

12.9.3. Pharmacovigilance audits

None

12.10. Periodic safety update reports (PSURs) & Union reference date (EURD) list

12.10.1. Periodic safety update reports

None

12.10.2. Granularity and Periodicity Advisory Group (GPAG)

PRAC lead: Menno van der Elst, Maia Uusküla

On behalf of the Granularity and periodicity advisory group (GPAG), the EMA Secretariat presented to PRAC an update on the EURD tool. As a reminder, the EURD tool is a statistical tool to support decision making for determining PSUR frequencies of EURD list entries centred on risk-based criteria as per GVP module VII on 'Periodic safety update'. In addition, the EMA Secretariat presented the GPAG workplan for 2022 as agreed by GPAG in January 2022. The GPAG workplan was adopted by PRAC.

12.10.3. PSURs repository

None

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

PRAC endorsed the draft revised EURD list, version February 2022, reflecting PRAC's comments impacting on the data lock point (DLP) and PSUR submission frequencies of the substances/combinations. PRAC endorsed the newly allocated Rapporteurs for upcoming PSUSAs in accordance with the principles previously endorsed by PRAC (see PRAC minutes April 2013).

Post-meeting note: following the PRAC meeting of February 2022, the updated EURD list was adopted by CHMP and CMDh at their February 2022 meetings and published on the EMA website, 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

PRAC was updated on the progress from the SMART Working Group meeting on processes held on 17 January 2022. The meeting focused on the handling of validation of COVID-19-related signals and coordination of their assessment. PRAC was also updated on the progress from the SMART Working Group meeting on methods. The presentation focused on the impact of COVID-19 case reports in different individual case safety report (ICSR) databases (e.g. VigiBase, EudraVigilance) and the strategy for monitoring the safety of COVID-19 vaccines. PRAC was also informed about the draft SMART methods workplan for 2022-2025. Further update will be planned in due course.

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

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 accordingly, 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

12.14.3. Coronavirus (COVID-19) pandemic - coreRMP19: update

PRAC lead: Jean-Michel Dogné, Brigitte Keller-Stanislawski, Zane Neikena, Hans Christian Siersted, Anette Kirstine Stark, Menno van der Elst, Ulla Wändel Liminga

The EMA Secretariat presented to PRAC (on behalf of a drafting group composed of PRAC members and EMA staff) the draft updated core-RMP19 document on RMP requirements and guidance for COVID-19 vaccines. The document reflects the knowledge acquired during the pandemic and the experience gained in assessing post-marketing data for the authorised COVID-19 vaccines. PRAC adopted the document.

On 8 February 2022, the EMA published on its website the: 'Consideration on core requirements for RMPs of COVID19 vaccines - coreRMP19 guidance v3.0' (EMA/PRAC/73244/2022).

12.15. Post-authorisation safety studies (PASS)

12.15.1. Post-authorisation Safety Studies – imposed PASS

None

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

None

12.16. Community procedures

12.16.1. Referral procedures for safety reasons

None

12.17. Renewals, conditional renewals, annual reassessments

None

12.18. Risk communication and transparency

12.18.1. Public participation in pharmacovigilance

None

12.18.2. Safety communication

None

12.19. Continuous pharmacovigilance

12.19.1. Incident management

None

12.20. Impact of pharmacovigilance activities

None

12.21. Others

12.21.1. EU pharmaceutical legislation – revision of Directive 2001/83/EC and Regulation (EC) No 726/2004

PRAC lead: Amelia Cupelli, Liana Gross-Martirosyan, Martin Huber, Maria del Pilar Rayon, Eva Segovia, Sabine Straus, Menno van der Elst, Ulla Wändel Liminga

The EMA Secretariat provided PRAC with an update on the status of concept papers to support the upcoming revision of Directive 2001/83/EC and Regulation (EC) No 726/2004. For background, see the European Commission (EC) roadmap for Revision of the EU general pharmaceuticals legislation. For background information, see PRAC minutes January 2022. Status updates will be given on a regular basis.

13. Any other business

None

14. Annex I – Signals assessment and prioritisation[69]

14.1. New signals detected from EU spontaneous reporting systems

None

14.2. New signals detected from other sources

None

14.3. Signals follow-up and prioritisation

None

14.4. Variation procedure(s) resulting from signal evaluation

14.4.1. Coronavirus (COVID-19) mRNA[70] vaccine (nucleoside-modified) - SPIKEVAX (CAP) - EMEA/H/C/005791/II/0028

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Hans Christian Siersted

Scope: Submission of an updated RMP (version 2.1) to include myocarditis and pericarditis in the list of the safety concerns as an important identified risk, as requested in the

[69] 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

[70] Messenger ribonucleic acid

outcome of the signal procedure on myocarditis and pericarditis (EPITT 19713) adopted in July 2021 (SDA 033)

15. Annex I – Risk management plans

15.1. Medicines in the pre-authorisation phase

As per the agreed criteria, 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/005574

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; first-line treatment of patients with unresectable advanced, metastatic or recurrent non-small cell lung cancer; first line treatment of patients with advanced and/or metastatic renal cell cancer

15.1.2. Dabigatran etexilate - EMEA/H/C/005639

Scope: Prevention of venous thromboembolic events

15.1.3. Insulin human - EMEA/H/W/005779

Scope: Treatment of diabetes mellitus

15.1.4. Insulin human - EMEA/H/W/005780

Scope: Treatment of diabetes mellitus

15.1.5. Pirfenidone - EMEA/H/C/005873

Scope: Treatment of mild to moderate idiopathic pulmonary fibrosis (IPF)

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

As per the agreed criteria, 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. Alogliptin - VIPIDIA (CAP) - EMEA/H/C/002182/WS2191/0029; alogliptin, metformin - VIPDOMET (CAP) - EMEA/H/C/002654/WS2191/0036; alogliptin, pioglitazone - INCRESYNC (CAP) - EMEA/H/C/002178/WS2191/0040

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Menno van der Elst

Scope: Submission of an updated RMP (version 11) in order to consolidate it within a single RMP for Vipidia (alogliptin), Vipdomet (alogliptin/metformin) and Incresync (alogliptin/pioglitazone) as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00010061/202104) finalised in November 2021. The consolidated RMP is also updated in line with revision 2 of GVP module V on 'Risk management systems' and the targeted follow up questionnaires (FUQ) of severe hypersensitivity and skin reactions, pancreatitis, hepatic events and follow up gastrointestinal events and infections is removed. Finally, the removal of the inverted black triangle as agreed other procedures is reflected in the RMP

15.2.2. Coronavirus (COVID-19) mRNA[71] vaccine (nucleoside-modified) - SPIKEVAX (CAP) - EMEA/H/C/005791/II/0022

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Hans Christian Siersted

Scope: Submission of an updated RMP (version 2.0) to include clinical safety data from study mRNA-1273 P203 (NCT04649151): a phase 2/3, randomised, observer-blind, placebo-controlled study evaluating the safety, reactogenicity and effectiveness of the mRNA-1273 vaccine in healthy adolescents aged ≥ 12 to < 18 years

15.2.3. Nintedanib - VARGATEF (CAP) - EMEA/H/C/002569/II/0044

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Georgia Gkegka

Scope: Submission of an updated RMP (version 10.0) in order to remove safety concerns that were classified as important identified risks, important potential risks and missing information, based on cumulative post-marketing experience. The MAH also proposed an update of the anatomical therapeutic chemical (ATC) code, an update of post-marketing exposure, the removal of adverse event follow-up forms and an update of search strategies

15.2.4. Pandemic influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) - FOCLIVIA (CAP) - EMEA/H/C/001208/WS2151/0068; prepandemic influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) - AFLUNOV (CAP) - EMEA/H/C/002094/WS2151/0071

Applicant: Seqirus S.r.l

PRAC Rapporteur: Amelia Cupelli

Scope: Submission of an updated RMP (version 3.9) in order to align safety concerns of Aflunov (prepandemic influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted)) and Foclivia (pandemic influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted)) and to reclassify some potential risks in line with revision 2 of GVP module V on 'Risk management systems'. In addition, reference to adverse drug reaction follow-up forms for routine pharmacovigilance activity are removed

[71] Messenger ribonucleic acid

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

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

15.3.1. Acalabrutinib - CALQUENCE (CAP) - EMEA/H/C/005299/X/0009/G

Applicant: AstraZeneca AB

PRAC Rapporteur: Željana Margan Koletić

Scope: Grouped application consisting of: 1) extension application to introduce a new pharmaceutical form, film-coated tablet; 2) change of the anatomical therapeutic chemical (ATC) code for acalabrutinib from L01XE51 to L01EL02. The RMP (version 4.1) is updated accordingly

15.3.2. Aflibercept - EYLEA (CAP) - EMEA/H/C/002392/II/0077/G

Applicant: Bayer AG

PRAC Rapporteur: Nathalie Gault

Scope: Grouped applications consisting of: 1) extension of indication to include as a paediatric indication retinopathy of prematurity (ROP). As a consequence, sections 2, 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2, 5.3 and 6.6 of the SmPC are updated. The package leaflet and the RMP (version 32.1) are updated in accordance. Separate package leaflet is proposed for the guardians of preterm babies; 2) addition of a stand-alone paediatric dosing device, which will be CE marked and cross-labelled to the EU product information

15.3.3. Apalutamide - ERLEADA (CAP) - EMEA/H/C/004452/II/0017

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Tiphaine Vaillant

Scope: Update of section 5.3 of the SmPC in order to update non-clinical information based on final results from study TOX11338 (in completion of MEA 006): a 2-year study to better characterize the carcinogenic potential of JNJ-56021927-AAA (apalutamide) by oral gavage in rats. The RMP (version 4.1) is updated accordingly. In addition, the MAH took the opportunity to include general information in the RMP regarding study TITAN (PCR3002): a phase 3 randomized, placebo-controlled, double-blind study of apalutamide plus androgen deprivation therapy (ADT) versus ADT in subjects with metastatic hormone-sensitive prostate cancer (mHSPC)

15.3.4. Axicabtagene ciloleucel - YESCARTA (CAP) - EMEA/H/C/004480/II/0042, Orphan

Applicant: Kite Pharma EU B.V., ATMP[72]

PRAC Rapporteur: Anette Kirstine Stark

Scope: Extension of indication to include the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) after three or more lines of systemic therapy. As a

[72] Advanced therapy medicinal product

consequence, sections 4.1, 4.8, 5.1 and 5.2 of the SmPC, Annex II-D on 'Conditions or restrictions with regard to the safe and effective use of the medicinal product' and the package leaflet are updated. The RMP (version 5.1) is updated in accordance. In addition, the applicant took the opportunity to make minor editorial corrections throughout the SmPC and package leaflet to align with the latest quality review of documents (QRD) template (version 10.2)

15.3.5. Axicabtagene ciloleucel - YESCARTA (CAP) - EMEA/H/C/004480/II/0046, Orphan

Applicant: Kite Pharma EU B.V., ATMP[73]

PRAC Rapporteur: Anette Kirstine Stark

Scope: Extension of indication to include treatment of adult patients with relapsed or refractory (r/r) diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL). As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 5.3) are updated in accordance. In addition, the MAH took the opportunity to update the product information with minor editorial changes

15.3.6. Baloxavir marboxil - XOFLUZA (CAP) - EMEA/H/C/004974/X/0003/G

Applicant: Roche Registration GmbH

PRAC Rapporteur: Sonja Hrabcik

Scope: Grouped applications consisting of: 1) extension application to add a new strength of 80 mg; 2) addition of a new pack size of 1 tablet for 40 mg strength. The RMP (version 1.2) is updated in accordance. Furthermore, the product information is brought in line with the latest quality review of documents (QRD) template (version 10.2) to update the local representatives with 'United Kingdom (Northern Ireland)'

15.3.7. Brolucizumab - BEOVU (CAP) - EMEA/H/C/004913/II/0010

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include treatment of visual impairment due to diabetic macular oedema (DME). As a consequence, sections 4.1, 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

15.3.8. Buprenorphine - BUVIDAL (CAP) - EMEA/H/C/004651/II/0017

Applicant: Camurus AB

PRAC Rapporteur: Tiphaine Vaillant

Scope: Extension of indication to include treatment of moderate to severe chronic pain in patients with opioid dependence. As a consequence, sections 4.1, 4.2, 4.5, 5.1 and 6.6 of the SmPC are updated. The package leaflet and the RMP (version 2.1) are updated accordingly

[73] Advanced therapy medicinal product

15.3.9. Cabozantinib - CABOMETYX (CAP) - EMEA/H/C/004163/II/0023

Applicant: Ipsen Pharma

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to include monotherapy treatment of adults and adolescent patients aged 12 years and older, with locally advanced or metastatic differentiated thyroid carcinoma (DTC), refractory or not eligible to radioactive iodine (RAI) who have progressed during or after prior systemic therapy. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 6.0) are updated in accordance

15.3.10. Cariprazine - REAGILA (CAP) - EMEA/H/C/002770/II/0023

Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Update of sections 4.4, 4.5, 4.6 and 5.2 of the SmPC in order to update pharmacokinetic information based on final results from RGH-188-302 (CAROLA) study (listed as a category 3 study in the RMP): an open-label, single-arm, fixed-sequence, phase 1 trial in female schizophrenia patients to investigate the effect of multiple-dose administration of cariprazine on the pharmacokinetics of a combined oral contraceptive containing ethinylestradiol and levonorgestrel. The package leaflet and the RMP (version 2.0) are updated accordingly. In addition, the MAH took the opportunity to implement minor editorial changes in the SmPC and the package leaflet

15.3.11. Cemiplimab - LIBTAYO (CAP) - EMEA/H/C/004844/II/0026

Applicant: Regeneron Ireland Designated Activity Company (DAC)

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to include monotherapy treatment of adult patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 3.0) are updated in accordance

15.3.12. Coronavirus (COVID-19) mRNA[74] vaccine (nucleoside-modified) - SPIKEVAX (CAP) - EMEA/H/C/005791/II/0041

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Hans Christian Siersted

Scope: Extension of indication to include use in children of 6-11 years of age based on data from study mRNA-1273-P204: an ongoing phase 2/3, 2-part, open-label, dose-escalation, age de-escalation and subsequent randomised, observer-blind, placebo-controlled expansion study to evaluate the safety, tolerability, reactogenicity, and effectiveness of mRNA-1273 in healthy children. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 1.3) are updated in

[74] Messenger ribonucleic acid

accordance

15.3.13. Crizotinib - XALKORI (CAP) - EMEA/H/C/002489/II/0072

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Tiphaine Vaillant

Scope: Extension of indication to include treatment of paediatric patients aged ≥ 6 to < 18 years with relapsed or refractory systemic anaplastic lymphoma kinase (ALK)-positive anaplastic large cell lymphoma (ALCL) and with unresectable, recurrent, or refractory ALK-positive inflammatory myofibroblastic tumour (IMT) based on the results from: 1) study ADVL0912: a phase 1/2 study of crizotinib, an oral small molecule inhibitor of ALK and C-Met, in children with relapsed/refractory solid tumours and anaplastic large cell lymphoma; 2) study A8081013: a phase 1b open-label study of the safety and clinical activity of crizotinib in tumours with genetic events involving the ALK gene locus. 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 8.0) are updated in accordance. In addition, the MAH took the opportunity to update the anatomical therapeutic chemical (ATC) code for crizotinib. Moreover, the MAH took the opportunity to implement a minor change in the list of local representatives in the package leaflet

15.3.14. Denosumab - PROLIA (CAP) - EMEA/H/C/001120/II/0093

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of sections 4.2 and 4.4 of the SmPC in order to change the posology recommendation for paediatric population and add a new warning on hypercalcaemia in paediatric patients with osteogenesis imperfecta (OI) following an urgent safety measure regarding the risk of hypercalcaemia reported very commonly in ongoing clinical trials in paediatric patients with OI treated with denosumab. The package leaflet and the RMP (version 29.0) are updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet and to implement minor editorial changes in the labelling

15.3.15. Doravirine - PIFELTRO (CAP) - EMEA/H/C/004747/WS2065/0019; doravirine, lamivudine, tenofovir disoproxil - DELSTRIGO (CAP) - EMEA/H/C/004746/WS2065/0026

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Extension of indication to extend the indication to the paediatric population weighing at least 35 kg. 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 2.1) are updated in accordance. In addition, the MAH took the opportunity to make minor editorial corrections and to update the list of local representatives in the package leaflet

15.3.16. Eribulin - HALAVEN (CAP) - EMEA/H/C/002084/II/0060

Applicant: Eisai GmbH

PRAC Rapporteur: Annika Folin

Scope: Update of sections 4.2, 5.1 and 5.2 of the SmPC in order to update efficacy and pharmacokinetic information based on results in the paediatric population (6 months to <18 years) from: 1) study E7389-A001-113: A phase 1 study of eribulin mesylate, a novel microtubule targeting chemotherapeutic agent in children with refractory or recurrent solid tumours, including lymphomas; 2) study E7389-G000-223: a phase 2, multicentre, open-label study to assess safety and preliminary activity of eribulin mesylate in paediatric subjects with relapsed/refractory rhabdomyosarcoma (RMS), non-rhabdomyosarcoma soft tissue sarcoma (NRSTS) and Ewing sarcoma (EWS); 3) study E7389-G000-213: a phase 1/2 single-arm study evaluating the safety and efficacy of eribulin mesilate in combination with irinotecan in children with refractory or recurrent solid tumours. The package leaflet and the RMP (version 6.0) are updated accordingly

15.3.17. Gilteritinib - XOSPATA (CAP) - EMEA/H/C/004752/II/0007, Orphan

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Martin Huber

Scope: Submission of the report of an integrated analysis to demonstrate the safety of long term treatment with gilteritinib when all patients enrolled in studies 2215-CL-0101, 2215-CL-0102 and 2215-CL-0301 have completed at least 3 years of treatment with gilteritinib or have withdrawn prior to completing at least 3 years of treatment. The studies refer to: 1) study 2215-CL-0101: a phase 1/2 open-label, dose escalation study investigating the safety, tolerability, pharmacokinetics, and pharmacodynamics of ASP2215 (gilteritinib) in patients with relapsed or refractory acute myeloid leukaemia (AML); 2) study 2215-CL-0102: a phase 1 open-label, dose escalation study investigating the safety, tolerability, pharmacokinetics, and pharmacodynamics of ASP2215 in Japanese patients with relapsed or refractory AML; 3) study 2215-CL-0301: a phase 3 open-label, multicentre, randomized study of ASP2215 versus salvage chemotherapy in patients with relapsed or refractory AML with FMS-like tyrosine kinase 3 (FLT3) mutation. The RMP (version 2.0) is updated in order to address the missing information regarding the safety of Xospata (gilteritinib)

15.3.18. Ipilimumab - YERVOY (CAP) - EMEA/H/C/002213/WS2113/0090; nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/WS2113/0108

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include first-line treatment of adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma (OSCC) for Opdivo (nivolumab) in combination with Yervoy (ipilimumab). As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 24.0 for Opdivo and version 33.0 for Yervoy) are updated in accordance

15.3.19. Ipilimumab - YERVOY (CAP) - EMEA/H/C/002213/WS2153/0093; nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/WS2153/0111

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of sections 4.2, 4.8 and 5.1 of the SmPC based on final results from study CA209908: a phase 1b/2 clinical trial of nivolumab monotherapy and nivolumab in combination with ipilimumab in paediatric subjects with high grade primary central nervous system (CNS) malignancies. The RMP (version 22.3 for Opdivo) is updated in accordance

15.3.20. Ivacaftor, tezacaftor, elexacaftor - KAFTRIO (CAP) - EMEA/H/C/005269/II/0017/G, Orphan

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Martin Huber

Scope: Grouped variations consisting of: 1) update of section 5.3 of the SmPC in order to update the non-clinical information based on final results from study VX-445-TX-015: a 2-year oral carcinogenicity study in rats evaluating the carcinogenic potential of up to 10 mg/kg/day of elexacaftor. The RMP (version 6.0) is updated accordingly; 2) submission of the final report for study VX-661-TX-038: a tezacaftor juvenile toxicity study

15.3.21. Lomitapide - LOJUXTA (CAP) - EMEA/H/C/002578/II/0046

Applicant: Amryt Pharmaceuticals DAC

PRAC Rapporteur: Menno van der Elst

Scope: Submission of an alternative study: an evaluation of the effect of lomitapide treatment on major adverse cardiovascular events (MACE) in patients with homozygous familial hypercholesterolemia (LILITH) to the currently agreed protocol for study on the effects of lomitapide on carotid and aortic atherosclerosis in patients treated with lomitapide in usual care (CAPTURE) in order to propose an evaluation of the effect of lomitapide treatment on MACE in patients with homozygous familial hypercholesterolemia. As a consequence, Annex II-D and the RMP (version 6.4) are updated accordingly. In addition, the MAH took the opportunity to bring the product information in line with the latest quality review of documents (QRD) template (version 10.2)

15.3.22. Lumasiran - OXLUMO (CAP) - EMEA/H/C/005040/II/0008, Orphan

Applicant: Alnylam Netherlands B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of sections 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC in order to clarify administration instructions, remove an existing warning on metabolic acidosis in patients with severe or end stage renal impairment, update the description of adverse reactions injection site reactions, abdominal pain and immunogenicity, update efficacy and pharmacokinetic information based on: 1) interim results from study ALN-GO1-005 (ILLUMINATE-C) (listed as a category 3 study in the RMP): a single arm study to evaluate efficacy, safety, pharmacokinetics, and pharmacodynamics of lumasiran in patients with

advanced primary hyperoxaluria type 1 (PH1); 2) available long-term efficacy and safety data from ongoing studies: study ALN-GO1-003 (ILLUMINATE-A): a phase 3 randomized, double-blind, placebo-controlled study with an extended dosing period to evaluate the efficacy and safety of lumasiran in children and adults with PH1 and study ALN-GO1-004 (ILLUMINATE-B): an open-label study to evaluate the efficacy, safety, pharmacokinetics, and pharmacodynamics of lumasiran in infants and young children with primary PH1; 3) study ALN-GO1-002: a phase 2, multicentre, open-label, extension study to evaluate the long-term administration of ALN-GO1 (lumasiran) in patients with PH. The package leaflet and the RMP (version 1.1) are updated in accordance

15.3.23. Mepolizumab - NUCALA (CAP) - EMEA/H/C/003860/X/0042

Applicant: GlaxoSmithKline Trading Services Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension application to introduce a new strength of 40 mg for Nucala (mepolizumab) solution for injection in a pre-filled syringe for subcutaneous use to be used in children aged 6 to 11 years. The RMP (version 8.0) is updated accordingly

15.3.24. Neratinib - NERLYNX (CAP) - EMEA/H/C/004030/II/0027

Applicant: Pierre Fabre Medicament

PRAC Rapporteur: Menno van der Elst

Scope: Update of section 5.1 of the SmPC in order to update the pharmacokinetic information with descriptive diarrhoea characteristics based on final results from study PUMA-NER-6201 (CONTROL) (listed as a category 3 study in the RMP):an open-label study to characterize the incidence and severity of diarrhoea in patients with early stage human epidermal growth factor receptor-2+ (HER2+) breast cancer treated with neratinib and loperamide. The RMP (version 2.1) is updated accordingly. In addition, the MAH took the opportunity to introduce editorial updates in the product information

15.3.25. Niraparib - ZEJULA (CAP) - EMEA/H/C/004249/II/0033, Orphan

Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Jan Neuhauser

Scope: Update of sections 4.4 and 4.8 of the SmPC in order to amend an existing warning and *add m*yelodysplastic syndrome *(*MDS*)/acute myeloid* leukaemia (AML) to the list of adverse drug reactions (ADRs) with a frequency common, and update of section 5.1 based on final results from study 213356 (NOVA): a phase 3 randomized double-blind trial of maintenance with niraparib versus placebo in patients with platinum sensitive ovarian cancer. In addition, the MAH also took this opportunity to amend section 4.4 and 4.6 to update information on contraception based on EMA and Clinical Trials Facilitation and Coordination Group (CTFG) recommendations. The package leaflet and the RMP (version 6.0) are updated accordingly

15.3.26. Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/II/0107

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include in combination with fluoropyrimidine- and platinum-based combination chemotherapy the first-line treatment of adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma (OSCC) based on study CA209648: a randomized phase 3 study of nivolumab plus ipilimumab or nivolumab combined with fluorouracil plus cisplatin versus fluorouracil plus cisplatin in subjects with unresectable advanced, recurrent or metastatic previously untreated oesophageal squamous cell carcinoma. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 6.6 of the SmPC are updated. The package leaflet and the RMP (version 25.0) are updated in accordance

15.3.27. Octocog alfa - KOVALTRY (CAP) - EMEA/H/C/003825/II/0038

Applicant: Bayer AG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of sections 4.8 and 5.1 of the SmPC to include data from LEOPOLD kids part B: a long term efficacy open-label programme in severe haemophilia A disease (previously submitted as Art 46; an addendum on biomarker data is included in this submission) and extension study results. In addition, an editorial revision in section 4.2 and a clarification in section 6.5 of the SmPC are proposed. The package leaflet is updated accordingly. The MAH took the opportunity to correct a typo in the Greek product information. The RMP (version 4.1) is updated and brought in line with revision 2.0.1 of the guidance on the format of RMP in the EU (template)

15.3.28. Padeliporfin - TOOKAD (CAP) - EMEA/H/C/004182/II/0015

Applicant: STEBA Biotech S.A

PRAC Rapporteur: Maia Uusküla

Scope: Submission of the clinical study report for study CLIN1001 PCM301FU5 (listed as a post-authorisation efficacy study (PAES), category 1 study in Annex II): a European randomised phase 3 study to assess the efficacy and safety of Tookad (padeliporfin) soluble for localised prostate cancer compared to active surveillance. Annex II is updated to remove reference to this study. The RMP (version 8.0) is updated accordingly

15.3.29. Palbociclib - IBRANCE (CAP) - EMEA/H/C/003853/II/0037

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Anette Kirstine Stark

Scope: Submission of the final report from study A5481027 (listed as a category 3 study in the RMP): a multicentre, randomized, double-blind, phase 3 study of palbociclib plus letrozole versus placebo plus letrozole for the treatment of previously untreated Asian postmenopausal women with estrogen receptor (ER)-positive, human epidermal growth factor receptor-2 (HER2)-negative advanced breast cancer to evaluate the effect of palbociclib on hyperglycaemia (in fulfilment of MEA 001). The RMP (version 1.8) is updated accordingly

15.3.30. Parathyroid hormone - NATPAR (CAP) - EMEA/H/C/003861/II/0029, Orphan

Applicant: Takeda Pharmaceuticals International AG

PRAC Rapporteur: Rhea Fitzgerald

Scope: Submission of the final results of study SHP634-101: an open-label, randomised, crossover study to assess the pharmacokinetic and pharmacodynamic profiles of once-daily and twice-daily dose regimens of recombinant human parathyroid hormone (rhPTH[1-84]) administered subcutaneously to subjects with hypoparathyroidism. Further clinical evaluation of an alternative dosing regimen is no longer warranted, as outlined in the current specific obligation (study SHP634-403). The conditional marketing authorisation can therefore be converted into a standard marketing authorisation (no longer subject to a specific obligation) valid for 5 years. The RMP (version 3.2) is updated accordingly

15.3.31. Polatuzumab vedotin - POLIVY (CAP) - EMEA/H/C/004870/II/0012, Orphan

Applicant: Roche Registration GmbH

PRAC Rapporteur: Annika Folin

Scope: Extension of indication to include treatment of adult patients with previously untreated diffuse large B-cell lymphoma (DLBCL) in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone based on the efficacy and safety data from pivotal study GO39942 (POLARIX): a phase 3, multicentre, randomized, double-blind, placebo-controlled trial comparing the efficacy and safety of polatuzumab vedotin in combination with rituximab and cyclophosphamide, doxorubicin and prednisone (CHP) (R-CHP) versus rituximab and cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) (R-CHOP) in previously untreated patients with diffuse large B-cell lymphoma. This submission fulfils SOB003 supporting the switch from conditional marketing authorisation to full marketing authorisation. As a consequence, the SmPC, Annex II and the package leaflet are revised. The RMP (version 2.0) is updated in accordance

15.3.32. Selpercatinib - RETSEVMO (CAP) - EMEA/H/C/005375/II/0011

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to include first-line treatment of rearranged during transfection (RET) fusion-positive non-small cell lung cancer (NSCLC) based on results from study LIBRETTO-001: an open-label, multicentre, global phase 1/2 study of selpercatinib in patients with RET-altered advanced solid tumours. As a consequence, sections 4.1, 4.5, 4.8 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 1.1) are updated in accordance

15.3.33. Tildrakizumab - ILUMETRI (CAP) - EMEA/H/C/004514/X/0023

Applicant: Almirall S.A

PRAC Rapporteur: Adam Przybylkowski

Scope: Extension application to introduce a new strength (200 mg solution for injection). The RMP (version 1.0) is updated accordingly

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

Based on the assessment of the following PSURs, 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 the agreed criteria, the procedures listed below were finalised at 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. Aclidinium bromide - BRETARIS GENUAIR (CAP); EKLIRA GENUAIR (CAP) - PSUSA/00009005/202107

Applicant(s): AstraZeneca AB

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.2. Alirocumab - PRALUENT (CAP) - PSUSA/00010423/202107

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.3. Asfotase alfa - STRENSIQ (CAP) - PSUSA/00010421/202107

Applicant: Alexion Europe SAS

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

16.1.4. Atazanavir - REYATAZ (CAP) - PSUSA/00000258/202106

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Nathalie Gault

Scope: Evaluation of a PSUSA procedure

16.1.5. Autologous peripheral blood T cells CD[75]4 and CD8 selected and CD3 and CD28 activated transduced with retroviral vector expressing anti-CD19 CD28/CD3-zeta

[75] Cluster of differentiation

chimeric antigen receptor and cultured - TECARTUS (CAP) - PSUSA/00010903/202107

Applicant: Kite Pharma EU B.V., ATMP[76]

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.6. Avapritinib - AYVAKYT (CAP) - PSUSA/00010878/202107

Applicant: Blueprint Medicines (Netherlands) B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.7. Beclometasone, formoterol, glycopyrronium bromide - RIARIFY (CAP); TRIMBOW (CAP); TRYDONIS (CAP) - PSUSA/00010617/202107

Applicant(s): Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.1.8. Birch bark extract[77] - EPISALVAN (CAP) - PSUSA/00010446/202107

Applicant: Amryt GmbH

PRAC Rapporteur: Zane Neikena

Scope: Evaluation of a PSUSA procedure

16.1.9. Brexpiprazole - RXULTI (CAP) - PSUSA/00010698/202107

Applicant: Otsuka Pharmaceutical Netherlands B.V.

PRAC Rapporteur: Marek Juracka

Scope: Evaluation of a PSUSA procedure

16.1.10. Brodalumab - KYNTHEUM (CAP) - PSUSA/00010616/202107

Applicant: LEO Pharma A/S

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

16.1.11. Budesonide[78] - JORVEZA (CAP) - PSUSA/00010664/202107

Applicant: Dr. Falk Pharma GmbH

[76] Advanced therapy medicinal product
[77] Centrally authorised product(s) only
[78] Centrally authorised product(s) only

PRAC Rapporteur: Zane Neikena

Scope: Evaluation of a PSUSA procedure

16.1.12. Canakinumab - ILARIS (CAP) - PSUSA/00000526/202106

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.13. Carfilzomib - KYPROLIS (CAP) - PSUSA/00010448/202107

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

16.1.14. Cenegermin - OXERVATE (CAP) - PSUSA/00010624/202107

Applicant: Dompe farmaceutici S.p.A.

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.1.15. Cladribine[79] - MAVENCLAD (CAP) - PSUSA/00010634/202107

Applicant: Merck Europe B.V.

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Evaluation of a PSUSA procedure

16.1.16. Gefitinib - IRESSA (CAP) - PSUSA/00001518/202107

Applicant: AstraZeneca AB

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

16.1.17. Glecaprevir, pibrentasvir - MAVIRET (CAP) - PSUSA/00010620/202107

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.1.18. Glucagon[80] - BAQSIMI (CAP); OGLUO (CAP) - PSUSA/00010826/202107

Applicant(s): Eli Lilly Nederland B.V. (Baqsimi), Tetris Pharma B.V. (Ogluo)

[79] For treatment of multiple sclerosis only
[80] Centrally authorised product(s) only

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

16.1.19. Guselkumab - TREMFYA (CAP) - PSUSA/00010652/202107

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.20. Human plasma protease C1 inhibitor - CINRYZE (CAP) - PSUSA/00010104/202106

Applicant: Shire Services BVBA

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.21. Idursulfase - ELAPRASE (CAP) - PSUSA/00001722/202107

Applicant: Shire Human Genetic Therapies AB

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.22. Imipenem, cilastatin, relebactam - RECARBRIO (CAP) - PSUSA/00010830/202107

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.23. Indacaterol, glycopyrronium, mometasone - ENERZAIR BREEZHALER (CAP); ZIMBUS BREEZHALER (CAP) - PSUSA/00010861/202107

Applicant(s): Novartis Europharm Limited

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.1.24. Inotersen - TEGSEDI (CAP) - PSUSA/00010697/202107

Applicant: Akcea Therapeutics Ireland Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

16.1.25. L-lysine hydrochloride, L-arginine hydrochloride - LYSAKARE (CAP) - PSUSA/00010786/202107

Applicant: Advanced Accelerator Applications

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.26. Lonoctocog alfa - AFSTYLA (CAP) - PSUSA/00010559/202107

Applicant: CSL Behring GmbH

PRAC Rapporteur: Sonja Hrabcik

Scope: Evaluation of a PSUSA procedure

16.1.27. Macimorelin - GHRYVELIN (CAP) - PSUSA/00010746/202107

Applicant: Consilient Health Limited

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.28. Mirabegron - BETMIGA (CAP) - PSUSA/00010031/202106

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

16.1.29. Neratinib - NERLYNX (CAP) - PSUSA/00010712/202107

Applicant: Pierre Fabre Medicament

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.30. Osilodrostat - ISTURISA (CAP) - PSUSA/00010820/202107

Applicant: Recordati Rare Diseases

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

16.1.31. Paliperidone - BYANNLI (CAP); INVEGA (CAP); TREVICTA (CAP); XEPLION (CAP) - PSUSA/00002266/202106

Applicant(s): Janssen-Cilag International N.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.32. Peginterferon beta-1a - PLEGRIDY (CAP) - PSUSA/00010275/202107

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.33. Romosozumab - EVENITY (CAP) - PSUSA/00010824/202107

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

16.1.34. Salmeterol, fluticasone propionate[81] - BROPAIR SPIROMAX (CAP); SEFFALAIR SPIROMAX (CAP) - PSUSA/00010928/202107

Applicant(s): Teva B.V.

PRAC Rapporteur: Ilaria Baldelli

Scope: Evaluation of a PSUSA procedure

16.1.35. Saxagliptin, dapagliflozin - QTERN (CAP) - PSUSA/00010520/202107

Applicant: AstraZeneca AB

PRAC Rapporteur: Ilaria Baldelli

Scope: Evaluation of a PSUSA procedure

16.1.36. Sofosbuvir, velpatasvir, voxilaprevir - VOSEVI (CAP) - PSUSA/00010619/202107

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.1.37. Spheroids of human autologous matrix-associated chondrocytes - SPHEROX (CAP) - PSUSA/00010630/202107

Applicant: CO.DON AG, ATMP[82]

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.38. Tagraxofusp - ELZONRIS (CAP) - PSUSA/00010896/202107

Applicant: Stemline Therapeutics B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

[81] Centrally authorised product(s) only
[82] Advanced therapy medicinal product

16.1.39. Tasimelteon - HETLIOZ (CAP) - PSUSA/00010394/202107

Applicant: Vanda Pharmaceuticals Netherlands B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.40. Tobramycin[83] - TOBI PODHALER (CAP) - PSUSA/00009315/202106

Applicant: Mylan IRE Healthcare Limited

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.41. Voretigene neparvovec - LUXTURNA (CAP) - PSUSA/00010742/202107

Applicant: Novartis Europharm Limited, ATMP[84]

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. 5-aminolevulinic acid[85] - AMELUZ (CAP); NAP - PSUSA/00010006/202106

Applicants: Biofrontera Bioscience GmbH (Ameluz), various

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.2.2. Amlodipine, valsartan - COPALIA (CAP), DAFIRO (CAP), EXFORGE (CAP), NAP; amlodipine, hydrochlorothiazide, valsartan - COPALIA HCT (CAP), DAFIRO HCT (CAP), EXFORGE HCT (CAP) - PSUSA/00010344/202106

Applicants: Novartis Europharm Limited (Copalia, Copalia HCT, Dafiro, Dafiro HCT, Exforge, Exforge HCT), various

PRAC Rapporteur: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

[83] Inhalation powder, capsules only
[84] Advanced therapy medicinal product
[85] For treatment of keratosis only

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

16.3.1. Betula verrucosa[86] [87] (NAP) - PSUSA/00010815/202107

Applicant(s): various

PRAC Lead: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

16.3.2. Bovine lung phospholipid (NAP) - PSUSA/00010791/202106

Applicant(s): various

PRAC Lead: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

16.3.3. Calcitonin salmon (NAP); synthetic analogue of eel calcitonin (NAP) - PSUSA/00000494/202106

Applicant(s): various

PRAC Lead: Eva Segovia

Scope: Evaluation of a PSUSA procedure

16.3.4. Cefepime (NAP) - PSUSA/00000593/202106

Applicant(s): various

PRAC Lead: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.3.5. Desogestrel (NAP) - PSUSA/00000966/202107

Applicant(s): various

PRAC Lead: Annika Folin

Scope: Evaluation of a PSUSA procedure

16.3.6. Dexchlorpheniramine (NAP) - PSUSA/00000989/202106

Applicant(s): various

PRAC Lead: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

[86] Allergen for therapy
[87] Sublingual tablet(s) only

16.3.7. Fosinopril (NAP); fosinopril, hydrochlorothiazide (NAP) - PSUSA/00010463/202107

Applicant(s): various

PRAC Lead: Eva Segovia

Scope: Evaluation of a PSUSA procedure

16.3.8. Glibenclamide, metformin hydrochloride (NAP) - PSUSA/00002002/202106

Applicant(s): various

PRAC Lead: Nathalie Gault

Scope: Evaluation of a PSUSA procedure

16.3.9. Human fibrinogen (NAP) - PSUSA/00001624/202106

Applicant(s): various

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.3.10. Ibuprofen, pseudoephedrine (NAP) - PSUSA/00001711/202107

Applicant(s): various

PRAC Lead: Nathalie Gault

Scope: Evaluation of a PSUSA procedure

16.3.11. Lidocaine hydrochloride, phenylephrine hydrochloride, tropicamide (NAP) - PSUSA/00010390/202107

Applicant(s): various

PRAC Lead: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

16.3.12. Manidipine (NAP) - PSUSA/00001932/202106

Applicant(s): various

PRAC Lead: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.3.13. Propranolol[88] (NAP) - PSUSA/00010251/202106

Applicant(s): various

PRAC Lead: Guðrún Stefánsdóttir

Scope: Evaluation of a PSUSA procedure

[88] All except centrally authorised product(s) only

16.3.14. Rabbit anti-human T-lymphocyte immunoglobulin (NAP) - PSUSA/00010252/202106

Applicant(s): various

PRAC Lead: Maia Uusküla

Scope: Evaluation of a PSUSA procedure

16.3.15. Solifenacin, tamsulosin (NAP) - PSUSA/00010285/202107

Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.3.16. Tamsulosin (NAP) - PSUSA/00002847/202107

Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.3.17. Thiocolchicoside (NAP); paracetamol, thiocolchicoside (NAP) - PSUSA/00010464/202107

Applicant(s): various

PRAC Lead: Ilaria Baldelli

Scope: Evaluation of a PSUSA procedure

16.3.18. Tianeptine (NAP) - PSUSA/00002943/202106

Applicant(s): various

PRAC Lead: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

16.3.19. Urapidil (NAP) - PSUSA/00003078/202107

Applicant(s): various

PRAC Lead: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

16.4. Follow-up to PSUR/PSUSA procedures

16.4.1. Sitagliptin - JANUVIA (CAP) - EMEA/H/C/000722/LEG 041.1

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to LEG 041.1 [cumulative review and analysis on the risk of malignancies/neoplasms particularly pancreatic carcinoma from clinical trials, literature and post-marketing data as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00010673/202008) adopted in March 2021] as per the request for supplementary information (RSI) adopted in September 2021

16.4.2. Sitagliptin - RISTABEN (CAP) - EMEA/H/C/001234/LEG 019.1

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to LEG 019 [cumulative review and analysis on the risk of malignancies/neoplasms particularly pancreatic carcinoma from clinical trials, literature and post-marketing data as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00010673/202008) adopted in March 2021] as per the request for supplementary information (RSI) adopted in September 2021

16.4.3. Sitagliptin - TESAVEL (CAP) - EMEA/H/C/000910/LEG 035.1

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to LEG 035 [cumulative review and analysis on the risk of malignancies/neoplasms particularly pancreatic carcinoma from clinical trials, literature and post-marketing data as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00010673/202008) adopted in March 2021] as per the request for supplementary information (RSI) adopted in September 2021

16.4.4. Sitagliptin - XELEVIA (CAP) - EMEA/H/C/000762/LEG 040.1

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to LEG 040 [cumulative review and analysis on the risk of malignancies/neoplasms particularly pancreatic carcinoma from clinical trials, literature and post-marketing data as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00010673/202008) adopted in March 2021] as per the request for supplementary information (RSI) adopted in September 2021

16.4.5. Sitagliptin, metformin hydrochloride - EFFICIB (CAP) - EMEA/H/C/000896/LEG 020.1

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to LEG 020 [cumulative review and analysis on the risk of malignancies/neoplasms particularly pancreatic carcinoma from clinical trials, literature and post-marketing data as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00010673/202008) adopted in March 2021] as per the request for supplementary information (RSI) adopted in September 2021

16.4.6. Sitagliptin, metformin hydrochloride - JANUMET (CAP) - EMEA/H/C/000861/LEG 020.1

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to LEG 020 [cumulative review and analysis on the risk of malignancies/neoplasms particularly pancreatic carcinoma from clinical trials, literature and post-marketing data as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00010673/202008) adopted in March 2021] as per the request for supplementary information (RSI) adopted in September 2021

16.4.7. Sitagliptin, metformin hydrochloride - RISTFOR (CAP) - EMEA/H/C/001235/LEG 016.1

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to LEG 016 [cumulative review and analysis on the risk of malignancies/neoplasms particularly pancreatic carcinoma from clinical trials, literature and post-marketing data as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00010673/202008) adopted in March 2021] as per the request for supplementary information (RSI) adopted in September 2021

16.4.8. Sitagliptin, metformin hydrochloride - VELMETIA (CAP) - EMEA/H/C/000862/LEG 020.1

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to LEG 020 [cumulative review and analysis on the risk of malignancies/neoplasms particularly pancreatic carcinoma from clinical trials, literature and post-marketing data as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00010673/202008) adopted in March 2021] as per the request for supplementary information (RSI) adopted in September 2021

16.5. Variation procedure(s) resulting from PSUSA evaluation

16.5.1. Macitentan - OPSUMIT (CAP) - EMEA/H/C/002697/II/0042, Orphan

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Eva Segovia

Scope: Update of Annex II of the product information and of the RMP (version 12.1) in line with the outcome of the last PSUR single assessment (PSUSA) procedure (PSUSA/00010115/202010) adopted in June 2021 to remove the controlled distribution system and prescriber kit (prescribing check list and healthcare professional (HCP) brochure) as additional risk minimisation measures (aRMM) while the patient alert card is kept as an aRMM. In addition, the RMP is updated to remove off-label use from the list of safety concerns, elderly patients aged over 75 years, patients with moderate to severe

hepatic impairment and patients with severe renal impairment and/or undergoing dialysis as missing information. The MAH took the opportunity to include in the RMP updated specific follow-up questionnaires forms (in line with internal company template. Finally, the MAH took the opportunity to bring the product information in line with the latest quality review of documents (QRD) template (version 10.2)

16.6. Expedited summary safety reviews[89]

16.6.1. Coronavirus (COVID-19) mRNA[90] vaccine (nucleoside-modified) - SPIKEVAX (CAP) - EMEA/H/C/005791/MEA 011.10

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Hans Christian Siersted

Scope: Eleventh expedited summary safety report (SSR) for Spikevax (COVID-19 mRNA vaccine (nucleoside-modified)) during the coronavirus disease (COVID-19) pandemic

16.6.2. Tozinameran - COMIRNATY (CAP) - EMEA/H/C/005735/MEA 002.11

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Twelfth expedited summary safety report (SSR) for Comirnaty (COVID-19 mRNA vaccine (nucleoside-modified)) during the coronavirus disease (COVID-19) pandemic

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, 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)[91]

17.1.1. Afamelanotide – SCENESSE (CAP) - EMEA/H/C/PSA/S/0076.1

Applicant: Clinuvel Europe Limited

PRAC Rapporteur: Martin Huber

Scope: MAH's response to PSA/S/0076 [substantial amendment to a protocol previously agreed in March 2016 (PSP/0022.1.A.1 (PSA/0002)) for study CUV-PA001: a post-authorisation disease registry safety study to generate data on the long-term safety and clinical effectiveness of Scenesse (afamelanotide) in patients with erythropoietic protoporphyria (EPP)] as per the request for supplementary information (RSI) adopted in October 2021

[89] Submission of expedited summary safety reports for review in addition to the requirements for submission of PSUR(s) falling within the pandemic period and requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC
[90] Messenger ribonucleic acid
[91] In accordance with Article 107n of Directive 2001/83/EC

17.1.2. Chlormadinone acetate, ethinylestradiol (NAP) – EMEA/H/N/PSA/J/0072.1

Applicant: Gedeon Richter PLC

PRAC Rapporteur: Martin Huber

Scope: MAH's response to PSA/J/0072 [substantial amendment to a joint protocol previously agreed in October 2018 for a case control study comparing levonorgestrel and chlormadinone acetate to compare the risk of venous thromboembolism (VTE) of combined hormonal contraceptives (COCs) containing chlormadinone (CMA) 2mg / ethinylestradiol (EE) 30 µg, compared to COCs containing levonorgestrel (LNG) 0.15mg, both combined with 30 µg ethinylestradiol (EE)] as per the request for supplementary information (RSI) adopted in July 2021

17.1.3. Levonorgestrel (NAP) - EMEA/H/N/PSA/S/0073.1

Applicant: Bayer Pharma AG (Jaydess, Luadei)

PRAC Rapporteur: Annika Folin

Scope: MAH's response to PSA/S/0073 [substantial amendment to a protocol previously agreed in November 2019 (PSA/S/0044) for study EURAS-LCS12: a European active surveillance study of LCS-12 (levonorgestrel intrauterine contraceptive system releasing 12 µg levonorgestrel/24h in vitro), an intra-uterine device (IUD) for Jaydess and Luadei (levonorgestrel) to investigate whether LCS-12 is associated with an increased risk of unintended pregnancy compared to Mirena (levonorgestrel-releasing intrauterine system) and to copper IUDs] as per the request for supplementary information (RSI) adopted in September 2021

17.1.4. Teduglutide - REVESTIVE (CAP) - EMEA/H/C/PSA/S/0082

Applicant: Shire Pharmaceuticals Ireland Limited

PRAC Rapporteur: Anette Kirstine Stark

Scope: Substantial amendment to a protocol previously agreed in July 2019 (PSA/S/0040) for study TED-R13-002: a prospective, multicentre registry for patients with short bowel syndrome

17.1.5. Tolvaptan - JINARC (CAP) - EMEA/H/C/PSA/S/0078.1

Applicant: Otsuka Pharmaceutical Europe Ltd

PRAC Rapporteur: Amelia Cupelli

Scope: MAH's response to PSA/S/0078 [substantial amendment to a protocol previously agreed in March 2016 (PSP/0028.2) for a 7.5-year, multicentre, non-interventional PASS to characterise and quantify the identified risk of idiosyncratic liver injury in Jinarc (tolvaptan) treated patients with autosomal dominant polycystic kidney disease (ADPKD) in routine clinical practice] as per the request for supplementary information (RSI) adopted in November 2021

17.2. Protocols of PASS non-imposed in the marketing authorisation(s)[92]

17.2.1. Filgotinib - JYSELECA (CAP) - EMEA/H/C/005113/MEA 011.1

Applicant: Galapagos N.V.

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: MAH's response to MEA 011 [protocol for study GS-EU-417-9050: a non-interventional post-authorisation cross-sectional safety study evaluating the effectiveness of the additional risk minimisation measures for filgotinib use in patients with rheumatoid arthritis within the German registry Rheumatoide Arthritis: Beobachtung der Biologika-Therapie (RABBIT)] as per the request for supplementary information (RSI) adopted in September 2021

17.2.2. Liraglutide - SAXENDA (CAP) - EMEA/H/C/003780/MEA 015.4

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Menno van der Elst

Scope: Amendment to a protocol previously agreed in September 2018 for study NN8022-4246: a drug utilisation study (DUS) in the United Kingdom using UK clinical practice research datalink (CPRD) database evaluating if liraglutide (Saxenda) is used according to approved indication and posology and if liraglutide (Victoza) is used for weight management

17.2.3. Naltrexone hydrochloride, bupropion hydrochloride - MYSIMBA (CAP) - EMEA/H/C/003687/MEA 003.11

Applicant: Orexigen Therapeutics Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: MAH's response to MEA 003.10 [third feasibility assessment report and protocol for study NB-451: an observational retrospective drug utilisation study (DUS) of Mysimba (naltrexone hydrochloride/bupropion hydrochloride) in Europe and the United States to describe the demographic and baseline characteristics of users of Mysimba (naltrexone hydrochloride/bupropion hydrochloride), evaluate patterns of Mysimba (naltrexone hydrochloride/bupropion hydrochloride) initiation and use] as per the request for supplementary information (RSI) adopted in September 2021

17.2.4. Risdiplam - EVRYSDI (CAP) - EMEA/H/C/005145/MEA 007.1

Applicant: Roche Registration GmbH

PRAC Rapporteur: Jan Neuhauser

Scope: MAH's response to MEA 007 [protocol for study BN42833 - Risdiplam pregnancy surveillance study: a phase 4, non-interventional surveillance study [final study report expected in Q4/2031] (from initial opinion/marketing authorisation (MA)] as per request for supplementary information (RSI) adopted in October 2021

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

17.2.5. Setmelanotide - IMCIVREE (CAP) - EMEA/H/C/005089/MEA 001

Applicant: Rhythm Pharmaceuticals Netherlands B.V.

PRAC Rapporteur: Marek Juracka

Scope: Protocol for study RM-IMC-901 (listed as a category 3 study in the RMP): a registry of patients with biallelic homozygous pro-opiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor (LEPR) deficiency obesity treated with setmelanotide (from initial opinion/marketing authorisation)

17.2.6. Tozinameran - COMIRNATY (CAP) - EMEA/H/C/005735/MEA 010.2

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to MEA 010.1 [amendment to a protocol previously agreed in the initial marketing authorisation application (MAA)/marketing authorisation for study C4591012 assessing the occurrence of safety events of interest, including severe or atypical COVID-19 in real-world use of COVID-19 mRNA vaccine to include the booster dose [final clinical study report (CSR) expected in December-2023]] as per the request for supplementary information (RSI) adopted in November 2021

17.2.7. Tozinameran - COMIRNATY (CAP) - EMEA/H/C/005735/MEA 041

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Protocol for study C4591036 (former paediatric heart network study): a safety surveillance study of myocarditis and myopericarditis associated with Comirnaty (tozinameran) in persons less than 21 years of age to characterize the clinical course, risk factors, long-term sequelae, and quality of life in children and young adults under 21 years with acute post-vaccine myocarditis

17.2.8. Upadacitinib – RINVOQ (CAP) – EMEA/H/C/004760/MEA 012

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Protocol for study P21-825: an evaluation of the effectiveness of additional risk minimisation measures for upadacitinib in the treatment of atopic dermatitis

17.2.9. Upadacitinib - RINVOQ (CAP) - EMEA/H/C/004760/MEA 013

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Protocol for study P20-390: a cohort study of long-term safety of upadacitinib in the treatment of atopic dermatitis in Denmark and Sweden

17.3. Results of PASS imposed in the marketing authorisation(s)[93]

None

17.4. Results of PASS non-imposed in the marketing authorisation(s)[94]

17.4.1. Axicabtagene ciloleucel - YESCARTA (CAP) - EMEA/H/C/004480/II/0040, Orphan

Applicant: Kite Pharma EU B.V., ATMP[95]

PRAC Rapporteur: Anette Kirstine Stark

Scope: Submission of the final study report for non-interventional study KT-EU-471-0116 (listed as category 3 study in the RMP): a quantitative testing of healthcare provider knowledge about Yescarta (axicabtagene ciloleucel) risk minimisation measures

17.4.2. Coronavirus (COVID-19) vaccine (ChAdOx1-S [recombinant]) - VAXZEVRIA (CAP) - EMEA/H/C/005675/II/0038

Applicant: AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: Submission of the final report from study MS1222-0003 (listed as a category 3 study in the RMP) as assessment of anti-platelet factor 4 (PF4) antibodies prior to, and following, vaccination with AZD1222: a study where sera of vaccinated individuals in study D8110C00001 are tested to elucidate whether vaccination with Vaxzevria (COVID-19 vaccine) leads to increased levels of circulating anti-PF4 antibodies, a key component of the hypothesised mechanism underlying thrombosis with thrombocytopenia syndrome (TTS)

17.4.3. Edoxaban - LIXIANA (CAP) - EMEA/H/C/002629/WS2078/0034; ROTEAS (CAP) - EMEA/H/C/004339/WS2078/0020

Applicant: Daiichi Sankyo Europe GmbH

PRAC Rapporteur: Nathalie Gault

Scope: Submission of the final report from study ETNA-VTE-EUROPE (DSE-EDO-05-14-EU), (listed as a category 3 study in the RMP): a non-interventional study on edoxaban treatment in routine clinical practice in patients with venous thromboembolism in Europe. The RMP (version 12.0) is updated accordingly

17.4.4. Empagliflozin - JARDIANCE (CAP) - EMEA/H/C/002677/WS2196/0063; empagliflozin, linagliptin - GLYXAMBI (CAP) - EMEA/H/C/003833/WS2196/0042; empagliflozin, metformin - SYNJARDY (CAP) - EMEA/H/C/003770/WS2196/0060

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Eva Segovia

Scope: Update of section 4.4 of the SmPC to delete the warning on lower limb amputations

[93] In accordance with Article 107p-q of Directive 2001/83/EC
[94] 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
[95] Advanced therapy medicinal product

based on the results from the final meta-analysis report of study 1245.171 (listed as category 3 study in the RMP): a meta-analysis of amputation risk in empagliflozin studies, namely: 1) study 1245.25 (EMPA-REG OUTCOME): a study in patients with type 2 diabetes mellitus (T2DM) and increased cardiovascular risk; 2) study 1245.110 (EMPEROR- HFpEF): a study in patients with chronic heart failure (HF) with preserved ejection fraction; 3) study 1245.121 (EMPEROR- HFrEF): a study in patients with chronic HF with reduced ejection fraction. The package leaflet and the RMP (version 17 for Jardiance, version 11 for Synjardy and version 6 for Glyxambi) are updated accordingly. The conduct of this meta-analysis was requested to MAHs of all sodium-glucose co-transporter-2 (SGLT2)-containing products as part of the outcome of the referral procedure (EMEA/H/A-20/1419) under Article 20 of Regulation (EC) No 726/2004 finalised in 2016

17.4.5. Etanercept - ENBREL (CAP) - EMEA/H/C/000262/II/0244

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Eva Segovia

Scope: Submission of the final report from study B1801310 (BIKER) (listed as a category 3 study in the RMP): an observational PASS of etanercept and methotrexate in the treatment of juvenile idiopathic arthritis (JIA) using data obtained from participants in the German Biologics JIA registry (BIKER) to monitor long-term safety and effectiveness of etanercept in the treatment of JIA in regular clinical practice

17.4.6. Human papillomavirus vaccine [types 16, 18] (recombinant, adjuvanted, adsorbed) – CERVARIX (CAP) - EMEA/H/C/000721/II/0114

Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Jean-Michel Dogné

Scope: Submission of the final report from study EPI-HPV-048 (listed as a category 3 study in the RMP): a surveillance study part of a two-phase national human papillomavirus vaccine (HPV) surveillance programme initiated in the UK by the Health Protection Agency in order to evaluate the impact of HPV vaccination on HPV type replacement and to assess the prevalence of type-specific HPV deoxyribonucleic acid (DNA) in young women in England since HPV immunisation using Cervarix (human papillomavirus vaccine) was introduced (in fulfilment of MEA 094). In addition, the submission includes the protocol for study EPI-HPV-099: an observational, retrospective database post-authorisation safety study (PASS) to assess trends and changes over time in incidence of anal cancer and feasibility for a case-control study in European countries that introduced Cervarix (human papillomavirus vaccine) in their National Immunisation Programmes (NIP) in order to address the safety concern of 'impact and effectiveness against anal lesions and cancer'. The RMP (version 25) is updated accordingly

17.4.7. Naltrexone hydrochloride, bupropion hydrochloride - MYSIMBA (CAP) - EMEA/H/C/003687/II/0054

Applicant: Orexigen Therapeutics Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: Submission of the final report from study NB-542 (listed as a category 3 study in

the RMP): a cross-sectional survey aimed to evaluate the effectiveness of the Mysimba (naltrexone hydrochloride/bupropion hydrochloride) physician prescribing checklist (PPC) among physicians in the EU. The RMP (version 12.6) is updated accordingly

17.4.8. Romiplostim - NPLATE (CAP) - EMEA/H/C/000942/II/0083

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Eva Segovia

Scope: Submission of the final report from study 20070797 (listed as a category 3 study in the RMP): an observational study assessing the long-term safety of romiplostim treatment in real-life clinical practice in three Nordic countries. The RMP (version 21.0) is updated accordingly

17.4.9. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/II/0091

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Submission of the final safety registry report from study CNTO1275PSO4007: pregnancy research initiative - exposure to ustekinumab during pregnancy: a review and analysis of birth outcomes from the Swedish, Danish, and Finnish medical birth registers (in fulfilment of MEA 024). The RMP (version 22.1) 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. Adalimumab - HUMIRA (CAP) - EMEA/H/C/000481/MEA 075.10

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Ulla Wändel Liminga

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

17.5.2. Adalimumab - HUMIRA (CAP) - EMEA/H/C/000481/MEA 080.8

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Ulla Wändel Liminga

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

17.5.3. Dapagliflozin - EDISTRIDE (CAP) - EMEA/H/C/004161/MEA 009.3

Applicant: AstraZeneca AB

PRAC Rapporteur: Annika Folin

Scope: Third interim report for study MB102-118 ST/D1690R00007 - (EUPAS12116): a pharmacoepidemiology study assessing the risk of cancer [final clinical study report (CSR) expected in 2024]

17.5.4. Dapagliflozin - FORXIGA (CAP) - EMEA/H/C/002322/MEA 004.8

Applicant: AstraZeneca AB

PRAC Rapporteur: Annika Folin

Scope: Third interim report for study MB102-118 ST/D1690R00007 (EUPAS12116): a pharmacoepidemiology study assessing the risk of cancer [final clinical study report (CSR) due in 2024]

17.5.5. Filgrastim - NIVESTIM (CAP) - EMEA/H/C/001142/MEA 015.6

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Kirsti Villikka

Scope: Fifth annual report for study ZOB-NIV-1513 (C1121008): a multinational, multicentre, prospective, non-interventional PASS in healthy donors (HDs) exposed to Nivestim (biosimilar filgrastim) for haematopoietic stem cell (HSC) mobilisation (NEST) [final clinical study report (CSR) expected in March 2023]

17.5.6. Pitolisant - WAKIX (CAP) - EMEA/H/C/002616/ANX 001.4

Applicant: Bioprojet Pharma

PRAC Rapporteur: Kirsti Villikka

Scope: Fourth annual interim study report for study P15-11: a 5-year multicentre, observational PASS to document the utilisation of Wakix (pitolisant) in the treatment of narcolepsy with or without cataplexy and to collect information on its long-term safety when used in routine medical practice [final results expected in 2023]

17.5.7. Sebelipase alfa - KANUMA (CAP) - EMEA/H/C/004004/ANX 001.5

Applicant: Alexion Europe SAS

PRAC Rapporteur: Ulla Wändel Liminga

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

17.5.8. Teriflunomide - AUBAGIO (CAP) - EMEA/H/C/002514/MEA 005.3

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Martin Huber

Scope: Annual progress reports 2021 for: 1) pregnancy registry OBS12751 (international): an international pregnancy exposure registry of women with multiple sclerosis (MS)

exposed to Aubagio (teriflunomide) and; 2) pregnancy registry OBS13499 (US/CA): teriflunomide pregnancy outcome exposure registry: a 'teratology information specialists (OTIS)' autoimmune diseases in pregnancy project

17.5.9. Turoctocog alfa pegol - ESPEROCT (CAP) - EMEA/H/C/004883/ANX 001.1

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: First annual progress report for study NN7088-4029: a multinational, prospective, open labelled, non-controlled, non-interventional PASS of turoctocog alfa pegol (N8-GP) during long-term routine prophylaxis and treatment of bleeding episodes in patients with haemophilia A

17.6. Others

17.6.1. Acalabrutinib - CALQUENCE (CAP) - EMEA/H/C/005299/MEA 002.2

Applicant: AstraZeneca AB

PRAC Rapporteur: Željana Margan Koletić

Scope: MAH's response to MEA 002.1 [protocol for study D8220C00008 (listed as a category 3 study in the RMP): a phase 3b, multicentre, open-label, single-arm study in subjects with chronic lymphocytic leukaemia (ASSURE) to address missing information around moderate to severe cardiac impaired patients in subjects treated with Calquence (acalabrutinib)] as per the request for supplementary information (RSI) adopted in October 2021

17.6.2. Coronavirus (COVID-19) vaccine (ChAdOx1-S [recombinant]) - VAXZEVRIA (CAP) - EMEA/H/C/005675/MEA 007.4

Applicant: AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: Statistical analysis plan (SAP) for study D8111R00006: a post-authorisation/post-marketing observational study using existing secondary health data sources to evaluate the association between exposure to Vaxzevria (AZD1222) and safety concerns

17.6.3. Eribulin - HALAVEN (CAP) - EMEA/H/C/002084/MEA 024.2

Applicant: Eisai GmbH

PRAC Rapporteur: Annika Folin

Scope: MAH's justification to request an extension of the due date of the final study report for study E7389-M044-504 (IRENE): an observational, post-authorisation, single-arm, prospective, multicentre cohort study to characterise and determine the incidence of eribulin-induced peripheral neuropathy (PN), and the frequency and time to resolution of eribulin-induced PN in adult patients treated with eribulin in a real-life setting with locally advanced or metastatic breast cancer who have progressed after at least one chemotherapeutic regimen for advanced disease

17.6.4. Insulin detemir - LEVEMIR (CAP) - EMEA/H/C/000528/MEA 045.11

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Anette Kirstine Stark

Scope: Submission of a statement to clinical overview addendum in order to correct some discrepancies related to post-marketing data from non-interventional study NN304-4016 (listed as a category 3 study in the RMP): a diabetes pregnancy registry study conducted to assess the long-term safety of insulin use in pregnant women (in fulfilment of MEA 045)

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 below-listed medicines and the CHMP Rapporteur's assessment report, 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 the agreed criteria, the procedures were finalised at PRAC level without further plenary discussion.

18.1. Annual reassessments of the marketing authorisation

18.1.1. Defibrotide - DEFITELIO (CAP) - EMEA/H/C/002393/S/0057 (with RMP)

Applicant: Gentium S.r.l.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Annual reassessment of the marketing authorisation

18.1.2. Lomitapide - LOJUXTA (CAP) - EMEA/H/C/002578/S/0048 (without RMP)

Applicant: Amryt Pharmaceuticals DAC

PRAC Rapporteur: Menno van der Elst

Scope: Annual reassessment of the marketing authorisation

18.1.3. Obiltoxaximab - OBILTOXAXIMAB SFL (CAP) - EMEA/H/C/005169/S/0004 (without RMP)

Applicant: SFL Pharmaceuticals Deutschland GmbH

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Annual reassessment of the marketing authorisation

18.1.4. Susoctocog alfa - OBIZUR (CAP) - EMEA/H/C/002792/S/0044 (without RMP)

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Annual reassessment of the marketing authorisation

18.1.5. Tafamidis - VYNDAQEL (CAP) - EMEA/H/C/002294/S/0076 (without RMP)

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Tiphaine Vaillant

Scope: Annual reassessment of the marketing authorisation

18.1.6. Tocofersolan - VEDROP (CAP) - EMEA/H/C/000920/S/0041 (without RMP)

Applicant: Recordati Rare Diseases

PRAC Rapporteur: Melinda Palfi

Scope: Annual reassessment of the marketing authorisation

18.2. Conditional renewals of the marketing authorisation

18.2.1. Onasemnogene abeparvovec - ZOLGENSMA (CAP) - EMEA/H/C/004750/R/0021 (without RMP)

Applicant: Novartis Gene Therapies EU Limited, ATMP[96]

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Conditional renewal of the marketing authorisation

18.2.2. Selumetinib - KOSELUGO (CAP) - EMEA/H/C/005244/R/0003 (without RMP)

Applicant: AstraZeneca AB

PRAC Rapporteur: Annika Folin

Scope: Conditional renewal of the marketing authorisation

[96] Advanced therapy medicinal product

18.3. Renewals of the marketing authorisation

18.3.1. Adalimumab - IMRALDI (CAP) - EMEA/H/C/004279/R/0050 (without RMP)

Applicant: Samsung Bioepis NL B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: 5-year renewal of the marketing authorisation

18.3.2. Atezolizumab - TECENTRIQ (CAP) - EMEA/H/C/004143/R/0069 (without RMP)

Applicant: Roche Registration GmbH

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: 5-year renewal of the marketing authorisation

18.3.3. Brodalumab - KYNTHEUM (CAP) - EMEA/H/C/003959/R/0019 (with RMP)

Applicant: LEO Pharma A/S

PRAC Rapporteur: Eva Segovia

Scope: 5-year renewal of the marketing authorisation

18.3.4. Cladribine - MAVENCLAD (CAP) - EMEA/H/C/004230/R/0022 (with RMP)

Applicant: Merck Europe B.V.

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: 5-year renewal of the marketing authorisation

18.3.5. Fampridine - FAMPYRA (CAP) - EMEA/H/C/002097/R/0050 (without RMP)

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: 5-year renewal of the marketing authorisation

18.3.6. Ivacaftor - KALYDECO (CAP) - EMEA/H/C/002494/R/0106 (without RMP)

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Maria del Pilar Rayon

Scope: 5-year renewal of the marketing authorisation

18.3.7. Meningococcal group b vaccine (recombinant, adsorbed) - TRUMENBA (CAP) - EMEA/H/C/004051/R/0036 (with RMP)

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Jean-Michel Dogné

Scope: 5-year renewal of the marketing authorisation

18.3.8. Midostaurin - RYDAPT (CAP) - EMEA/H/C/004095/R/0023 (without RMP)

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: 5-year renewal of the marketing authorisation

18.3.9. Rituximab - BLITZIMA (CAP) - EMEA/H/C/004723/R/0049 (without RMP)

Applicant: Celltrion Healthcare Hungary Kft.

PRAC Rapporteur: Anette Kirstine Stark

Scope: 5-year renewal of the marketing authorisation

18.3.10. Sarilumab - KEVZARA (CAP) - EMEA/H/C/004254/R/0029 (with RMP)

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Eva Segovia

Scope: 5-year renewal of the marketing authorisation

18.3.11. Sofosbuvir, velpatasvir, voxilaprevir - VOSEVI (CAP) - EMEA/H/C/004350/R/0053 (with RMP)

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: 5-year renewal of the marketing authorisation

18.3.12. Spheroids of human autologous matrix-associated chondrocytes - SPHEROX (CAP) - EMEA/H/C/002736/R/0024 (with RMP)

Applicant: CO.DON AG, ATMP[97]

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: 5-year renewal of the marketing authorisation

18.3.13. Telotristat ethyl - XERMELO (CAP) - EMEA/H/C/003937/R/0032 (without RMP)

Applicant: Ipsen Pharma

PRAC Rapporteur: Adam Przybylkowski

Scope: 5-year renewal of the marketing authorisation

19. Annex II – List of participants

including any restrictions with respect to involvement of members / alternates / experts following evaluation of declared interests for the 07-10 February 2022 meeting.

[97] Advanced therapy medicinal product

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Sabine Straus	Chair	Netherlands	No interests declared	Full involvement
Jan Neuhauser	Member	Austria	No interests declared	Full involvement
Sonja Hrabcik	Alternate	Austria	No interests declared	Full involvement
Jean-Michel Dogné	Member	Belgium	No interests declared	Full involvement
Laurence de Fays	Alternate	Belgium	No interests declared	Full involvement
Maria Popova-Kiradjieva	Member	Bulgaria	No interests declared	Full involvement
Nikica Mirošević Skvrce	Member	Croatia	No interests declared	Full involvement
Željana Margan Koletić	Alternate	Croatia	No interests declared	Full involvement
Elena Kaisis	Member	Cyprus	No interests declared	Full involvement
Panagiotis Psaras	Alternate	Cyprus	No interests declared	Full involvement
Eva Jirsová	Member	Czechia	No interests declared	Full involvement
Jana Lukacisinova	Alternate	Czechia	No interests declared	Full involvement
Anette Kirstine Stark	Member	Denmark	No interests declared	Full involvement
Hans Christian Siersted	Alternate	Denmark	No participation in discussion, final deliberations and voting on:	15.3.23. Mepolizumab - NUCALA (CAP) - EMEA/H/C/003860/X/0042
Maia Uusküla	Member	Estonia	No interests declared	Full involvement
Krõõt Aab	Alternate	Estonia	No interests declared	Full involvement
Kirsti Villikka	Member	Finland	No interests declared	Full involvement
Kimmo Jaakkola	Alternate	Finland	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
Tiphaine Vaillant	Member	France	No interests declared	Full involvement
Nathalie Gault	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
Sofia Trantza	Member	Greece	No interest declared	Full involvement
Georgia Gkegka	Alternate	Greece	No interest declared	Full involvement
Melinda Palfi	Member	Hungary	No interests declared	Full involvement
Julia Pallos	Alternate	Hungary	No restrictions applicable to this meeting	Full involvement
Guðrún Stefánsdóttir	Member	Iceland	No participation in discussion, final deliberations and voting on:	15.3.14. Denosumab - PROLIA (CAP) - EMEA/H/C/001120/II/0093 16.1.13. Carfilzomib - KYPROLIS (CAP) - PSUSA/00010448/202107 17.4.8. Romiplostim - NPLATE (CAP) - EMEA/H/C/000942/II/0083
Rhea Fitzgerald	Member	Ireland	No interests declared	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

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Rugile Pilviniene	Member	Lithuania	No interests declared	Full involvement
Nadine Petitpain	Member	Luxembourg	No restrictions applicable to this meeting	Full involvement
John Joseph Borg	Member	Malta	No interests declared	Full involvement
Menno van der Elst	Member	Netherlands	No interests declared	Full involvement
Liana Gross-Martirosyan	Alternate	Netherlands	No interests declared	Full involvement
David Olsen	Member	Norway	No participation in final deliberations and voting on:	4.3.3. Sorafenib - NEXAVAR (CAP) - EMEA/H/C/000690/SDA/041 15.3.2. Aflibercept - EYLEA (CAP) - EMEA/H/C/002392/II/0077/G 15.3.27. Octocog alfa - KOVALTRY (CAP) - EMEA/H/C/003825/II/0038 16.3.6. Dexchlorpheniramine (NAP) - PSUSA/00000989/202106 17.1.3. Levonorgestrel (NAP) - EMEA/H/N/PSA/S/0073.1
Karen Pernille Harg	Alternate	Norway	No interests declared	Full involvement
Adam Przybylkowski	Member	Poland	No interests declared	Full involvement
Ana Sofia Diniz Martins	Member	Portugal	No interests declared	Full involvement
Marcia Sofia Sanches de Castro Lopes Silva	Alternate	Portugal	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
Roxana Dondera	Member	Romania	No interests declared	Full involvement
Alexandra - Maria Spurni	Alternate	Romania	No interests declared	Full involvement
Marek Juracka	Member	Slovakia	No interests declared	Full involvement
Anna Mareková	Alternate	Slovakia	No interests declared	Full involvement
Milena Radoha-Bergoc	Alternate	Slovenia	No restrictions applicable to this meeting	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
Annalisa Capuano	Member	Independent scientific expert	No interests declared	Full involvement
Milou Daniel Drici	Member	Independent scientific expert	No restrictions applicable to this meeting	Full involvement
Maria Teresa Herdeiro	Member	Independent scientific expert	No interests declared	Full involvement
Patricia McGettigan	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
Raymond Anderson	Member	Healthcare Professionals' Representative	No interests declared	Full involvement
Roberto Frontini	Alternate	Healthcare Professionals' Representative	No participation in final deliberations and voting on:	16.3.9. Human fibrinogen (NAP) - PSUSA/00001624/202106 16.3.14. Rabbit anti-human T-lymphocyte

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				immunoglobulin (NAP) - PSUSA/00010252/202106
Cathalijne van Doorne	Member	Patients' Organisation Representative	No interests declared	Full involvement
Virginie Hivert	Alternate	Patients' Organisation Representative	No restrictions applicable to this meeting	Full involvement
Jamila Hamdani	Expert	Belgium	No interests declared	Full involvement
Martine Sabbe	Expert	Belgium	No interests declared	Full involvement
Françoise Wuillaume	Expert	Belgium	No interests declared	Full involvement
Melita Dumančić	Expert	Croatia	No restrictions applicable to this meeting	Full involvement
Barbara Kovačić	Expert	Croatia	No interests declared	Full involvement
Nina Lalić	Expert	Croatia	No restrictions applicable to this meeting	Full involvement
Ivana Ljubičić	Expert	Croatia	No restrictions applicable to this meeting	Full involvement
Petra Kaftanová	Expert	Czechia	No interests declared	Full involvement
Jitka Vokrouhlická	Expert	Czechia	No interests declared	Full involvement
Helle Esbjørn Kristensen	Expert	Denmark	No interests declared	Full involvement
Marianne Hald Clemmensen	Expert	Denmark	No restrictions applicable to this meeting	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Marie Louise Schougaard Christiansen	Expert	Denmark	No interests declared	Full involvement
Ditte Søgaard	Expert	Denmark	No restrictions applicable to this meeting	Full involvement
Emma Stadsbjerg	Expert	Denmark	No interests declared	Full involvement
Josiane Uwera	Expert	Denmark	No restrictions applicable to this meeting	Full involvement
Samuel Crommelynck	Expert	France	No restrictions applicable to this meeting	Full involvement
Vincent Gazin	Expert	France	No interests declared	Full involvement
Mathilde Geynet-Kovacs	Expert	France	No interests declared	Full involvement
Camille De Kervasdoue	Expert	France	No interests declared	Full involvement
Jean-Michel Race	Expert	France	No restrictions applicable to this meeting	Full involvement
Youssef Shaim	Expert	France	No restrictions applicable to this meeting	Full involvement
Marie Tardieu	Expert	France	No interests declared	Full involvement
Faustine Vidil	Expert	France	No interests declared	Full involvement
Nicole Bick	Expert	Germany	No interests declared	Full involvement
Jelena Katic	Expert	Germany	No interests declared	Full involvement
Dennis Lex	Expert	Germany	No restrictions applicable to this meeting	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Julian Paesler	Expert	Germany	No interests declared	Full involvement
Natalie Welter	Expert	Germany	No restrictions applicable to this meeting	Full involvement
Susanne Winterscheid	Expert	Germany	No interests declared	Full involvement
Grainne Kirwan	Expert	Ireland	No interests declared	Full involvement
Laura Galatti	Expert	Italy	No interests declared	Full involvement
Kora Doorduyn-van der Stoep	Expert	Netherlands	No interests declared	Full involvement
Marianne Klanker	Expert	Netherlands	No interests declared	Full involvement
Tina Leguijt	Expert	Netherlands	No interests declared	Full involvement
Paul ten Berg	Expert	Netherlands	No interests declared	Full involvement
Susanne Dertz	Expert	Norway	No interests declared	Full involvement
Lars Peter Engeset Austdal	Expert	Norway	No interests declared	Full involvement
Gunnar Fløan Rimul	Expert	Norway	No interests declared	Full involvement
María Martínez Gonzalez	Expert	Spain	No restrictions applicable to this meeting	Full involvement
Consuelo Mejías Pavón	Expert	Spain	No interests declared	Full involvement
Charlotte Backman	Expert	Sweden	No interests declared	Full involvement
Kristina Dunder	Expert	Sweden	No interests declared	Full involvement
Karin Hellgren	Expert	Sweden	No restrictions applicable to this meeting	Full involvement
Gunilla Sjölin-Forsberg	Expert	Sweden	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	
Anna Vikerfors	Expert	Sweden	No restrictions applicable to this meeting	Full involvement
A representative from the European Commission attended the meeting				
Meeting run with support from relevant EMA staff				

Experts were 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/