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Pharmacovigilance Risk Assessment Committee (PRAC) Minutes of PRAC meeting on 26-29 November 2018

Chair: Sabine Straus – Vice-Chair: Martin Huber

Health and safety information

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

Disclaimers

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

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

Note on access to documents

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



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1. Introduction

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

The Chairperson opened the 26-29 November 2018 meeting by welcoming all participants.

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

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

1.2. Agenda of the meeting on 26-29 November 2018

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

1.3. Minutes of the previous meeting on 29-31 October 2018

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

Post-meeting note: the PRAC minutes of the meeting held on 29-31 October 2018 were published on the EMA website on 20 December 2018 ([EMA/PRAC/822441/2018](https://www.ema.europa.eu/en/press-room/2018/12/2018-12-20-prac-minutes)).

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

2.1. Newly triggered procedures

None

2.2. Ongoing procedures

None

2.3. Procedures for finalisation

None

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

3.1. Newly triggered procedures

None

3.2. Ongoing procedures

None

3.3. Procedures for finalisation

None

3.4. Re-examination procedures¹

None

3.5. Others

None

4. Signals assessment and prioritisation²

4.1. New signals detected from EU spontaneous reporting systems

See Annex I 14.1.

4.2. New signals detected from other sources

See also Annex I 14.2.

4.2.1. Inactivated poliomyelitis vaccine³ (NAP)

Applicant(s): various

PRAC Rapporteur: Doris Stenver

Scope: Signal of case reports from outside the EU of immune thrombocytopenic purpura

EPITT 19336 – New signal

Lead Member State(s): DK

Background

¹ Re-examination of PRAC recommendation under Article 32 of Directive 2001/83/EC

² 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

³ Including combination vaccines

Inactivated poliomyelitis vaccines are indicated for immunisation against poliomyelitis. The exposure for inactivated poliomyelitis vaccines is estimated to have been more than 52.3 million doses worldwide, in the period from July 2009 to July 2012.

During routine signal detection activities, a signal of immune thrombocytopenic purpura (ITP) was identified by Denmark, based on 19 cases retrieved from EudraVigilance. Denmark confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information on the cases of ITP and agreed that the number of possible cases of ITP with inactivated poliomyelitis vaccine is low given the large patient exposure. The PRAC agreed that more information is necessary in order to clarify the background for the occurrence of these cases.

The PRAC appointed Doris Stenver as Rapporteur for the signal.

Summary of recommendation(s)

- The MAH Sanofi Pasteur for Imovax Polio (inactivated poliomyelitis vaccine) should submit to EMA, within 60 days, a cumulative review of the signal, including an analysis of all case reports of ITP and related terms and an observed versus expected analysis stratified by age and region, local epidemiology of infectious diseases, genetic characteristics and any other relevant factors. Depending on the outcome of the review, the MAH should consider any appropriate regulatory actions.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.2.2. Vascular endothelial growth factor (VEGF) inhibitors: aflibercept – EYLEA (CAP), ZALTRAP (CAP); axitinib – INLYTA (CAP); bevacizumab – AVASTIN (CAP), MVASI (CAP); cabozantinib – CABOMETYX (CAP), COMETRIQ (CAP); lenvatinib - KISPLYX (CAP), LENVIMA (CAP); nintedanib – OFEV (CAP), VARGATEF (CAP); pazopanib – VOTRIENT (CAP); pegaptanib – MACUGEN (CAP); ponatinib – ICLUSIG (CAP); ramucirumab – CYRAMZA (CAP); ranibizumab – LUCENTIS (CAP); regorafenib – STIVARGA (CAP); sorafenib – NEXAVAR (CAP); sunitinib – SUTENT (CAP); tivozanib – FOTIVDA (CAP); vandetanib – CAPRELSA (CAP)

Applicant(s): Amgen Europe B.V. (Mvasi), Bayer AG (Eylea, Nexavar, Stivarga), Boehringer Ingelheim (Ofev, Vargatef), Eisai Europe Ltd. (Kispalyx, Lenvima), Eli Lilly Nederland B.V. (Cyramza), EUSA Pharma (UK) Limited (Fotivda), Genzyme Europe BV (Caprelsa), Incyte Biosciences Distribution (Iclusig), Ipsen Pharma (Cabometyx, Cometriq), Novartis Europharm Limited (Lucentis, Votrient), Pfizer Europe MA EEIG (Inlyta, Sutent), PharmaSwiss Ceska Republika (Macugen), Roche Registration GmbH (Avastin), Sanofi-aventis groupe (Zaltrap)

PRAC Rapporteur: Annika Folin

Scope: Signal of artery dissections and aneurysms

EPITT 19330 – New signal

Lead Member State(s): BE, DE, DK, FR, GR, HR, IT, LT, NL, NO, SE, UK

Background

Vascular endothelial growth factor (VEGF) inhibitors are a class of medicinal products directed against vascular endothelial growth factor which is a potent mitogenic, chemotactic, and vascular permeability factors for endothelial cells.

Avastin (bevacizumab) and Mvasi (bevacizumab), Cyramza (ramucirumab) and Zaltrap (aflibercept) are medicinal products targeting VEGF and are indicated, under certain conditions, for the treatment of colorectal cancer, non-small cell lung cancer, breast cancer, ovary, fallopian tube, peritoneum and cervix cancer, renal cell carcinoma, gastric cancer or gastro-oesophageal junction adenocarcinoma.

Eylea (aflibercept), Macugen (pegaptanib) and Lucentis (ranibizumab) and are medicinal products targeting VEGF and are indicated, under certain conditions, for the treatment of age-related macular degeneration and visual impairment due to macular oedema or neovascularisation.

Sutent (sunitinib), Nexavar (sorafenib), Votrient (pazopanib), Kispalyx (lenvatinib) and Lenvima (lenvatinib), Caprelsa (vandetanib), Iclusig (ponatinib), Stivarga (regorafenib), Cabometyx (cabozantinib) and Cometriq (cabozantinib), Ofev (nintedanib) and Vargatef (nintedanib) and Fotivda (tivozanib) are inhibitors of multiple tyrosine kinases receptors and are indicated, under certain conditions, for the treatment of renal cell carcinoma, thyroid cancer, gastrointestinal stromal tumours, hepatic cell carcinoma, pancreatic neuroendocrine tumours, soft tissue sarcoma, chronic myeloid leukaemia, acute lymphoblastic leukaemia, colorectal cancer, non-small cell lung cancer and idiopathic pulmonary fibrosis.

Inlyta (axitinib) is a tyrosine kinase inhibitor of VEGF receptors indicated for the treatment of renal cell carcinoma.

The exposure for Avastin (bevacizumab) is estimated to have been more than 3,099,396 patients worldwide, in the period from first authorisation in 2004 to 2018. The exposure for Cyramza (ramucirumab) is estimated to have been more than 75,800 patients worldwide, in the period from first authorisation in 2014 to 2018. The exposure for Eylea and Zaltrap (aflibercept) is estimated to have been more than 2,504,885 patient-years and 39,980 patients, respectively, worldwide, in the period from first authorisation in 2011 to 2017. The exposure for Macugen (pegaptanib) is estimated to have been more than 131,890 patients worldwide, in the period from first authorisation in 2004 to 2018. The exposure for Lucentis (ranibizumab) is estimated to have been more than 4,293,995 patient-years worldwide, in the period from first authorisation in 2006 to 2016. The exposure for Sutent (sunitinib) is estimated to have been more than 404,657 patients worldwide, in the period from first authorisation in 2006 to 2018. The exposure for Nexavar (sorafenib) is estimated to have been more than 500,315 patients worldwide, in the period from first authorisation in 2005 to 2016. The exposure for Votrient (pazopanib) is estimated to have been more than 72,590 patient-years worldwide, in the period from first authorisation in 2009 to 2017. The exposure for Kispalyx and Lenvima (lenvatinib) is estimated to have been more than 2.3 million patient-days worldwide, in the period from first authorisation in 2015 to 2018. The exposure for Caprelsa (vandetanib) is estimated to have been more than 12,155 patients worldwide, in the period from first authorisation in 2011 to 2018. The exposure for Iclusig (ponatinib) is estimated to have been more than 5,723 patient-years worldwide, in the period from first authorisation in 2012 to 2017. The exposure for Stivarga (regorafenib) is estimated to have more than 123,750 patients worldwide, in the period from first authorisation in 2012 to 2017. The exposure for Cabometyx and Cometriq (cabozantinib) is estimated to have been more than 8,116 patients and 2,449 patients, respectively, worldwide, in the period from first authorisation in 2012 to 2017. The exposure for Ofev and Vargatef (nintedanib) is

estimated to have been more than 32,394 patient-years and 2,183 patient-years, respectively, worldwide, in the period from first authorisation in 2014 to 2017. The exposure for Fotivda (tivozanib) is estimated to have been 71.5 patient-years worldwide, in the period from first authorisation in 2017 to 2018. The exposure for Inlyta (axitinib) is estimated to have been more than 66,617 patients worldwide, in the period from first authorisation in 2012 to 2018.

During routine signal detection activities, a signal of artery dissections and aneurysms was identified by the EMA, based on communication from Health Canada and cases retrieved from EudraVigilance⁴ as follows: 256 cases for bevacizumab, 249 for ranibizumab, 13 for aflibercept, 7 for ramucirumab, 2 for and pegaptanib, 79 for sunitinib, 43 for sorafenib, 17 for nintedanib, 17 for pazopanib, 14 for axitinib, 12 for lenvatinib, 8 for cabozantinib, 7 for regorafenib, 2 for ponatinib and 1 for vandetanib. Sweden confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information on the cases of artery dissections and aneurysms and noted that for some medicinal products regulatory actions have been already taken. The PRAC agreed that due to the evidence, a plausible mechanism and the severity of the reactions, a class review was warranted which should include VEGF receptors tyrosine kinase inhibitors as well as biological medicinal products targeting VEGF. The review should determine whether the identified and potential risks are sufficiently characterised and the risk minimisation activities are appropriate.

The PRAC appointed Annika Folin as Rapporteur for the signal.

Summary of recommendation(s)

- The Rapporteur should analyse the data on artery dissections and aneurysms contained in EudraVigilance for all the medicinal products included in the class of substances that inhibit VEGF signal transduction.
- A 90-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.3. Signals follow-up and prioritisation

4.3.1. Canagliflozin – INVOKANA (CAP) – EMEA/H/C/002649/SDA/017; dapagliflozin - FORXIGA (CAP) – EMEA/H/C/002322/SDA/026; empagliflozin - JARDIANCE (CAP) – EMEA/H/C/002677/SDA/016; ertugliflozin – STEGLATRO (CAP) – EMEA/H/C/004315/SDA/005

Applicant(s): AstraZeneca AB (Forxiga), Boehringer Ingelheim International GmbH (Jardiance), Janssen-Cilag International NV (Invokana), Merck Sharp & Dohme B.V. (Steglatro)

PRAC Rapporteur: Martin Huber

Scope: Signal of Fournier's gangrene

EPITT 19308 – Follow-up to October 2018

⁴ No cases retrieved for tivozanib

Background

For background information, see [PRAC minutes October 2018](#).

The MAHs replied to the request for information on the signal of Fournier's gangrene and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence on Fournier's gangrene, the PRAC agreed that the data demonstrates a possible causal association between Fournier's gangrene and sodium-glucose cotransporter-2 (SGLT-2) inhibitors.

Summary of recommendation(s)

- The MAHs for Invokana (canagliflozin), Vokanamet (canagliflozin/metformin), Edistride and Forxiga (dapagliflozin), Ebymect and Xigduo (dapagliflozin/metformin), Xigduo (dapagliflozin/metformin) Qtern (saxagliptin/dapagliflozin), Jardiance (empagliflozin), Glyxambi (empagliflozin/linagliptin), Synjardy (empagliflozin/metformin), Steglatro (ertugliflozin), Segluromet (ertugliflozin/metformin), Steglujan (ertugliflozin/sitagliptin) should submit to EMA, within 60 days, a variation to amend their product information⁵.
- The MAHs should also distribute a single direct healthcare professional communication (DHPC) according to the text and communication plan agreed with the PRAC.

For the full PRAC recommendation, see [EMA/PRAC/826440/2018](#) published on 04/01/2019 on the EMA website.

4.3.2. Carbimazole (NAP); thiamazole (NAP)

Applicant(s): various

PRAC Rapporteur: Martin Huber

Scope: New information on the known risk of birth defects and neonatal disorders in case of exposure during pregnancy

EPITT 19238 – Follow-up to June 2018

Background

For background information, see [PRAC minutes June 2018](#).

The MAHs replied to the request for information on the signal of birth defects and neonatal disorders in case of exposure during pregnancy and the responses were assessed by the Rapporteur.

Discussion

Based on the assessment of the available data from epidemiological studies and case reports, the PRAC considered that the data strengthens the evidence that carbimazole and thiamazole are suspected to cause congenital malformations when administered during pregnancy. The PRAC agreed on the importance of adequate treatment of hyperthyroidism during pregnancy to prevent serious maternal and foetal complications and the need for warnings to be provided in the product information.

⁵ Update of SmPC sections 4.4 and 4.8. The package leaflet is to be updated accordingly

Summary of recommendation(s)

- The MAHs for carbimazole- and thiamazole-containing products should submit to the relevant national competent authorities of the Member States, within 60 days, a variation to amend their product information⁶.
- The MAHs should also distribute a single direct healthcare professional communication⁷ (DHPC) according to the text and communication plan agreed with the PRAC.

For the full PRAC recommendation, see [EMA/PRAC/826440/2018](#) published on 04/01/2019 on the EMA website.

4.3.3. Carbimazole (NAP); thiamazole (NAP)

Applicant(s): various

PRAC Rapporteur: Martin Huber

Scope: Signal of pancreatitis

EPITT 19274 – Follow-up to July 2018

Background

For background information, see [PRAC minutes July 2018](#).

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

Discussion

Having considered the available evidence on pancreatitis, the PRAC considered that the data demonstrates an association between thiamazole and carbimazole and pancreatitis. The PRAC agreed on the need for warnings on pancreatitis to be included in the product information and to avoid re-exposure of patients who experienced pancreatitis on treatment with carbimazole or thiamazole previously.

Summary of recommendation(s)

- The MAHs for carbimazole and thiamazole-containing products should submit to the relevant national competent authorities of the Member States, within 60 days, a variation to amend their product information⁸.
- The MAHs should also distribute a single direct healthcare professional communication⁹ (DHPC) according to the text and communication plan agreed with the PRAC.

For the full PRAC recommendation, see [EMA/PRAC/826440/2018](#) published on 04/01/2019 on the EMA website.

4.3.4. Certolizumab pegol – CIMZIA (CAP) - EMEA/H/C/001037/SDA/031; etanercept – ENBREL (CAP) - EMEA/H/C/000262/SDA/169, LIFMIOR (CAP) - EMEA/H/C/004167/SDA/003; golimumab – SIMPONI (CAP) -

⁶ Update of SmPC sections 4.4 and 4.6. The package leaflet is to be updated accordingly

⁷ One joint DHPC is to be circulated combining information from the evaluation of the risk of pancreatitis (see under 4.3.3.) and the risk of birth defects and neonatal disorders in case of exposure during pregnancy (see under 4.3.2.)

⁸ Update of SmPC sections 4.3, 4.4 and 4.8. The package leaflet is to be updated accordingly

⁹ One joint DHPC is to be circulated combining information from the evaluation of the risk of pancreatitis (see under 4.3.3.) and the risk of birth defects and neonatal disorders in case of exposure during pregnancy (see under 4.3.2.)

Applicant(s): Janssen Biologics B.V. (Remicade, Simponi), Pfizer Europe MA EEIG (Enbrel, Lifmior), UCB Pharma S.A. (Cimzia)

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of lichenoid skin reactions for tumour necrosis factor alfa (TNF α) inhibitors

EPITT 19128 – Follow-up to July 2018

Background

For background information, see [PRAC minutes July 2018](#).

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

Discussion

Having considered the available evidence of lichenoid skin reactions and the known association of tumour necrosis factor alfa (TNF α) inhibitors with skin reactions, the PRAC agreed that a causal association with TNF α inhibitors is possible.

Summary of recommendation(s)

- The MAHs for Remicade (infliximab), Simponi (golimumab), Enbrel and Lifmior (etanercept) as well as Cimzia (certolizumab pegol) should submit to EMA, within 60 days, a variation to amend their product information¹⁰.

For the full PRAC recommendation, see [EMA/PRAC/826440/2018](#) published on 04/01/2019 on the EMA website.

4.3.5. Dasabuvir – EXVIERA (CAP) - EMA/H/C/003837/SDA/012; ombitasvir, paritaprevir, ritonavir - VIEKIRAX (CAP) - EMA/H/C/003839/SDA/014

Applicant(s): AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Signal of interstitial lung disease

EPITT 19257 – Follow-up to July 2018

Background

For background information, see [PRAC minutes July 2018](#).

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

Discussion

Having considered the available evidence from EudraVigilance, the literature and the responses from the MAH, the PRAC agreed that there is insufficient evidence of a causal relationship between ombitasvir/paritaprevir/ritonavir and dasabuvir and interstitial lung

¹⁰ Update of SmPC section 4.8. The package leaflet is to be updated accordingly

disease. Therefore, the PRAC concurred that no further regulatory action is warranted at this stage.

Summary of recommendation(s)

- The MAH for the Viekirax (ombitasvir/paritaprevir/ritonavir) and Exviera (dasabuvir) should continue to monitor these events as part of routine safety surveillance.

4.3.6. Dulaglutide – TRULICITY (CAP); exenatide – BYDUREON (CAP), BYETTA (CAP); liraglutide – VICTOZA (CAP), SAXENDA (CAP)

Applicant(s): AstraZeneca AB (Bydureon, Byetta), Eli Lilly Nederland B.V. (Trulicity), Novo Nordisk A/S (Victoza), Novo Nordisk A/S (Saxenda)

PRAC Rapporteur: Amelia Cupelli

Scope: Signal of diabetic ketoacidosis (DKA)

EPITT 19237 – Follow-up to June 2018

Background

For background information, see [PRAC minutes June 2018](#).

The MAHs replied to the request for information on the signal of diabetic ketoacidosis (DKA) and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence, the PRAC agreed that the occurrence of DKA is consistent in a number of cases and could be attributed to the abrupt dose reduction or discontinuation from insulin while initiating exenatide, liraglutide or dulaglutide, resulting in a poor glycaemic control. The PRAC agreed to provide further guidance for prescribers and patients in adopting a stepwise dose-reduction of insulin and/or close monitoring of blood glucose levels.

Summary of recommendation(s)

- The MAHs for Bydureon (exenatide), Byetta (exenatide), Trulicity (dulaglutide), Victoza (liraglutide) and Saxenda (liraglutide) should submit to EMA, within 60 days, a variation to amend their product information¹¹.

For the full PRAC recommendation, see [EMA/PRAC/826440/2018](#) published on 04/01/2019 on the EMA website.

4.3.7. Olmesartan (NAP)

Applicant(s): various

PRAC Rapporteur: Martin Huber

Scope: Signal of risk of autoimmune hepatitis

EPITT 19258 - Follow-up to July 2018

Background

¹¹ Update of SmPC sections 4.2 and 4.4. The package leaflet is to be updated accordingly (except for Saxenda)

For background information, see [PRAC minutes July 2018](#).

The MAH Daiichi-Sankyo Europe replied to the request for information on the signal of autoimmune hepatitis and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence, the PRAC agreed that the number of well documented possible cases of autoimmune hepatitis with a temporal relationship with olmesartan is very low and that the likelihood of a causal relationship is not sufficiently strong in light of the current knowledge. Therefore, the PRAC concurred that no further regulatory action is warranted at this stage.

Summary of recommendation(s)

- The MAHs for olmesartan-containing products should continue to monitor these events as part of routine safety surveillance.

4.3.8. Perindopril (NAP)

Applicant(s): various

PRAC Rapporteur: Doris Stenver

Scope: Signal of Raynaud's phenomenon

EPITT 19248 – Follow-up to July 2018

Background

For background information, see [PRAC minutes July 2018](#).

The MAH Les Laboratoires Servier replied to the request for information on the signal of Raynaud's phenomenon and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence on Raynaud's phenomenon based on post-marketing cases including cases with a positive dechallenge, the PRAC agreed that the causal association between perindopril and Raynaud's phenomenon is possible.

Summary of recommendation(s)

- The MAHs for perindopril-containing products should submit to the relevant national competent authorities of the Member States, within 60 days, a variation to amend their product information¹².

For the full PRAC recommendation, see [EMA/PRAC/826440/2018](#) published on 04/01/2019 on the EMA website.

4.3.9. Propranolol (NAP)

Applicant(s): various

PRAC Rapporteur: Karen Pernille Harg

Scope: Signal of increased risk of Parkinson's disease

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

EPITT 19223 – Follow-up to July 2018

Background

For background information, see [PRAC minutes July 2018](#).

The MAH AstraZeneca AB and the study authors *Mittal et al*¹³ replied to the requests for information on the signal of Parkinson's disease and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence from the cumulative review provided by the MAH, the responses from the study authors *Mittal et al* and analysis from the Norwegian prescription database, the PRAC agreed that the current evidence is insufficiently strong to warrant changes in the product information.

Summary of recommendation(s)

- The MAHs of propranolol-containing products should review the findings from any new publications in the next PSUR. The PRAC recommended that the PSUR submission frequency for propranolol should be amended to 3-yearly, with the next data lock point (DLP) set to 30/06/2021.

4.3.10. Ranibizumab – LUCENTIS (CAP) - EMEA/H/C/000715/SDA/074

Applicant(s): Novartis Europharm Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of angioedema

EPITT 19245 – Follow-up to July 2018

Background

For background information, see [PRAC minutes July 2018](#).

The MAH for Lucentis (ranibizumab) replied to the request for information on the signal of angioedema and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence from the review provided by the MAH for Lucentis (ranibizumab), the PRAC agreed that the likelihood of a causal relationship between ranibizumab and angioedema is insufficiently strong at this stage due to the low number of possible cases with a temporal relationship in relation to the exposure and considering the confounding effect of other substances used during the administration procedure. Therefore, the PRAC concurred that no further regulatory action is warranted at this stage.

Summary of recommendation(s)

- The MAH for Lucentis (ranibizumab) should continue to monitor angioedema events as part of routine safety surveillance.

¹³ Mittal S, Bjørnevik K, Doo Soon I, et al. β 2-adrenoceptor is a regulator of the α -synuclein gene driving risk of Parkinson's disease. *Science* 2017; 357: 891-98

Applicant(s): Roche Registration GmbH

PRAC Rapporteur: Annika Folin

Scope: Signal of cardiac failure

EPITT 19268 – Follow-up to July 2018

Background

For background information, see [PRAC minutes July 2018](#).

The MAH for Zelboraf (vemurafenib) replied to the request for information on the signal of cardiac failure and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence from the cumulative review provided by the MAH for Zelboraf (vemurafenib), the PRAC agreed that a causal relationship between vemurafenib and cardiac failure, cardiomyopathies and cardiac arrhythmias other than QTc prolongation (already labelled) cannot be established based on the current data and also considering the multifactorial aetiology of these cardiac events. Therefore, the PRAC concurred that no further regulatory action is warranted at this stage.

Summary of recommendation(s)

- The MAH for Zelboraf (vemurafenib) should continue to monitor cardiac failure events as part of routine safety surveillance.

5. Risk management plans (RMPs)

5.1. Medicines in the pre-authorisation phase

The PRAC provided the CHMP with advice on the proposed RMPs for a number of products (identified by active substance below) that are under evaluation for initial marketing authorisation. 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. Avacopan - EMEA/H/C/004487, Orphan

Applicant: ChemoCentryx Ltd

Scope: Induction of response in adult patients with granulomatosis with polyangiitis (Wegener's) (GPA) or microscopic polyangiitis (MPA)

5.1.2. Ibalizumab - EMEA/H/C/004961

Scope (accelerated assessment): Treatment of adults infected with human immunodeficiency virus 1 (HIV-1) resistant to at least 1 agent in 3 different classes

5.1.3. Larotrectinib - EMEA/H/C/004919, Orphan

Applicant: Bayer AG

Scope (accelerated assessment): Treatment of adult and paediatric patients with locally advanced or metastatic solid tumours

5.1.4. Pegvaliase - EMEA/H/C/004744, Orphan

Applicant: BioMarin International Limited

Scope: Treatment of adults with phenylketonuria (PKU) with inadequate blood phenylalanine control

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. Dapagliflozin - EDISTRIDE (CAP) - EMEA/H/C/004161/WS1344/0025; FORXIGA (CAP) - EMEA/H/C/002322/WS1344/0044

Applicant: AstraZeneca AB

PRAC Rapporteur: Annika Folin

Scope: Extension of indication to include the treatment of insufficiently controlled type 1 diabetes mellitus (T1DM) as an adjunct to insulin, when insulin does not provide adequate glycaemic control, for Forxiga and Edistride (dapagliflozin). As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8 and 5.1 of the SmPC are updated. The package leaflet and RMP (version 16) are updated accordingly. In addition, the MAH took the opportunity to introduce minor editorial changes to the SmPC and package leaflet

Background

Dapagliflozin is a selective and reversible inhibitor of sodium-glucose cotransporter-2 (SGLT2) indicated, as Edistride and Forxiga, two centrally authorised products, in adults aged 18 years and older with type 2 diabetes mellitus (T2DM) to improve glycaemic control when diet and exercise alone do not provide adequate glycaemic control in patients for whom use of metformin is considered inappropriate due to intolerance. It is also indicated in combination with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control.

The CHMP is evaluating a worksharing application consisting of an extension of the therapeutic indication for Edistride and Forxiga, centrally authorised products containing dapagliflozin, to include a new indication for the treatment of insufficiently controlled type 1 diabetes mellitus (T1DM) as an adjunct to insulin, when insulin does not provide adequate glycaemic control. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this extension of indication. For further background, see [PRAC minutes May 2018](#) and [PRAC minutes October 2018](#).

Summary of advice

- The RMP for Edistride and Forxiga (dapagliflozin) in the context of the worksharing variation procedure under evaluation by the CHMP could be considered acceptable provided that an update to RMP version 16.4 and satisfactory responses to the request for supplementary information (RSI), in particular in relation to the additional pharmacovigilance activities and the additional risk minimisation measures (aRMM) are submitted.
- With regard to additional pharmacovigilance activities, the PRAC considered that the proposed cohort study 'to determine the effectiveness of the aRMMs in place for diabetic ketoacidosis (DKA) in T1DM European patients who are treated with dapagliflozin' should have its secondary objective (i.e. comparing of incidence of DKA in dapagliflozin users with the incidence in non-users of dapagliflozin) changed to a primary objective and should have an increase of the study size. In addition, the PRAC did not support the proposed cross-sectional survey to assess the knowledge and understanding of the aRMM for DKA in healthcare-professionals and patients. In terms of aRMMs, the PRAC suggested some refinement in the proposed key elements for educational materials (guide for healthcare professionals, guide for patients/carers and patient alert card). The MAH should revise the proposed educational materials accordingly.

5.3.2. Irinotecan hydrochloride trihydrate - ONIVYDE (CAP) - EMEA/H/C/004125/II/0008

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: David Olsen

Scope: Update of sections 1, 2, 4.2, 4.8, 4.9, 5.1, 5.2, 5.3 and 6.6 of the SmPC in order to reflect the expression of strength based on irinotecan anhydrous free-base. The labelling, package leaflet and the RMP (version 2.1) are updated accordingly. In addition, the MAH took the opportunity to introduce minor editorial changes throughout the product information

Background

Irinotecan is a topoisomerase I inhibitor indicated, as Onivyde, a centrally authorised product, for the treatment of metastatic adenocarcinoma of the pancreas, in combination with 5-fluorouracil (5-FU) and leucovorin (LV), in adult patients who have progressed following gemcitabine based therapy.

The CHMP is evaluating a type II variation for Onivyde, a centrally authorised product containing irinotecan, in order to reflect the expression of strength based on irinotecan anhydrous free-base instead of irinotecan hydrochloride trihydrate. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this variation. For further background, see [PRAC minutes September 2018](#).

Summary of advice

- The RMP for Onivyde (irinotecan) in the context of the variation procedure under evaluation by the CHMP could be considered acceptable provided that an update to RMP version 2.5 is submitted.
- The PRAC agreed on the distribution of a direct healthcare professional communication (DHPC) in order to warn healthcare professionals (HCPs) on the risk of medication error. The PRAC agreed the content of the DHPC together with a communication plan.

- The PRAC also considered that the dosing flash card needed to be removed from the proposed risk minimisations measures as it was not found of added value considering that the information on dosing is stated in the DHPC and in the updated product information.

5.3.3. Rituximab - MABTHERA (CAP) - EMEA/H/C/000165/II/0152

Applicant: Roche Registration GmbH

PRAC Rapporteur: Doris Stenver

Scope: Update of sections 4.2 and 4.4 of the SmPC following the submission of the final study report for the non-interventional drug utilisation study (DUS) BA28478: MabThera drug utilisation study and patient alert card evaluation in non-oncology patients in Europe: an infusion centre-based approach. Annex II-E is updated to remove the patient alert card as an additional risk minimisation measure for the risks of progressive multifocal leukoencephalopathy (PML) and infections for the non-oncology indications. The package leaflet and the RMP (version 18) are updated accordingly. This submission fulfils FUM-68.1 and FUM-71

Background

Rituximab is a monoclonal antibody that binds specifically to the transmembrane antigen, CD20, a non-glycosylated phosphoprotein, located on pre-B and mature B lymphocytes. It is indicated, as Mabthera a centrally authorised product, in adults for the treatment of non-Hodgkin's lymphoma (NHL), chronic lymphocytic leukaemia (CLL), rheumatoid arthritis (RA) as well for the treatment of granulomatosis with polyangiitis and microscopic polyangiitis under certain conditions.

The CHMP is evaluating a type II variation for Mabthera, a centrally authorised product containing rituximab, in order to assess the proposed update to the product information and the proposed removal of the patient alert card as an additional risk minimisation measure (aRMM) for the risks of progressive multifocal leukoencephalopathy (PML) and infections for the non-oncology indications based on the evaluation of the final study report of the non-interventional drug utilisation study (DUS) BA28478. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this variation. For further background, see [PRAC minutes September 2018](#).

Summary of advice

- The RMP for Mabthera (rituximab) in the context of the variation procedure under evaluation by the CHMP could be considered acceptable provided that an update to RMP version 18.0 is provided.
- Taking into account the very low incidence of PML in approved non-oncology indications and the knowledge gathered over the years amongst healthcare professionals prescribing this medicine, the PRAC considered that only educational material informing patients on the risk of PML and infections in approved non-oncology indications should remain as aRMM. The MAH should continue to evaluate and further improve the educational material in light of the results of study BA28478. The evaluation should be performed with regard to both the dissemination of the materials and the awareness of the risks (PML, serious infection, administration route errors) among patients in all relevant indications.

- The PRAC supported consulting targeted patient groups to evaluate the preferences of patients regarding the ways of receiving information PML and infections during rituximab treatment.

Post-meeting note: On 04/12/2018, the PRAC adopted by written procedure a list of questions (LoQ) in the framework of the consultation with patients taking rituximab on the educational materials available for risks of infections and PML. Patients can complete the on-line questionnaire in English until 22 January 2019 on:

https://ec.europa.eu/eusurvey/runner/MabThera_rituximab

6. Periodic safety update reports (PSURs)

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

See also Annex I 16.1.

6.1.1. Abiraterone - ZYTIGA (CAP) - PSUSA/00000015/201804

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

Background

Abiraterone is an androgen biosynthesis inhibitor indicated, as Zytiga a centrally authorised product, with prednisone or prednisolone for the treatment of newly diagnosed high risk metastatic hormone sensitive prostate cancer (mHSPC) in adult men in combination with androgen deprivation therapy (ADT), for the treatment of metastatic castration resistant prostate cancer (mCRPC) in adult men who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated as well as for the treatment of mCRPC in adult men whose disease has progressed on or after a docetaxel-based chemotherapy regimen.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Zytiga, a centrally authorised medicine containing abiraterone 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 Zytiga (abiraterone) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add a new contraindication of the use of abiraterone and prednisone or prednisolone in combination with radium Ra-223 dichloride and to add a warning to reflect that such combination is contraindicated due to an increased risk of fractures and a trend for increased mortality among asymptomatic or mildly symptomatic prostate cancer patients as observed in clinical trials. Therefore, it is recommended that subsequent treatment with radium Ra-223 dichloride is not initiated for at least 5 days after the last administration of abiraterone acetate in combination with prednisone/prednisolone. Furthermore, the existing warning on skeletal muscle effects should be refined to reflect that cases of

rhabdomyolysis have also been reported with patients treated with abiraterone. Therefore, the current terms of the marketing authorisation(s) should be varied¹⁴.

- In the next PSUR, the MAH should provide a summary of adverse events associated with medication error especially those of drug prescribing error and incorrect dose administered and discuss the relevance of the findings. The MAH should keep open the following topics: blood and lymphatic disorders, serious cutaneous adverse drug reactions (SCARs), thromboembolic events, anaemia and sudden.

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

6.1.2. Apixaban - ELIQUIS (CAP) - PSUSA/00000226/201805

Applicant: Bristol-Myers Squibb / Pfizer EEIG

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

Background

Apixaban is a factor Xa inhibitor, direct oral anticoagulant (DOAC) indicated, as Eliquis a centrally authorised product, for the prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective hip or knee replacement surgery, for the prevention of stroke and systemic embolism (SE) in adult patients with non-valvular atrial fibrillation (NVAF), with one or more risk factors, such as prior stroke or transient ischaemic attack (TIA); age \geq 75 years; hypertension; diabetes mellitus; symptomatic heart failure (NYHA¹⁵ class \geq II). It is also indicated for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Eliquis, a centrally authorised medicine containing apixaban, 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 Eliquis (apixaban) 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 60 days, a detailed review of cases of alopecia and a detailed review of cases of worsening of renal function in patients using apixaban, including for both reviews cases with a possible or probable relationship due to some missing information, together with a proposal to update the product information as applicable.
- In the next PSUR, the MAH should provide a cumulative review on the interaction between fluconazole and apixaban, and a cumulative safety review of cases of

¹⁴ Update of SmPC sections 4.3 and 4.4. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

¹⁵ New York Heart Association

hypereosinophilia or eosinophilia in patients using apixaban including information from literature, clinical and nonclinical studies, as well as causality assessment of post-marketing cases. The MAH should make a proposal to update the product information as applicable.

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. [Artemimol, piperazine tetraphosphate - EURARTESIM \(CAP\) - PSUSA/00001069/201804](#)

Applicant: Alfasigma S.p.A.

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

Background

Artemimol is an antimalarial and piperazine a bisquinoline. In combination as Eurartesim, a centrally authorised product, artemimol/piperazine tetraphosphate is indicated for the treatment of uncomplicated *Plasmodium falciparum* malaria in adults, adolescents, children and infants 6 months and over and weighing 5 kg or more.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Eurartesim, a centrally authorised medicine containing artemimol/piperazine tetraphosphate 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 Eurartesim (artemimol/piperazine tetraphosphate) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add a warning about the risk of delayed haemolytic anaemia to alert healthcare professionals (HCPs), patients and caregivers to be vigilant for relevant signs and symptoms of post-treatment haemolysis such as pallor, jaundice, dark-coloured urine, fever, fatigue, shortness of breath, dizziness, and confusion. Therefore, the current terms of the marketing authorisation(s) should be varied¹⁶.

The frequency of PSUR submission should be revised from yearly to 18-monthly and the next PSUR should be submitted to the EMA within 90 days of the data lock point. The list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC is updated accordingly.

6.1.4. [Atezolizumab - TECENTRIQ \(CAP\) - PSUSA/00010644/201805 \(with RMP\)](#)

Applicant: Roche Registration GmbH

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

¹⁶ Update of SmPC section 4.4. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

Scope: Evaluation of a PSUSA procedure

Background

Atezolizumab is a programmed death-ligand 1 (PD-L1) inhibitor indicated, as Tecentriq a centrally authorised product, for the treatment in monotherapy of adult patients with locally advanced or metastatic urothelial carcinoma (UC) after prior platinum-containing chemotherapy, or who are considered cisplatin ineligible, and whose tumours have a PD-L1 expression $\geq 5\%$. It is also indicated as monotherapy for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Tecentriq, a centrally authorised medicine containing atezolizumab 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 Tecentriq (atezolizumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add immune-related nephritis as an undesirable effect with frequency 'rare' and as a warning together with dose modification advice for Tecentriq (atezolizumab) in line with the type of nephritis grades patients experience. In addition, immune-related nephritis should be added to the guide for healthcare professionals (HCPs) and to the patient alert card as an additional risk minimisation measure. Therefore, the current terms of the marketing authorisation(s) should be varied¹⁷.
- In the next PSUR, the MAH should provide an analysis of any possible cases of haemophagocytic syndrome and haemophagocytic lymphohistiocytosis. In addition, a detailed review of reported events of cardiac disorders should be presented. Finally, the MAH should keep under close monitoring 'potential pharmacodynamic interaction with systemic immunosuppressants including corticosteroids' and consider it as an important potential risk.

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

6.1.5. Decitabine - DACOGEN (CAP) - PSUSA/00009118/201805

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

Background

Decitabine is a cytidine deoxynucleoside analogue indicated, as Dacogen a centrally authorised product, for the treatment of adult patients with newly diagnosed de novo or

¹⁷ Update of SmPC sections 4.2, 4.4 and 4.8. The package leaflet is updated accordingly. Annex II on 'conditions or restrictions with regard to the safe and effective use of the medicinal product' is also updated. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

secondary acute myeloid leukaemia (AML), according to the World Health Organisation (WHO) classification, who are not candidates for standard induction chemotherapy.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Dacogen, a centrally authorised medicine containing decitabine 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 Dacogen (decitabine) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add 'cardiomyopathy' as an undesirable effect with frequency 'uncommon' and to revise the existing warning on 'cardiac disease' to reflect that cases of cardiomyopathy have been reported and patients, especially those with cardiac disease history, should be monitored for signs and symptoms of heart failure. Therefore, the current terms of the marketing authorisation(s) should be varied¹⁸.
- In the next PSUR, the MAH should closely monitor cases of off-label use.

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

6.1.6. Emicizumab - HEMLIBRA (CAP) - PSUSA/00010668/201805

Applicant: Roche Registration GmbH

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

Background

Emicizumab bridges activated factor IX and factor X to restore the function of missing activated factor VIII that is needed for effective haemostasis. It is indicated, as Hemlibra a centrally authorised product, for routine prophylaxis of bleeding episodes in patients with haemophilia A with factor VIII inhibitors.

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

¹⁸ Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

- Nevertheless, the product information should be updated to include the reported frequencies of anti-drug antibodies (ADA) and ADA with neutralising potential. Therefore, the current terms of the marketing authorisation(s) should be varied¹⁹.
- In the next PSUR, the MAH should monitor and discuss cases reporting fatal haemorrhagic events. In addition, the MAH should provide cases of immunogenicity collected from phase 3 studies BH29884²⁰, BH29992²¹, BH30071²² and BO39182²³ and 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.

6.1.7. Fluticasone furoate - AVAMYS (CAP) - PSUSA/00009154/201804

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

Background

Fluticasone furoate is a synthetic trifluorinated corticosteroid indicated in adults, adolescents and children (6 years and over), as Avamys a centrally authorised product, for the treatment of the symptoms of allergic rhinitis.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Avamys, a centrally authorised medicine containing fluticasone furoate 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 Avamys (fluticasone furoate) 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 90 days, a cumulative review of cases of respiratory, thoracic and mediastinal disorders together with a cumulative review of lower respiratory tract infections. In addition, the MAH should also submit a cumulative review of cases of drug dependence.
- In the next PSUR, the MAH should closely monitor cases with fatal outcome.

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.

¹⁹ Update of SmPC section 5.1. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

²⁰ A randomized, multicentre, open-label, phase 3 clinical trial to evaluate the efficacy, safety, and pharmacokinetics of prophylactic emicizumab versus no prophylaxis in hemophilia A patients with inhibitors

²¹ A multicentre, open-label, phase 3 clinical trial to evaluate the efficacy, safety, and pharmacokinetics of subcutaneous (SC) administration of emicizumab in hemophilia A pediatric patients with inhibitors

²² A randomized, multicentre, open-label, phase 3 clinical trial to evaluate the efficacy, safety, and pharmacokinetics of prophylactic emicizumab versus no prophylaxis in hemophilia A patients without inhibitors

²³ A multicentre, open-label, phase 3 study to evaluate the efficacy, safety, pharmacokinetics, and pharmacodynamics of emicizumab given every 4 weeks in patients with hemophilia A

6.1.8. Interferon beta-1a - AVONEX (CAP); REBIF (CAP) - PSUSA/00009198/201805

Applicant(s): Biogen Netherlands B.V. (Avonex), Merck Europe B.V. (Rebif)

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

Background

Interferon beta-1a is a recombinant interferon, a glycoprotein endowed with immunomodulatory, antiviral and antiproliferative properties. It is indicated, as Avonex and Rebif, two centrally authorised products, for the treatment of patients diagnosed with relapsing multiple sclerosis (MS) and for the treatment of patients with a single demyelinating event with an active inflammatory process under certain conditions.

Based on the assessment of the PSURs, the PRAC reviewed the benefit-risk balance of Avonex and Rebif, centrally authorised medicines containing interferon beta-1a 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 Avonex and Rebif (interferon beta-1a) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- The MAH for Rebif (interferon beta-1a) should submit to EMA, within 60 days, a detailed justification regarding the decrease of spontaneous reports during the period covered by the PSUSA procedure. In addition, the MAH should submit a cumulative review of cases of panniculitis and propose to update the product information as warranted.
- In the next PSUR, the MAHs should provide an analysis of cases of device medication errors as well as a cumulative review of cases of chronic lymphocytic leukaemia (CLL) with a special focus on all available literature. In addition, the MAH for Avonex (interferon beta-1a) should closely monitor cases of thromboembolism. The MAH for Rebif (interferon beta-1a) should provide a cumulative review of cases of acute coronary syndrome.

The PRAC considered that PSURs for Avonex (interferon beta-1a) and Rebif (interferon beta-1a) should be assessed in the future in separate PSUSA procedures as the biological origin of these medicinal products entails different immunogenic properties and the distinct route of administration involves differences in the bioavailability of the active substance, leading to variations of the safety profile between them. Therefore, the EURD list is updated accordingly, keeping the same data lock point (DLP) for both entries. The next PSURs should be submitted in accordance with the requirements set out in the EURD list.

6.1.9. Pixantrone - PIXUVRI (CAP) - PSUSA/00009261/201805

Applicant: CTI Life Sciences Limited

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

Background

Pixantrone is a cytotoxic aza-anthracenedione indicated, as Pixuvri, a centrally authorised product, for the treatment in monotherapy of adult patients with multiply relapsed or refractory aggressive non-Hodgkin B-cell Lymphomas (NHL).

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Pixuvri, a centrally authorised medicine containing pixantrone 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 Pixuvri (pixantrone) 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 60 days, a detailed review for all phase 3 trials including study PIX306²⁴ as well as for study PIXreal²⁵ of the number and proportion of patients for each study with information on possible dose lowering and/or dose omission/skipping. With regard to PIX306, the MAH should also provide a discussion of the rate of dose omission together with a rationale for the differences in dose modification criteria in the study compared to that in the pivotal studies and the guideline on summary of product characteristics (SmPC). Based on these reviews, the MAH should discuss whether changes to the product information or any other risk minimisation measures are 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. The frequency of submission of the subsequent PSURs should be changed from 6-monthly to yearly and the list of Union reference dates (EURD list) will be updated accordingly.

6.1.10. Sunitinib - SUTENT (CAP) - PSUSA/00002833/201804

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

Background

Sunitinib is a multiple receptor tyrosine kinase (RTK) inhibitor indicated, as Sutent, a centrally authorised product, for the treatment of unresectable and/or metastatic malignant gastrointestinal stromal tumour (GIST) in adults after failure of imatinib treatment due to resistance or intolerance, for the treatment of advanced/metastatic renal cell carcinoma (MRCC) in adults, for the treatment of unresectable or metastatic, well-differentiated pancreatic neuroendocrine tumours (pNET) with disease progression in adults as well as for the treatment of unresectable or metastatic, well-differentiated pancreatic neuroendocrine tumours (pNET) with disease progression in adults.

²⁴ A randomised multicentre study comparing pixantrone + rituximab with gemcitabine + rituximab in patients with aggressive B-cell non-Hodgkin lymphoma who have relapsed after therapy with CHOP-R (cyclophosphamide, doxorubicin hydrochloride, vincristine, prednisone - rituximab) or an equivalent regimen and are ineligible for stem cell transplant

²⁵ An observational, multicentre, open label study of pixantrone 50mg/m² given on days 1, 8, and 15 of each 28 day cycle for up to 6 cycles for the treatment of adult patients with multiple relapsed or refractory aggressive B cell non-Hodgkin lymphomas

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Sutent, a centrally authorised medicine containing sunitinib 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 Sutent (sunitinib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning on aortic aneurysms and dissections, and to add 'aortic aneurysms and dissections' as an undesirable effect with a frequency 'not known' as well as 'colitis and ischaemic colitis' with a frequency 'uncommon'. Therefore, the current terms of the marketing authorisation(s) should be varied²⁶.
- In the next PSUR, the MAH should provide cumulative reviews of cases reporting second primary malignancy, hypokalaemia, hypercalcaemia, diabetes, loss of consciousness, and cardiac arrest. The MAH should also provide a cumulative review of cases of drug interaction with flecainide and propose to update the product information as warranted. In addition, the MAH should include a review on cases of overdose, including a discussion whether a specific pattern can be identified.

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

6.1.11. Tolvaptan²⁷ - JINARC (CAP) - PSUSA/00010395/201805

Applicant: Otsuka Pharmaceutical Netherlands B.V.

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

Background

Tolvaptan is a vasopressin antagonist indicated, as Jinarc, a centrally authorised product, to slow the progression of cyst development and renal insufficiency of autosomal dominant polycystic kidney disease (ADPKD) in adults with chronic kidney disease (CKD) stage 1 to 4 at initiation of treatment with evidence of rapidly progressing disease.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Jinarc, a centrally authorised medicine containing tolvaptan 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 Jinarc (tolvaptan) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add gout as an undesirable effect with a frequency 'common'. Therefore, the current terms of the marketing authorisation(s) should be varied²⁸.

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

²⁷ Indicated for adults with autosomal dominant polycystic kidney disease (ADPKD) only

- In the next PSUR, the MAH should provide detailed reviews of cases of sleep disorder and of cases of acute renal failure, renal failure and renal impairment.

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

6.1.12. Vedolizumab - ENTYVIO (CAP) - PSUSA/00010186/201805

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

Background

Vedolizumab is a gut-selective immunosuppressive biologic, indicated as Entyvio, a centrally authorised product, for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a tumour necrosis factor- α (TNF α) antagonist, as well as for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a TNF α antagonist.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Entyvio, a centrally authorised medicine containing vedolizumab 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 Entyvio (vedolizumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add herpes zoster infection as an undesirable effect with a frequency 'uncommon'. Therefore, the current terms of the marketing authorisation(s) should be varied²⁹.
- In the next PSUR, the MAH should provide a cumulative review of cases of delayed onset or long-term breathlessness, pneumonitis and associated allergic lung conditions. In addition, the MAH should discuss the biological impact of α 4 β 7 inhibition on the lung, including innate lymphoid cells and the role in allergic airway inflammation, and should propose to update the product information as warranted.

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

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

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

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. Bortezomib - BORTEZOMIB ACCORD (CAP); BORTEZOMIB HOSPIRA (CAP); BORTEZOMIB SUN (CAP); VELCADE (CAP); NAP - PSUSA/00000424/201804

Applicants: Accord Healthcare Limited (Bortezomib Accord), Janssen-Cilag International NV (Velcade), Pfizer Europe MA EEIG (Bortezomib Hospira), Sun Pharmaceutical Industries Europe B.V. (Bortezomib SUN), various

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

Background

Bortezomib is a proteasome inhibitor indicated as monotherapy or in combination for the treatment of progressive or untreated multiple myeloma in adult patients under certain conditions, as well as for the treatment of adult patients with previously untreated mantle cell lymphoma who are unsuitable for haematopoietic stem cell transplantation, in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone.

Based on the assessment of the PSURs, the PRAC reviewed the benefit-risk balance of Bortezomib Accord, Bortezomib Hospira, Bortezomib Sun and Velcade, centrally authorised medicine(s) containing bortezomib, and nationally authorised medicines containing bortezomib, 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 bortezomib-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information relating to the multiple myeloma indication should be updated to include chalazion and blepharitis as undesirable effects with a frequency 'uncommon' and to include 'thrombotic microangiopathy, including thrombocytopenic purpura' with a frequency 'rare'. Therefore, the current terms of the marketing authorisations should be varied³⁰.
- In the next PSUR, the MAH(s) should provide cumulative reviews of cases of syndrome of inappropriate secretion of antidiuretic hormone (SIADH) and of cases of capillary leak syndrome and should propose to update the product information as warranted. The MAHs should also provide a cumulative review and discussion on plausible mechanism related to hepatitis C reactivation and bortezomib.

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.

³⁰ Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

6.2.2. Capecitabine - CAPECITABINE ACCORD (CAP); CAPECITABINE MEDAC (CAP); ECANSYA (CAP); XELODA (CAP); NAP - PSUSA/00000531/201804

Applicants: Accord Healthcare Limited (Capecitabine Accord), Krka, d.d., Novo mesto (Ecansya), Medac Gesellschaft für klinische Spezialpräparate mbH (Capecitabine medac), Roche Registration GmbH (Xeloda), various

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Capecitabine is a non-cytotoxic fluoropyrimidine carbamate, which functions as an orally administered precursor of the cytotoxic moiety 5-fluorouracil (5-FU) indicated for the adjuvant treatment of patients following surgery of stage III (Dukes' stage C) colon cancer, for the treatment of metastatic colorectal cancer, for first-line treatment of advanced gastric cancer in combination with a platinum based regimen and finally as monotherapy or in combination with docetaxel for the treatment of patients with locally advanced or metastatic breast cancer under certain conditions.

The PRAC is currently reviewing the benefit-risk balance of Capecitabine Accord, Capecitabine medac, Ecansya and Xeloda, centrally authorised medicines containing capecitabine, and nationally authorised medicines containing capecitabine, in the framework of the assessment of a PSUR single assessment (PSUSA) procedure due for PRAC recommendation at the PRAC meeting in January 2019.

Summary of conclusions

- The PRAC Rapporteur presented the preliminary assessment of the currently ongoing PSUSA procedure, which is due to complete at the following PRAC meeting. Further discussion and adoption of a recommendation is planned at the January 2019 PRAC meeting.

6.2.3. Efavirenz - STOCRIN (CAP); SUSTIVA (CAP); NAP - PSUSA/00001200/201804

Applicant(s): Merck Sharp & Dohme B.V. (Stocrin), Bristol-Myers Squibb Pharma EEIG (Sustiva)

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

Background

Efavirenz is a non-nucleoside reverse transcriptase inhibitor (NNRTI) indicated in antiviral combination treatment of human immunodeficiency virus-1 (HIV-1) infected adults, adolescents and children 3 years of age and older.

Based on the assessment of the PSURs, the PRAC reviewed the benefit-risk balance of Stocrin and Sustiva, centrally authorised medicines containing efavirenz, and nationally authorised medicines containing efavirenz 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 efavirenz-containing medicinal products in the approved indications remains unchanged.
- The current terms of the marketing authorisation(s) for Stocrin (efavirenz) should be maintained.
- Nevertheless, the product information should be updated for Sustiva (efavirenz) and efavirenz-nationally authorised medicines to refine the information on interaction between efavirenz and etonogestrel implant. Therefore, the current terms of the marketing authorisations should be varied³¹.
- In the next PSUR, the MAHs should evaluate the potential interaction with the antimalarial drugs dihydroartemisinin (DHA)-piperazine or piperazine alone, following the identification of five scientific publications^{32,33,34,35,36} that describe and analyse this potential drug-drug interaction. In addition, the MAHs should provide a detailed cumulative review of cases of neurotoxicity, especially in populations of CYP2B6³⁷ slow metaboliser genotypes, and propose to update the product information as warranted.
- The PRAC considered the drug-drug interaction with etonogestrel implant is also relevant for fixed dose combination products containing emtricitabine/tenofovir disoproxil. Further consideration is to be given at the level of the CMDh.

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

6.2.4. Tacrolimus³⁸ - ADVAGRAF (CAP); ENVARSUS (CAP); MODIGRAF (CAP); NAP - PSUSA/00002839/201803 (with RMP)

Applicants: Astellas Pharma Europe B.V. (Advagraf, Modigraf), Chiesi Farmaceutici S.p.A. (Envarsus), various

PRAC Rapporteur: Ronan Grimes

Scope: Evaluation of a PSUSA procedure

Background

Tacrolimus is an immunosuppressive agent indicated in prophylaxis of transplant rejection in adult and paediatric kidney, liver or heart allograft recipients as well as for the treatment of allograft rejection resistant to treatment with other immunosuppressive medicinal products in adult and paediatric patients.

³¹ Update of SmPC section 4.5. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

³² R Kajubi et al. Antiretroviral therapy with efavirenz accentuates pregnancy-associated reduction of dihydroartemisinin-piperazine exposure during malaria chemoprevention. Volume 102 number 3/September 2017, doi:10.1002/cpt.664

³³ Olusola Olafuyi; Michael Coleman; Raj K.S. Badhan. The application of physiologically based pharmacokinetic modelling to assess the impact of antiretroviral-mediated drug–drug interactions on piperazine antimalarial therapy during pregnancy. *Biopharm Drug Dispos.* 2017 Nov; 38(8):464-478. doi: 10.1002/bdd.2087. Epub 2017 Sep 29

³⁴ Nugehally R. Srinivas. Letter to the editor: antiretroviral therapy with efavirenz in human immunodeficiency virus (HIV)-infected pregnant women: understanding the possible mechanisms for drug–drug interaction. *Clin Pharmacol Ther.* 2018 Apr; 103(4):570. doi: 10.1002/cpt.961. Epub 2018 Jan 11

³⁵ Wallender, E. et al (2017). Predicting optimal dihydroartemisinin-piperazine regimens to prevent malaria during pregnancy for human immunodeficiency virus–infected women receiving efavirenz. *The Journal of Infectious Diseases*, 217, 964–972

³⁶ Banda, C. et al (2018). Pharmacokinetics of piperazine and safety profile of dihydroartemisinin-piperazine coadministered with antiretroviral therapy in malaria-uninfected HIV-positive Malawian adults. *Antimicrobial Agents and Chemotherapy*, 62, e00634-18

³⁷ Cytochrome P450 2B6

³⁸ Systemic formulations only

Based on the assessment of the PSURs, the PRAC reviewed the benefit-risk balance of Advagraf, Envarsus and Modigraf, centrally authorised medicines containing tacrolimus, and nationally authorised medicines containing tacrolimus 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 tacrolimus-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to add a warning on optic neuropathy and to refine the interaction between tacrolimus and isavuconazole, cobicistat, ritonavir in combination with ombitasvir, paritaprevir +/- dasabuvir indicated for the treatment of hepatitis C, mycophenolic acid, as well as the tyrosine kinase inhibitors nilotinib and imatinib. In addition, the product information should be updated to include optic neuropathy as an undesirable effect with a frequency 'not known', and thrombotic microangiopathy with a frequency 'rare'. Therefore, the current terms of the marketing authorisations should be varied³⁹.
- In the next PSUR, the MAH should provide a cumulative review of the impact of CYP3A5⁴⁰ on tacrolimus pharmacokinetics and the risk of rejection and of toxicity. In addition, the MAHs should provide a cumulative review of cases of interaction with midostaurin and nafcillin which may induce CYP3A4⁴⁰, and with cilostazol which may inhibit CYP3A4, and evaluate the potential pharmacokinetic interaction with tacrolimus. The MAH should also provide a cumulative review on cases reporting cytomegalovirus (CMV) infection as CMV infection may influence the risk of rejection. Lastly, MAH Chiesi should provide a root cause analysis of cases of medication errors involving inappropriate schedule of drug administration.

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. Chlorprothixene (NAP) - PSUSA/00000717/201803

Applicant(s): various

PRAC Lead: Zane Neikena

Scope: Evaluation of a PSUSA procedure

Background

Chlorprothixene is a sedative neuroleptic indicated for the treatment of schizophrenia and other psychoses with psychomotor unrest, agitation and anxiety. In addition, chlorprothixene

³⁹ Update of SmPC sections 4.4, 4.5 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

⁴⁰ Cytochrome P450 3A5

is indicated, in low doses, for the treatment of psychiatric disorders characterised by anxiety-depression unrest, and associated psychosomatic symptoms.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing chlorprothixene 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 chlorprothixene-containing medicinal products in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAH(s) should provide a cumulative review and detailed analysis of the risk of suicidal reactions associated with the use of chlorprothixene. When addressing the strengths and limitations of the available epidemiological data, the MAH(s) should discuss the possible differences in indications for prescription of chlorprothixene as compared to indications of the comparator products, taking into account the psychiatric comorbidities and the fact that chlorprothixene may be used by patients with substance abuse. The MAH(s) should propose to update the product information as warranted.

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

6.3.2. Deoxycholic acid (NAP) - PSUSA/00010525/201804

Applicant(s): various

PRAC Lead: Annika Folin

Scope: Evaluation of a PSUSA procedure

Background

Deoxycholic acid is an endogenous secondary bile acid indicated for the treatment of moderate to severe convexity or fullness associated with submental fat (SMF) in adults when the presence of SMF has an important psychological impact for the patient.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing deoxycholic 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 deoxycholic acid-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add a warning on injection site necrosis and to include 'injection site necrosis' and 'injection site artery necrosis' as

undesirable effects with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied⁴¹.

- In addition, Member States shall ensure that the condition on MAH(s) of medicinal products containing deoxycholic acid and related substances to develop and submit educational materials according to agreed core elements, is fulfilled within 90 days of the date of finalisation of the PSUSA procedure. These materials should ensure that prescribers are informed and the patients understand and acknowledge the risks associated with deoxycholic acid.
- In the next PSUR, the MAH(s) should provide cumulative reviews of cases of lymphadenopathy, ear pain and hypoaesthesia oral. The MAH(s) should also closely monitor cases of pyoderma gangrenosum.
- The PRAC agreed on the distribution of a direct healthcare professional communication (DHPC) in order to warn healthcare professionals (HCPs) of the risks of injection-site necrosis and injection site artery necrosis. The PRAC agreed the content of the DHPC together with a communication plan.

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

6.3.3. Isotretinoin⁴² (NAP) - PSUSA/00010488/201805

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

Background

Isotretinoin is a stereoisomer of all-trans retinoic acid (tretinoin) indicated⁴³ for the treatment of severe forms of acne (nodular or conglobate acne, or acne at risk of permanent scarring) and acne which has failed to respond to standard therapies with systemic antibiotics and topical therapy.

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

⁴¹ Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

⁴² Oral formulations only

⁴³ Oral formulations

- Nevertheless, the product information should be updated to include gynaecomastia as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied⁴⁴.
- In the next PSUR, the MAH(s) should provide cumulative reviews of cases of pyoderma gangrenosum, Raynaud's phenomenon and of vulvovaginal dryness. In addition, the MAH(s) should provide a cumulative review of cases of neurodevelopmental symptoms without evidence of central nervous system malformation in the children of women taking isotretinoin. The MAH(s) 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.

6.3.4. Ivermectin⁴⁵ (NAP) - PSUSA/00010376/201804

Applicant(s): various

PRAC Lead: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

Background

Ivermectin is a semi-synthetic derivative of avermectins, macrocyclic lactones produced by a soil bacterium, indicated⁴⁶ for the treatment of inflammatory lesions of rosacea (papulopustular) in adult patients.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of ivermectin-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include transaminase increased as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied⁴⁷.

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

6.3.5. Metamizole (NAP) - PSUSA/00001997/201804

Applicant(s): various

⁴⁴ Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

⁴⁵ Topical use only

⁴⁶ Topical use

⁴⁷ Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

PRAC Lead: Julia Pallos

Scope: Evaluation of a PSUSA procedure

Background

Metamizole is a non-opioid pyrazolone derivative indicated for the treatment of severe or resistant pain and for the treatment of high fever not responding to general therapeutic measures.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing metamizole 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 metamizole-containing medicinal product(s) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAH(s) should provide a cumulative review of the potential interaction of metamizole and relevant CYP2B6⁴⁸ substrates and propose to update the product information as warranted. In addition, MAH Sanofi should provide a detailed cumulative review of the potential role of metamizole in drug-induced liver injury (DILI) including a comprehensible causality assessment. The MAH should propose to update the product information as warranted.

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

6.3.6. Nadroparin (NAP) - PSUSA/00002104/201803

Applicant(s): various

PRAC Lead: Eva Segovia

Scope: Evaluation of a PSUSA procedure

Background

Nadroparin is a low molecular weight heparin (LMWH) indicated for the prophylaxis and treatment of thromboembolic disorders, the prevention of clotting during hemodialysis, the treatment of unstable angina and non-Q-wave myocardial infarction.

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

⁴⁸ Cytochrome P450 2B6

- Nevertheless, the product information should be updated to include 'headache' as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied⁴⁹.

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

6.3.7. Nortriptyline (NAP) - PSUSA/00002192/201803

Applicant(s): various

PRAC Lead: Maia Uusküla

Scope: Evaluation of a PSUSA procedure

Background

Nortriptyline is a tricyclic antidepressant indicated for the treatment of major depression and depressive states in schizophrenia. It is also indicated in the treatment of nocturnal enuresis.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing nortriptyline 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 nortriptyline-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add an interaction between nortriptyline and valproic acid as nortriptyline plasma concentration can be increased by sodium valproate and valpromide. Therefore, the current terms of the marketing authorisation(s) should be varied⁵⁰.

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

6.3.8. Oxaliplatin (NAP) - PSUSA/00002229/201804

Applicant(s): various

PRAC Lead: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

Background

Oxaliplatin is an antineoplastic drug. In combination with 5-fluorouracil (5-FU) and folinic acid (FA) (FOLFOX), oxaliplatin is indicated for the treatment of stage III (Duke's C) colon

⁴⁹ Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

⁵⁰ Update of SmPC section 4.5. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

cancer after complete resection of primary tumour and for the treatment of advanced/metastatic colorectal cancer.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing oxaliplatin 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 oxaliplatin-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add 'fall' as an undesirable effect with a frequency 'common' and 'acute coronary syndrome (including myocardial infarction and coronary arteriospasm and angina pectoris in patients treated with oxaliplatin in combination with 5-FU and bevacizumab)' and 'oesophagitis' as undesirable effects with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied⁵¹.
- In the next PSUR, the MAH(s) should closely monitor cases of cardiac arrhythmias, cardiomyopathy, cardiac failure, adverse reactions that occurred in the context of intra-arterial chemotherapy/chemoembolisation and hyperthermic intraperitoneal chemotherapy increased bilirubin, drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, Stevens-Johnson syndrome (SJS), cholangitis, tumour lysis syndrome and sudden death. In addition, the MAH(s) should provide a comprehensive review of cases of Guillain Barre syndrome (GBS) and discuss the chronology, concomitant treatments and confounding factors.

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.

6.3.9. Oxycodone (NAP) - PSUSA/00002254/201804

Applicant(s): various

PRAC Lead: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

Background

Oxycodone is a semi-synthetic opioid indicated for the treatment of pain under certain conditions.

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

Summary of recommendation(s) and conclusions

⁵¹ Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

- Based on the review of the data on safety and efficacy, the benefit-risk balance of oxycodone-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add an interaction with serotonergic agents as this may cause serotonin toxicity. Therefore, the current terms of the marketing authorisation(s) should be varied⁵².
- In the next PSUR, the MAH Mundipharma should provide cumulative reviews of cases of abuse, dependence, withdrawal and overdose and cases of opioid-induced apnoea and propose to update the product information as warranted.

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

6.3.10. Paracetamol⁵³ (NAP) - PSUSA/00002311/201805

Applicant(s): various

PRAC Lead: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

Background

Paracetamol is a para-aminophenol derivative indicated⁵⁴ for the short-term treatment of moderate pain.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing paracetamol 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 paracetamol-containing medicinal product(s) IV formulation in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be refined to delete a mention regarding pregnancies exposed to overdose of paracetamol. Therefore, the current terms of the marketing authorisation(s) should be varied⁵⁵.
- The PRAC considered that the deletion of the mention regarding pregnancies exposed to overdose of paracetamol is warranted to all formulations/presentations of paracetamol-containing medicinal products. Further consideration is to be given at the level of the CMDh.
- In the next PSUR, the MAH(s) should closely monitor paediatric cases of paracetamol used for fever prophylaxis in the context of vaccination. In addition, the MAH(s) should

⁵² Update of SmPC section 4.5. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

⁵³ Intravenous (IV) formulation only

⁵⁴ IV formulation

⁵⁵ Update of SmPC section 4.6. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

provide a detailed review of cases of hepatobiliary disorders and abnormal liver functions as well as a cumulative review of cases of renal disorders in a context of paracetamol overdose and should propose 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 the EMA within 90 days of the data lock point. The list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC is updated accordingly.

6.4. Follow-up to PSUR/PSUSA procedures

None

7. Post-authorisation safety studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)⁵⁶

See also Annex I 17.1.

7.1.1. Tisagenlecleucel – KYMRIAH (CAP) - EMEA/H/C/PSP/S/0066

Applicant: Novartis Europharm Ltd, ATMP⁵⁷

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Protocol for non-interventional study CCTLO19B2401 with secondary use of data from two registries conducted by the 'European Society for Blood and Marrow Transplantation' (EBMT) and 'Centre for International Blood and Marrow Transplant Research' (CIBMTR) to evaluate the long term safety of patients with B lymphocyte malignancies treated with tisagenlecleucel (chimeric antigen receptor (CAR)-T cell therapy) in a real-world setting

Background

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

In order to further characterise its safety (including long-term safety), the marketing authorisation of Kymriah (tisagenlecleucel) is subject to the obligation to conduct, as a post-authorisation measure, a non-interventional PASS based on data from a disease registry in ALL and DLBCL patients. In order to fulfil the obligation to conduct a PASS imposed in accordance with Article 107n of Directive 2001/83/EC, the MAH, Novartis Europharm Ltd, submitted on 14 September 2018 a PASS protocol version V01 to EMA for non-interventional study CCTLO19B2401 with secondary use of data from two registries conducted by the European Society for Blood and Marrow Transplantation (EBMT) and the Centre for

⁵⁶ In accordance with Article 107n of Directive 2001/83/EC

⁵⁷ Advanced therapy medicinal product

International Blood & Marrow Transplant Research (CIBMTR) to evaluate the long term safety of patients with B lymphocyte malignancies treated with tisagenlecleucel (chimeric antigen receptor (CAR)-T cell therapy) in a real-world setting. The evaluation procedure started on 1 October 2018.

Endorsement/Refusal of the protocol

- The PRAC, having reviewed the PASS protocol version V01, dated 27 August 2018, and in accordance with Article 107n of Directive 2001/83/EC, considered that the PASS protocol for Kymriah (tisagenlecleucel) could be endorsed, provided that satisfactory responses are provided regarding the case definitions and severity grading of adverse reactions specified in the RMP safety specification, details of communication and actions between the MAH, the registry holders and healthcare professionals (HCPs) in the case of occurrence of a secondary malignancy, data collections forms in the registry, individual case safety report (ICSR) reporting description, quality control procedures descriptions, as well as description of follow-up of pregnancies and infants. Moreover, a first interim report needs to be submitted earlier than proposed (i.e. earlier than 5 years).
- The MAH should submit a revised PASS protocol within 60 days to the EMA. A 60 day-assessment timetable will be followed.

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

See Annex I 17.2.

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

None

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

See Annex I 17.4.

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

See Annex I 17.5.

7.6. Others

See Annex I 17.6.

7.7. New Scientific Advice

None

⁵⁸ In accordance with Article 107m of Directive 2001/83/EC, supervised by PRAC in accordance with Article 61a (6) of Regulation (EC) No 726/2004

⁵⁹ In accordance with Article 107p-q of Directive 2001/83/EC

⁶⁰ In accordance with Article 61a (6) of Regulation (EC) No 726/2004, in line with the revised variations regulation for any submission as of 4 August 2013

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)

None

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

9.1.1. Risk-based programme for routine pharmacovigilance inspections of marketing authorisation holders connected with human centrally authorised products

Scope: Pharmacovigilance inspection programme 2018-2021 (second revision for 2018)

The PRAC agreed the list of planned pharmacovigilance inspections for 2018-2021, the second revision having been agreed by the Pharmacovigilance Inspector Working Group ([PhV IWG](#)) and reviewed according to a risk-based approach. This list is subsequently due for adoption at CHMP. For further background, see [PRAC minutes July 2018](#).

Post-meeting note: On 13 December 2018, the CHMP adopted the pharmacovigilance inspection programme 2018-2021, second revision.

9.2. Ongoing or concluded pharmacovigilance inspections

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

9.3. Others

None

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

10.1. Safety related variations of the marketing authorisation

10.1.1. Febuxostat - ADENURIC (CAP) - EMEA/H/C/000777/II/0051

Applicant: Menarini International Operations Luxembourg S.A.

PRAC Rapporteur: Jan Neuhauser

Scope: PRAC consultation in a variation to update section 5.1 of the SmPC in order to include the results of the clinical safety study CARES (TMX-67_301) to compare the cardiovascular outcomes of febuxostat and allopurinol in subjects with gout and cardiovascular comorbidities. This is a multicentre, randomized, active-control, phase 3B study. In addition, the MAH took the opportunity to provide a consolidated Module 2.7.6 in order to list all the synopsis of individual studies in a unique tabular format

Background

Febuxostat is a non-purine selective inhibitor of xanthine oxidase (NP-SIXO). Adenuric (febuxostat) is a centrally authorised product indicated in adults for the treatment of chronic hyperuricaemia in conditions where urate deposition has already occurred (including a history, or presence of, tophus and/or gouty arthritis) and for the treatment for the prevention and treatment of hyperuricaemia in adult patients undergoing chemotherapy for haematologic malignancies at intermediate to high risk of tumour lysis syndrome (TLS).

A type II variation is under evaluation at the CHMP proposing to update the product information of Adenuric (febuxostat) with the results of the clinical post-authorisation safety study CARES (TMX-67_301)⁶¹ to evaluate the cardiovascular safety of Adenuric (febuxostat) and allopurinol in subjects with gout and cardiovascular comorbidities. The PRAC was requested to provide advice on the possible need, in the context of this variation, for a direct healthcare professional communication (DHPC) to inform the prescriber of the results of the post-approval safety study CARES.

Summary of advice

- Based on the review of the available information, the PRAC considered that the data from the CARES study raised important safety concerns most importantly the increase in mortality that would need to be communicated to healthcare professionals (HCPs), especially in those patients where treatment with allopurinol is also possible.
- However, the PRAC also agreed that there are a number of issues in the CARES study and that further MAH's responses are needed before distributing a DHPC in order to include relevant and specific clinical recommendations to HCPs.
- The PRAC also suggested requesting the MAH to submit to EMA interim results for the FAST⁶² study due for finalisation in 2020.

⁶¹ Performed in USA, Canada and Mexico by the Sponsor Takeda (MAH of febuxostat registration in US) in order to fulfil a post-approval commitment for Uloric (febuxostat) requested by the US FDA

⁶² A multicentre prospective, randomised, open-label, blinded endpoint trial comparing the cardiovascular safety of allopurinol and febuxostat in patients with symptomatic hyperuricaemia

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

None

10.3. Other requests

None

10.4. Scientific Advice

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

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

11.1. Safety related variations of the marketing authorisation

11.1.1. Esomeprazole, naproxen (NAP) - NL/H/1848/001/II/026

Applicant: AstraZeneca B.V. (Vimovo)

PRAC Lead: Liana Gross-Martirosyan

Scope: PRAC consultation on a variation procedure proposing to change the current warning related to naproxen on the cardiovascular and cerebrovascular risk profile

Background

Naproxen is a propionic acid derivative and non-steroidal anti-inflammatory non-selective cyclooxygenase 1-2 (COX 1-2) inhibitor drug (NSAID) used to treat a variety of inflammatory conditions and symptoms that are due to excessive inflammation, such as pain and fever (naproxen has fever-reducing or antipyretic properties in addition to its anti-inflammatory activity). Inflammatory sources of pain that may respond to naproxen's anti-inflammatory activity are conditions such as migraine, osteoarthritis, kidney stones, rheumatoid arthritis, psoriatic arthritis, gout, ankylosing spondylitis, menstrual cramps, tendinitis, and bursitis.

Due to emerging safety data, various reviews including referrals procedures ([CHMP/323166/05](#), [EMA/H/A-5.3/800](#), [EMA/H/A-5\(3\)/1319](#), [EMA/H/A-31/1344](#)), have been conducted for coxibs and NSAIDs regarding cardiovascular safety, leading to various updates of the product information. In the context of the recent PSUR single assessment (PSUSA) procedure for naproxen (PSUSA/00002125/201708), a meta-analysis of four epidemiological studies published by *Bally et al.*⁶³ observing an increased odd ratio (OR) of acute myocardial infarction when naproxen doses >750 mg/day were used short term (8-30 days) compared to non-use was reviewed. The PRAC considered that the study alone was not sufficient to change previous conclusions on the cardiovascular risks. No update of the product information was considered warranted at that time. For further background, see [PRAC minutes April 2018](#).

⁶³ Bally et al. Risk of acute myocardial infarction with NSAIDs in real world use: bayesian meta-analysis of individual patient data. BMJ. 2017

In the context of the evaluation of a type II work sharing variation procedure (NL/H/1848/001/II/026) for Vimovo⁶⁴, a nationally authorised fixed dose combination product containing naproxen/esomeprazole to change the current warning regarding cardiovascular and cerebrovascular risk in the product information, the Netherlands, as Reference Member State (RMS), requested PRAC advice on its assessment.

Summary of advice

- Based on the review of the available information, the PRAC did not support the assessment and proposal from the RMS to amend the product information.
- In particular, the PRAC noted that the studies presented⁶⁵ have important limitations and that no substantial new information has become available since the discussion of the same cardiovascular safety data in both the latest PSUSA procedure concluded in April 2018 (PSUSA/00002125/201708) and in the PRAC advice on celecoxib to Member States adopted in September 2018 (see [PRAC minutes September 2018](#)) where the PRECISION study was discussed in detail. The proposed changes are not substantiated by the available evidence.

11.2. Other requests

11.2.1. Atorvastatin (NAP) - DE/H/PSUFU/00010347/201710/A

Applicant: Pfizer

PRAC Lead: Martin Huber

Scope: PRAC consultation on a worksharing PSUR follow-up (PSU FU) procedure on the safety concern of 'systemic lupus erythematosus/lupus erythematosus/lupus-like syndrome' and causal association of atorvastatin as discussed at PRAC and agreed by CMDh following the conclusion of the PSUSA procedure on atorvastatin (PSUSA/00010347/201710) concluded in June 2018

Background

Atorvastatin is a synthetic lipid-lowering agent indicated for the prevention of cardiovascular diseases as well as for the treatment of hypercholesterolaemia under certain conditions.

Based on the assessment of the recent PSUR single assessment (PSUSA) procedure for atorvastatin (PSUSA/00010347/201710) concluded in June 2018, the PRAC considered that the safety concerns of 'systemic lupus erythematosus/lupus erythematosus/lupus-like syndrome' needed to be further assessed. For further background, see [PRAC minutes June 2018](#).

On request of the CMDh, the originator MAH for atorvastatin-containing product, Pfizer, submitted a safety review of all cases issued from clinical studies, post-marketing exposure

⁶⁴ Indicated for the symptomatic treatment of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis, in patients who are at risk for developing non-steroidal anti-inflammatory drug (NSAID)-associated gastric and/or duodenal ulcers and where treatment with lower doses of naproxen or of other NSAIDs is not considered sufficient

⁶⁵ Nissen et al 2016. PRECISION trial. Cardiovascular safety of celecoxib, naproxen, or ibuprofen for arthritis. *N Engl J Med* 2016; 375(26):2519-29

Chan et al 2017. Gastrointestinal safety of celecoxib versus naproxen in patients with cardiothrombotic diseases and arthritis after upper gastrointestinal bleeding (CONCERN): an industry-independent, double-blind, double-dummy, randomised trial. *Lancet* 2017; 389(10087):237 5-82

Bally et al 2017. Risk of acute myocardial infarction with NSAIDs in real world use: bayesian meta-analysis of individual patient data. *BMJ* 2017; 357:j1909

including causality assessment with de- and rechallenge data as well as literature together with a thorough discussion of the possible pathomechanism for evaluation within a worksharing periodic safety update (PSU) follow-up procedure. In the context of the ongoing evaluation of the PSU FU procedure (DE/H/PSUFU/00010347/201710/A), Germany, as lead Member State (LMS), requested PRAC advice on its assessment.

Summary of advice

- Based on the assessment provided by the LMS, the PRAC supported the conclusions by the LMS and concurred that there was sufficient available evidence at this stage to support a possible causal relationship between 'lupus-related events' and atorvastatin. Consequently, the PRAC supported the conclusion from the RMS to update the product information in order to include 'lupus-like syndrome' as an undesirable effect with a frequency 'very rare'.

11.2.2. Cabergoline (NAP)

Applicant: Pfizer Limited

PRAC Lead: Amelia Cupelli

Scope: PRAC consultation on the evaluation of the final report for the 'study on the utilisation of cabergoline for compliance with risk minimisation activities (SUCRE)' requested as an outcome of the referral procedure under Article 31 of Directive 2001/83/EC on ergot-derived dopamine agonists concluded in 2008 (EMA/H/A-31/881)

Background

Cabergoline is an ergot derivative and a dopamine D2-agonist used for the inhibition of physiologic lactation soon after parturition, suppression of established physiologic lactation, and for the treatment of hyperprolactinemic disorders including dysfunctions such as amenorrhea, oligomenorrhea, anovulation and galactorrhea. Cabergoline is also indicated in patients with prolactin-secreting pituitary adenomas (micro- and macroprolactinomas), idiopathic hyperprolactinemia, or empty sella syndrome with associated hyperprolactinemia, which represent the basic underlying pathologies contributing to the above clinical manifestations. In addition, cabergoline is indicated in the management of Parkinson's disease as monotherapy, or as an adjunct to levodopa therapy to reduce 'end-of-dose' or 'on-off' fluctuations in response.

As part of the outcome of the referral procedure under Article 31 of Directive 2001/83/EC on the review of ergot-derived dopamine agonists concluded in 2008 (see [EMA/CHMP/319054/2008](#)), an obligation for cabergoline-containing medicines to perform a study for the long term follow-up on the adherence to and effectiveness of the changes to the product information, was included as a condition of the marketing authorisations (MA) of cabergoline-containing medicines. Changes to prescribing information included a warning stating that patients must be monitored for signs of cardiac valve fibrosis with echocardiography before treatment is started and regularly (every 6 months) during treatment, a reduction of the maximum recommended dose to 3 mg per day and a statement that cardiac valve fibrosis is 'a very common' undesirable effect. In the context of the evaluation of a worksharing procedure to assess the final study report for the 'SUCRE' study, a study designed with this purpose, Italy requested PRAC advice on its assessment in October 2014. The PRAC supported the submission of a revised study report addressing clarifications on the results. For further background, see [PRAC minutes October 2014](#).

In the context of the review, Italy, as the lead Member State (LMS) for the evaluation of the revised study report submitted by the MAH, requested further PRAC advice on its assessment.

Summary of advice

- Based on the review of the available information, the PRAC supported the LMS conclusions that the SUCRE study objectives (a full assessment of the effect of product information changes and prescription guidelines on both compliance in performing echocardiography and prevalence of cardiac valvulopathy in patients receiving cabergoline) have not been fully achieved.
- Nevertheless, given the substantial decline of cabergoline use (despite some evidence of persisting first line prescription for Parkinson's disease), partially explaining the study small sample size and presented to PRAC as part of the PSUR single assessment (PSUSA) procedure concluded in November 2018 (PSUSA/00000477/201803, see [PRAC minutes November 2018 \(29-31 October 2018\)](#)), the Committee advised that no further data collection was needed.

11.2.3. Paroxetine (NAP) - NL/H/PSUFU/00002319/201712

Applicant: GlaxoSmithKline (Seroxat)

PRAC Lead: Liana Gross-Martirosyan

Scope: PRAC consultation on a worksharing PSUR follow-up (PSU FU) procedure on a detailed review of cases of drug reaction with eosinophilia and systemic symptoms (DRESS) as discussed at PRAC and agreed by CMDh following the conclusion of the PSUSA procedure on paroxetine (PSUSA/00002319/201712) concluded in July 2018

Background

Paroxetine is a selective serotonin re-uptake inhibitor (SSRI) indicated for the treatment of major depressive disorder (MDD), obsessive compulsive disorder (OCD), panic disorder with and without agoraphobia, social anxiety disorder (SAD), generalised anxiety disorder (GAD) and post-traumatic stress disorder (PTSD). Paroxetine controlled-release (CR) formulation is indicated for MDD, premenstrual dysphoric disorder (PMDD), panic disorder and social anxiety disorder/social phobia.

Based on the assessment the assessment of the recent PSUR single assessment (PSUSA) procedure for paroxetine (PSUSA/00002319/201712) concluded in July 2018, the PRAC considered that the signal on 'DRESS' needed to be further assessed (for further background, see [PRAC minutes July 2018](#)). The originator MAH for paroxetine-containing product was requested by CMDh to submit a cumulative review of cases of DRESS (including cases from clinical trials and post marketing and literature publications) as a worksharing PSU follow-up (PSU FU) procedure. In the context of the evaluation of the worksharing PSU FU procedure, the Netherlands as lead Member State (LMS), requested PRAC advice on its assessment.

Summary of advice

- Based on the review of the available information, the PRAC supported the conclusions from the LMS stating that the currently available data do not provide sufficient evidence for a possible causal relationship between onset of DRESS and paroxetine. As a consequence, no update of the product information or the RMP is considered warranted at this stage. However, the PRAC concurred that the MAH should continue to monitor

cases discussing onset of DRESS in patients receiving paroxetine via routine pharmacovigilance activities and provide an update on this matter as soon as new and relevant information becomes available.

12. Organisational, regulatory and methodological matters

12.1. Mandate and organisation of the PRAC

None

12.2. Coordination with EMA Scientific Committees or CMDh-v

None

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

None

12.4. Cooperation within the EU regulatory network

12.4.1. Brexit – EMA knowledge sharing package to support UK portfolio transfer

At the organisational matters teleconference held on 13 December 2018, and in the context of the regular status updates to Committees on 'Brexit preparedness business continuity plan including Committees' operational preparedness activities in view of the withdrawal of the UK from the European Union' (for further background, see last update [PRAC minutes May 2018](#)), the EMA Secretariat presented to PRAC information on 'knowledge sharing package to support UK portfolio transfer'. PRAC was informed that EMA created a library in sharepoint to be used as a repository for the medicinal products due for Rapporteurship transfers. For each product, background knowledge on the regulatory and evaluation history is made available. Additional information or documents can be also requested 'ad-hoc' to EMA as needed.

12.4.2. PRAC strategic review and learning meeting (SRLM), Vienna, Austria, 25-26 September 2018 - report

PRAC lead: Jan Neuhauser

As a follow-up to the recent PRAC strategic review and learning meeting (SRLM) held in September 2018 under the Austrian presidency of the Council of the EU, the Austrian PRAC member presented for information and consideration to PRAC a list of action points resulting from the SRLM.

12.5. Cooperation with International Regulators

None

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

None

12.7. PRAC work plan

12.7.1. PRAC work plan 2019 – preparation

PRAC lead: Sabine Straus, Martin Huber

At the organisational matters teleconference held on 13 December 2018, and as a follow-up the last PRAC discussion (for further background, see [PRAC minutes November 2018 \(29-31 October 2018\)](#)), the EMA Secretariat presented to PRAC a draft PRAC work plan for 2019. PRAC members were invited to provide written comments by 4 January 2019. Further discussion will take place in January 2019.

12.8. Planning and reporting

None

12.9. Pharmacovigilance audits and inspections

12.9.1. Pharmacovigilance systems and their quality systems

None

12.9.2. Pharmacovigilance inspections

None

12.9.3. Pharmacovigilance audits

None

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

12.10.1. Periodic safety update reports

None

12.10.2. Granularity and Periodicity Advisory Group (GPAG)

PRAC lead: Menno van der Elst, Maia Uusküla

The PRAC noted that the January 2018 meeting of the GPAG, focussing on harmonising and streamlining the EURD list, was cancelled.

12.10.3. PSURs repository

None

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

The PRAC endorsed the draft revised EURD list, version December 2018, reflecting the PRAC's comments impacting on the data lock point (DLP) and PSUR submission frequencies of the substances/combinations. The PRAC endorsed the newly allocated Rapporteurs for upcoming PSUSAs in accordance with the principles previously endorsed by the PRAC (see [PRAC minutes April 2013](#)).

Post-meeting note: following the PRAC meeting December 2018 (held on 26-29 November 2018), the updated EURD list was adopted by the CHMP and CMDh at their December 2018 meetings and published on the EMA website on 19/12/2018, 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 \(PSURs\)](#)

12.10.5. Good Pharmacovigilance Practice (GVP) module V on 'Risk management systems' and module VII on 'Periodic safety update report' – clarifications on safety specification

See under 12.14.2.

12.11. Signal management

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

PRAC lead: Menno van der Elst

The PRAC was updated on the signal management review technical (SMART) working group meeting held on 26 November 2018. The main discussion focussed on preliminary results of the survey among National Competent Authorities (NCAs) and EMA concerning the monitoring of scientific literature and also implementation plan for MAHs' signals. It was reminded that the evaluation of the pilot on signal detection in EudraVigilance (EV) by MAHs will cover 1 year data starting from 22 February 2018. The data will be analysed and discussed in the months following February 2019, with a view to report to the European Commission (EC) by September 2019 and communicate on the next steps by December 2019. Enhanced training of MAHs will be needed to support the next phase of the implementation. PRAC will be involved in the decision-making process. In addition, the SMART working group discussed the transfer of UK Rapporteurship/lead Membership.

12.11.2. Signal Management Review Technical (SMART) methods activities - update

At the organisational matters teleconference held on 13 December 2018, and in line with the [PRAC work plan 2018](#), the EMA Secretariat presented to the Committee on each topic of the SMART work programme, namely on unexpected increase of frequency, methodologies in signal detection for paediatric, statistical correction of bias, mechanisms of action and signals outcome and analysis. The PRAC noted the status update for 2018.

12.12. Adverse drug reactions reporting and additional monitoring

12.12.1. Management and reporting of adverse reactions to medicinal products

None

12.12.2. Additional monitoring

None

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

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

Post-meeting note: The updated additional monitoring list was published on 19/12/2018 on the EMA website (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. Good Pharmacovigilance Practice (GVP) module V on 'Risk management systems' and module VII on 'Periodic safety update report' – clarifications on safety specification

PRAC lead: Menno van der Elst

Following the recent introduction of revision 2.01 of the guidance on the format of RMP in the EU (template) (for further background, see [PRAC minutes November 2018 \(29-31 October 2018\)](#)), the EMA Secretariat brought some clarification to PRAC on how the safety specification should be approached in RMP and in the periodic benefit risk evaluation report (PBRER) single assessments (PSUSA). As a conclusion, it was highlighted that safety specification in RMP and PBRER can differ with the new RMP template. The new 'active management' approach to risks in the new RMP template as per revision 2 of GVP module V on 'Risk management systems' does not apply to PBRER, for which GVP module VII on 'Periodic safety update report' applies. Furthermore, stand-alone assessments of safety specifications in RMP are not part of the PSUR procedure/assessment. Only RMP updates based on the data presented in PBRER should be mentioned in PSUSA conclusions.

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

None

12.15. Post-authorisation safety studies (PASS)

12.15.1. Post-authorisation Safety Studies – imposed PASS

None

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

None

12.16. Community procedures

12.16.1. Referral procedures for safety reasons

None

12.17. Renewals, conditional renewals, annual reassessments

None

12.18. Risk communication and transparency

12.18.1. Public participation in pharmacovigilance

None

12.18.2. Safety communication

None

12.19. Continuous pharmacovigilance

12.19.1. Incident management

None

12.20. Others

12.20.1. EMA relocation to Amsterdam, the Netherlands – meeting premises

As a follow-up to the previous discussion on the EMA relocation in 2019 to Amsterdam, the Netherlands (for further background, see [PRAC minutes July 2018](#)), the EMA Secretariat further updated the PRAC on the meeting premises in the interim building in Amsterdam as of March 2019.

12.20.2. EMA relocation to Amsterdam, the Netherlands – adjustment to March 2019 meeting start time

Due to the EMA relocation in Amsterdam in March 2019, the PRAC was informed that the date of the first PRAC plenary meeting in the Netherlands was slightly refined and will take place on 12-15 March 2019.

See also 12.20.1.

12.20.3. Patient registry initiative and cross-committee task force on registries – update

At the organisational matters teleconference held on 13 December 2018, and in line with the [PRAC work plan 2018](#), the EMA Secretariat presented to the Committee a status update on the 'EMA patient registry initiative and the cross-committee task force on registries'. The PRAC was reminded that the 'cross-committee task force' was set up in September 2015, aiming at facilitating use of disease registries by introducing and supporting a systematic approach to their contribution to the benefit-risk evaluation of medicines. This includes the promotion of dialogue between regulators, companies and registry holders to understand barriers and opportunities of using disease registries as well as the provision of guidance to clarify methodological concepts and regulatory requirements. Several patient registries workshop took place at EMA in 2017-2018, an inventory of disease registries is conducted and several qualification opinion and scientific advice have been issued. Overall, it is considered that discussion and agreement on the use of registries should happen at early stages in the regulatory process to authorize a medicinal product. To this end, an internal EMA process is in place. The discussion paper on 'use of patient disease registries for regulatory purposes – methodological and operational considerations' ([EMA/763513/2018](#)) from the 'cross-committee task force' is currently under public consultation until 30 June 2019.

13. Any other business

None

14. Annex I – Signals assessment and prioritisation⁶⁶

14.1. New signals detected from EU spontaneous reporting systems

As per agreed criteria for new signal(s), the PRAC adopted without further plenary discussion the recommendation of the Rapporteur to request MAH(s) to submit a cumulative review following standard timetables⁶⁷.

⁶⁶ 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

⁶⁷ Either MA(s)'s submission within 60 days followed by a 60 day-timetable assessment or MAH's submission cumulative review within an ongoing or upcoming PSUR/PSUSA procedure (if the DLP is within 90 days), and no disagreement has been raised before the meeting

14.1.1. Alectinib – ALECENSA (CAP)

Applicant(s): Roche Registration GmbH

PRAC Rapporteur: Patrick Batty

Scope: Signal of erythema multiforme

EPITT 19321 – New signal

Lead Member State(s): UK

14.1.2. Benralizumab – FASENRA (CAP)

Applicant(s): AstraZeneca AB

PRAC Rapporteur: David Olsen

Scope: Signal of anaphylactic reaction

EPITT 19319 – New signal

Lead Member State(s): NO

14.1.3. Idelalisib – ZYDELIG (CAP)

Applicant(s): Gilead Sciences Ireland UC

PRAC Rapporteur: Patrick Batty

Scope: Signal of arthritis and arthralgia

EPITT 19312 – New signal

Lead Member State(s): UK

14.1.4. Ivacaftor – KALYDECO (CAP); ivafactor, tezacaftor – SYMKEVI (CAP)

Applicant(s): Vertex Pharmaceuticals (Europe) Ltd.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Signal of increased blood creatine phosphokinase (CPK)

EPITT 19316 – New signal

Lead Member State(s): ES, IE

14.1.5. Trastuzumab emtansine – KADCYLA (CAP)

Applicant(s): Roche Registration GmbH

PRAC Rapporteur: Doris Stenver

Scope: Signal of sepsis

EPITT 19326 – New signal

Lead Member State(s): DK

14.2. New signals detected from other sources

- 14.2.1. Clopidogrel – CLOPIDOGREL APOTEX (CAP), CLOPIDOGREL BGR (CAP), CLOPIDOGREL HCS (CAP), CLOPIDOGREL KRKA (CAP), CLOPIDOGREL KRKA D.D. (CAP), CLOPIDOGREL MYLAN (CAP), CLOPIDOGREL RATIOPHARM (CAP), CLOPIDOGREL RATIOPHARM GMBH (CAP), CLOPIDOGREL TAD (CAP), CLOPIDOGREL TEVA (CAP), CLOPIDOGREL ZENTIVA (CAP), GREPID (CAP), ISCOVER (CAP), PLAVIX (CAP), ZYLLT (CAP); NAP; clopidogrel/acetylsalicylic acid – CLOPIDOGREL/ACETYLSALICYLIC ACID ZENTIVA (CAP), DUOPLAVIN (CAP); NAP Lopinavir, ritonavir – KALETRA (CAP), LOPINAVIR/RITONAVIR MYLAN (CAP), NAP; ritonavir – NORVIR (CAP), RITONAVIR (CAP), NAP
-

Applicant(s): AbbVie Deutschland GmbH & Co. KG (Kaletra, Norvir), Apotex Europe BV (Clopidogrel Apotex), Archie Samuel s.r.o. (Clopidogrel Ratiopharm GmbH), HCS bvba (Clopidogrel HCS), Krka, d.d., Novo mesto (Clopidogrel Krka, Clopidogrel Krka d.d., Zyllt), Laboratoires Biogaran (Clopidogrel BGR), Mylan S.A.S (Clopidogrel Mylan, Lopinavir/Ritonavir Mylan, Ritonavir Mylan), Pharmathen S.A. (Grepid), Sanofi-aventis groupe (Clopidogrel/Acetylsalicylic acid Zentiva, Iscover), Sanofi Clir SNC (Duoplavin, Plavix), TAD Pharma GmbH (Clopidogrel TAD), Teva B.V. (Clopidogrel Ratiopharm, Clopidogrel Teva), Zentiva k.s. (Clopidogrel Zentiva), various

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Signal of interaction with ritonavir boosted antiviral human immunodeficiency virus (HIV) therapy leading to insufficient inhibition of platelet aggregation

EPITT 19325 – New signal

Lead Member State(s): FR, NL, PT

- 14.2.2. Selective serotonin reuptake inhibitors (SSRI): citalopram (NAP); escitalopram (NAP)
-

Applicant(s): various

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of drug interaction with fluconazole

EPITT 19327 – New signal

Lead Member State(s): SE

- 14.2.3. Sorafenib – NEXAVAR (CAP)
-

Applicant(s): Bayer AG

PRAC Rapporteur: Annika Folin

Scope: Signal of acute generalised exemanthous pustulosis (AGEP)

EPITT 18109 – New signal

Lead Member State(s): SE

- 14.2.4. Natalizumab – TYSABRI (CAP)
-

Applicant(s): Biogen Netherlands B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Signal of human papillomavirus (HPV) infection and complications

EPITT 19329 – New signal

Lead Member State(s): DE

15. Annex I – Risk management plans

15.1. Medicines in the pre-authorisation phase

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

15.1.1. Febuxostat - EMEA/H/C/004773

Scope: Treatment of hyperuricaemia

15.1.2. Pegfilgrastim - EMEA/H/C/004556

Scope: Reduction in the duration of neutropenia and the incidence of febrile neutropenia

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

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

15.2.1. Aclidinium - BRETARIS GENUAIR (CAP) - EMEA/H/C/002706/WS1402/0038; EKLIRA GENUAIR (CAP) - EMEA/H/C/002211/WS1402/0038

Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

Scope: Update of the RMP (version 7.0) in order to reflect changes in the categorisation of safety concerns and missing information in line with revision 2 of GVP module V on 'Risk management systems' and revision 2 of the guidance on the format of RMP in the EU (template)

15.2.2. Aclidinium, formoterol fumarate dihydrate - BRIMICA GENUAIR (CAP) - EMEA/H/C/003969/WS1403/0023; DUAKLIR GENUAIR (CAP) - EMEA/H/C/003745/WS1403/0023

Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

Scope: Update of the RMP (version 4.0) in order to reflect changes in the categorisation of safety concerns and missing information in line with revision 2 of GVP module V on 'Risk

management systems' and revision 2 of the guidance on the format of RMP in the EU (template)

15.2.3. Ambrisentan - VOLIBRIS (CAP) - EMEA/H/C/000839/II/0055

Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Eva Segovia

Scope: Update of the RMP (version 7.6) in order to remove the educational materials for healthcare professionals given the information provide in the product information and the experience gained in using ambrisentan, as requested by PRAC in the PSUR single assessment procedure (PSUSA/00000129/201706) concluded in January 2018. Annex II of the product information is updated accordingly. In addition, the MAH took the opportunity to update Annex II to include minor changes including the correction of typographical errors

15.2.4. Darbepoetin alfa - ARANESP (CAP) - EMEA/H/C/000332/II/0148

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Martin Huber

Scope: Update of Annex II-D on 'conditions or restrictions with regard to the safe and effective use of the medicinal product' to implement information on education material proposal to address the incorrect self-administration of Aranesp (darbepoetin alfa) via the SureClick pre-filled pen and associated dosing errors. The RMP (version 9.1) is updated accordingly and in line with revision 2 of GVP module V on 'Risk management systems' and revision 2 of the guidance on the format of RMP in the EU (template)

15.2.5. Emtricitabine - EMTRIVA (CAP) - EMEA/H/C/000533/II/0127

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Julie Williams

Scope: Update of the RMP (version 9.1) in order to reflect changes in the categorisation of safety concerns in line with revision 2 of the guidance on the format of RMP in the EU (template). In addition, updates have been made to the Antiretroviral Pregnancy Registry (APR) and the Mitochondrial Collaborative Committee (MITOC) study: a cross-sectional study of human immunodeficiency virus (HIV) negative children aged 18-24 months born to HIV-1 infected mothers in Europe. Finally, the RMP is also updated to reflect the approved transfer of the marketing authorisation from Gilead Sciences International Ltd, Cambridge (GSIL) to Gilead Sciences Ireland UC, Cork (GSIUC)

15.2.6. Evolocumab - REPATHA (CAP) - EMEA/H/C/003766/II/0028

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Kimmo Jaakkola

Scope: Update of the RMP (version 5.0) in order to provide the final results of study 20120332 (GAUSS-3, part C) (listed as a category 3 study in the RMP): a 3-part, phase 3, multicentre, randomized, double-blind, ezetimibe-controlled, parallel-group study. Part C was a 2-year, open-label extension that evaluated the long-term safety and efficacy of

evolocumab in hypercholesterolemic subjects unable to tolerate an effective dose of a statin. As a consequence, the MAH proposes to remove missing information of use in patients with severe hepatic impairment (Child-Pugh class C) and use in patients with hepatitis C

15.2.7. Human fibrinogen, human thrombin - EVICEL (CAP) - EMEA/H/C/000898/II/0063

Applicant: Omrix Biopharmaceuticals N. V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of the RMP (version 14.2) in order to bring it in line with revision 2 of the guidance on the format of RMP in the EU (template) to update exposure data, and to remove 'lack of efficacy' as an identified risk as requested by PRAC in the outcome of the PSUR single assessment procedure (PSUSA/00010297/201706) concluded in January 2018

15.2.8. Pegfilgrastim - NEULASTA (CAP) - EMEA/H/C/000420/II/0099

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Patrick Batty

Scope: Update of the RMP (version 5.1) in order to add study 20160176 (listed as category 3 in the RMP): a retrospective cohort study of female breast cancer patients aged 66 years and over selected from the US Surveillance, Epidemiology and End Results (SEER)-Medicare database to investigate the association between granulocyte colony stimulating factor (G-CSF) use and myelodysplastic syndrome (MDS) or acute myeloid leukaemia (AML), as a new pharmacovigilance activity. In addition, the MAH submitted a draft protocol for study 20160176

15.2.9. Pregabalin - LYRICA (CAP) - EMEA/H/C/000546/WS1364/0092; PREGABALIN PFIZER (CAP) - EMEA/H/C/003880/WS1364/0021

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Update of the RMP (version 12.0) in order to update the safety specifications and risk minimisation measures as requested in the outcome of the PSUR single assessment procedure (PSUSA/00002511/201701) finalised in September 2017. The pharmacovigilance plan is also updated. The draft protocol for a non-interventional non-imposed PASS (study A0081359) entitled 'a population-based cohort study of pregabalin to characterize pregnancy outcomes' is submitted. The MAH took the opportunity to include minor updates and to align the RMP in line with revision 2 of the guidance on the format of RMP in the EU (template)

15.2.10. Saxagliptin - ONGLYZA (CAP) - EMEA/H/C/001039/II/0048

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Update of the RMP (version 14) in order to reflect changes in the categorisation of safety concerns in line with revision 2 of the guidance on the format of RMP in the EU

(template)

- 15.2.11. Sitagliptin - JANUVIA (CAP) - EMEA/H/C/000722/WS1357/0063; RISTABEN (CAP) - EMEA/H/C/001234/WS1357/0055; TESAVEL (CAP) - EMEA/H/C/000910/WS1357/0063; XELEVIA (CAP) - EMEA/H/C/000762/WS1357/0067; sitagliptin, metformin hydrochloride - EFFICIB (CAP) - EMEA/H/C/000896/WS1357/0089; JANUMET (CAP) - EMEA/H/C/000861/WS1357/0089; RISTFOR (CAP) - EMEA/H/C/001235/WS1357/0076; VELMETIA (CAP) - EMEA/H/C/000862/WS1357/0092
-

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Update of the RMP (version 9.1) in order to remove 'theoretic carcinogenic potential' currently classified as missing information from the list of safety concerns in line with revision 2 of GVP module V on 'Risk management systems' and revision 2 of the guidance on the format of RMP in the EU (template)

- 15.2.12. Talimogene laherparepvec - IMLYGIC (CAP) - EMEA/H/C/002771/II/0028
-

Applicant: Amgen Europe B.V., ATMP⁶⁸

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of the RMP (version 4.0) in order to reflect changes in the categorisation of safety concerns and missing information in line with revision 2 of GVP module V on 'Risk management systems' and revision 2 of the guidance on the format of RMP in the EU (template)

- 15.2.13. Trastuzumab emtansine - KADCYLA (CAP) - EMEA/H/C/002389/II/0042/G
-

Applicant: Roche Registration GmbH

PRAC Rapporteur: Doris Stenver

Scope: Grouped variations consisting of an update of the RMP (version 8) in order to: 1) remove MoTHER pharmacovigilance activities (MEA 011): 'an observational study of pregnancy and pregnancy outcomes in women with breast cancer treated with trastuzumab, pertuzumab in combination with trastuzumab or pertuzumab during pregnancy or within 7 months prior to conception'; and use the global enhanced pharmacovigilance pregnancy programme to fulfil the commitment; 2) change the due date of final results for the provision of the final study report for BO27938 (KATHERINE) (a category 3 study in the RMP): a randomized, multicentre, open label phase 3 study to evaluate the efficacy and safety of trastuzumab emtansine versus trastuzumab as adjuvant therapy for patients with human epidermal growth factor receptor 2 (HER2)-positive primary breast cancer who have residual tumour present pathologically in the breast or axillary lymph nodes following preoperative therapy to address the following safety concerns: left ventricular dysfunction, safety in elderly patients, immunogenicity (anti-therapeutic antibodies [ATAs]). In addition, the MAH took the opportunity to update the RMP in line with revision 2 of GVP module V on 'Risk

⁶⁸ Advanced therapy medicinal product

management systems' and include an update of Kadcyła (trastuzumab emtansine) educational material to reflect changes in the prescribing information following the completion of the renewal procedure of the marketing authorisation in July 2018

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

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

15.3.1. Abatacept - ORENCIA (CAP) - EMEA/H/C/000701/X/0117/G

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Kimmo Jaakkola

Scope: Grouped applications consisting of: 1) extension application to add two new strengths of 50 mg and 87.5 mg for solution for injection in a pre-filled syringe with needle guard for subcutaneous (SC) administration; 2) variation to include paediatric use of polyarticular juvenile idiopathic arthritis (2 years and above) for solution for injection (50 mg, 87.5 mg and 125 mg). The RMP (version 25.0) is updated accordingly. In addition, the MAH took the opportunity to implement minor editorial changes in the product information

15.3.2. Ataluren - TRANSLARNA (CAP) - EMEA/H/C/002720/II/0047, Orphan

Applicant: PTC Therapeutics International Limited

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Extension of indication to include non-ambulatory patients with Duchenne muscular dystrophy. As supportive data, the variation includes the final results of the long term clinical study PTC-124-GD-019-DMD: an open-label study for previously treated ataluren (PTC124) patients with nonsense mutation dystrophinopathy. As a consequence, sections 4.1, 4.2, 4.8, and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 8.0) are updated accordingly

15.3.3. Brentuximab vedotin - ADCETRIS (CAP) - EMEA/H/C/002455/II/0055, Orphan

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to include the frontline treatment of adult patients with CD30+ advanced Hodgkin lymphoma (HL) in combination with chemotherapy, based on data from ECHELON-1 (C25003): a phase 3 multicentre, randomised, open-label study comparing the modified progression-free survival (mPFS) obtained with brentuximab vedotin, doxorubicin, vinblastine and dacarbazine versus the mPFS obtained with doxorubicin, bleomycin, vinblastine and dacarbazine. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated. The package leaflet and the RMP (version 13) are updated accordingly. Furthermore, the MAH took the opportunity to bring the product information in line with the latest QRD template (version 10)

15.3.4. Ceritinib - ZYKADIA (CAP) - EMEA/H/C/003819/II/0026

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Annika Folin

Scope: Update of section 4.5 of the SmPC in order to update the safety information based on the final results from study CLDK378A2103 (listed as a category 3 study in the RMP, MEA 002): a phase I, multicentre, open label, drug-drug interaction study to assess the effect of ceritinib on the pharmacokinetics of warfarin and midazolam administered as a two-drug cocktail in patients with anaplastic lymphoma kinase (ALK)-positive advanced tumours including non-small cell lung cancer (NSCLC). The package leaflet and the RMP (version 14) are updated accordingly

15.3.5. Cinacalcet - MIMPARA (CAP) - EMEA/H/C/000570/II/0062/G

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Grouped variations consisting of: 1) update of section 4.4 of the SmPC to provide additional information on switching from etelcalcetide to Mimpara (cinacalcet) as requested by PRAC in the PSUR single assessment procedure for etelcalcetide (PSUSA/00010533/201711) concluded in May 2018; 2) update of section 6.1 of the SmPC to replace the term 'silica, dental type' by 'amorphous silicon dioxide'. The RMP is updated (version 9.0) in order to reflect changes in the categorisation of safety concerns in line with revision 2 of the guidance on the format of RMP in the EU (template)

15.3.6. Daratumumab - DARZALEX (CAP) - EMEA/H/C/004077/II/0020, Orphan

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Submission of study report of study SMM2001: a randomised phase 2 trial to evaluate 3 daratumumab dose schedules in smouldering multiple myeloma. As a consequence, the RMP is updated (version 4.1) in order to remove QTc prolongation as an important potential risk

15.3.7. Dasatinib - SPRYCEL (CAP) - EMEA/H/C/000709/II/0059

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Doris Stenver

Scope: Extension of indication to include Philadelphia chromosome positive (Ph+) acute lymphoblastic leukaemia for the treatment of paediatric patients. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 16.0) are updated accordingly. In addition, the MAH took the opportunity to make minor editorial changes to the product information

15.3.8. Decitabine - DACOGEN (CAP) - EMEA/H/C/002221/II/0033, Orphan

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Ghania Chamouni

Scope: Update of section sections 4.2, 4.8, 5.1 and 5.2 of the SmPC to reflect the results from the paediatric study DACOGENAML2004: 'a phase 1-2 safety and efficacy study of Dacogen (decitabine) in sequential administration with cytarabine in children with relapsed or refractory acute myeloid leukaemia' as per the requirement of Article 46 of Regulation (EC) No1901/2006. The RMP (version 3.1) is updated accordingly and in line with revision 2 of the guidance on the format of RMP in the EU (template). In addition, the MAH took the opportunity to update section 4.4 of the SmPC to align the safety warning related to sodium excipient with the Annex to the revised European Commission guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use'. The package leaflet is updated accordingly. Moreover, the contact details of the local representative in Slovenia are updated in the package leaflet

15.3.9. [Deferiprone - FERRIPROX \(CAP\) - EMEA/H/C/000236/II/0128](#)

Applicant: Apotex Europe BV

PRAC Rapporteur: Ghania Chamouni

Scope: Update of section 4.4 of the SmPC and the patient/carer reminder card in order to update and change the recommended frequency of absolute neutrophil count (ANC) monitoring throughout Ferriprox (deferiprone) treatment from a weekly basis to every week for the first six months of therapy, once every two weeks after six months and to monthly after one year of therapy. The package leaflet and the RMP (version 13.2) are updated accordingly. In addition, the MAH took the opportunity to update minor linguistic amendments in the Hungarian and Maltese product information

15.3.10. [Denosumab - XGEVA \(CAP\) - EMEA/H/C/002173/II/0065](#)

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of section 4.8 of the SmPC to modify the frequency category of atypical femoral fracture (AFF) as an adverse drug reaction (ADR) from 'rare' to 'uncommon' and to add descriptive language regarding latency observed in clinical studies. The package leaflet and the RMP (version 33) are updated accordingly. In addition, the MAH took the opportunity to remove the black triangle and corresponding text from the Annexes as Xgeva (denosumab) is no longer under additional monitoring. The MAH also took the opportunity to implement editorial changes in the annexes and to update the contact details of the local representative in Ireland in the package leaflet

15.3.11. [Eftrenonacog alfa - ALPROLIX \(CAP\) - EMEA/H/C/004142/II/0021, Orphan](#)

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of sections 4.8 and 5.1 of the SmPC to include new clinical efficacy and safety data on long-term treatment with Alprolix (eftrenonacog alfa) based on the data from extension study 9HB01EXT (BYOND): an open-label, multicentre evaluation of the long-term safety and efficacy of recombinant, human coagulation factor IX fusion protein (rFIXFc) in the prevention and treatment of bleeding episodes in previously treated subjects

with haemophilia B as well data from the pivotal parent studies. The package leaflet and the RMP (version 1.4) are updated accordingly. In addition, the MAH took the opportunity to update the product information to comply with the latest version of the European Commission (EC) guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use'. In addition, the MAH took the opportunity to update the list of local representatives and to introduce minor editorial changes in the package leaflet

15.3.12. [Elotuzumab - EMLICITI \(CAP\) - EMEA/H/C/003967/II/0012](#)

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include treatment in combination with pomalidomide and dexamethasone of adult patients with multiple myeloma. As a consequence, sections 4.1, 4.2, 4.4, 4.6, 4.8, 4.9, 5.1, 5.2 and 6.6 of the SmPC are updated. The package leaflet and the RMP (version 2.0) are updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet

15.3.13. [Emicizumab - HEMLIBRA \(CAP\) - EMEA/H/C/004406/II/0002](#)

Applicant: Roche Registration GmbH

PRAC Rapporteur: Amelia Cupelli

Scope: Extension of indication to include routine prophylaxis of bleeding episodes in patients with haemophilia A without factor VIII (FVIII) inhibitors. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated with efficacy and safety information of the following pivotal trials: 1) study BH30071 (HAVEN 3): an ongoing, multicentre, open-label, randomized phase 3 clinical study evaluating the efficacy, safety and pharmacokinetic (PK) of emicizumab prophylaxis at doses of 1.5 mg/kg/week (QW) and 3 mg/kg/every 2 weeks (Q2W) versus no prophylaxis in adults and adolescent patients (age of 12 or above) with haemophilia A without inhibitors against FVIII; 2) study BO39182 (HAVEN 4): an ongoing multicentre, open-label, non-randomized phase 3 study evaluating the efficacy, safety and PK of emicizumab given as the dose of 6 mg/kg/every 4 weeks (Q4W) in adults and adolescent patients (age of 12 or above) with haemophilia A with or without FVIII inhibitors; 3) study BH29992 (HAVEN 2): a multicentre, open-label, non-randomized phase 3 study evaluating the efficacy, safety and PK of emicizumab at the QW dose in paediatric patients (<12 years old or 12-17 years old and <40kg) with haemophilia A with FVIII inhibitors. The package leaflet and the RMP (version.2.0) are updated accordingly. In addition, the MAH took the opportunity to introduce minor corrections and clarity to sections 4.4, 4.5 and 4.6 of the SmPC

15.3.14. [Empagliflozin, linagliptin - GLYXAMBI \(CAP\) - EMEA/H/C/003833/WS1461/0017;](#) [Linagliptin, metformin - JENTADUETO \(CAP\) - EMEA/H/C/002279/WS1461/0047;](#) [Linagliptin - TRAJENTA \(CAP\) - EMEA/H/C/002110/WS1461/0035](#)

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Update of sections 4.4, 4.8 and 5.1 of the SmPC to update the warnings related to acute pancreatitis and bullous pemphigoid as well as the efficacy and safety information

based on the final results from study CARMELINA (listed as a category 3 study in the RMP): a multicentre, international, randomised, parallel group, double blind, placebo-controlled Cardiovascular Safety & Renal Microvascular outcome study with LINagliptin, 5 mg once daily in patients with type 2 diabetes mellitus (T2DM) at high vascular risk. The RMP is updated accordingly (Trajenta and Jentaduetto version 12, Glyxambi version 4.0) and in line with revision 2 of the guidance on the format of RMP in the EU (template)

15.3.15. Erenumab - AIMOVIG (CAP) - EMEA/H/C/004447/X/0001

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Kirsti Villikka

Scope: Extension application to add a new strength of 140 mg. The RMP (version 2.0) is updated accordingly

15.3.16. Etelcalcetide - PARSABIV (CAP) - EMEA/H/C/003995/II/0010

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Amelia Cupelli

Scope: Update of section 4.8 to add 'convulsions secondary to hypocalcaemia' as an adverse drug reaction with a frequency uncommon and to reflect further information on reports related to hypersensitivity reactions. The package leaflet is updated accordingly. The RMP (version 2) is also updated accordingly and in line with revision 2 of the guidance on the format of RMP in the EU (template) introducing some changes in the categorisation of safety concerns. In addition, the MAH took the opportunity to introduce minor editorial changes in SmPC

15.3.17. Golimumab - SIMPONI (CAP) - EMEA/H/C/000992/X/0083/G

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Grouped applications consisting of: 1) extension application to add a new strength of 100 mg/ml solution for injection for paediatric use; 2) extension of indication to include paediatric patients from the age of 2 years and older for the treatment of polyarticular juvenile idiopathic arthritis (pJIA) with Simponi (golimumab) 100 mg/ml solution for injection. As a consequence, sections 4.1, 4.2, 5.1 and section 4.1 of the 50mg strength are updated; 3) update of the RMP (version 18.0) to delete the following safety concerns: vasculitis, psoriasis (new onset or worsening of pre-existing), and sarcoidosis/sarcoid like reaction as requested in the outcome of variation II/068/G concluded in May 2016; 4) update of the RMP (version 18.0) to change the due date of study MK-8259-050 (listed as a category 3 study in the RMP) as requested by CHMP in the conclusion of MEA 033 dated April 2017. Finally, the MAH took the opportunity to update the product information in line with the latest QRD template (version 10) to implement the recommendations stated in the revised Annex to the European Commission (EC) guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use' with regard to the excipient sorbitol (E420); to add a statement in section 4.4 of the SmPC to record the name and the batch number of the administered product in line with GVP Module P.II on 'Biological medicinal products' (EMA/168402/2014 Corr*)

15.3.18. [Guselkumab - TREMFYA \(CAP\) - EMEA/H/C/004271/II/0005](#)

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of sections 4.4 and 4.8 of the SmPC in order to add hypersensitivity and rash as adverse drug reactions with the frequency uncommon, together with a statement describing the characteristics of the serious hypersensitivity events. The package leaflet and the RMP (version 3.0) are updated accordingly

15.3.19. [Insulin glargine - TOUJEO \(CAP\) - EMEA/H/C/000309/II/0105/G](#)

Applicant: Sanofi-Aventis Deutschland GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Grouped variations to introduce a new 3 ml pre-filled pen. Introduction of four new pack sizes: packs of 1, 3, 6 (multipack) and 9 pens (multipack). As a consequence, Annex A, I, IIA and IIIB are amended. In addition, the RMP (version 5.0) in line with revision 2 of the guidance on the format of RMP in the EU (template) is updated accordingly

15.3.20. [Nivolumab - OPDIVO \(CAP\) - EMEA/H/C/003985/WS1372/0053;](#) [Ipilimumab - YERVOY \(CAP\) - EMEA/H/C/002213/WS1372/0057](#)

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include first-line treatment of adult patients with metastatic non-small cell lung carcinoma (NSCLC). As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated in order to add information from pivotal study CA209227: an open-label, randomised phase 3 trial of nivolumab, or nivolumab plus ipilimumab, or nivolumab plus platinum doublet chemotherapy versus platinum doublet chemotherapy in subjects with chemotherapy-naïve stage IV or recurrent NSCLC. The package leaflet and RMP (version 14.0 for Opdivo and version 21.0 for Yervoy) are updated accordingly. In addition, the MAH took the opportunity to introduce minor editorial and formatting revisions in the product information

15.3.21. [Macitentan - OPSUMIT \(CAP\) - EMEA/H/C/002697/II/0029, Orphan](#)

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Eva Segovia

Scope: Extension of indication to include treatment of patients with inoperable chronic thromboembolic pulmonary hypertension (CTEPH), based on: 1) pivotal study MERIT-1 (AC-055E201): a prospective, randomized, placebo-controlled, double-blind, multicentre, parallel-group, 24-week study to assess the efficacy, safety and tolerability of macitentan in subjects with inoperable CTEPH; 2) 6 months of efficacy and safety data (cut-off date 17 October 2017) from its ongoing open-label extension study MERIT-2 (AC-055E202): a long term, multicentre, single-arm, open-label extension study of the merit-1 study, to assess the safety, tolerability and efficacy of macitentan in subjects with inoperable CTEPH; 3) drug-drug interaction (DDI) study AC-055-122: a single-centre, open-label, one-sequence,

two-treatment study to investigate the effect of macitentan at steady state on the pharmacokinetics (PK) of rosuvastatin in healthy male subjects; 4) DDI study AC-055-123: a single-center, open-label, one-sequence, two-treatment study to investigate the effect of macitentan at steady state on the PK of riociguat in healthy male subjects; 5) observational data from the OPUS registry (OPsumit USers Registry; cut-off date of 17 April 2018): safety and tolerability of macitentan in a real-world setting. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8 and 5.1 are updated. The package leaflet and the RMP (version 9.2) are updated accordingly. In addition, the MAH took the opportunity to implement editorial changes, to align the annexes with the latest QRD template and to update the contact details of the local representatives in the package leaflet

15.3.22. Niraparib - ZEJULA (CAP) - EMEA/H/C/004249/II/0006, Orphan

Applicant: Tesaro UK Limited

PRAC Rapporteur: Patrick Batty

Scope: Update of sections 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC in order to optimise the starting dose of niraparib and clarify dose modification information, modify the existing warning on haematologic adverse reactions, amend the description of thrombocytopenia and amend existing efficacy and pharmacokinetics information, respectively. The changes are based on the integrated population clinical report that contains information from: 1) completed phase 3 study NOVA (submitted as part of the initial application): a phase 3 randomized double-blind trial of maintenance with niraparib versus placebo in patients with platinum-sensitive ovarian cancer; 2) supportive information from ongoing study PR-30-5020-C (QUADRA): a phase 2, open-label, single-arm study to evaluate the safety and efficacy of niraparib in patients with advanced, relapsed, high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who have received three or four previous chemotherapy regimens; 3) study 300-PN-162-01-001 (TOPACIO): a phase 1/2 clinical study of niraparib in combination with pembrolizumab (MK-3475) in patients with advanced or metastatic triple-negative breast cancer and in patients with recurrent ovarian cancer. The package leaflet and the RMP (version 1.1) are updated accordingly. The RMP is also updated in line with revision 2 of the guidance on the format of RMP in the EU (template) and the outcome of the PSUR single assessment procedure (PSUSA/00010655/201803) finalised in October 2018

15.3.23. Olaparib - LYNPARZA (CAP) - EMEA/H/C/003726/II/0020

Applicant: AstraZeneca AB

PRAC Rapporteur: Amelia Cupelli

Scope: Extension of indication to include the use of Lynparza (olaparib) tablets as monotherapy for the treatment of adult patients with BRCA-1/2-mutated human epidermal growth factor receptor 2 (HER2) negative metastatic breast cancer who have previously been treated with chemotherapy. These patients could have received chemotherapy in the neoadjuvant, adjuvant or metastatic setting. 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 16) are updated accordingly

15.3.24. Olaparib - LYNPARZA (CAP) - EMEA/H/C/003726/II/0023

Applicant: AstraZeneca AB

PRAC Rapporteur: Amelia Cupelli

Scope: Extension of indication to include the use of Lynparza (olaparib) as a monotherapy for the maintenance treatment of adult patients with newly diagnosed advanced BRCA-mutated high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete response or partial response) to first-line platinum-based chemotherapy. As a consequence, sections 4.1 and 4.8 of the SmPC are updated in order to include information from single pivotal study D0818C00001 (SOLO 1): a phase 3, randomised, double blind, placebo controlled, multicentre study of olaparib maintenance monotherapy in patients with BRCA mutated advanced (FIGO⁶⁹ stage III-IV) ovarian cancer following first line platinum based chemotherapy. The package leaflet and the RMP (version 17) are updated accordingly

15.3.25. Omalizumab - XOLAIR (CAP) - EMEA/H/C/000606/II/0093

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Annika Folin

Scope: Update of section 4.6 of the SmPC based on the data from the Xolair Pregnancy Registry (EXPECT): an observational study of the use and safety of Xolair (omalizumab) during pregnancy; and the final study report for study Q2952g (listed as a category 3 study in the RMP): an observational study to evaluate pregnancy outcomes and estimate the incidence of spontaneous foetal loss in pregnant women exposed to omalizumab prenatally and to explore the potential risk to newborn infants exposed via breast milk. The package leaflet and the RMP (version 14.0) are updated accordingly

15.3.26. Plerixafor - MOZOBIL (CAP) - EMEA/H/C/001030/II/0034, Orphan

Applicant: Genzyme Europe BV

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to include paediatric patients aged 1 to 18 years for Mozobil (plerixafor). As a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The package leaflet and the RMP (version 10) are updated accordingly

15.3.27. Rituximab - MABTHERA (CAP) - EMEA/H/C/000165/II/0157

Applicant: Roche Registration GmbH

PRAC Rapporteur: Doris Stenver

Scope: Update of Annex II-D on 'conditions or restrictions with regard to the safe and effective use of the medicinal product' resulting from the obligation fulfilment for the rituximab subcutaneous (SC) formulation at a dose of 1,400 mg by the submission of the final clinical study report for study BO22334 (SABRINA, listed as a category 1 study) including reports on long-term safety in relation to body surface area (BSA) (as a measure

⁶⁹ International Federation of Gynaecology and Obstetrics

for exposure variation) and to gender. SABRINA is a two-stage phase 3, international, multicentre, randomized, controlled, open-label study investigating the pharmacokinetics (PK), efficacy and safety of rituximab SC in combination with cyclophosphamide, doxorubicin, vincristine, prednisolone (CHOP) chemotherapy or cyclophosphamide, vincristine, prednisolone (CVP) chemotherapy versus rituximab intravenous (IV) in combination with CHOP or CVP chemotherapy followed by maintenance treatment with either rituximab SC or rituximab IV. The RMP (version 19.0) is updated accordingly. In addition, the MAH took the opportunity to include other changes to the RMP including the fulfilment of the previous information on concluded commitments such as the prolonged B-cell depletion and immunogenicity associated with the subcutaneous formulation

15.3.28. Rituximab - MABTHERA (CAP) - EMEA/H/C/000165/II/0158

Applicant: Roche Registration GmbH

PRAC Rapporteur: Doris Stenver

Scope: Update of Annex II-D on 'conditions or restrictions with regard to the safe and effective use of the medicinal product', resulting from the obligation fulfilment for the rituximab subcutaneous formulation at a dose of 1,400 mg by the submission of the final clinical study report for study BO25341 (SAWYER, listed as a category 1 study) including reports on long-term safety in relation to body surface area (BSA) (as a measure for exposure variation) and to gender. SAWYER is a phase Ib adaptive, comparative, randomized, parallel-group, multicentre study of subcutaneous (SC) rituximab versus intravenous (IV) rituximab both in combination with chemotherapy (fludarabine and cyclophosphamide), in patients with previously untreated chronic lymphocytic leukaemia (CLL). The RMP (version 19.0) is updated accordingly. In addition, the MAH took the opportunity to include the changes on the concluded commitment such as the prolonged B-cell depletion and immunogenicity associated with the subcutaneous formulation

15.3.29. Rucaparib - RUBRACA (CAP) - EMEA/H/C/004272/II/0001, Orphan

Applicant: Clovis Oncology UK Limited

PRAC Rapporteur: Annika Folin

Scope: Extension of indication to include a new indication for Rubraca (rucaparib) 'as monotherapy for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy'. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated with the expanded clinical efficacy and safety data. The package leaflet and the RMP (version 2.0) are updated accordingly. In addition, the applicant took the opportunity to propose to move one paragraph from section 4.4 to 5.1 in the SmPC for consistency with other SmPC for agents in the class with this indication

15.3.30. Tenofovir disoproxil - VIREAD (CAP) - EMEA/H/C/000419/II/0191

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Adrien Inoubli

Scope: Extension of indication to include as a new indication treatment of chronic hepatitis B (CHB) in paediatric patients aged 6 to < 12 years (film coated tablets 123 mg; 163 mg;

204 mg) and to extend the existing CHB indication to include treatment of CHB in paediatric patients aged 2 to < 12 years (granules 33 mg/g), based on results from interim week 48 clinical study report (CSR) for study GS-US-174-0144: a randomized, double-blind evaluation of the antiviral efficacy, safety and tolerability of tenofovir disoproxil fumarate versus placebo in paediatric patients with CHB infection. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated for Viread (tenofovir disoproxil) 123 mg, 163 mg and 204 mg; sections 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC for Viread (tenofovir disoproxil) 245 mg; and sections 4.1, 4.2, 4.4, 5.1 and 5.2 for Viread (tenofovir disoproxil) granules 33 mg/g. The package leaflet and the RMP (version 22.1) are updated accordingly

15.3.31. Thalidomide - THALIDOMIDE CELGENE (CAP) - EMEA/H/C/000823/II/0056, Orphan

Applicant: Celgene Europe BV

PRAC Rapporteur: Ghania Chamouni

Scope: Update of the RMP (version 19) in line with revision 2 of GVP module V on 'Risk management systems' and revision 2 of the guidance on the format of RMP in the EU (template) to propose the reclassification and/or renaming of known safety concerns associated with the use of Thalidomide Celgene (thalidomide). Consequently, Annex II-D on 'conditions or restrictions with regard to the safe and effective use of the medicinal product', section 4.4 and 4.6 of the SmPC as well as the package leaflet are updated accordingly

15.3.32. Vedolizumab - ENTYVIO (CAP) - EMEA/H/C/002782/II/0034

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Adam Przybylkowski

Scope: Update of section 5.1 of the SmPC in order to provide the final efficacy results up to week 348 regarding clinical study c13008 (listed as a category 3 study in the RMP): a phase 3, open-label study to determine the long-term safety and efficacy of vedolizumab in subjects with ulcerative colitis and Crohn's disease. The RMP is updated accordingly (version 4.0)

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

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

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

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

16.1.1. Basiliximab - SIMULECT (CAP) - PSUSA/00000301/201804

Applicant: Novartis Europharm Limited
PRAC Rapporteur: Brigitte Keller-Stanislawski
Scope: Evaluation of a PSUSA procedure

16.1.2. Benralizumab - FASENRA (CAP) - PSUSA/00010661/201805

Applicant: AstraZeneca AB
PRAC Rapporteur: David Olsen
Scope: Evaluation of a PSUSA procedure

16.1.3. Cerliponase alfa - BRINEURA (CAP) - PSUSA/00010596/201804

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

16.1.4. Cobicistat, elvitegravir, emtricitabine, tenofovir alafenamide - GENVOYA (CAP) - PSUSA/00010449/201805

Applicant: Gilead Sciences Ireland UC
PRAC Rapporteur: Amelia Cupelli
Scope: Evaluation of a PSUSA procedure

16.1.5. Daratumumab - DARZALEX (CAP) - PSUSA/00010498/201805

Applicant: Janssen-Cilag International NV
PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva
Scope: Evaluation of a PSUSA procedure

16.1.6. Darunavir, cobicistat - REZOLSTA (CAP) - PSUSA/00010315/201805

Applicant: Janssen-Cilag International NV
PRAC Rapporteur: Amelia Cupelli
Scope: Evaluation of a PSUSA procedure

16.1.7. Delamanid - DELTYBA (CAP) - PSUSA/00010213/201804

Applicant: Otsuka Novel Products GmbH
PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.8. [Dinutuximab beta - QARZIBA \(CAP\) - PSUSA/00010597/201805](#)

Applicant: EUSA Pharma (UK) Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.9. [Empagliflozin, linagliptin - GLYXAMBI \(CAP\) - PSUSA/00010539/201805](#)

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.10. [Epoetin theta - BIOPOIN \(CAP\); EPORATIO \(CAP\) - PSUSA/00001240/201804](#)

Applicant(s): Teva GmbH (Biopoin), Ratiopharm GmbH (Eporatio)

PRAC Rapporteur: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

16.1.11. [Etelcalcetide - PARSABIV \(CAP\) - PSUSA/00010533/201805](#)

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.1.12. [Fentanyl⁷⁰ - IONSYS⁷¹ - PSUSA/00010453/201805](#)

Applicant: Incline Therapeutics Europe Ltd

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

16.1.13. [Fluticasone furoate, vilanterol - RELVAR ELLIPTA \(CAP\); REVINTY ELLIPTA \(CAP\) - PSUSA/00010099/201805](#)

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

16.1.14. [Insulin glargine, lixisenatide - SULIQUA \(CAP\) - PSUSA/00010577/201805](#)

Applicant: Sanofi-aventis groupe

⁷⁰ Transdermal system - centrally authorised product(s) only

⁷¹ European Commission (EC) decision on the MA withdrawal of Ionsys dated 27 September 2018

PRAC Rapporteur: Julie Williams
Scope: Evaluation of a PSUSA procedure

16.1.15. Ixazomib - NINLARO (CAP) - PSUSA/00010535/201805

Applicant: Takeda Pharma A/S
PRAC Rapporteur: Annika Folin
Scope: Evaluation of a PSUSA procedure

16.1.16. Ketoconazole⁷² - KETOCONAZOLE HRA (CAP) - PSUSA/00010316/201805

Applicant: Laboratoire HRA Pharma
PRAC Rapporteur: Željana Margan Koletić
Scope: Evaluation of a PSUSA procedure

16.1.17. Laronidase - ALDURAZYME (CAP) - PSUSA/00001830/201804

Applicant: Genzyme Europe BV
PRAC Rapporteur: Patrick Batty
Scope: Evaluation of a PSUSA procedure

16.1.18. Letemovir - PREVYMIS (CAP) - PSUSA/00010660/201805

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

16.1.19. Lidocaine, prilocaine⁷³ - FORTACIN (CAP) - PSUSA/00010110/201805

Applicant: Recordati Ireland Ltd
PRAC Rapporteur: Maria del Pilar Rayon
Scope: Evaluation of a PSUSA procedure

16.1.20. Linagliptin - TRAJENTA (CAP); linagliptin, metformin - JENTADUETO (CAP); - PSUSA/00010427/201805

Applicant: Boehringer Ingelheim International GmbH
PRAC Rapporteur: Menno van der Elst
Scope: Evaluation of a PSUSA procedure

⁷² Centrally authorised product(s) only

⁷³ Centrally authorised product(s) only

16.1.21. Lumacaftor, ivacaftor - ORKAMBI (CAP) - PSUSA/00010455/201805

Applicant: Vertex Pharmaceuticals (Europe) Ltd.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

16.1.22. Meningococcal group B vaccine (recombinant, adsorbed) - TRUMENBA (CAP) - PSUSA/00010607/201805

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

16.1.23. Necitumumab - PORTRAZZA (CAP) - PSUSA/00010471/201805

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

16.1.24. Padeliporfin - TOOKAD (CAP) - PSUSA/00010654/201805

Applicant: Steba Biotech S.A

PRAC Rapporteur: Maia Uusküla

Scope: Evaluation of a PSUSA procedure

16.1.25. Pandemic influenza vaccine (H5N1) (live attenuated, nasal) - PANDEMIC INFLUENZA VACCINE H5N1 ASTRAZENECA (CAP) - PSUSA/00010501/201805

Applicant: AstraZeneca AB

PRAC Rapporteur: Daniela Philadelphia

Scope: Evaluation of a PSUSA procedure

16.1.26. Pandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) - ADJUPANRIX (CAP); prepandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) - PREPANDRIX (CAP) - PSUSA/00002281/201805

Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.27. Prasterone⁷⁴ - INTRAROSA (CAP) - PSUSA/00010672/201805

Applicant: Endoceutics Limited

⁷⁴ Pessary, vaginal use only

PRAC Rapporteur: Menno van der Elst
Scope: Evaluation of a PSUSA procedure

16.1.28. Radium (²²³Ra) dichloride - XOFIGO (CAP) - PSUSA/00010132/201805

Applicant: Bayer AG
PRAC Rapporteur: Patrick Batty
Scope: Evaluation of a PSUSA procedure

16.1.29. Ruriococog alfa pegol - ADYNOVI (CAP) - PSUSA/00010663/201805

Applicant: Baxalta Innovations GmbH
PRAC Rapporteur: Menno van der Elst
Scope: Evaluation of a PSUSA procedure

16.1.30. Shingles (herpes zoster) vaccine (live) - ZOSTAVAX (CAP) - PSUSA/00009289/201805

Applicant: MSD Vaccins
PRAC Rapporteur: Brigitte Keller-Stanislawski
Scope: Evaluation of a PSUSA procedure

16.1.31. Susoctocog alpha - OBIZUR (CAP) - PSUSA/00010458/201805

Applicant: Baxalta Innovations GmbH
PRAC Rapporteur: Brigitte Keller-Stanislawski
Scope: Evaluation of a PSUSA procedure

16.1.32. Tafamidis - VYNDAQEL (CAP) - PSUSA/00002842/201805

Applicant: Pfizer Europe MA EEIG
PRAC Rapporteur: Ghania Chamouni
Scope: Evaluation of a PSUSA procedure

16.1.33. Talimogene laherparepvec - IMLYGIC (CAP) - PSUSA/00010459/201804

Applicant: Amgen Europe B.V., ATMP⁷⁵
PRAC Rapporteur: Brigitte Keller-Stanislawski
Scope: Evaluation of a PSUSA procedure

⁷⁵ Advanced therapy medicinal product

16.1.34. Tenofovir alafenamide - VEMLIDY (CAP) - PSUSA/00010575/201805

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.1.35. Tilmanocept - LYMPHOSEEK (CAP) - PSUSA/00010313/201805

Applicant: Norgine B.V.

PRAC Rapporteur: Jolanta Gulbinovic

Scope: Evaluation of a PSUSA procedure

16.1.36. Tofacitinib - XELJANZ (CAP) - PSUSA/00010588/201805

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.37. Tolvaptan⁷⁶ - SAMSCA (CAP) - PSUSA/00002994/201805

Applicant: Otsuka Pharmaceutical Netherlands B.V.

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.38. Ulipristal⁷⁷ - ELLAONE (CAP) - PSUSA/00003074/201805

Applicant: Laboratoire HRA Pharma

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

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

16.2.1. Enoxaparin⁷⁸ - INHIXA (CAP); THORINANE (CAP); NAP - PSUSA/00010553/201804

Applicants: Techdow Europe AB (Inhixa), Techdow Pharma Netherlands B.V. (Thorinane), various

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

⁷⁶ Indicated for adults with hyponatraemia secondary to syndrome of inappropriate antidiuretic hormone secretion (SIADH) only

⁷⁷ indicated in female emergency contraception only

⁷⁸ Biosimilar products only

16.2.2. Hydrochlorothiazide, telmisartan - KINZALKOMB (CAP); MICARDISPLUS (CAP); PRITORPLUS (CAP); telmisartan - KINZALMONO (CAP); MICARDIS (CAP); PRITOR (CAP); NAP - PSUSA/00002882/201804

Applicants: Bayer AG (Kinzalkomb, Kinzalmono, Pritor, PritorPlus), Boehringer Ingelheim International GmbH (Micardis, MicardisPlus), various

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.2.3. Ivabradine - CORLENTOR (CAP); IVABRADINE ANPHARM (CAP); PROCORALAN (CAP); NAP - PSUSA/00001799/201804

Applicants: Anpharm Przedsiębiorstwo Farmaceutyczne S.A. (Ivabradine Anpharm), Les Laboratoires Servier (Corlentor, Procoralan), various

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.2.4. Mycophenolate mofetil - CELLCEPT (CAP); MYCLAUSEN (CAP); MYCOPHENOLATE MOFETIL TEVA (CAP); MYFENAX (CAP); NAP mycophenolic acid (NAP) - - PSUSA/00010550/201805

Applicants: Passauer Pharma GmbH (Myclausen), Roche Registration GmbH (CellCept), Teva B.V. (Mycophenolate mofetil Teva, Myfenax), various

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

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

16.3.1. Acarbose (NAP) - PSUSA/00000017/201803

Applicant(s): various

PRAC Lead: Eva Segovia

Scope: Evaluation of a PSUSA procedure

16.3.2. Amlodipine besilate, ramipril (NAP) - PSUSA/00000181/201803

Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.3.3. Benzyl nicotinate, camphor, dimethyl sulfoxide, nonivamide, turpentine oil (NAP) - PSUSA/00010584/201803

Applicant(s): various

PRAC Lead: Zane Neikena

Scope: Evaluation of a PSUSA procedure

16.3.4. [Calcium chloride, glutamic acid, glutathione, histidine, lactobionic acid, magnesium chloride, mannitol, potassium chloride, sodium hydroxide \(NAP\) - PSUSA/00009162/201803](#)

Applicant(s): various

PRAC Lead: Maria Popova-Kiradjieva

Scope: Evaluation of a PSUSA procedure

16.3.5. [Dihydroergotamine \(NAP\) - PSUSA/00001075/201804](#)

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.3.6. [Dihydroergotoxine \(NAP\) - PSUSA/00001079/201804](#)

Applicant(s): various

PRAC Lead: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

16.3.7. [Enalapril \(NAP\) - PSUSA/00001211/201803](#)

Applicant(s): various

PRAC Lead: Annika Folin

Scope: Evaluation of a PSUSA procedure

16.3.8. [Felodipine, ramipril \(NAP\) - PSUSA/00001358/201803](#)

Applicant(s): various

PRAC Lead: Annika Folin

Scope: Evaluation of a PSUSA procedure

16.3.9. [Foscarnet \(NAP\) - PSUSA/00001472/201803](#)

Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.3.10. [Human anti-D immunoglobulin \(NAP\) - PSUSA/00001614/201803](#)

Applicant(s): various

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.3.11. [Ivabradine, metoprolol \(NAP\) - PSUSA/00010381/201804](#)

Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.3.12. [Mepivacaine \(NAP\); mepivacaine hydrochloride, epinephrine \(NAP\); mepivacaine, norepinephrine \(NAP\) - PSUSA/00001979/201803](#)

Applicant(s): various

PRAC Lead: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

16.3.13. [Metformin \(NAP\) - PSUSA/00002001/201804](#)

Applicant(s): various

PRAC Lead: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

16.3.14. [Methylphenobarbital \(NAP\) - PSUSA/00002025/201803](#)

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.3.15. [Nebivolol \(NAP\) - PSUSA/00002129/201803](#)

Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.3.16. [Nitrendipine \(NAP\) - PSUSA/00002171/201803](#)

Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.3.17. [Ofloxacin⁷⁹ \(NAP\) - PSUSA/00002203/201804](#)

Applicant(s): various

⁷⁹ Systemic use only

PRAC Lead: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

16.3.18. Ofloxacin⁸⁰ (NAP) - PSUSA/00002204/201804

Applicant(s): various

PRAC Lead: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

16.4. Follow-up to PSUR/PSUSA procedures

17. Annex I – Post-authorisation safety studies (PASS)

Based on the assessment of the following PASS protocol(s), result(s), interim result(s) or feasibility study(ies), and following endorsement of the comments received, the PRAC adopted the conclusion of the Rapporteurs on their assessment for the medicines listed below without further plenary discussion.

17.1. Protocols of PASS imposed in the marketing authorisation(s)⁸¹

17.1.1. Eliglustat – CERDELGA (CAP) - EMEA/H/C/PSA/S/0035

Applicant: Genzyme Europe BV

PRAC Rapporteur: Eva Segovia

Scope: Protocol for a prospective multicentre observational post authorisation safety sub-registry to characterize the long-term safety profile of commercial use of Cerdelga (eliglustat) in adult patients with Gaucher disease

17.1.2. Lenalidomide – REVLIMID (CAP) - EMEA/H/C/PSA/S/0034

Applicant: Celgene Europe Limited

PRAC Rapporteur: Ghania Chamouni

Scope: Amendment to a previously agreed protocol in April 2014 (ANX 041.4) for a prospective non-interventional PASS, designed as a disease registry of patients with transfusion dependent international prognostic scoring system (IPSS) low or intermediate-1-risk myelodysplastic syndromes (MDS) and isolated del(5q)

17.2. Protocols of PASS non-imposed in the marketing authorisation(s)⁸²

17.2.1. Baricitinib - OLUMIANT (CAP) - EMEA/H/C/004085/MEA 009

Applicant: Eli Lilly Nederland B.V.

⁸⁰ Topical use only

⁸¹ In accordance with Article 107n of Directive 2001/83/EC

⁸² In accordance with Article 107m of Directive 2001/83/EC, supervised by PRAC in accordance with Article 61a (6) of Regulation (EC) No 726/2004

PRAC Rapporteur: Patrick Batty

Scope: PASS protocol for study I4V-MC-B0166: assessment of off-label use in paediatric patients in the UK in the Clinical Practice Research Datalink (CPRD) database

17.2.2. Benralizumab - FASENRA (CAP) - EMEA/H/C/004433/MEA 003.1

Applicant: AstraZeneca AB

PRAC Rapporteur: David Olsen

Scope: MAH's response to MEA 003.1 [PASS protocol for study D3250R00026 'the benralizumab pregnancy exposure study': a post-marketing surveillance study on vaccines and medications in pregnancy surveillance system (VAMPSS)] as per the request for supplementary information (RSI) adopted in June 2018

17.2.3. Brodalumab - KYNTHEUM (CAP) - EMEA/H/C/003959/MEA 002.2

Applicant: LEO Pharma A/S

PRAC Rapporteur: Eva Segovia

Scope: MAH's response to MEA 002.1 [protocol for study NIS-KYNTHEUM-1345: an observational PASS of suicidal behaviour, serious infections, major adverse cardiovascular events (MACE) and malignancy in psoriasis patients treated with brodalumab. The brodalumab assessment of hazards: a multinational safety (BRAHMS) study in electronic healthcare databases [final report expected in Q3 2030]] as per the request for supplementary information (RSI) adopted in June 2018

17.2.4. Burosumab - CRYSVITA (CAP) - EMEA/H/C/004275/MEA 004.1

Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: MAH's response to MEA 002.1 [protocol for a non-interventional prospective cohort study in the treatment of children with X-linked hypophosphataemia (XLH) to assess the long term safety of Crysvida (burosumab) during routine clinical care using data collected in a European disease registry for XLH [final report expected in December 2028]] as per the request for supplementary information (RSI) adopted in June 2018

17.2.5. Canagliflozin - INVOKANA (CAP) - EMEA/H/C/002649/MEA 013.3

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Martin Huber

Scope: MAH's response to MEA 013.2 [PASS protocol for a US epidemiology database study to further characterise the incidence of below-knee lower limb amputation in patients taking canagliflozin (listed as a category 3 study in RMP) as per the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on lower limb amputation in relation to the use of sodium-glucose co-transporter-2 (SGLT-2) inhibitors completed in February 2017 (EMEA/H/A-20/1442)] as per the request for supplementary information (RSI) adopted in July 2018

17.2.6. [Canagliflozin, metformin - VOKANAMET \(CAP\) - EMEA/H/C/002656/MEA 012.3](#)

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to MEA 012.2 [PASS protocol for a US epidemiology database study to further characterise the incidence of below-knee lower limb amputation in patients taking canagliflozin (listed as a category 3 study in RMP) as per the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on lower limb amputation in relation to the use of sodium-glucose co-transporter-2 (SGLT-2) inhibitors completed in February 2017 (EMEA/H/A-20/1442)] as per the request for supplementary information (RSI) adopted in July 2018

17.2.7. [Defibrotide - DEFITELIO \(CAP\) - EMEA/H/C/002393/LEG 010](#)

Applicant: Gentium S.r.l.

PRAC Rapporteur: Julie Williams

Scope: Protocol for study DF-VOD2013-03-REG: a multicentre, multinational, prospective, non-interventional registry to record safety and outcome data in patients diagnosed with severe veno-occlusive disease (VOD) following hematopoietic stem cell transplantation (HSCT) treated or not with Defitelio (defibrotide) describing the objectives and methodology for the literature review and analysis of data from the Center for International Blood and Marrow Transplant Research (CIBMTR), as requested in the outcome of variation I1/27 concluded in June 2018

17.2.8. [Emicizumab - HEMLIBRA \(CAP\) - EMEA/H/C/004406/MEA 001.1](#)

Applicant: Roche Registration GmbH

PRAC Rapporteur: Amelia Cupelli

Scope: MAH's response to MEA 001 [protocol for study GO40162: a PASS based on the European Haemophilia Safety Surveillance (EUHASS) registry to characterise the safety profile of patients with haemophilia A exposed to emicizumab under real-world conditions, including an estimate of event rates of the following important risks: thromboembolic events, thrombotic microangiopathy, systemic hypersensitivity, anaphylaxis and anaphylactoid events [final clinical study report: (CSR) expected in June 2024]] as per the request for supplementary information (RSI) adopted in July 2018

17.2.9. [Emtricitabine, tenofovir disoproxil - TRUVADA \(CAP\) - EMEA/H/C/000594/MEA 045.6](#)

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Julie Williams

Scope: MAH's response to MEA 045.5, including an enrolment progress report [PASS protocol for study GS-EU-276-4027, a drug utilisation study (DUS) to characterize: 1) prescribers' level of knowledge about the key risks of Truvada for a pre-exposure prophylaxis (PrEP) indication and assess the effectiveness of risk minimisation measures; 2) prescribing practices in routine clinical practice of Truvada for PrEP by describing the

demographics of human immunodeficiency virus 1 (HIV-1) uninfected individuals who were prescribed Truvada for PrEP, and the prescribed dosing schedule for Truvada for PrEP as reported by the prescriber] as per the request for supplementary information (RSI) adopted in July 2018

17.2.10. Florbetaben (¹⁸F) - NEURACEQ (CAP) - EMEA/H/C/002553/MEA 001.7

Applicant: Life Radiopharma Berlin GmbH

PRAC Rapporteur: Patrick Batty

Scope: MAH's response to MEA 003 [amended protocol to previously agreed protocol in September 2016 for PASS study FBB-01_03_13 (PASS 2): a non-interventional, prospective observational multicentre, multi-country registry to observe usage pattern, safety and tolerability of the diagnostic agent NeuraCeq (florbetaben (¹⁸F)) in clinical practice [final clinical study report (CSR) expected in Q2/2020]] as per the request for supplementary information adopted in June 2018

17.2.11. Golimumab - SIMPONI (CAP) - EMEA/H/C/000992/MEA 026.6

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Amended protocol (version 2) to a previously agreed protocol in April 2015 for study MK-8259-013, the ulcerative colitis (UC) Nordic registry: a non-interventional observational longitudinal PASS of Simponi (golimumab) in the treatment of UC using Nordic national health registries

17.2.12. Naloxegol - MOVENTIG (CAP) - EMEA/H/C/002810/MEA 006.6

Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: MAH's response to MEA 006.5 [amendment for study D3820R00009 (previously study D2288R00084) to a protocol previously agreed in June 2016: an observational PASS of Moventig (naloxegol) among patients aged 18 years and older treated with opioids chronically] as per the request for supplementary information (RSI) adopted in July 2018

17.2.13. Niraparib - ZEJULA (CAP) - EMEA/H/C/004249/MEA 003.1

Applicant: Tesaro UK Limited

PRAC Rapporteur: Patrick Batty

Scope: MAH's response to MEA 003 [protocol and statistical analysis plan for a non-interventional non-imposed PASS: a pooled analysis of the incidence of acute myelogenous leukaemia, myelodysplastic syndrome, and other secondary primary malignancies in patients treated with niraparib] as per the request for supplementary information (RSI) adopted in July 2018

17.2.14. Pegfilgrastim - NEULASTA (CAP) - EMEA/H/C/000420/MEA 059.1

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Patrick Batty

Scope: MAH's response to MEA 045.1 [protocol for study 20170701: an observational study to assess the effectiveness of the Neulasta (pegfilgrastim) patient alert card (PAC) and to measure medication errors related to the use of the on-body injector (OBI) to assess respondent awareness of key safety messages and behavioural intent to carry out recommended actions as described in the PAC and to estimate the proportion of OBI administrations associated with medication error [final study report expected in March 2022]] as per the request for supplementary information (RSI) adopted in July 2018

17.2.15. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/MEA 045.2

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Patrick Batty

Scope: MAH's response to MEA 045.1 [protocol for study RRA-20745: a PASS to investigate the long-term safety in adult patients with moderately to severely active Crohn's disease] as per the request for supplementary information (RSI) adopted in June 2018

17.3. Results of PASS imposed in the marketing authorisation(s)⁸³

None

17.4. Results of PASS non-imposed in the marketing authorisation(s)⁸⁴

17.4.1. Atazanavir, atazanavir sulfate - REYATAZ (CAP) - EMEA/H/C/000494/II/0117

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Adrien Inoubli

Scope: Submission of the final reports for studies AI424397 (PRINCE I) and AI424451 (PRINCE II) listed as a category 3 studies in the RMP. These studies were phase 3b, prospective, single arm, open-label, international, multicentre studies to evaluate the safety, efficacy and pharmacokinetics of atazanavir powder boosted with ritonavir and administered with an optimised nucleoside reverse transcriptase inhibitor (NRTI) background therapy, in human immunodeficiency virus (HIV) infected paediatric patients. The RMP is updated accordingly (version 15.0). In addition, the MAH took the opportunity to bring the RMP in line with revision 2 of the guidance on the format of RMP in the EU (template)

17.4.2. Canagliflozin - INVOKANA (CAP) - EMEA/H/C/002649/II/0039

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Martin Huber

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

⁸⁴ In accordance with Article 61a (6) of Regulation (EC) No 726/2004, in line with the revised variations regulation for any submission as of 4 August 2013

Scope: Submission of the final study report for non-interventional study RRA-21430: a retrospective cohort study exploring acute pancreatitis in patients with type 2 diabetes mellitus (T2DM) who are new users of canagliflozin as compared with new users of other antihyperglycemic agents (AHAs) using large claim databases in the US

17.4.3. Canagliflozin, metformin - VOKANAMET (CAP) - EMEA/H/C/002656/II/0040

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Menno van der Elst

Scope: Submission of the final study report for non-interventional study RRA-21430: a retrospective cohort study exploring acute pancreatitis in patients with type 2 diabetes mellitus (T2DM) who are new users of canagliflozin as compared with new users of other antihyperglycemic agents (AHAs) using large claim databases in the US

17.4.4. Ocriplasmin - JETREA (CAP) - EMEA/H/C/002381/II/0042/G

Applicant: Oxurion NV

PRAC Rapporteur: Julie Williams

Scope: Grouped variations consisting of: 1) submission of the final report from study (TG-MV-018) 'ocriplasmin research to better inform treatment (ORBIT)': a multicentre, prospective, observational study which assesses clinical outcomes and safety of Jetrea (ocriplasmin) administered in a real-world setting for the treatment of symptomatic vitreomacular adhesion (VMA); 2) submission of the final report from a prospective drug utilisation study TG-MV-017 (listed as a category 3 study in the RMP): a European, multicentre, observational study exploring the utilisation patterns of intravitreal Jetrea (ocriplasmin) in real-life clinical practice. The study includes two parts, a drug utilisation study (DUS) and the patient educational material evaluation survey (PEMES); 3) submission of the final report from study INJECT (investigation of Jetrea (ocriplasmin) in patients with confirmed vitreomacular traction): a non-interventional, multicentre, worldwide study in patients treated with Jetrea (ocriplasmin) in order to evaluate safety, clinical effectiveness, and health-related quality of life (HRQoL) outcomes in a real world setting among a large population of patients exposed to ocriplasmin across different countries according to country's approved indications. The RMP (version 7.2) is updated accordingly and in line with revision 2 of the guidance on the format of RMP in the EU (template)

17.4.5. Orlistat - ALLI (CAP) - EMEA/H/C/000854/II/0058

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Julie Williams

Scope: Submission of the final report for non-interventional PASS study 204675 (listed as a category 3 study in the RMP): 'evaluating the effectiveness of the revised alli (orlistat) pack information in helping pharmacy staff within the EU supply alli appropriately'. In addition, the RMP is updated (version 17) in line with revision 2 of the guidance on the format of RMP in the EU (template)

17.4.6. Sofosbuvir, velpatasvir - EPCLUSA (CAP) - EMEA/H/C/004210/WS1476/0028; Ledipasvir, sofosbuvir - HARVONI (CAP) - EMEA/H/C/003850/WS1476/0070;

Sofosbuvir - SOVALDI (CAP) - EMEA/H/C/002798/WS1476/0052;
Sofosbuvir, velpatasvir, voxilaprevir - VOSEVI (CAP) -
EMA/H/C/004350/WS1476/0016

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Submission of the final report from study GS-US-334-0154 (listed as a category 3 study in the RMP): a phase 2b randomized, open-label study of 200 mg or 400 mg sofosbuvir + ribavirin for 24 weeks in genotype 1 or 3 hepatitis C virus (HCV)-infected subjects with renal insufficiency. The RMPs are updated accordingly (Eplclusa version 3.2, Harvoni version 4.1, Sovaldi version 7.1 and Vosevi version 1.1)

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 075.7

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Sixth 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 080.6

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Fourth 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. Dulaglutide - TRULICITY (CAP) - EMEA/H/C/002825/MEA 002.4

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Amelia Cupelli

Scope: MAH's response to MEA 002.3 [third progress report and first interim report for study H9X-MC-B009: dulaglutide European modified prescription-event monitoring and network database study: a multi-database collaborative research programme of observational studies to monitor the utilisation and safety of dulaglutide in the EU] as per the request for supplementary information (RSI) adopted in June 2018

17.5.4. Estrogens conjugated, bazedoxifene - DUAVIVE (CAP) - EMEA/H/C/002314/MEA 002.9

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Martin Huber

Scope: MAH's response to MEA 002.9 [third interim study report for a US (listed as a category 3 study in the RMP) non-interventional PASS (B2311060 study): an active surveillance of conjugated oestrogens (CE)/bazedoxifene acetate (BZA) using US healthcare data] as per the request for supplementary information (RSI) adopted in June 2018

17.5.5. [Estrogens conjugated, bazedoxifene - DUAVIVE \(CAP\) - EMEA/H/C/002314/MEA 003.5](#)

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Martin Huber

Scope: MAH's response to MEA 003.4 [first interim report for a drug utilisation study (DUS) on conjugated oestrogens/ bazedoxifene (CE/BZA) in the European Union (EU) to describe baseline characteristics and utilisation patterns of EU patients initiating Duavive (CE/BZA) or oestrogen + progestin (E+P) combination hormone replacement therapy (HRT)]

17.5.6. [Follitropin alfa - OVALEAP \(CAP\) - EMEA/H/C/002608/MEA 002.3](#)

Applicant: Teva B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Interim report for study XM17-WH-50005 (SOFIA): a non-interventional multinational prospective observational study to assess the safety of Ovaleap (follitropin alfa) compared to Gonal-F (follitropin alfa) in one treatment cycle with respect to the incidence rates of ovarian hyperstimulation syndrome (OHSS) in infertile women undergoing superovulation for assisted reproductive technologies (ART)

17.5.7. [Nivolumab - OPDIVO \(CAP\) - EMEA/H/C/003985/MEA 008.4](#)

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Second annual interim report for study CA209234 (listed as a category 3 study in the RMP): a PASS exploring the pattern of use, safety, and effectiveness of nivolumab in routine oncology practice [final clinical study report (CSR) due date: 31 December 2024] (from initial opinion/MA)

17.5.8. [Sacubitril, valsartan - ENTRESTO \(CAP\) - EMEA/H/C/004062/MEA 004.4](#)

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Julie Williams

Scope: MAH's response to MEA 004.3 [first interim report for study CLCZ696B2015 (PASS 3) (listed as a category 3 study in the RMP): a non-interventional post-authorisation European multi-database safety study to assess the risk of myotoxicity, hepatotoxicity and acute pancreatitis in statin-exposed heart failure patients with or without concomitant use of Entresto/Neparvis (sacubitril/valsartan) [final report expected in Q2/2020]] as per the request for supplementary information (RSI) adopted in July 2018

17.5.9. [Sacubitril, valsartan - NEPARVIS \(CAP\) - EMEA/H/C/004343/MEA 003.1](#)

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Julie Williams

Scope: MAH's response to MEA 003 [First interim report for study CLCZ696B2015 (PASS 3) (listed as a category 3 study in the RMP): a non-interventional post-authorisation European multi-database safety study to assess the risk of myotoxicity, hepatotoxicity and acute pancreatitis in statin-exposed heart failure patients with or without concomitant use of Entresto/Neparvis (sacubitril/valsartan) [final report expected in Q2/2020]] as per the request for supplementary information (RSI) adopted in July 2018

17.5.10. [Somatropin - OMNITROPE \(CAP\) - EMEA/H/C/000607/MEA 012.2](#)

Applicant: Sandoz GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Second interim report for study EP00-501 (PATRO Children): a non-interventional post-marketing surveillance study to collect long-term safety and efficacy of Omnitrope (somatropin) in infants, children and adolescents with growth hormone deficiency and treated within routine clinical practice in Europe

17.6. Others

17.6.1. [Canagliflozin - INVOKANA \(CAP\) - EMEA/H/C/002649/MEA 014](#)

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Martin Huber

Scope: Protocol for a meta-analysis of amputation events from clinical trials DIA3008 (CANVAS: a randomized, multicentre, double-blind, parallel, placebo-controlled study of the effects of JNJ-28431754 (canagliflozin) on cardiovascular outcomes in adult subjects with type 2 diabetes mellitus (T2DM)), DIA4003 (CANVAS-R: a randomized, multicentre, double-blind, parallel, placebo-controlled study of the effects of canagliflozin on renal endpoints in adult subjects with T2DM), and DNE3001 (CREDENCE: a randomised, double-blind, event-driven, placebo-controlled, multicentre study of the effects of canagliflozin on renal and cardiovascular outcomes in subjects with T2DM and diabetic nephropathy), as per the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on lower limb amputation in relation to the use of sodium-glucose co-transporter-2 (SGLT-2) inhibitors completed in February 2017 (EMA/H/A-20/1442)

17.6.2. [Canagliflozin, metformin - VOKANAMET \(CAP\) - EMEA/H/C/002656/MEA 013](#)

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Menno van der Elst

Scope: Protocol for a meta-analysis of amputation events from clinical trials DIA3008 (CANVAS: a randomized, multicentre, double-blind, parallel, placebo-controlled study of the effects of JNJ-28431754 (canagliflozin) on cardiovascular outcomes in adult subjects with type 2 diabetes mellitus (T2DM)), DIA4003 (CANVAS-R: a randomized, multicentre, double-

blind, parallel, placebo-controlled study of the effects of canagliflozin on renal endpoints in adult subjects with T2DM), and DNE3001 (CREDENCE: a randomised, double-blind, event-driven, placebo-controlled, multicentre study of the effects of canagliflozin on renal and cardiovascular outcomes in subjects with T2DM and diabetic nephropathy), as per the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on lower limb amputation in relation to the use of sodium-glucose co-transporter-2 (SGLT-2) inhibitors completed in February 2017 (EMA/H/A-20/1442)

[17.6.3. Dasabuvir - EXVIERA \(CAP\) - EMA/H/C/003837/MEA 001.5](#)

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Maria del Pilar Rayon

Scope: MAH's response to MEA 001.3 and MEA 001.4 [interim results and proposal for termination of study P15-421: a prospective, observational cohort study utilising the hepatitis C therapeutic registry and research network (HCV-TARGET) data to evaluate the clinical impact and real world frequency of grade 3+ alanine transaminase (ALT) elevations in patients being treated for hepatitis C with paritaprevir with ritonavir (paritaprevir/ritonavir), ombitasvir and dasabuvir (2 direct-acting antiviral (DAA) regimen) or paritaprevir/ritonavir and ombitasvir (3-DAA regimen) with or without ribavirin for hepatitis C infection (HCV) (SHORT – evaluation of the potential for and clinical impact of increased ALT in patients using the AbbVie 2-DAA or 3-DAA regimens in a real world setting] as per the request for supplementary information (RSI) adopted in July 2018

[17.6.4. Ocrelizumab - OCREVUS \(CAP\) - EMA/H/C/004043/MEA 005.1](#)

Applicant: Roche Registration GmbH

PRAC Rapporteur: Julie Williams

Scope: MAH's response to MEA 005 [PASS protocol for study WA40404 (listed as category 3 study in the RMP): a phase 3b multicentre, randomised, double-blind, placebo controlled study to evaluate the efficacy and safety of ocrelizumab in adults with primary progressive multiple sclerosis later in their disease course] as per the request for supplementary information (RSI) adopted in July 2018

[17.6.5. Ombitasvir, paritaprevir, ritonavir - VIEKIRAX \(CAP\) - EMA/H/C/003839/MEA 001.5](#)

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Maria del Pilar Rayon

Scope: MAH's response to MEA 001.3 and MEA 001.4 [interim results and proposal for termination of study P15-421: a prospective, observational cohort study utilising the hepatitis C therapeutic registry and research network (HCV-TARGET) data to evaluate the clinical impact and real world frequency of grade 3+ alanine transaminase (ALT) elevations in patients being treated for hepatitis C with paritaprevir with ritonavir (paritaprevir/ritonavir), ombitasvir and dasabuvir (2 direct-acting antiviral (DAA) regimen) or paritaprevir/ritonavir and ombitasvir (3-DAA regimen) with or without ribavirin for hepatitis C infection (HCV) (SHORT – evaluation of the potential for and clinical impact of increased ALT in patients using the AbbVie 2-DAA or 3-DAA regimens in a real world

setting] as per the request for supplementary information (RSI) adopted in July 2018

17.7. New Scientific Advice

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

17.8. Ongoing Scientific Advice

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

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

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

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

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

18.1. Annual reassessments of the marketing authorisation

18.1.1. Antithrombin alfa - ATRYN (CAP) - EMEA/H/C/000587/S/0035 (without RMP)

Applicant: Laboratoire Francais du Fractionnement et des Biotechnologies

PRAC Rapporteur: Adrien Inoubli

Scope: Annual reassessment of the marketing authorisation

18.1.2. Asfotase alfa - STRENSIQ (CAP) - EMEA/H/C/003794/S/0032 (without RMP)

Applicant: Alexion Europe SAS

PRAC Rapporteur: Rhea Fitzgerald

Scope: Annual reassessment of the marketing authorisation

18.2. Conditional renewals of the marketing authorisation

18.2.1. Bosutinib - BOSULIF (CAP) - EMEA/H/C/002373/R/0035 (without RMP)

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Martin Huber

Scope: Conditional renewal of the marketing authorisation

18.2.2. Delamanid - DELTYBA (CAP) - EMEA/H/C/002552/R/0033 (without RMP)

Applicant: Otsuka Novel Products GmbH

PRAC Rapporteur: Julie Williams

Scope: Conditional renewal of the marketing authorisation

18.3. Renewals of the marketing authorisation

18.3.1. Brinzolamide, brimonidine - SIMBRINZA (CAP) - EMEA/H/C/003698/R/0014 (without RMP)

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: 5-year renewal of the marketing authorisation

18.3.2. Empagliflozin - JARDIANCE (CAP) - EMEA/H/C/002677/R/0040 (with RMP)

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Eva Segovia

Scope: 5-year renewal of the marketing authorisation

18.3.3. Mifamurtide - MEPACT (CAP) - EMEA/H/C/000802/R/0047 (without RMP)

Applicant: Takeda France SAS

PRAC Rapporteur: Menno van der Elst

Scope: 5-year renewal of the marketing authorisation

18.3.4. Oseltamivir - EBILFUMIN (CAP) - EMEA/H/C/003717/R/0012 (without RMP)

Applicant: Actavis Group PTC ehf

PRAC Rapporteur: Kirsti Villikka

Scope: 5-year renewal of the marketing authorisation

18.3.5. Sevelamer carbonate - RENVELA (CAP) - EMEA/H/C/000993/R/0046 (without RMP)

Applicant: Genzyme Europe BV

PRAC Rapporteur: Laurence de Fays

Scope: 5-year renewal of the marketing authorisation

18.3.6. Siltuximab - SYLVANT (CAP) - EMEA/H/C/003708/R/0029 (without RMP)

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: 5-year renewal of the marketing authorisation

18.3.7. Trametinib - MEKINIST (CAP) - EMEA/H/C/002643/R/0029 (without RMP)

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Patrick Batty

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 26-29 November 2018 meeting.

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Sabine Straus	Chair	The Netherlands	No interests declared	Full involvement
Jan Neuhauser	Member	Austria	No interests declared	Full involvement
Jean-Michel Dogné	Member	Belgium	No interests declared	Full involvement
Laurence de Fays	Alternate	Belgium	No interests declared	Full involvement
Yuliyán Eftimov	Alternate	Bulgaria	No interests declared	Full involvement
Željana Margan Koletić	Alternate	Croatia	No interests declared	Full involvement
Andri Andreou	Member	Cyprus	No restrictions applicable to this meeting	Full involvement
Eva Jirsovà	Member	Czech Republic	No interests declared	Full involvement
Doris Stenver	Member	Denmark	No interests declared	Full involvement
Anette Stark	Alternate	Denmark	No restrictions applicable to this meeting	Full involvement
Maia Uusküla	Member	Estonia	No interests declared	Full involvement
Kirsti Villikka	Member	Finland	No interests declared	Full involvement
Kimmo Jaakkola	Alternate	Finland	No interests declared	Full involvement
Ghania Chamouni	Member	France	No restrictions applicable to this meeting	Full involvement
Adrien Inoubli	Alternate	France	No interests declared	Full involvement
Martin Huber	Member	Germany	No interests	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
	(Vice-Chair)		declared	
Brigitte Keller-Stanislawski	Alternate	Germany	No interests declared	Full involvement
Sophia Trantza	Alternate	Greece	No restrictions applicable to this meeting	Full involvement
Julia Pallos	Member	Hungary	No interests declared	Full involvement
Melinda Palfi	Alternate - via telephone*	Hungary	No interests declared	Full involvement
Guðrún Stefánsdóttir	Member	Iceland	No participation in final deliberations and voting on:	6.2.4. Tacrolimus - ADVAGRAF (CAP); ENVARSUS (CAP); MODIGRAF (CAP); NAP
Rhea Fitzgerald	Member	Ireland	No restrictions applicable to this meeting	Full involvement
Ronan Grimes	Alternate	Ireland	No interests declared	Full involvement
Amelia Cupelli	Member	Italy	No interests declared	Full involvement
Zane Neikena	Member	Latvia	No interests declared	Full involvement
Jolanta Gulbinovic	Member	Lithuania	No interests declared	Full involvement
Ruta Dubosiene	Alternate	Lithuania	No interests declared	Full involvement
Marcel Bruch	Member	Luxembourg	No interests declared	Full involvement
Anne-Cécile Vuillemin	Alternate - via telephone*	Luxembourg	No restrictions applicable to this meeting	Full involvement
Benjamin Micallef	Alternate	Malta	No interests declared	Full involvement
Menno van der Elst	Member	Netherlands	No interests declared	Full involvement
Liana Gross-Martirosyan	Alternate	Netherlands	No interests declared	Full involvement
David Olsen	Member	Norway	No participation in final deliberations and voting on:	6.3.10. Paracetamol (NAP) - PSUSA/0000231 1/201805 14.2.3. Sorafenib – NEXAVAR (CAP)

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				4.2.2. VEGF inhibitors: aflibercept – EYLEA (CAP), ZALTRAP (CAP); axitinib – INLYTA (CAP); bevacizumab – AVASTIN (CAP), MVASI (CAP); cabozantinib – CABOMETYX (CAP), COMETRIQ (CAP); lenvatinib - KISPLYX (CAP), LENVIMA (CAP); nintedanib – OFEV (CAP), VARGATEF (CAP); pazopanib – VOTRIENT (CAP); pegaptanib – MACUGEN (CAP); ponatinib – ICLUSIG (CAP); ramucirumab – CYRAMZA (CAP); ranibizumab – LUCENTIS (CAP); regorafenib – STIVARGA (CAP); sorafenib – NEXAVAR (CAP); sunitinib – SUTENT (CAP); tivozanib – FOTIVDA (CAP); vandetanib – CAPRELSA (CAP)
Karen Pernille Harg	Alternate	Norway	No interests declared	5.1.3. Larotrectinib - VITRAKVI (CAP MAA) - EMEA/H/C/004919, Orphan Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Adam Przybylkowski	Member	Poland	No interests declared	Full involvement
Ana Diniz Martins	Member	Portugal	No interests declared	Full involvement
Marcia Silva	Alternate	Portugal	No interests declared	Full involvement
Michal Radik	Member	Slovakia	No restrictions applicable to this meeting	Full involvement
Gabriela Jazbec	Member	Slovenia	No interests declared	Full involvement
Eva Segovia	Member	Spain	No interests declared	Full involvement
Maria del Pilar Rayon	Alternate	Spain	No interests declared	Full involvement
Ulla Wändel Liminga	Member	Sweden	No interests declared	Full involvement
Annika Folin	Alternate	Sweden	No interests declared	Full involvement
Julie Williams	Member	United Kingdom	No interests declared	Full involvement
Patrick Batty	Alternate	United Kingdom	No interests declared	Full involvement
Birgitta Grundmark	Member	Independent scientific expert	No interests declared	Full involvement
Daniel Morales	Member	Independent scientific expert	No interests declared	Full involvement
Hedvig Nordeng	Member	Independent scientific expert	No interests declared	Full involvement
Antoine Pariente	Member	Independent scientific expert	No participation in final deliberations and voting on:	6.3.10. Paracetamol (NAP) - PSUSA/0000231 1/201805
Stefan Weiler	Member	Independent scientific expert	No restrictions applicable to this meeting	Full involvement
Raymond Anderson	Member	Healthcare Professionals' Representative	No interests declared	Full involvement
Kirsten Myhr	Alternate	Healthcare Professionals' Representative	No interests declared	Full involvement
Marco Greco	Member	Patients' Organisation Representative	No restrictions applicable to this meeting	Full involvement
Maxim Frizler	Expert - via telephone*	Germany	No interests declared	Full involvement
Kerstin Loeschcke	Expert - via telephone*	Germany	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Valerie Strassman	Expert - in person*	Germany	No interests declared	Full involvement
Niamh Buckley	Expert - via telephone*	Ireland	No interests declared	Full involvement
Fakhredin Sayed Tabatabaei	Expert - in person*	Netherlands	No interests declared	Full involvement
Inge Zomerdijk	Expert - via telephone*	Netherlands	No interests declared	Full involvement
Gunnar Rimul	Expert - in person*	Norway	No interests declared	Full involvement
João Freire	Expert - in person*	Portugal	No restrictions applicable to this meeting	Full involvement
Charlotte Backman	Expert - in person*	Sweden	No interests declared	Full involvement
Karin Bolin	Expert - via telephone*	Sweden	No interests declared	Full involvement
Annika Ekbohm Schnell	Expert - via telephone*	Sweden	No restrictions applicable to this meeting	Full involvement
Natalie Bando	Expert - in person*	United Kingdom	No interests declared	Full involvement
Rory Littlebury	Expert - via telephone*	United Kingdom	No interests declared	Full involvement
Graham Lunn	Expert - in person*	United Kingdom	No restrictions applicable to this meeting	Full involvement
Kiernan Trevett	Expert - via telephone*	United Kingdom	No interests declared	Full involvement
A representative from the European Commission attended the meeting				
Meeting run with support from relevant EMA staff				

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

20. Annex III - List of acronyms and abbreviations

For a list of acronyms and abbreviations used in the PRAC minutes, see:

[Home>Committees>PRAC>Agendas, minutes and highlights](#)

21. Explanatory notes

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

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

(Items 2 and 3 of the PRAC minutes)

A referral is a procedure used to resolve issues such as concerns over the safety or benefit-risk balance of a medicine or a class of medicines. In a referral, the EMA is requested to conduct a scientific assessment of a particular medicine or class of medicines on behalf of the European Union (EU). For further detailed information on safety related referrals please see:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000150.jsp&mid=WC0b01ac05800240d0

Signals assessment and prioritisation

(Item 4 of the PRAC minutes)

A safety signal is information on a new or incompletely documented adverse event that is potentially caused by a medicine and that warrants further investigation. Signals are generated from several sources such as spontaneous reports, clinical studies and the scientific literature. The evaluation of safety signals is a routine part of pharmacovigilance and is essential to ensuring that regulatory authorities have a comprehensive knowledge of a medicine's benefits and risks.

The presence of a safety signal does not mean that a medicine has caused the reported adverse event. The adverse event could be a symptom of another illness or caused by another medicine taken by the patient. The evaluation of safety signals is required to establish whether or not there is a causal relationship between the medicine and the reported adverse event.

The evaluation of safety signals may not necessarily conclude that the medicine caused the adverse event in question. In cases where a causal relationship is confirmed or considered likely, regulatory action may be necessary and this usually takes the form of an update of the summary of product characteristics and the package leaflet.

Risk Management Plans (RMPs)

(Item 5 of the PRAC minutes)

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

Assessment of Periodic Safety Update Reports (PSURs)

(Item 6 of the PRAC minutes)

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

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

Post-authorisation Safety Studies (PASS)

(Item 7 of the PRAC minutes)

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

Product related pharmacovigilance inspections

(Item 9 of the PRAC minutes)

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

More detailed information on the above terms can be found on the EMA website:

<http://www.ema.europa.eu/ema/>