15 March 2019
EMA/PRAC/216303/2019
Inspections, Human Medicines Pharmacovigilance and Committees Division

Pharmacovigilance Risk Assessment Committee (PRAC)

Minutes of PRAC meeting on 11-14 February 2019

Chair: Sabine Straus – Vice-Chair: Martin Huber

Health and safety information

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

Disclaimers

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

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

Note on access to documents

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

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1. Introduction

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

The Chairperson opened the 11-14 February 2019 meeting by welcoming all participants.

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

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

The PRAC Chair welcomed Rugile Pilviniene, replacing Jolanta Gulbinovic, as the new member for Lithuania. In addition, the PRAC Chair announced that it was the last PRAC meeting for Doris Stenver as the member for Denmark, Marco Greco as the member representing patients' organisations, Albert van der Zeijden as the alternate representing patients' organisations as well as Kirsten Myhr as the alternate representing healthcare professionals. The PRAC thanked them for their valuable contribution to the work of the PRAC.

1.2. Agenda of the meeting on 11-14 February 2019

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

1.3. Minutes of the previous meeting on 14-17 January 2019

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

Post-meeting note: the PRAC minutes of the meeting held on 14-17 January 2019 were published on the EMA website on 25 March 2019 (EMA/PRAC/190876/2019).

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

2.1. Newly triggered procedures

2.1.1. Fenspiride (NAP) - EMEA/H/A-107i/1480

Applicant(s): various

PRAC Rapporteur: Julia Pallos; PRAC Co-rapporteur: Adrien Inoubli

Scope: Review of the benefit-risk balance following notification by France of a referral under Article 107i of Directive 2001/83/EC, based on pharmacovigilance data

Background

Fenpsiride is a bronchodilator indicated for the symptomatic treatment of cough and expectoration related to bronchopulmonary diseases.

The French Medicine Agency (ANSM) sent a letter of notification dated 08/02/2019, along with a scientific background (rationale), triggering an urgent Union procedure under Article 107i of Directive 2001/83/EC for the review of fenspiride-containing products. The review was initiated following the results of two non-clinical studies, requested in the conclusions of the periodic safety update report single assessment (PSUSA) procedure PSUSA/00001368/201804 concluded in November 2018. For further background, see PRAC minutes November 2018 (29-31 October 2018). The results show that fenspiride can induce an inhibition of hERG[1] tail current *in vitro*, and increase the corrected QT (QTc) intervals in isolated and perfused guinea pig heart. In addition, calculated safety margins between the hERG inhibition concentration and the effective therapeutic plasma concentration are below the acceptable margin. In light of these new safety findings, taking into account the indication of fenspiride and the seriousness of the risk of QT prolongation, the ANSM considered that the benefit-risk ratio of fenspiride-containing medicinal products is no longer favourable in the treatment of symptoms related to bronchopulmonary diseases, and suspended the marketing authorisations of these medicinal products in France. Therefore, the ANSM triggered an urgent Union procedure resulting from pharmacovigilance data, and requested the PRAC to assess the impact of the above concerns on the benefit-risk balance of fenspiride-containing products.

Discussion

The PRAC noted the notification letter and the scientific background from ANSM. The PRAC appointed Julia Pallos as Rapporteur and Adrien Inoubli as Co-Rapporteur for the procedure.

The PRAC discussed the results of the two non-clinical studies and the need for temporary measures to protect public health as well as lists of questions to be addressed during the procedure together with a timetable for conducting the review. The PRAC also discussed the need for a public hearing.

With regard to temporary measures, the PRAC reviewed the information currently available to the Committee on the risk of QT prolongation and proarrhythmia potential, particularly the new findings from non-clinical studies which are supportive of a previously suspected association between the use of fenspiride and the occurrence of QT prolongation in humans. The PRAC also considered cumulative data from post marketing cases which provided further evidence of a possible causal relationship between fenspiride and QT prolongation/proarrhythmia. The PRAC noted that QT prolongation and proarrhythmia are life-threatening and unpredictable conditions, and considered that, taking into account that the medicinal product is only authorised to treat benign symptoms, the only appropriate risk minimisation measure to protect patients while the review is ongoing is the suspension of the marketing authorisations. The PRAC considered that at present the risk of QT prolongation and proarrhythmia potential outweighs the benefits of fenspiride in its authorised indications.

[1] Human ether-a-go-go-related gene

Summary of recommendation(s)/conclusions

- The Committee recommended the suspension of the marketing authorisations for fenspiride-containing products as a temporary measure, without prejudice to the final conclusions of the ongoing procedure under Article 107i of Directive 2001/83/EC. See EMA press release (EMA/114407/2019) entitled 'Suspension of fenspiride medicines due to potential risk of heart rhythm problems'.
- The PRAC also agreed on distribution of a direct healthcare professional communication (DHPC) together with a communication plan.
- The Committee adopted a list of questions (LoQ) to MAHs (EMA/PRAC/100387/2019) and a LoQ to stakeholders[2] (EMA/PRAC/100386/2019). In addition, the PRAC adopted a timetable for the ongoing procedure (EMA/PRAC/100392/2019).
- The PRAC discussed the option to conduct a public hearing in the context of the Article 107i procedure on medicinal products containing-fenspiride, according to the pre-defined criteria set out in the rules of procedure[3] (EMA/363479/2015). It was agreed by the Committee that at this stage in the assessment, in light of the currently available data and the need to determine the appropriate approach to stakeholder engagement, a public hearing would not be appropriate. The PRAC can come back to reconsider this at a later stage of the procedure as needed.

2.2. Ongoing procedures

None

2.3. Procedures for finalisation

None

2.4. Planned public hearings

None

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

3.1. Newly triggered procedures

None

3.2. Ongoing procedures

3.2.1. Methotrexate - JYLAMVO (CAP), NORDIMET (CAP); NAP - EMEA/H/A-31/1463

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

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

[2] E.g. healthcare professionals, patients' organisations or general public
[3] Rules of procedure on the organisation and conduct of public hearings at the PRAC

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

Background

A referral procedure under Article 31 of Directive 2001/83/EC is ongoing for methotrexate-containing medicines (oral and parenteral formulations) following reports of overdose toxicity as a consequence of daily intake in error instead of weekly intake. The ongoing review also assesses the risk minimisation measures taken nationally over recent years to fully elucidate the issue and to take appropriate measures. For further background see PRAC minutes April 2018, PRAC minutes October 2018 and PRAC minutes January 2019.

Summary of recommendation(s)/conclusions

- The PRAC discussed the joint assessment report by the Rapporteurs.
- The PRAC adopted a second list of outstanding issues (LoOI), to be addressed by the MAHs in accordance with a revised timetable (EMA/PRAC/199744/2018 Rev 2).

3.3. Procedures for finalisation

None

3.4. Re-examination procedures[4]

None

3.5. Others

None

4. Signals assessment and prioritisation[5]

4.1. New signals detected from EU spontaneous reporting systems

See Annex I **Error! Reference source not found.**

4.2. New signals detected from other sources

See also Annex I 14.2.

4.2.1. Angiotensin converting enzyme (ACE) inhibitors: benazepril (NAP), captopril (NAP), cilazapril (NAP), delapril (NAP), enalapril (NAP), fosinopril (NAP), imidapril (NAP), lisinopril (NAP), moexipril (NAP), perindopril (NAP), quinapril (NAP), ramipril (NAP), trandolapril (NAP), zofenopril (NAP)

Applicant(s): various

PRAC Rapporteur: Ronan Grimes

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

[5] 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

Scope: Evaluation of data on risk of lung cancer from a population based cohort study

EPITT 19346 – New signal

Lead Member State(s): DE, DK, ES, IE, IT, NL, PT, SE, SK, UK

Background

Medicines containing angiotensin converting enzyme (ACE) inhibitors benazepril, captopril, cilazapril, delapril, enalapril, fosinopril, imidapril, lisinopril, moexipril, perindopril, quinapril, ramipril, trandolapril and zofenopril are indicated, under certain conditions, for the treatment of hypertension, heart failure, acute myocardial infarction and renal complications of diabetes mellitus.

The exposure for benazepril-containing products is estimated to have been more than 33.3 million patient-years worldwide, in the period from 1998 to 2015. The exposure for captopril-containing products is estimated to have been more than 45.2 million patients worldwide, in the period from first authorisation in 1980 to 2015. The exposure for cilazapril-containing products is estimated to have been more than 39.8 million patients worldwide, in the period from first authorisation in 1990 to 2018.The exposure for delapril-containing products is estimated to have been more than 1.58 million patient-years worldwide, in the period from first authorisation in 1989 to 2017. The exposure for enalapril-containing products is estimated to have been more than 327.55 million patient-years worldwide, in the period from first authorisation in 2004 to 2018. The exposure for fosinopril-containing products is estimated to have been more than 38.9 million patient-years worldwide, in the period from first authorisation in 1990 to 2018. The exposure for perindopril-containing products is estimated to have been more than 96.2 million patient-years worldwide, in the period from first authorisation in 1988 to 2015. The exposure for quinapril-containing products is estimated to have been more than 35.7 million patient-years worldwide, in the period from first authorisation in 1989 to 2016.

Following the publication in British Medical Journal by *Hicks et al.*[6], a signal of lung cancer was identified by Italy, suggesting that the use of ACE inhibitors was associated with an increased risk of lung cancer. Ireland confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information from the observational cohort study by *Hicks et al.* in the context of other published studies on the association between ACE inhibitors and the risk of lung cancer. Considering the potential for residual confounding, the possibility of ascertainment bias and information bias, lack of information on relationship with dose, the inconsistent relationship with lung cancer observed in the literature to date, and conflicting findings in non-clinical studies, the PRAC agreed that there is currently insufficient evidence for a causal association between ACE inhibitors and lung cancer. Therefore, the PRAC concurred that no regulatory action is currently warranted.

The PRAC appointed Ronan Grimes as Rapporteur for the signal.

[6] Hicks BM, Filion KB, Yin H, Udell JA, Azoulay L. Angiotensin converting enzyme inhibitors and risk of lung cancer: population based cohort study. BMJ. 2018;363:k4209. doi: 10.1136/bmj.k4209

Summary of recommendation(s)

- The MAHs for benazepril-, captopril-, cilazapril-, delapril-, enalapril-, fosinopril-, imidapril-, lisinopril-, moexipril-, perindopril-, quinapril-, ramipril-, trandolapril- and zofenopril-containing products should continue to monitor these events as part of routine safety surveillance.

4.2.2. Armodafinil (NAP), modafinil (NAP)

Applicant(s): various

PRAC Rapporteur: Martin Huber

Scope: Evaluation of data on foetal outcomes including congenital anomalies from a single observational study in the US

EPITT 19367 – New signal

Lead Member State(s): DE

Background

Armodafinil and modafinil are centrally acting sympathomimetics indicated for the treatment of excessive sleepiness associated with narcolepsy with or without cataplexy.

The exposure for modafinil-containing products is estimated to have been more than 2.96 million patient-years, in the period from first authorisation in 1992 to 2017.

Based on information received from the MAH Teva summarising data deriving from a pregnancy registry and supplemented by 51 cases in EudraVigilance, a signal of congenital anomalies was identified. Germany confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information on the cases of congenital anomalies in the context of existing warnings in the product information regarding the use during pregnancy and agreed to request further information from the MAH.

The PRAC appointed Martin Huber as Rapporteur for the signal.

Summary of recommendation(s)

- The MAH Teva for modafinil-containing products should submit to the EMA, within 30 days, answers to a list of questions (LoQ) agreed by the PRAC and a proposal to amend the product information and/or RMP as applicable, as well as a proposal for a direct healthcare professional communication (DHPC) and a communication plan.
- A 30-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.2.3. Propylthiouracil (NAP)

Applicant(s): various

PRAC Rapporteur: Martin Huber

Scope: Signal of risk of congenital anomalies

EPITT 19358 – New signal

Lead Member State(s): EE

Background

Propylthiouracil is an antithyroid drug that depresses the formation of thyroid hormone indicated for the treatment of hyperthyroidism.

During routine signal detection activities, a signal of congenital anomalies was identified by Germany, based on 142 cases in EudraVigilance and a review of epidemiological studies[7] on the association of use of propylthiouracil in pregnancy and congenital anomalies. Estonia confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information from the epidemiological studies of congenital anomalies and agreed to request a cumulative review of all data as regards congenital anomalies, with a view to amending the product information for propylthiouracil-containing medicines.

The PRAC appointed Martin Huber as Rapporteur for the signal.

Summary of recommendation(s)

- The MAHs Uni-Pharma Kleon Tsetis Pharmaceutical Laboratories, RPH Pharmaceuticals, Takeda and Admeda Arzneimittel for originator propylthiouracil-containing products should submit to the EMA, within 60 days, a comprehensive review of all relevant data from non-clinical studies, clinical trials, and epidemiological studies as regards congenital anomalies in association with the use of propylthiouracil during pregnancy and a proposal to amend the product information.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.2.4. Sulfasalazine (NAP)

Applicant(s): various

PRAC Rapporteur: Anette Kirstine Stark

Scope: Signal of interference with dihydronicotinamide-adenine dinucleotide / dihydronicotinamide-adenine dinucleotide phosphate (NADH/NADP) reaction assays

EPITT 19351 – New signal

Lead Member State(s): DK

Background

Sulfasalazine is an anti-inflammatory agent indicated for the treatment of ulcerative colitis and active Crohn's Disease, and for the treatment of rheumatoid arthritis which has failed to respond to nonsteroidal anti-inflammatory drugs.

[7] Seo GH, Kim TH and Chung JH. Antithyroid drugs and congenital malformations: a nationwide Korean cohort study. Ann Intern Med. 2018; 168(6):405–413
Andersen SL, Olsen J, Wu CS and Laurberg P. Birth defects after early pregnancy use of antithyroid drugs: a Danish nationwide study. J Clin Endocrinol Metab. 2013; 98(11):4373–81
Yoshihara A, Noh J, Yamaguchi T et al. Treatment of Graves' disease with antithyroid drugs in the first trimester of pregnancy and the prevalence of congenital malformation. J Clin Endocrinol Metab. 2012; 97(7):2396–403

During routine signal detection activities, a signal of interference with dihydronicotinamide-adenine dinucleotide/dihydronicotinamide-adenine dinucleotide phosphate (NADH/NADP) reaction assays was identified by Denmark, based on information received from manufacturers of certain NADH and/or NADP reaction assays that are registered as medical devices in the EU. Denmark confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information on the interference with NADH and/or NADP reaction assays, potentially leading to false results in patient samples and agreed to request a cumulative review of such interference with a view to amending the product information for sulfasalazine-containing medicines.

The PRAC appointed Anette Kirstine Stark as Rapporteur for the signal.

Summary of recommendation(s)

- The MAH Pfizer of the innovator sulfasalazine-containing product(s) should submit to the EMA, within 60 days, a cumulative analysis of all available information on the interference with NADH/NADP reaction assays with sulfasalazine (i.e. spontaneous reports, literature and clinical trials), and a proposal to amend the product information.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.3. Signals follow-up and prioritisation

4.3.1. Olanzapine – OLANZAPINE APOTEX (CAP), OLANZAPINE GLENMARK (CAP), OLANZAPINE GLENMARK EUROPE (CAP), OLANZAPINE MYLAN (CAP), OLANZAPINE TEVA (CAP), OLAZAX (CAP), OLAZAX DISPERZI (CAP), ZALASTA (CAP) - EMEA/H/C/000792/SDA/007, ZYPADHERA (CAP) - EMEA/H/C/000890/SDA/029, ZYPREXA (CAP) - EMEA/H/C/000115/SDA/050, ZYPREXA VELOTAB (CAP) - EMEA/H/C/000287/SDA/043; NAP

Applicant(s): Apotex Europe BV (Olanzapine Apotex), Eli Lilly Nederland B.V. (Zypadhera, Zyprexa, Zyprexa Velotab), Glenmark Arzneimittel GmbH (Olanzapine Glenmark, Olanzapine Glenmark Europe), Glenmark Pharmaceuticals (Olazax, Olazax Disperzi), Krka, d.d. (Zalasta), Mylan S.A.S (Olanzapine Mylan), Teva B.V. (Olanzapine Teva), various

PRAC Rapporteur: Kimmo Jaakkola

Scope: Signal of gestational diabetes

EPITT 19306 – Follow up to October 2018

Background

For background information, see PRAC minutes October 2018.

The MAH of Zypadhera, Zyprexa and Zyprexa Velotab (olanzapine) replied to the request for information on the signal of gestational diabetes and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence from the cumulative review provided by the MAH, and taking into account the limitations of the study by *Park et al.*[8], the PRAC agreed that the risk of gestational diabetes associated with the use of olanzapine during pregnancy cannot be fully distinguished from the overall metabolic effects of olanzapine. Therefore, the PRAC concurred that no regulatory action is currently warranted.

Summary of recommendation(s)

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

4.3.2. Tocilizumab – ROACTEMRA (CAP) - EMEA/H/C/000955/SDA/054

Applicant(s): Roche Registration GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Signal of facial paralysis

EPITT 19295 – Follow up to October 2018

Background

For background information, see PRAC minutes October 2018.

The MAH for RoActemra (tocilizumab) replied to the request for information on the signal of facial paralysis and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence, including the data submitted by the MAH, the PRAC agreed that the MAH should provide further responses to a list of questions (LoQ) agreed by the PRAC.

Summary of recommendation(s)

- The MAH for RoActemra (tocilizumab) should submit to EMA, within 30 days, responses to the LoQ agreed by the PRAC.
- A 30-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

Post-meeting note: Further to a request from the MAH, the PRAC agreed to extend by additional 30 days the timelines for submission to EMA of the requested responses to the LoQ.

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

[8] Park Y, Hernandez-Diaz S, Bateman BT, et al: Continuation of atypical antipsychotic medication during early pregnancy and the risk of gestational diabetes. Am J Psychiatry 2018; 175: 564–574

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. Avatrombopag - EMEA/H/C/004722

Scope: Treatment of thrombocytopenia

5.1.2. Crisaborole - EMEA/H/C/004863

Scope: Treatment of mild to moderate atopic dermatitis

5.1.3. Edaravone - EMEA/H/C/004938, Orphan

Applicant: Mitsubishi Tanabe Pharma Europe Ltd

Scope: Treatment of amyotrophic lateral sclerosis (ALS)

5.1.4. Onasemnogene abeparvovec - EMEA/H/C/004750, Orphan

Applicant: AveXis Netherlands B.V., ATMP[9]

Scope (accelerated assessment): Treatment of spinal muscular atrophy (SMA)

5.1.5. Ravulizumab - EMEA/H/C/004954, Orphan

Applicant: Alexion Europe SAS

Scope: Treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH)

5.1.6. Talazoparib - EMEA/H/C/004674

Scope: Treatment of adult patients with germline breast cancer susceptibility gene (BRCA) mutated human epidermal growth factor receptor 2 (HER2) negative locally advanced or metastatic breast cancer

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

Applicant: Roche Registration GmbH

[9] Advanced therapy medicinal product

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 and PRAC minutes December 2018 (26-29 November 2018).

Summary of advice

- The RMP version 19.1 for Mabthera (rituximab) in the context of the variation procedure under evaluation by the CHMP is acceptable with the deletion of safety concern on 'off label use in autoimmune disease'.
- The PRAC concluded that the MAH's proposal to remove the patient alert card (PAC) was not acceptable as the results of non-interventional drug utilisation study BA28478 showed that most patients did not receive a PAC nor were aware of PML being a rare side effect of the medicine. In addition, the outcome of the consultation with targeted patient groups to evaluate 'patient preferences regarding the ways of receiving information on PML and infections during rituximab treatment' showed that the patients supported the need for a PAC. As a result, the MAH should ensure that HCPs and patients are appropriately informed on the risk and patients receive the additional risk minimisation measures (aRMM). The MAH should continue to monitor the effectiveness of the PAC and patient brochure by process indicators, dissemination of the educational material and awareness of the risks (PML, serious infections, administration route errors). The PRAC considered that the issue regarding the appropriateness of having both a PAC and a patient brochure could be further discussed once further data are gathered on the effectiveness of the additional risk minimisation measures.

5.3.2. 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

Background

Thalidomide is immunomodulatory and anti-inflammatory agent with potential anti-neoplastic activities. It is indicated, as Thalidomide Celgene, a centrally authorised medicine, in combination with melphalan and prednisone, as first line treatment of patients with untreated multiple myeloma, aged ≥ 65 years or ineligible for high dose chemotherapy.

The CHMP is evaluating a type II variation for Thalidomide Celgene, a centrally authorised product containing thalidomide, in order to assess the update of the RMP in line with revision 2 of GVP module V 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. 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 October 2018 and PRAC minutes December 2018 (26-29 November 2018).

Summary of advice

- The RMP version 19.2 for Thalidomide Celgene (thalidomide) in the context of the variation procedure under evaluation by the CHMP is considered acceptable.
- The PRAC agreed with the proposed reclassification of the safety concerns. Teratogenicity, severe infections (sepsis, septic shock and viral reactivation of hepatitis B), acute myeloid leukaemia and myelodysplastic syndromes are reclassified as 'important identified risks' and ischaemic heart disease (including myocardial infarction), other second primary malignancies, hepatic disorders (hepatocellular and cholestatic liver injury), and off-label use as 'important potential risks'. The condition and requirements in terms of 'pregnancy prevention programme (PPP)' remains unchanged.

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. Asparaginase[10] - SPECTRILA (CAP) - PSUSA/00010445/201807

Applicant: Medac Gesellschaft fur klinische Spezialpraparate mbH

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

Background

Asparaginase is an enzyme hydrolysing asparagine, indicated, as Spectrila, as a component of antineoplastic combination therapy for the treatment of acute lymphoblastic leukaemia (ALL) in paediatric patients from birth to 18 years and adults.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Spectrila, a centrally authorised medicine containing asparaginase 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 Spectrila (asparaginase) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning in order to improve traceability of the product including the batch number. Therefore, the current terms of the marketing authorisation(s) should be varied[11].
- In the next PSUR, the MAH should provide a summary review of fatal reports (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. 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.

6.1.2. Carfilzomib - KYPROLIS (CAP) - PSUSA/00010448/201807

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

Background

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

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

[10] Centrally authorised product(s) only
[11] 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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Kyprolis (carfilzomib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include cytomegalovirus infection as an undesirable effect with frequency 'uncommon'. Therefore, the current terms of the marketing authorisation(s) should be varied[12].
- In the next PSUR, the MAH should provide the details of the search strategy for potential cases of off-label use, perform an analysis of off-label use of carfilzomib in paediatric patients, provide a cumulative analysis of cases of osteonecrosis, rhabdomyolysis/myopathy, gastrointestinal obstruction, Stevens-Johnson syndrome (SJS), progressive multifocal leukoencephalopathy (PML) and cardiac toxicity, cardio-respiratory arrest, pulmonary oedema and cases of dyspnoea 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. 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.

6.1.3. Evolocumab - REPATHA (CAP) - PSUSA/00010405/201807

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

Background

Evolocumab is a human monoclonal antibody to proprotein convertase subtilisin/kexin type 9 (PCSK9), indicated as Repatha, alone or in combination with other lipid-lowering therapies, for the treatment of hypercholesterolaemia under certain conditions. It is also indicated for the reduction of cardiovascular risk in adult patients with established atherosclerotic cardiovascular disease.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Repatha (evolocumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include angioedema as an undesirable effect with frequency 'rare'. In addition, the instructions for use of the package leaflet should be updated for the 140 mg solution for injection in pre-filled pen

[12] 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

to include the correct technique for using SureClick. Therefore, the current terms of the marketing authorisation(s) should be varied[13].

- In the next PSUR, the MAH should provide reviews of myalgia and flu like symptoms, anaphylaxis and evaluate clinical trial data on pneumonia, prostate cancer, cataract, chronic obstructive pulmonary disease, acute pancreatitis, osteoarthritis, and hip fracture.

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

6.1.4. Glecaprevir, pibrentasvir - MAVIRET (CAP) - PSUSA/00010620/201807

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

Background

Glecaprevir is a pan-genotypic inhibitor of the chronic hepatitis C virus (HCV) NS3/4A protease and pibrentasvir is a pan-genotypic inhibitor of HCV NS5A. Glecaprevir/pibrentasvir is indicated, as Maviret, for the treatment of chronic hepatitis C virus (HCV) infection in adults.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Maviret, a centrally authorised medicine containing glecaprevir/pibrentasvir 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 Maviret (glecaprevir/pibrentasvir) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include pruritus as an undesirable effect with the frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[14].
- In the next PSUR, the MAH should closely monitor future cases of angioedema and closely monitor the cases of cardiac disorders, the events of rash and toxicoderma and psychiatric disorders and discuss any new relevant information.

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. Ingenol mebutate - PICATO (CAP) - PSUSA/00010035/201807 (with RMP)

Applicant: LEO Laboratories Ltd

[13] 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
[14] 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

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

Background

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

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Picato (ingenol mebutate) in the approved indication(s) remains unchanged.
- Nevertheless, Annex II-D on 'conditions or restrictions with regard to the safe and effective use of the medicinal product' should be updated to include two new imposed studies[15], one an interventional vehicle-controlled study and the other an observational cohort study, to further investigate the risk of skin malignancy. Therefore, the current terms of the marketing authorisation(s) should be varied[16].
- The MAH should submit to EMA, by end of 2019, results from studies on *in vitro* colony formation and migration in keratinocytes and squamous cell carcinoma (SCC) cell lines, and in immortalised actinic keratosis (AK) cell lines, using ingenol mebutate and appropriate controls. The MAH should also conduct a literature review of evidence of any potential carcinogenic effects of ingenol mebutate high occupancy targets as identified in the study by *Parker et al.*[17].
- The MAH should submit to EMA the protocols for the observational and interventional studies within 90 and 180 days, respectively.
- In the next PSUR, the MAH should present a summary of all cases of localised skin reactions in which pre-treatment with laser therapy is mentioned, provide a review of all reported cases of urticaria, focusing on any cases in which urticaria occurred away from the treatment area and continue to monitor the literature and report any new findings regarding the potential role in carcinogenesis.

[15] 1. PASS: In order to further investigate the incidence of treatment area skin malignancy, particularly squamous cell carcinoma, the MAH should conduct and submit the results of a randomised, double-blind trial in patients treated with ingenol mebutate compared with vehicle control, over at least 18 months of follow-up. The study should be based on an agreed protocol
2. Non-interventional PASS: In order to investigate the rate of skin malignancies (squamous cell carcinoma, Bowen's disease, basal cell carcinoma, keratoacanthoma, malignant melanoma) in patients with actinic keratosis treated with ingenol mebutate, the MAH should conduct and submit the results of a cohort study comparing patients treated with ingenol mebutate with patients exposed to other actinic keratosis treatments

[16] Update of Annex II of the product information. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

[17] Parker CG et al. Chemical proteomics identifies SLC25A20 (mitochondrial carnitine-acylcarnitine translocase) as a functional target of the ingenol class of actinic keratosis drugs. ACS Cent Sci. 2017; 3(12):1276-1285

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

6.1.6. Lipegfilgrastim - LONQUEX (CAP) - PSUSA/00010111/201807

Applicant: Teva B.V.

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

Background

Lipegfilgrastim is a covalent conjugate of filgrastim with a single methoxy polyethylene glycol (PEG) molecule indicated, as Lonquex, for reduction in the duration of neutropenia and the incidence of febrile neutropenia in patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes).

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Lonquex, a centrally authorised medicine containing lipegfilgrastim 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 Lonquex (lipegfilgrastim) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include nausea as an undesirable effect with a frequency 'very common' and include a description of severe musculoskeletal pain reactions with patients requiring hospitalisation. Therefore, the current terms of the marketing authorisation(s) should be varied[18].

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.

6.1.7. Natalizumab - TYSABRI (CAP) - PSUSA/00002127/201808 (with RMP)

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

Background

Natalizumab is a selective immunosuppressive agent indicated, as Tysabri, as single disease modifying therapy (DMT) in adults with highly active relapsing remitting multiple sclerosis for patients with highly active disease despite a full and adequate course of treatment with at least one DMT or for patients with rapidly evolving severe relapsing remitting multiple

[18] 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

sclerosis defined by two or more disabling relapses in one year, and with one or more gadolinium enhancing lesions on brain magnetic resonance imaging (MRI) or a significant increase in T2 lesion load as compared to a previous recent MRI.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Tysabri, a centrally authorised medicine containing natalizumab 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 Tysabri (natalizumab) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAH should provide a cumulative review of pregnancy and foetal outcomes together with review of the literature according to natalizumab exposure during pregnancy.
- The MAH should submit to EMA, within 30 days, detailed analyses of skin melanoma.

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

6.1.8. Pegaspargase[19] - ONCASPAR (CAP) - PSUSA/00010457/201807 (with RMP)

Applicant: Les Laboratoires Servier

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

Background

Pegaspargase is a modified asparaginase enzyme indicated, as Oncaspar, as a component of antineoplastic combination therapy in acute lymphoblastic leukaemia (ALL).

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Oncaspar, a centrally authorised medicine containing pegaspargase 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 Oncaspar (pegaspargase) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include gamma-glutamyl transferase increased as an undesirable effect with a frequency 'common' and add a warning on traceability of the product in the package leaflet. Therefore, the current terms of the marketing authorisation(s) should be varied[20].
- In the next PSUR, the MAH should provide a cumulative review of cases of dehydration, and consider each event of pain in the light of adverse drug reactions (ADRs) of

[19] Centrally authorised product(s) only
[20] 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

abdominal pain and pain in extremities which are already listed in the product information. In addition, the MAH should discuss the events of anaphylactic shock and provide cumulative reviews of second primary malignancy, tachycardia and hyponatraemia.

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

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

6.2.1. 5-aminolevulinic acid[21] - AMELUZ (CAP); NAP - PSUSA/00010006/201806

Applicants: Biofrontera Bioscience GmbH (Ameluz), various

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

5-aminolevulinic acid is a sensitizer used in photodynamic therapy indicated for the treatment of actinic keratosis of mild to moderate severity on the face and scalp and of field cancerisation in adults, and for the treatment of superficial and/or nodular basal cell carcinoma unsuitable for surgical treatment due to possible treatment-related morbidity and/or poor cosmetic outcome in adults.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Ameluz, a centrally authorised medicine containing 5-aminolevulinic acid, and nationally authorised medicines containing 5-aminolevulinic acid and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

- Based on the PRAC review of data on safety and efficacy, the PRAC considered that the benefit-risk balance of medicinal products containing 5-aminolevulinic acid (plaster formulations) remains unchanged and therefore recommends the maintenance of the marketing authorisation(s).
- Based on the PRAC review of data on safety and efficacy, the PRAC considers that the benefit-risk balance of medicinal products containing 5-aminolevulinic acid (gel formulations) remains unchanged. Nevertheless, the product information should be updated to include application site hypersensitivity as an undesirable effect with frequency 'uncommon'. Additionally, the frequency of transient global amnesia is updated from 'not known' to 'uncommon'. Therefore, the current terms of the marketing authorisations should be varied[22].
- In the next PSUR, the MAH should provide a review and discussion on non-melanoma skin cancer and hypertension.

[21] For treatment of keratosis only
[22] Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

The 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.

6.2.2. Aripiprazole - ABILIFY (CAP); ABILIFY MAINTENA (CAP); ARIPIPRAZOLE SANDOZ (CAP); NAP - PSUSA/00000234/201807

Applicants: Otsuka Pharmaceutical Netherlands B.V. (Abilify, Abilify Maintena), Sandoz GmbH (Aripiprazole Sandoz), various

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

Background

Aripiprazole is an antipsychotic agent indicated for the treatment of schizophrenia, manic or mixed episodes associated with bipolar I disorder, as monotherapy or adjunctive to lithium or valproate. It is also indicated as an adjunctive treatment of major depressive disorder and for the treatment of agitation associated with schizophrenia or bipolar mania.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Abilify, Abilify Maintena and Aripiprazole Sandoz, centrally authorised medicines containing aripiprazole, and nationally authorised medicines containing aripiprazole 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 aripiprazole-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include a warning on the risk of falls. In addition, the product information of aripiprazole-containing product(s) for immediate release should be amended to include oculogyric crisis as an undesirable effect with frequency 'not known'. Therefore, the current terms of the marketing authorisations should be varied[23].
- In the next PSUR, the MAHs should provide a cumulative review of photophobia and related events. The MAH Otsuka Pharmaceutical Netherlands B.V. should discuss the data on serum triglycerides and high-density lipoprotein (HDL) cholesterol levels depending on the administration of aripiprazole in the evening versus in the morning.

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.

[23] Update of SmPC sections 4.4. In addition, update of section 4.8 for aripiprazole-containing product(s) for immediate release is implemented. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

6.3.1. Daunorubicin (NAP) - PSUSA/00000936/201806

Applicant(s): various

PRAC Lead: Daniela Philadelphy

Scope: Evaluation of a PSUSA procedure

Background

Daunorubicin is an anthracycline cytostatic antineoplastic agent indicated for the treatment of acute myelogenous leukaemia (AML), acute lymphocytic leukaemias (ALL), erythroleukaemia, chronic myelogenous leukaemia (CML), non-Hodgkin's lymphoma and Hodgkin's lymphoma and treatment of acquired immune deficiency syndrome (AIDS)-related Kaposi's sarcoma.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing daunorubicin 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 daunorubicin-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning on the occurrence of posterior reversible encephalopathy syndrome (PRES) when daunorubicin is used in combination chemotherapy and to include a clarification in the existing text on the undesirable effect of infections. Therefore, the current terms of the marketing authorisation(s) should be varied[24].

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

6.3.2. Ibuprofen, pseudoephedrine (NAP) - PSUSA/00001711/201807

Applicant(s): various

PRAC Lead: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

Background

Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID) with analgesic, antipyretic and anti-inflammatory properties. Pseudoephedrine is a sympathomimetic agent which, when administered systemically, acts as a nasal decongestant. Ibuprofen/pseudoephedrine is indicated for the symptomatic relief of nasal and/or sinus congestion with headache, fever and pain associated with the common cold and flu.

[24] 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

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing ibuprofen/pseudoephedrine 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 ibuprofen/pseudoephedrine-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning on ischaemic colitis and to add ischaemic colitis as an undesirable effect with frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[25].
- The PRAC considered the risk of ischaemic colitis to be also relevant for single agent or fixed dose combinations containing pseudoephedrine. Further consideration is to be given at the level of the CMDh.
- In the next PSUR, the MAHs should provide a cumulative review of cases of ischemia with the MedDRA SOC[26] 'eye disorders' reported with ibuprofen/pseudoephedrine-containing products and provide a cumulative review of pulmonary arterial hypertension.

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. Manidipine (NAP) - PSUSA/00001932/201806

Applicant(s): various

PRAC Lead: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

Background

Manidipine is a long-acting calcium channel inhibitor indicated for the treatment of hypertension.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing manidipine 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 manidipine-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include myalgia and gynaecomastia as undesirable effects with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[27].

[25] 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
[26] Medical Dictionary for Regulatory Activities Terminology – System Organ Class

- In the next PSUR, the MAHs should provide an updated review of the cases of photosensitivity. The MAHs should monitor and discuss cases of extrapyramidal syndrome, cases of peripheral oedema and pulmonary oedema in pregnant women treated off-label for tocolysis.

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. Metyrapone (NAP) - PSUSA/00002046/201806

Applicant(s): various

PRAC Lead: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

Background

Metyrapone is a diagnostic and therapeutic agent which inhibits the biosynthesis of cortisol and to a lesser extent aldosterone, indicated for the differential diagnosis of adrenocorticotropic hormone (ACTH)-dependent Cushing's syndrome and for the treatment of patients with Cushing's syndrome.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing metyrapone 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 metyrapone-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to replace the undesirable effect bone marrow failure by leukopenia, anaemia and thrombocytopenia with a frequency 'not known'. The information on the treatment of overdose is to be also updated in line with current treatment guidelines for routine poisoning management. Therefore, the current terms of the marketing authorisation(s) should be varied[28].

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. Paracetamol, pseudoephedrine (NAP) - PSUSA/00002307/201806

Applicant(s): various

PRAC Lead: Laurence de Fays

Scope: Evaluation of a PSUSA procedure

[27] 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
[28] Update of SmPC sections 4.8 and 4.9. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

Background

Paracetamol is an analgesic and antipyretic indicated for the treatment of mild to moderate pain and febrile conditions e.g. headache, toothache, colds, influenza, rheumatic pain and dysmenorrhoea. Pseudoephedrine is a sympathomimetic agent which, when administered systemically, acts as a nasal decongestant. Paracetamol/pseudoephedrine is indicated for the symptomatic relief of the symptoms of cold and flu symptoms and nasal/sinus congestion (blocked nose and sinuses).

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing paracetamol/pseudoephedrine 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/pseudoephedrine-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning on ischaemic colitis and to add ischaemic colitis as an undesirable effect with frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[29].
- In the next PSUR, the MAH should include, if not already done, ischaemic conditions including ischaemic colitis and concomitant use with sympathomimetics and vasoconstrictive medicinal agents (as important identified risks) and myocardial infarction or neurovascular events (as important potential risk) and use in pregnancy and lactation as missing information in the summary of safety concerns.

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

6.3.6. Pseudoephedrine (NAP); acetylsalicylic acid, pseudoephedrine (NAP) - PSUSA/00010667/201806

Applicant(s): various

PRAC Lead: Maia Uusküla

Scope: Evaluation of a PSUSA procedure

Background

Pseudoephedrine is a sympathomimetic agent which, when administered systemically, acts as a nasal decongestant and is indicated for the symptomatic relief of conditions such as allergic rhinitis, vasomotor rhinitis, the common cold and influenza. Acetylsalicylic acid is a nonsteroidal anti-inflammatory agent with analgesic, antipyretic and anti-inflammatory properties. In combination, acetylsalicylic acid/pseudoephedrine is indicated for the symptomatic relief of the symptoms of colds and influenza including feverishness, aches and pains, headache, nasal and sinus congestion (blocked nose and sinuses).

[29] 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

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing pseudoephedrine and acetylsalicylic acid/pseudoephedrine 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 pseudoephedrine- and acetylsalicylic acid/pseudoephedrine-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning on ischaemic colitis and to add ischaemic colitis as an undesirable effect with frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[30].
- In the next PSUR, the MAHs should discuss the risk of stroke, myocardial infarction and myocardial ischaemia in patients with pre-existing cardiovascular diseases. The MAHs should include, if not already done, ischaemic colitis and concomitant use with sympathomimetics and vasoconstrictive medicinal agents (as important identified risks) and cardiovascular events including stroke, myocardial infarction or myocardial ischaemia (as important potential risk) in the summary of safety concerns.

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. Rabbit anti-human T-lymphocyte immunoglobulin (NAP) - PSUSA/00010252/201806

Applicant(s): various

PRAC Lead: Maia Uusküla

Scope: Evaluation of a PSUSA procedure

Background

Rabbit anti-human T-lymphocyte immunoglobulin is a concentrated, highly purified, polyclonal anti-human T-lymphocyte immunoglobulin preparation derived from rabbits indicated for the prevention and treatment of graft rejection after solid organ transplantation (SOT), prevention of acute and chronic graft-versus-host disease (GvHD) after haematopoietic stem cell transplantation (HSCT), the treatment of steroid resistant, acute GvHD and for the treatment of aplastic anaemia.

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

[30] 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

- Nevertheless, the product information should be updated to include as undesirable effects hyperbilirubinaemia with frequency 'not known' and anaemia with frequency 'very common'. Therefore, the current terms of the marketing authorisation(s) should be varied[31].
- In the next PSUR, the MAHs should monitor and provide a cumulative review on the occurrence of bradycardia during treatment with rabbit anti-human T-lymphocyte immunoglobulin.

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. Tianeptine (NAP) - PSUSA/00002943/201806

Applicant(s): various

PRAC Lead: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

Background

Tianeptine is an antidepressant indicated for the treatment of major depressive episodes (MDE) in adults.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing tianeptine 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 tianeptine-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning on withdrawal symptoms and hyponatremia. Therefore, the current terms of the marketing authorisation(s) should be varied[32].
- In the next PSUR, the MAHs should provide publications reporting cases of drug abuse related to tianeptine and assess any potential relevant safety findings.

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

6.4. Follow-up to PSUR/PSUSA procedures

See also Annex I 16.4.

[31] 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
[32] Update of SmPC sections 4.2 and 4.4. The package leaflet is updated accordingly. he PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

6.4.1. Fingolimod - GILENYA (CAP) - EMEA/H/C/002202/LEG 037

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ghania Chamouni

Scope: Review of the potential benefit of Gilenya (fingolimod) use in pregnant women and women of child-bearing potential (WCBP) not using effective contraception, as well as up-to-date information on reproductive toxicity, as requested in the conclusions of PSUSA/00001393/201802 adopted in September 2018

Background

Fingolimod is a sphingosine 1-phosphate receptor modulator indicated, as Gilenya a centrally authorised medicine, as single disease modifying therapy in highly active relapsing remitting multiple sclerosis (RRMS) in adult patients and paediatric patients aged 10 years and older with highly active disease despite a full and adequate course of treatment with at least one disease modifying therapy (DMT), or with rapidly evolving severe RRMS defined by 2 or more disabling relapses in one year, and with 1 or more gadolinium enhancing lesions on brain magnetic resonance imaging (MRI) or a significant increase in T2 lesion load as compared to a previous recent MRI.

Following the evaluation of the most recently submitted PSUR(s) for the above mentioned medicine(s), the PRAC requested the MAH to submit further data on the potential benefit of Gilenya (fingolimod) use in pregnant women and women of child-bearing potential (WCBP) not using effective contraception. For further background, see PRAC minutes September 2018 and PRAC minutes January 2019.

Summary of advice/conclusion(s)

- The PRAC discussed the responses from the Scientific Advisory Group on Neurology (SAG-N) held on 4 February 2019 to the list of questions (LoQ) adopted by the PRAC.
- Based on the review of the available information and the feedback from the SAG-N, the PRAC agreed to request an update of the product information to include a contraindication in pregnant women and women of childbearing potential (WCBP) not using effective contraception. In addition, the product information should be updated to include a warning on the need for an effective contraception in WCBP, a pregnancy test before initiating treatment with fingolimod and further information regarding the 2-fold increase risk of malformation and the types of malformations[33].
- In terms of additional risk minimisation measures (aRMM), the PRAC also considered the need for a pregnancy prevention programme (PPP). To this end, the MAH should update the existing physician checklist with information on malformative risk with fingolimod, contraindications and the need for patient counselling before treatment initiation. The MAH should introduce a specific patient card dedicated to pregnancy. Furthermore, the MAH should update the existing general patient card to introduce information regarding the contraindication and to make a reference to the specific pregnancy patient card.
- In view of the new additional and routine RMMs proposed and in addition to the existing ongoing pharmacovigilance activities, taking into account revision 2 of GVP module XVI on 'risk minimisation measures: selection of tools and effectiveness indicators', the MAH

[33] Update of SmPC sections 4.3, 4.4 and 4.6. The package leaflet is to be updated accordingly

should present these measures in the context of a PPP. The RMP, educational material and Annex II-D on 'conditions or restrictions with regard to the safe and effective use of the medicinal product' are to be updated accordingly.

- Finally, the PRAC considered that the MAH should provide a direct healthcare professional communication (DHPC) and communication plan for review to inform healthcare professionals (HCPs) on this new risk in humans and the implementation of the PPP and its related risk minimisation measures.

7. Post-authorisation safety studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)[34]

See also Annex I 17.1.

7.1.1. Blinatumomab - BLINCYTO (CAP) - EMEA/H/C/PSP/S/0071

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Eva Jirsová

Scope: Protocol for study 20180130: an observational PASS to describe the long-term safety profile of first-relapse B-precursor acute lymphoblastic leukaemia (ALL) paediatric patients who have been treated with blinatumomab or chemotherapy prior to undergoing haematopoietic stem cell transplant

Background

Blinatumomab is a bispecific T-cell engager antibody, indicated as Blincyto, a centrally authorised medicine, as monotherapy for the treatment of adults with Philadelphia chromosome negative CD[35]19 positive relapsed or refractory B-precursor acute lymphoblastic leukaemia (ALL). It is also indicated as monotherapy for the treatment of paediatric patients aged 1 year or older with Philadelphia chromosome negative CD19 positive B-cell precursor ALL which is refractory or in relapse after receiving at least two prior therapies or in relapse after receiving prior allogeneic hematopoietic stem cell transplantation.

The obligation to conduct a PASS for the MAH of Blincyto (blinatumomab) was imposed as a condition of the marketing authorisation(s) when the paediatric indication was granted in 2018. In order to fulfil the obligation to conduct a PASS imposed in accordance with Article 107n(3) of Directive 2001/83/EC, the MAH submitted PASS protocol version 1 for a non-interventional observational study of blinatumomab aiming to investigate the long-term safety profile of blinatumomab in children, by providing 12 years of follow-up of patients treated with either blinatumomab or chemotherapy followed by hematopoietic stem cell transplantation (HSCT).

Endorsement/Refusal of the protocol

- The PRAC, having reviewed PASS protocol version 1 and in accordance with Article 107n of Directive 2001/83/EC, considered that the PASS is non-interventional but the study

[34] In accordance with Article 107n of Directive 2001/83/EC
[35] Cluster of differentiation

design does not fulfil the study objectives at this stage. The protocol for Blincyto (blinatumomab) PASS could be acceptable provided that satisfactory responses are provided regarding in particular the feasibility to recruit a sufficient number of patients in the study and the measurement of psychomotor development and other development impairment.

- The MAH should submit a revised PASS protocol within 60 days to the EMA. A 60 day-assessment timetable will be followed.

7.1.2. Damoctocog alfa pegol - JIVI (CAP) - EMEA/H/C/PSP/S/0070

Applicant: Bayer AG

PRAC Rapporteur: Menno van der Elst

Scope: Protocol for an observational study to assess the effectiveness and long term safety of prophylaxis with damoctocog alfa pegol in real-world settings through the collection of total bleeding events and analysis of the annualised bleeding rate (ABR) in the different prophylaxis regimens (following approved local label or any other regimen prescribed by the physician as part of normal clinical practice) in patients with haemophilia A

Background

Damoctocog alfa pegol is a PEGylated[36] form of recombinant factor VIII (rFVIII) indicated, as Jivi, a centrally authorised medicine, for the treatment and prophylaxis of bleeding in previously treated patients ≥ 12 years of age with haemophilia A (congenital factor VIII deficiency).

The obligation to conduct a PASS for the MAH of Jivi (damoctocog alfa pegol) was imposed as a condition of the marketing authorisation(s) in order to provide long-term safety data to investigate the potential effects of PEG accumulation in the choroid plexus of the brain and other tissues/organs. In order to fulfil the obligation to conduct a PASS imposed in accordance with Article 107n(3) of Directive 2001/83/EC, the MAH submitted PASS protocol version 1.0 for an observational study evaluating the effectiveness and safety of real-world treatment with damoctocog alfa pegol in previously treated patients with haemophilia A (HEM-POWR).

Endorsement/Refusal of the protocol

- The PRAC, having reviewed PASS protocol version 1.0, and in accordance with Article 107n of Directive 2001/83/EC, considered that the PASS is non-interventional but, the study design does not fulfil the study objectives at this stage. The protocol for Jivi (damoctocog alfa pegol) PASS could be acceptable provided that satisfactory responses are provided regarding in particular the need to review the research questions and objectives. Notably, the MAH should review the proposed primary objective of the study and ensure it is replaced with assessment of the long term safety of prophylaxis with damoctocog alfa pegol in patients with haemophilia A in the real-world setting through the collection and analysis of adverse events (AEs) of special interest potentially indicative of PEG accumulation (hypersensitivity reactions, loss of drug effect, renal impairment, neurocognitive disorders, and inhibitor development), AEs, serious adverse

[36] Polyethylene glycol

events (SAEs) and adverse reactions (ARs). The study design should be further adjusted.

- The MAH should submit a revised PASS protocol within 60 days to the EMA. A 60 day-assessment timetable will be followed.

7.1.3. Valproate (NAP) - EMEA/H/N/PSP/J/0072

Applicant: Sanofi-aventis Recherche & Development (on behalf of a consortium)

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Protocol for a retrospective observational study to investigate the association between paternal exposure to valproate and the risk of congenital anomalies and neurodevelopmental disorders including autism in offspring, as required in the outcome of the referral procedure under Article 31 of Directive 2001/83/EC on valproate-containing products completed in February 2018 (EMEA/H/A-31/1454)

Background

Sodium valproate is indicated for the treatment of epilepsy and for the treatment of manic episodes when lithium is contraindicated or not tolerated. Valproate is also indicated in some EU Member States in prophylaxis of migraine attacks.

In line with the conclusions reached in 2018 of the referral procedure under Article 31 of Directive 2001/83/EC (EMEA/H/A-31/1454) conducted by the PRAC for valproate-containing medicines, MAHs were required as a condition to the marketing authorisation(s) (Annex IV) to conduct a retrospective observational study to investigate the association between paternal exposure to valproate and the risk of congenital anomalies and neurodevelopmental disorders including autism in the offspring. For further background, see PRAC minutes February 2018.

The MAH Sanofi-Aventis Recherche & Développement on behalf of a consortium submitted to EMA protocol version 1.0 of a PASS entitled: 'evaluation of paternal exposure to valproate and the risk of congenital abnormalities and neurodevelopmental disorders including autism spectrum disorders in children – a population-based retrospective study'.

Endorsement/Refusal of the protocol

- The PRAC considered that the choice of the study design is in line with the condition to the marketing authorisation(s). Nevertheless, the PRAC agreed that clarifications and complementary information are needed before drawing final conclusions on the protocol. The consortium of MAHs is requested to implement major amendments to the PASS protocol to adjust the study objectives, design and setting, definition of variables, study size and statistical analysis plan.
- The MAH should submit a revised PASS protocol within 60 days to the EMA. A 60 day-assessment timetable will be followed.

7.1.4. Valproate (NAP) - EMEA/H/N/PSP/J/0073

Applicant: Sanofi-aventis Recherche & Development (on behalf of a consortium)

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Protocol for a survey among healthcare professionals (HCP) to assess the knowledge

of HCP and behaviour with regard to the pregnancy prevention programme (PPP), the receipt/use of direct healthcare professional communication (DHPC) and educational materials as well as for a survey among patients to assess the knowledge of patients with regards to PPP and receipt/use of educational materials, as required in the outcome of the referral procedure under Article 31 of Directive 2001/83/EC on valproate-containing products completed in February 2018 (EMEA/H/A-31/1454)

Background

Sodium valproate is indicated for the treatment of epilepsy and for the treatment of manic episodes when lithium is contraindicated or not tolerated. Valproate is also indicated in some EU Member States in prophylaxis of migraine attacks.

In line with the conclusions reached in 2018 of the referral procedure under Article 31 of Directive 2001/83/EC (EMEA/H/A-31/1454) conducted by the PRAC for valproate-containing medicines, MAHs were required as a condition to the marketing authorisation(s) (Annex IV) to measure the effectiveness of the risk minimisation measures set to avoid exposure of offspring to valproate medicines in the womb due to the risk of malformations and developmental problems. For further background, see PRAC minutes February 2018.

The MAH Sanofi-Aventis Recherche & Développement on behalf of a consortium submitted to EMA protocol version 1.0 of a PASS entitled: 'surveys among healthcare professionals (HCPs) and patients to assess their knowledge and behaviour with respect to the new (2018) risk minimisation measures for valproate use in Europe'.

Endorsement/Refusal of the protocol

- The PRAC agreed that clarifications and complementary information are needed before drawing final conclusions on the protocol. The consortium of MAHs is requested to amend the protocol to ensure that inclusion of additional HCPs is in line with the target group, the sample size for the HCP survey is increased, additional EU Member States are included, exclusion/inclusion criteria for recruiting patients are refined as well as the pre-defined success criteria/threshold levels are provided.
- The MAH should submit a revised PASS protocol within 60 days to the EMA. A 60 day-assessment timetable will be followed.

7.1.5. Valproate (NAP) - EMEA/H/N/PSP/J/0074

Applicant: Sanofi-aventis Recherche & Development (on behalf of a consortium)

PRAC Rapporteur: Jean-Michel Dogné

Scope: Protocol for an observational study to evaluate and identify the best practices for switching of valproate in clinical practice, as required in the outcome of the referral procedure under Article 31 of Directive 2001/83/EC on valproate-containing products completed in February 2018 (EMEA/H/A-31/1454)

Background

Sodium valproate is indicated for the treatment of epilepsy and for the treatment of manic episodes when lithium is contraindicated or not tolerated. Valproate is also indicated in some EU Member States in prophylaxis of migraine attacks.

In line with the conclusions reached in 2018 of the referral procedure under Article 31 of Directive 2001/83/EC (EMEA/H/A-31/1454) conducted by the PRAC for valproate-containing medicines, MAHs were required as a condition to the marketing authorisation(s) (Annex IV) to conduct an observational study to evaluate and identify the best practices for switching of valproate in clinical practice. For further background, see PRAC minutes February 2018.

The MAH Sanofi-Aventis Recherche & Développement on behalf of a consortium submitted to EMA protocol version 1.0 of a PASS entitled: 'a non-interventional retrospective longitudinal study in the UK and France to evaluate and identify the best practices for switching of valproate and related substances in clinical practice'.

Endorsement/Refusal of the protocol

- The PRAC agreed that clarifications and complementary information are needed before drawing final conclusions on the protocol. The consortium of MAHs is requested to amend the protocol including a refined primary objective, description of 'treatment patterns' for valproate switching, a revised statistical analysis plan, and clarifications on valproate withdrawal and follow-up period as well as data available in the databases.
- The MAH should submit a revised PASS protocol within 60 days to the EMA. A 60 day-assessment timetable will be followed.

7.1.6. Valproate (NAP) - EMEA/H/N/PSP/J/0075

Applicant: Sanofi-aventis Recherche & Development (on behalf of a consortium)

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Protocol for a drug utilisation study (DUS) to assess the effectiveness of the new risk minimisation measures and to further characterise the prescribing patterns for valproate as required in the outcome of the referral procedure under Article 31 of Directive 2001/83/EC on valproate-containing products completed in February 2018 (EMEA/H/A-31/1454)

Background

Sodium valproate is indicated for the treatment of epilepsy and for the treatment of manic episodes when lithium is contraindicated or not tolerated. Valproate is also indicated in some EU Member States in prophylaxis of migraine attacks.

In line with the conclusions reached in 2018 of the referral procedure under Article 31 of Directive 2001/83/EC (EMEA/H/A-31/1454) conducted by the PRAC for valproate-containing medicines, MAHs were required as a condition to the marketing authorisation(s) (Annex IV) to adapt and continue the ongoing drug utilisation study (DUS) to assess the effectiveness of the updated risk minimisation measures including the pregnancy prevention programme conditions and to further characterise the prescribing patterns for valproate with a pre- and post-implementation analysis. For further background, see PRAC minutes February 2018.

The MAH Sanofi-Aventis Recherche & Développement on behalf of a consortium submitted to EMA a protocol version 1.0 for a drug utilisation study extension of valproate and related substances in Europe, using databases.

Endorsement/Refusal of the protocol

- The PRAC agreed that clarifications and complementary information are needed before drawing final conclusions on the protocol. The consortium of MAHs is requested to amend the protocol by amending the study objectives, the proposed data sources, the study design (i.e. the exact study periods to be used in the analyses), the data sources (i.e. suitability of the newly proposed French database; consideration for inclusion of South and East-European country database) and the alignment between defined objectives and the proposed data analysis.
- 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)[37]

See also Annex I 17.2.

7.2.1. Obinutuzumab - GAZYVARO (CAP) - EMEA/H/C/002799/MEA 007.1

Applicant: Roche Registration GmbH

PRAC Rapporteur: Annika Folin

Scope: Protocol for study BO41031: a survey to prescribers, with the objective to evaluate the effectiveness of Gazyvaro (obinutuzumab) routine risk minimisation activities of important identified risks in the SmPC by investigating healthcare professionals' (HCPs) awareness and knowledge of the important identified risks of infusion related reactions (IRR), tumour lysis syndrome (TLS), thrombocytopenia, worsening of pre-existing cardiac conditions, progressive multifocal leukoencephalopathy (PML), hepatitis B virus (HBV) reactivation, neutropenia and infection

Background

Obinutuzumab is a recombinant monoclonal humanised and glycoengineered type II anti-CD[38]20 antibody of the immunoglobulin G1 (IgG1) isotype. It is indicated, as Gazyvaro, a centrally authorised medicine, in combination with chlorambucil for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL) and with comorbidities making them unsuitable for full-dose fludarabine based therapy. It is also indicated in combination with bendamustine followed by obinutuzumab maintenance for the treatment of patients with follicular lymphoma (FL) who did not respond or who progressed during or up to 6 months after treatment with rituximab or a rituximab-containing regimen.

As part of the RMP for Gazyvaro (obinutuzumab), the MAH planned to conduct a survey to prescribers as an effectiveness measure to investigate the awareness and knowledge of obinutuzumab label and guidance among prescribers of the important identified risks of infusion related reactions (IRR), tumour lysis syndrome (TLS), thrombocytopenia, worsening of pre-existing cardiac conditions, progressive multifocal leukoencephalopathy (PML), hepatitis B (HBV) reactivation, neutropenia and infections, together with their risk minimisation measures (RMMs).

[37] 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
[38] Cluster of differentiation

The MAH submitted a protocol for Gazyvaro (obinutuzumab) for the evaluation of this survey which was assessed by the Rapporteur. The PRAC was requested to provide advice to CHMP on the protocol submitted by the MAH.

Summary of advice

- The PRAC considered that the survey does not adequately answer the relevant question of effectiveness of the RMMs on a patient level in daily clinical practice. In addition, the PRAC expressed concern regarding potential promotional aspects. Therefore, the Committee did not consider the survey of relevance from a safety perspective and advised to have it removed from the RMP. An updated RMP should be submitted accordingly at the next regulatory opportunity.

7.3. Results of PASS imposed in the marketing authorisation(s)[39]

None

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

See Annex I 17.4.

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

See Annex I 17.5.

7.6. Others

See Annex I 17.6.

7.7. New Scientific Advice

None

7.8. Ongoing Scientific Advice

None

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

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.

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

8.2. Conditional renewals of the marketing authorisation

See Annex I 18.2.

8.3. Renewals of the marketing authorisation

See Annex I 18.3.

9. Product related pharmacovigilance inspections

9.1. List of planned pharmacovigilance inspections

None

9.2. Ongoing or concluded pharmacovigilance inspections

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

9.3. Others

None

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

10.1. Safety related variations of the marketing authorisation

10.1.1. Cobicistat - TYBOST (CAP) - EMEA/H/C/002572/WS1401/0044; cobicistat, elvitegravir, emtricitabine, tenofovir alafenamide - GENVOYA (CAP) - EMEA/H/C/004042/WS1401/0047; Cobicistat, elvitegravir, emtricitabine, tenofovir disoproxil - STRIBILD (CAP) - EMEA/H/C/002574/WS1401/0094

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Amelia Cupelli

Scope: Consultation on a type II variation to update section 4.6 the SmPC for Tybost (cobicistat), Stribild (cobicistat/elvitegravir/emtricitabine/tenofovir disoproxil) and Genvoya (cobicistat/elvitegravir/emtricitabine/tenofovir alafenamide) based on pharmacokinetics data in pregnancy from study P1026s (NCT00042289 or IMPAACT): an ongoing, non-randomized, open-label, parallel-group, multicentre phase 4 prospective study of antiretroviral (ARV) pharmacokinetics (PK) and safety in human immunodeficiency virus-1 (HIV-1) infected pregnant women that includes an arm for elvitegravir/cobicistat (EVG/COBI). The package leaflet is updated accordingly. In addition, the MAH took the opportunity to bring the product information in line with the latest QRD template (version 10)

Background

Cobicistat is CYP3A[41] inhibitor and is indicated, as Tybost, a centrally authorised medicine, as a pharmacokinetic enhancer of atazanavir 300 mg once daily or darunavir 800 mg once daily as part of antiretroviral combination therapy in human immunodeficiency virus-1 (HIV-1) infected adults.

Elvitegravir is an HIV-1 integrase strand transfer inhibitor (INSTI) and emtricitabine a nucleoside analogue of cytidine. Tenofovir alafenamide is converted *in vivo* to tenofovir, a nucleoside monophosphate (nucleotide) analogue of adenosine monophosphate. Cobicistat/elvitegravir/emtricitabine/tenofovir disoproxil in combination as Stribild and cobicistat/elvitegravir/emtricitabine/tenofovir alafenamide as Genvoya, centrally authorised medicines, are indicated for the treatment of HIV-1 infection without any known mutations associated with resistance to any of the three antiretroviral agents under certain conditions.

A worksharing variation proposing to update the product information of Tybost (cobicistat), Stribild (cobicistat/elvitegravir/emtricitabine/tenofovir disoproxil) and Genvoya (cobicistat/elvitegravir/emtricitabine/tenofovir alafenamide) to reflect pharmacokinetic data in pregnancy based on results from study IMPAACT is under evaluation at the CHMP. The PRAC was requested to provide advice on this variation.

Summary of advice

- Based on the review of the available information, the PRAC agreed on the distribution of a direct healthcare professional communication (DHPC) in order to warn healthcare professionals (HCPs) of an increased risk of treatment failure and an increased risk of mother to child transmission of HIV infection due to low exposure values of cobicistat and elvitegravir during the second and third trimesters of pregnancy. Therefore, HCPs should not initiate cobicistat/elvitegravir in pregnancy and alternative regimens are to be used. The PRAC agreed the content of the DHPC together with a communication plan.

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.

[41] Cytochrome P450 subfamily 3A4

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

11.1. Safety related variations of the marketing authorisation

11.1.1. Leuprorelin (NAP) - DE/H/0580/001-003/II/077, DE/H/0580/001-003/II/078

Applicant: Astellas Pharma (Eligard)

PRAC Lead: Martin Huber

Scope: PRAC consultation on national variations on RMP updates proposing the removal of additional risk minimisation measure (aRMM) on the development of a new product presentation, the addition of new risk minimisation measures and pharmacovigilance activities updating the product information with monitoring the response to Eligard (leuprorelin) by measuring the serum concentrations of testosterone, on request of Germany

Background

Leuprorelin is a gonadotrophin-releasing hormone (GnRH) analogue indicated for the treatment of advanced hormone-dependent prostate cancer.

In 2014, a signal of 'wrong technique in drug usage process' (EPITT 17753) leading to lack of efficacy for Eligard (leuprorelin) with a new safety needle was concluded at PRAC. Since 2014, several risk minimisation measures (RMMs) have been introduced to reduce the number of handling errors. The current device was modified to reduce handling errors due to a stopper remaining in the device, educational material (poster, video, website) was introduced and the product information updated. Although the number of cases of handling errors was reduced, cases were still reported. Therefore, further measures were put in place, i.e. update of the existing educational materials, introduction of QR[42] codes into the product information and poster. For further background, see PRAC minutes November 2014 and PRAC minutes November 2017 (23-26 October 2017).

In order to identify patients experiencing lack of efficacy after administration of Eligard (leuprorelin) and to allow for early intervention, variations are currently assessed to further update the product information with recommendations for intensified serum testosterone monitoring and to distribute a direct healthcare professional communication (DHPC) together with further updated educational materials. In addition, a PASS was proposed to evaluate the effectiveness of the RMMs and to evaluate the occurrence of lack of efficacy in patients treated with Eligard in comparison to other leuprorelin-containing products. Germany requested PRAC advice on its assessment.

Summary of advice

- Based on the review of the available information, the PRAC supported to request the MAH to provide further analyses regarding the nature of medication errors leading to lack of efficacy. In addition, the PRAC expressed a number of concerns with regards to the proposed PASS (e.g. no collection of information of medication errors, lack of link between handling errors and lack of efficacy, interventional nature of the study creating

[42] Quick Response

bias). Therefore, it was considered that the proposed PASS is unlikely to provide decision-relevant information in a timely manner and therefore, it was not supported at this stage. It was also considered that the further review will inform the need for a PASS or any further regulatory actions. Furthermore, the Committee highlighted that the proposed recommendation for intensified monitoring of serum testosterone is unlikely to reduce the risk of medication errors, but is rather likely to allow for an early detection of a potential lack of efficacy in order for healthcare professionals (HCPs) to take appropriate action. At this stage, the PRAC considered it was premature to distribute a DHPC. The PRAC advised that this new measure should be re-evaluated after a thorough review of the data. As an outcome of the review, the PRAC also advised to consider the need for further additional measures.

11.2. Other requests

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

Applicant: Pfizer Ltd (Ator, Ator Pfizer, Atorvasa, Atorvastatin Pfizer, Liprimar, Sortis)

PRAC Lead: Martin Huber

Scope: PRAC consultation on a worksharing PSUR follow-up (PSU FU) procedure on the safety concern of 'muscle rupture/torn muscle' 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 selective, potent and competitive inhibitor of 3-hydroxy 3-methylglutaryl coenzyme A (HMG-CoA) reductase, and is indicated for the prevention of cardiovascular diseases and 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 'muscle rupture/torn muscle' needed to be further assessed. For further background, see PRAC minutes June 2018. The originator MAH for atorvastatin-containing product(s) was requested by CMDh to submit safety reviews of cases of 'muscle rupture/ torn muscle' from clinical studies, post-marketing exposure and literature, together with a thorough discussion of the possible patho-mechanisms, as part of a worksharing PSUR follow-up (PSU FU) procedure. In the context of the evaluation of the worksharing PSU FU procedure, Germany 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 and concurred that there was sufficient available evidence at this stage to support a possible causal relationship between 'muscle rupture' with atorvastatin. As a consequence, the PRAC supported the conclusion of the LMS to update the product information in order to include 'muscle rupture' as an undesirable effect with a frequency 'rare'.
- The PRAC agreed with the LMS that MAHs of atorvastatin-fixed dose combination (FDC) medicinal products should be requested to add to their product information 'muscle rupture' as an undesirable effect.

12. Organisational, regulatory and methodological matters

12.1. Mandate and organisation of the PRAC

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

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

In line with the adopted PRAC best practice guidance (BPG) on Committee efficiency (see PRAC minutes May 2016 and PRAC minutes June 2018) and the adopted implementation plan for the BPG including goals to measure compliance with the recommendations (see PRAC minutes June 2016 and PRAC minutes June 2018), the PRAC was updated at the organisational matters teleconference held on 28 February 2019 on quantitative measures collected for the fourth 2018 quarter of PRAC meetings. For previous update, see PRAC minutes November 2018 (29-31 October 2018).

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. European Network Training Centre (EU NTC) - Pharmacovigilance - Training curriculum (TC) – Strategy for 2019

The EMA Secretariat updated the PRAC on the training opportunities being made available to the European regulatory network through the European Network Training Centre (EU NTC) and specifically on the EU NTC learning management system. For further background, see PRAC minutes June 2018. An overview of planned trainings for 2019 was presented. As next steps, the PRAC was informed that currently the 'Operation of Pharmacovigilance in the EU' (EU PVOP) training curriculum is in the process of identifying new topic area leads, in collaborating in the organisation of events concerning relevant areas (e.g. yearly PRAC trainings to assessors) and in continuing identifying existing training programmes at National Competent Authorities (NCA) and network levels. The PRAC will be kept informed on a regular basis.

12.5. Cooperation with International Regulators

None

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

None

12.7. PRAC work plan

None

12.8. Planning and reporting

12.8.1. PRAC workload statistics – Q4 2018

The EMA secretariat presented, at the organisational matters teleconference held on 28 February 2019, quarterly and cumulative figures to estimate the evolution of the workload of the PRAC, by reflecting on the number of procedures and agenda items covered at each PRAC plenary meeting. See previous update, PRAC minutes November 2018 (29-31 October 2018).

12.9. Pharmacovigilance audits and inspections

12.9.1. Pharmacovigilance systems and their quality systems

None

12.9.2. Pharmacovigilance inspections

None

12.9.3. Pharmacovigilance audits

None

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

12.10.1. Periodic safety update reports

None

12.10.2. Granularity and Periodicity Advisory Group (GPAG)

PRAC lead: Menno van der Elst, Maia Uusküla

The PRAC was updated on the activities of the GPAG, focussing on harmonising and streamlining the EURD list. The PRAC endorsed the GPAG work plan 2019.

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 February 2019, reflecting the PRAC's comments impacting on the data lock point (DLP) and PSUR submission frequencies of the substances/combinations. The PRAC endorsed the newly allocated Rapporteurs for

upcoming PSUSAs in accordance with the principles previously endorsed by the PRAC (see PRAC minutes April 2013).

Post-meeting note: following the PRAC meeting in February 2019, the updated EURD list was adopted by the CHMP and CMDh at their February 2019 meetings and published on the EMA website on 06/03/2019, see:

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

12.11. Signal management

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

PRAC lead: Menno van der Elst

The PRAC was updated on the outcome of the SMART Working Group (SMART WG) Processes meeting held on 11 February 2019. The SMART WG initiated a discussion on signals and effectiveness of risk minimisation measures (RMM) and also interference of drugs with laboratory tests. Follow-up discussion is planned in April 2019.

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 27/02/2019 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

12.13.2. EudraVigilance – annual report 2018

At the organisational matters teleconference on 28 February 2019, the EMA secretariat presented to the PRAC the 2018 EudraVigilance annual report for the European Parliament, the Council and the Commission in line with Article 24(2), paragraph 2 of Regulation (EC) No. 726/2004. Following the next EMA Management Board meeting in March 2019, the report will be submitted to the EU institutions and published on the EMA website.

Post-meeting note: On 27 March 2019, the EudraVigilance annual report 2018 (EMA/906394/2019) was published on the EMA website.

12.14. Risk management plans and effectiveness of risk minimisations

12.14.1. Risk management systems

None

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

None

12.15. Post-authorisation safety studies (PASS)

12.15.1. Post-authorisation Safety Studies – imposed PASS

None

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

None

12.16. Community procedures

12.16.1. Referral procedures for safety reasons

None

12.17. Renewals, conditional renewals, annual reassessments

None

12.18. Risk communication and transparency

12.18.1. Public participation in pharmacovigilance

None

12.18.2. Safety communication

None

12.19. Continuous pharmacovigilance

12.19.1. Incident management

None

12.20. Others

12.20.1. Guideline on good pharmacovigilance practices (GVP) Product- or Population-Specific considerations III: risk management in pregnant and breastfeeding women

The topic was postponed to May/June 2019.

12.20.2. EMA relocation to Amsterdam, the Netherlands – Questions & Answers (Q&As)

As a follow-up to previous presentations on the EMA relocation in 2019 to Amsterdam, the Netherlands (for further background, see PRAC minutes July 2018 and PRAC minutes December 2018 (26-29 November 2018)), the EMA Secretariat further updated the PRAC on the new meeting premises in the interim building in Amsterdam in use as of March 2019. The EMA Secretariat shared with PRAC the orientation guide for delegates.

13. Any other business

None

14. Annex I – Signals assessment and prioritisation[43]

14.1. New signals detected from EU spontaneous reporting systems

As per agreed criteria for new signal(s), the PRAC adopted without further plenary discussion the recommendation of the Rapporteur to request MAH(s) to submit a cumulative review following standard timetables[44].

14.1.1. Bevacizumab - AVASTIN (CAP), MVASI (CAP)

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

PRAC Rapporteur: Doris Stenver

Scope: Signal of splenic infarction

EPITT 19344 – New signal

Lead Member State(s): DK

[43] 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

[44] 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

14.1.2. Secukinumab – COSENTYX (CAP)

Applicant(s): Novartis Europharm Limited

PRAC Rapporteur: Eva Segovia

Scope: Signal of dermatitis exfoliative generalised

EPITT 19354 – New signal

Lead Member State(s): ES

14.2. New signals detected from other sources

14.2.1. Olanzapine - OLANZAPINE APOTEX (CAP), OLANZAPINE GLENMARK (CAP), OLANZAPINE GLENMARK EUROPE (CAP), OLANZAPINE MYLAN (CAP), OLANZAPINE TEVA (CAP), OLAZAX (CAP), OLAZAX DISPERZI (CAP), ZALASTA (CAP), ZYPADHERA (CAP), ZYPREXA (CAP), ZYPREXA VELOTAB (CAP); NAP

Applicant(s): Apotex Europe BV (Olanzapine Apotex), Eli Lilly Nederland B.V. (Zypadhera, Zyprexa, Zyprexa Velotab), Glenmark Arzneimittel GmbH (Olanzapine Glenmark, Olanzapine Glenmark Europe), Glenmark Pharmaceuticals (Olazax, Olazax Disperzi), Krka, d.d. (Zalasta), Mylan S.A.S (Olanzapine Mylan), Teva B.V. (Olanzapine Teva), various

PRAC Rapporteur: Kimmo Jaakkola

Scope: Signal of salivary hypersecretion

EPITT 19357 – New signal

Lead Member State(s): FI

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. Ambrisentan - EMEA/H/C/004985

Scope: Treatment of pulmonary arterial hypertension (PAH)

15.1.2. Cabazitaxel - EMEA/H/C/004951

Scope: Treatment of prostate cancer

15.1.3. Ioflupane (123I) - EMEA/H/C/004745

Scope: Detection of loss of functional dopaminergic neuron terminals in the striatum

15.1.4. Posaconazole - EMEA/H/C/005005

Scope: Treatment of fungal infections

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

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

15.2.1. Abacavir - ZIAGEN (CAP) - EMEA/H/C/000252/WS1521/0105; abacavir, lamivudine - KIVEXA (CAP) - EMEA/H/C/000581/WS1521/0079; abacavir, lamivudine, zidovudine - TRIZIVIR (CAP) - EMEA/H/C/000338/WS1521/0112

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Adrien Inoubli

Scope: Submission of an RMP (version 1.0) combining the RMPs for Ziagen (abacavir), Kivexa (abacavir/lamivudine) and Trizivir (abacavir/lamivudine/zidovudine) into one RMP specific to abacavir-active substance

15.2.2. 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 provided 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

15.2.3. Cangrelor - KENGREXAL (CAP) - EMEA/H/C/003773/II/0015

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Amelia Cupelli

Scope: Update of the RMP (version 2.0) in order to update the requirements for a planned study (listed as a category 3 in the RMP): a multicentre, observational, non-interventional European study of patients undergoing percutaneous coronary intervention (PCI) who receive cangrelor and transition to either clopidogrel, prasugrel or ticagrelor. In addition, the MAH took the opportunity to bring the RMP in line with revision 2 of the guidance on the format of RMP in the EU (template)

15.2.4. 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. Deferasirox - EXJADE (CAP) - EMEA/H/C/000670/II/0064

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ghania Chamouni

Scope: Update of the RMP (version 16.0) to bring the RMP in line with revision 2 of the guidance on the format of RMP in the EU (template) and consequential removal of the food interaction and drug-drug interactions (DDI) from the list of important identified risks. In addition, 'drug reaction with eosinophilia and systemic symptoms (DRESS)' is reclassified from important potential risk to important identified risk as requested in the conclusions of PSUSA/00000939/201710 procedure adopted in May 2018. Furthermore, the healthcare professional (HCP) guide is also updated. The MAH took the opportunity to include minor changes throughout the RMP

15.2.6. Fluciclovine (^{18}F) - AXUMIN (CAP) - EMEA/H/C/004197/II/0010

Applicant: Blue Earth Diagnostics Ltd

PRAC Rapporteur: Rugile Pilviniene

Scope: Update of the RMP (version 2.0) in order to bring it 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). In addition, the MAH updated the RMP to include new exposure details from clinical trials and exposure from US and EU in real-world setting and corrected the effectiveness measurement of the image interpretation training from a review of self-assessments scores to standard pharmacovigilance activities

15.2.7. Herpes zoster vaccine (recombinant, adjuvanted) - SHINGRIX (CAP) - EMEA/H/C/004336/II/0011

Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Daniela Philadelphy

Scope: Update of the RMP (version 2) in order to extend the due dates of four category 3 studies, namely: study ZOSTER-002: an observer-blind study to evaluate efficacy, safety, and immunogenicity of Shingrix (herpes zoster vaccine) in adult autologous haematopoietic stem cell transplant (HCT) recipients; study ZOSTER-039: an observer blind study to evaluate safety and immunogenicity of Shingrix (herpes zoster vaccine) in adults aged 18 years and older with haematologic malignancies, study ZOSTER-041: an observer-blind study to evaluate immunogenicity and safety of Shingrix (herpes zoster vaccine) in adults aged 18 years and older with renal transplant; study ZOSTER-028: an observer-blind study to evaluate immunogenicity and safety of Shingrix (herpes zoster vaccine) in adults aged 18 years and older with solid tumours receiving chemotherapy. In addition, the RMP is updated to change the study design and due dates of category 3 study EPI-ZOSTER-030

VS: a targeted safety study (TSS) to evaluate the safety of Shingrix (herpes zoster vaccine) in adults 50 years of age and older. Furthermore, the MAH took the opportunity to bring the RMP in line with revision 2 of the guidance on the format of RMP in the EU (template)

15.2.8. Human papillomavirus vaccine [types 6, 11, 16, 18, 31, 33, 45, 52, 58] (recombinant, adsorbed) - GARDASIL 9 (CAP) - EMEA/H/C/003852/II/0029

Applicant: MSD Vaccins

PRAC Rapporteur: Jean-Michel Dogné

Scope: Update of the RMP (version 3.1) in order to bring it in line with revision 2 of the guidance on the format of RMP in the EU (template). As a result, the safety concerns are updated

15.2.9. Panobinostat - FARYDAK (CAP) - EMEA/H/C/003725/II/0013, Orphan

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Patrick Batty

Scope: Update of the RMP (version 5.0) in order to remove the commitment to conduct study LBH589D2408 (listed as a category 3 study in the RMP): a non-interventional PASS of panobinostat use in relapsed or relapsed/refractory multiple myeloma patients who have received at least two prior regimens including bortezomib and an immunomodulatory agent in a real-world setting according to the current EU prescribing information and document adherence to dosing regimen (including the dosing card, blister pack) by describing clinical characteristics, frequency and severity of medication error events

15.2.10. Piperaquine tetraphosphate, artenimol - EURARTESIM (CAP) - EMEA/H/C/001199/II/0032

Applicant: Alfasigma S.p.A.

PRAC Rapporteur: Julie Williams

Scope: Update of the RMP (version 15.2) to close the pregnancy registry 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 include the 'distribution of a new version of the educational material', to add 'delayed haemolytic anaemia' and 'severe cutaneous adverse reactions (SCARs)' such as Stevens-Johnson syndrome and toxic epidermal necrolysis as important potential risks, to limit the reproductive risk to the first trimester of pregnancy; to update on several studies, to include Eurartesim (piperaquine tetraphosphate/artenimol) into the WHO[45] list of essential medicines and to update the details of the MAH

15.2.11. Pramipexole - MIRAPEXIN (CAP) - EMEA/H/C/000134/WS1510/0089; SIFROL (CAP) - EMEA/H/C/000133/WS1510/0080

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Anette Kirstine Stark

[45] World Health Organization

Scope: Update of the RMP (version 9) to implement changes as requested in the conclusions of PSUSA/00002491/201604 procedure and in connection with a PRAC signal assessment procedure. In addition, the RMP is in order to bring it in line with revision 2 of the guidance on the format of RMP in the EU (template). Furthermore, the MAH took the opportunity to adapt the medical search strategies and data retrieval approach without any impact on the overall safety conclusion

15.2.12. 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)

15.2.13. Semaglutide - OZEMPIC (CAP) - EMEA/H/C/004174/II/0006

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Annika Folin

Scope: Update of the RMP (version 3.0) in order to reflect that the first milestones (i.e. final protocol submissions) are fulfilled for study NN9535-4447: a cohort study based on Nordic registry data to assess the risk of pancreatic cancer associated with the use of Ozempic (semaglutide) in patients with type 2 diabetes mellitus (T2DM) and study NN9535-4352: a randomised, double-masked parallel-group, placebo-controlled trial assessing the long-term effects of Ozempic (semaglutide) on diabetic retinopathy in subjects with T2DM. In addition, the RMP is updated in line with revision 2 of the guidance on the format of RMP in the EU (template) and in line with revision 2 of GVP module V on 'Risk management systems'

15.2.14. Tolcapone - TASMAR (CAP) - EMEA/H/C/000132/II/0061

Applicant: Meda AB

PRAC Rapporteur: Rhea Fitzgerald

Scope: Update of the RMP (version 7) in order to reflect currently available data from post-marketing experience and patient exposure data, to align the RMP with revision 2 of GVP module V on 'Risk management systems' as well as to remove 'dopaminergic effects due to increased bioavailability of co-administered levodopa (e.g. dyskinesia)' as an important identified risk and 'drug interactions with significant clinical consequence including sudden sleep onset' as a potential risk

15.2.15. 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 management systems' and include an update of Kadcyla (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. Anakinra - KINERET (CAP) - EMEA/H/C/000363/II/0064/G

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Anette Kirstine Stark

Scope: Update of section 4.4 of the SmPC in order to add a warning on pulmonary events based on post-marketing data. The package leaflet is updated accordingly. Consequently, the important potential risks and the list of target medical events in the RMP (version 4.6) are updated to include pulmonary events and a specific follow-up questionnaire is introduced. The RMP is also revised in line with revision 2 of the guidance on the format of RMP in the EU (template). In addition, the due date for submission of the final study report for study Sobi ANAKIN-302 (listed as a category 3 in the RMP): 'a non-interventional study to follow-up long term safety including macrophage activation syndrome MAS in paediatric patients with Still's disease (PRINTO/Pharmachild registry)' is proposed to be extended. Furthermore, the MAH took the opportunity to move the text about MAS and malignancies from section 4.8 to section 4.4 of the SmPC

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. Beclometasone dipropionate, formoterol fumarate dehydrate, glycopyrronium - RIARIFY (CAP) - EMEA/H/C/004836/WS1554/0002; TRYDONIS (CAP) - EMEA/H/C/004702/WS1554/0002

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Jan Neuhauser

Scope: Extension of indication based on results from two Phase 3 studies, namely Triple 7 (CCD-05993AA1-07): 'a multinational, multicentre, randomised, open-label, active-controlled, 26-week, 2-arm, parallel group study to evaluate the non-inferiority of fixed combination of beclomethasone dipropionate plus formoterol fumarate plus glycopyrronium bromide (Riarify/Trydonis (CHF 5993)) administered via pressurized metered-dose inhaler (pMDI) versus fixed combination of fluticasone furoate plus vilanterol administered via dry powder inhaler (DPI) (Relvar) plus tiotropium bromide (Spiriva) for the treatment of patients with chronic obstructive pulmonary disease' and Triple 8 (CCD-05993AA1-08): '52-week, double blind, randomized, 2 active parallel arms study of fixed combination CHF 5993 administered vs glycopyrronium bromide/indacaterol maleate (Ultibro) in chronic obstructive pulmonary disease (COPD) patients' in order to include maintenance treatment in adult patients with moderate to severe COPD who are not adequately treated by combination of a long-acting beta2-agonist and a long-acting muscarinic antagonist. As a consequence, sections 4.1, 4.4, 4.8 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 6.0) are updated accordingly

15.3.4. Bedaquiline - SIRTURO (CAP) - EMEA/H/C/002614/II/0028, Orphan

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of section 4.4 of the SmPC in order to update the safety information with inclusion of a statement on bedaquiline resistance in line with the outcome of the PSUSA procedure (PSUSA/00010074/201709) finalised in April 2018. The RMP (version 3.0) is updated based on the data triggering the SmPC update and to reflect completion of studies which were assessed in previous procedures. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet

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

Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension of indication to include patients aged 5 years and older in the current approved indication for the powder for solution for infusion 120 mg/mL and 400 mg/mL based on the results of study BEL114055: a multicentre, randomized parallel group, placebo-controlled double-blind trial to evaluate the safety, efficacy, and pharmacokinetics of belimumab, a human monoclonal anti-BLyS antibody, plus standard therapy in paediatric patients with systemic lupus erythematosus (SLE). As a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated with safety and efficacy information. In addition, sections 4.2, 5.1 and 5.2 of the SmPC for the solution for injection in pre-filled

pen and pre-filled syringe, 200 mg are updated to reflect the paediatric data available for the intravenous formulation. The package leaflet is updated accordingly. Furthermore, the RMP (version 28.0) is updated accordingly and with revision 2 of the guidance on the format of RMP in the EU (template). Finally, the MAH took the opportunity to introduce some editorial changes in the product information and bring it in line with the latest QRD template (version 10.0)

15.3.6. Benralizumab - FASENRA (CAP) - EMEA/H/C/004433/II/0014/G

Applicant: AstraZeneca AB

PRAC Rapporteur: David Olsen

Scope: Grouped variation consisting of: 1) addition of an auto-injector delivery device, Fasenra 30 mg solution for injection in pre-filled pen, 2) update of sections 4.2, 6.4, 6.5 and 6.6 of the SmPC in order to update the information for self-administration for Fasenra 30 mg solution for injection in pre-filled syringe. The labelling and the package leaflet are updated accordingly. In addition, the RMP (version 2.0) is updated to reflect the information about the new presentation, to include additional information on completed studies, namely: study ALIZE: 'a multicentre, randomized, double-blind, parallel group, placebo-controlled, phase 3b study to evaluate the potential effect of benralizumab on the humoral immune response to the seasonal influenza vaccination in adolescent and young adult patients with severe asthma'; study GREGALE: a multicentre, open-label, functionality, reliability, and performance study of an accessorized pre-filled syringe with home-administered subcutaneous benralizumab in adult patients with severe asthma; study AMES: a multicentre, randomised, open-label, parallel group, phase 1 study designed to compare benralizumab pharmacokinetics exposure in healthy subjects following single subcutaneous administration of a fixed 30 mg dose of benralizumab when using an autoinjector and accessorised pre-filled syringe; study GRECO: a multicentre, open-label, functionality, reliability and performance study of a single-use auto-injector with home-administered subcutaneous benralizumab in adult patients with severe asthma. The RMP is also updated with exposure data post marketing authorisation (MA) approval, and additional details on the following post-authorisation safety studies: study D3250R00026 (pregnancy registry): benralizumab pregnancy exposure study: a Vaccines and Medications in Pregnancy Surveillance System (VAMPSS) post marketing surveillance study, and study D3250R00042 (malignancy PASS): a descriptive study of the incidence of malignancy in patients with severe asthma overall and among those receiving benralizumab and other biologic therapy. Furthermore, the RMP is updated in line with revision 2 of the guidance on the format of RMP in the EU (template)

15.3.7. Ceftaroline fosamil - ZINFORO (CAP) - EMEA/H/C/002252/II/0041

Applicant: Pfizer Ireland Pharmaceuticals

PRAC Rapporteur: Maia Uusküla

Scope: Extension of indication to include paediatric patients from birth to less than 2 months old based on results from study D3720C00009 (C2661002) an open-label, multicentre study to evaluate the safety, tolerability, pharmacokinetics, and efficacy of ceftaroline in neonates and young infants with late-onset sepsis. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. In addition, the package leaflet and the RMP (version 17.0) are updated accordingly

15.3.8. Ciclosporin - IKERVIS (CAP) - EMEA/H/C/002066/WS1490/0014; VERKAZIA (CAP) - EMEA/H/C/004411/WS1490/0001

Applicant: Santen Oy

PRAC Rapporteur: Jan Neuhauser

Scope: Update of the RMP (version 7.0) in order to bring the RMP in line with revision 2 of the guidance on the format of RMP in the EU (template). The milestones for the Verkazia (ciclosporin) PASS on: quantification of the risk of periocular skin cancer, conjunctival or corneal neoplasia in children treated with Verkazia (ciclosporin) for vernal keratoconjunctivitis (VKC), have also been updated. In addition, the MAH proposed to align Ikervis (ciclosporin) SmPC section 4.4 on concomitant therapy and effects on immune system with Verkazia (ciclosporin) SmPC in order to harmonise the routine risk minimisation measures for both medicinal products. The MAH took this opportunity to implement the latest QRD template and the safety features for Ikervis (ciclosporin)

15.3.9. Daclatasvir - DAKLINZA (CAP) - EMEA/H/C/003768/II/0031

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Update of section 5.1 of the SmPC in order to add information on long-term efficacy and drug resistance based on final results from study AI444046 (listed as a category 3 study in the RMP): a phase 3 non-randomized, open-label, long-term follow-up and observational study of durability of efficacy, resistance and characterization of progression of liver disease in subjects with chronic hepatitis C previously treated with daclatasvir and/or asunaprevir. In addition, the MAH took the opportunity to postpone the due date of safety study AI444427: a post-authorisation safety study of early recurrence of hepatocellular carcinoma in hepatitis C virus (HCV)-infected patients after direct-acting antiviral therapy (DAA PASS) evaluating recurrence of hepatocellular carcinoma from Q2 2021 to Q2 2023. Annex II and the RMP (version 6.0) are updated accordingly

15.3.10. Eltrombopag - REVOLADE (CAP) - EMEA/H/C/001110/II/0049

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Eva Segovia

Scope: Extension of indication to include first line treatment of adult and paediatric patients aged 2 years and older with severe aplastic anaemia. 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 50.0) are updated accordingly

15.3.11. 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

15.3.12. 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

15.3.13. Guanfacine - INTUNIV (CAP) - EMEA/H/C/003759/II/0015

Applicant: Shire Pharmaceuticals Ireland Limited

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Update of section 4.5 of the SmPC in order to remove the statement on potential drug interactions with drugs that inhibit organic cation transporter 1 (OCT1) based on final results from study V8953M-SPD503: a non-clinical study to investigate the rate limiting step (hepatic uptake or hepatic metabolism) in the elimination of guanfacine. The RMP (version 3.0) is updated accordingly

15.3.14. 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

15.3.15. Ibrutinib - IMBRUVICA (CAP) - EMEA/H/C/003791/II/0046, Orphan

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Extension of indication to include treatment of adult patients with Waldenström's macroglobulinaemia (WM) in combination with rituximab, based on the results of the final clinical study report of study PCYC-1127-CA: a randomized, double-blind, placebo-controlled, phase 3 study of ibrutinib or placebo in combination with rituximab in subjects with WM (iNNOVATE study). As a consequence, sections 4.1 and 4.8 of the SmPC are updated accordingly. The RMP (version 12) is updated accordingly. In addition, the MAH took the opportunity to update the SmPC and package leaflet with minor editorial/administrative changes

15.3.16. Ibrutinib - IMBRUVICA (CAP) - EMEA/H/C/003791/II/0047, Orphan

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Extension of indication to extend the existing indication on chronic lymphocytic leukaemia (CLL) to include the combination use with obinutuzumab for the treatment of adult patients with previously untreated CLL, based on the data from study PCYC-1130-CA: a randomized, multicentre, open-label, phase 3 study of the Bruton's tyrosine kinase inhibitor ibrutinib in combination with obinutuzumab versus chlorambucil in combination with obinutuzumab in subjects with treatment-naïve CLL or small lymphocytic lymphoma. As a consequence, sections 4.1, 4.8 and 5.1 of the SmPC are updated. The package leaflet is updated accordingly. The RMP (version 12) is updated accordingly. In addition, the MAH took the opportunity to update the SmPC and package leaflet with minor editorial/administrative changes

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

Applicant: Merck Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Grouped variations consisting of: 1) update of sections 4.3, 4.6 and 5.3 of the SmPC in order to add information about pregnancy and update the statement regarding breast-feeding following the completion of the European interferon beta (IFN-β) pregnancy registry (eighth annual and final report) and the final clinical study report (CSR) of the register-based study in the Nordic countries (EUPAS13054: multiple sclerosis pregnancy study - pregnancy outcomes in multiple sclerosis populations exposed and unexposed to interferon beta - a register-based study in the Nordic countries); 2) update of section 4.6 of the SmPC in order to update the statement regarding breast-feeding following a review of studies, case reports and literature articles. The package leaflet is updated accordingly (fulfilment of MEA 43.2 and 39). The RMP (version 10.0) is updated accordingly, including the deletion of the important potential risk 'pregnancy outcomes'. The RMP is also updated to bring it in line with revision 2 of the guidance on the format of RMP in the EU (template)

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

Applicant: Bayer AG

PRAC Rapporteur: Martin Huber

Scope: Grouped variations consisting of: 1) update of sections 4.3 and 4.6 of the SmPC in order to add information on pregnancy and update the statement regarding breast-feeding following the completion of the European interferon beta (IFN-β) pregnancy registry (eighth annual and final report) and the final clinical study report (CSR) of the register-based study in the Nordic countries (EUPAS13054: multiple sclerosis pregnancy study - pregnancy outcomes in multiple sclerosis populations exposed and unexposed to interferon beta - a register-based study in the Nordic countries); 2) update of section 4.6 of the SmPC in order to update the statement regarding breast-feeding following a review of studies, case reports and literature articles. The package leaflet has been updated accordingly (fulfilment of MEA 024.2 and 21). The RMP (version 4.1) is updated accordingly, including the deletion of the important potential risk 'pregnancy outcomes'. The RMP is also updated to bring it in

line with revision 2 of the guidance on the format of RMP in the EU (template)

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

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Martin Huber

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

15.3.20. Lacosamide - VIMPAT (CAP) - EMEA/H/C/000863/II/0073/G

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Grouped variations consisting of: 1) update of sections 4.4, 4.5 and 4.8 of the SmPC in order to include new safety information on cardiac arrhythmias based on safety signal assessment report (SSAR); 2) update of section 4.8 of the SmPC to update the frequency of some adverse events (AEs) based on data obtained from the updated safety pool analysis (Pool DBC-1) which consists of the combined data from SP667, SP754, SP755, and EP0008. All of these studies were randomized, double-blind, placebo-controlled, parallel-group, adjunctive therapy studies in subjects with epilepsy. The package leaflet and the RMP (version 13.0) are updated accordingly

15.3.21. Meningococcal group B vaccine (recombinant, adsorbed) - TRUMENBA (CAP) - EMEA/H/C/004051/II/0013

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Jean-Michel Dogné

Scope: Extension of indication to include active immunisation of children 1-9 years old. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated based on the results from the two pivotal studies, namely B1971017: a phase 2, randomized, controlled, observer-blinded study to describe the immunogenicity, safety, and tolerability of *Neisseria meningitidis* serogroup b bivalent recombinant lipoprotein 2086 vaccine (bivalent rLP2086 (Trumenba)) in healthy subjects aged ≥24 months to <10 years; and study B1971035: a phase 2, randomized, controlled, observer-blinded study conducted to describe the immunogenicity, safety, and tolerability of a *Neisseria meningitidis* serogroup B bivalent recombinant lipoprotein 2086 vaccine (bivalent rLP2086 (Trumenba)) when administered to healthy toddlers aged 12 to <18 months or 18 to <24 months, and the safety and

immunogenicity of a booster dose of bivalent rLP2086. The package leaflet and the RMP (version 2.0) are updated accordingly. In addition, the MAH took the opportunity to submit a corrected version of the final report of study B1971016: a phase 3, randomized, placebo-controlled, observer-blinded, trial to assess the safety, tolerability, and immunogenicity of bivalent rLP2086 vaccine (Trumenba) when administered as a 3-dose regimen in healthy young adults aged >=18 to <26 years, which was included in the initial marketing authorisation application (MAA)

15.3.22. Modified vaccinia Ankara virus - IMVANEX (CAP) - EMEA/H/C/002596/II/0036

Applicant: Bavarian Nordic A/S

PRAC Rapporteur: Julie Williams

Scope: Update of sections 4.4, 4.8 and 5.1 of the SmPC in order to update the safety information and to provide confirmation in terms of immunogenicity based on the results from study POX-MVA-006 (listed as an obligation in Annex II (ANX 004)): a randomized, open-label phase 3 non-inferiority trial to compare indicators of efficacy for smallpox vaccine to the US licensed replicating smallpox vaccine in 18-42 year old healthy vaccinia-naïve subjects. The package leaflet and the RMP (version 7.2) are updated accordingly

15.3.23. Naltrexone hydrochloride, bupropion hydrochloride - MYSIMBA (CAP) - EMEA/H/C/003687/II/0029/G

Applicant: Orexigen Therapeutics Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: Grouped variations consisting of: 1) update of section 4.8 to adjust the list of adverse drug reactions and their corresponding frequencies in line with the outcome of the PSUSA procedure (PSUSA/00010366/201709) finalised in April 2018 ; 2) update of sections 4.2, 4.4 and 5.2 of the SmPC to add results from a phase 1 open label parallel study to evaluate the pharmacokinetics of a single oral dose of extended-release combination of naltrexone and bupropion in subjects with normal hepatic function or varying degrees of impaired hepatic function and remove the recommendation to not use naltrexone/bupropion in patients with mild hepatic impairment. The existing warning is updated accordingly. The warning related to contraindications is aligned to section 4.3 to add end-stage renal failure patients. As a consequence, the RMP is updated accordingly (version 11). In addition, the MAH took the opportunity to update the warning on lactose in accordance with the European Commission (EC) guideline on 'excipients in the labelling and package leaflet of medicinal products for human use'

15.3.24. Nelarabine - ATRIANCE (CAP) - EMEA/H/C/000752/II/0046/G

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Anette Kirstine Stark

Scope: Grouped variations consisting of: 1) update to Annex II to remove the specific obligation (SOB) based on the final results from study NLR506AUS02T (COG-AALL0434): 'intensified methotrexate, nelarabine and augmented Berlin-Frankfurt-Munster (BFM) therapy for children and young adults with newly diagnosed T-cell acute lymphoblastic leukaemia (T-ALL) and T-cell lymphoblastic lymphoma (T-LBL)'. As a consequence, sections

4.8 and 5.1 of the SmPC are updated; 2) update of section 4.6 of the SmPC to revise information on male and female contraception taking into consideration available non-clinical and clinical safety data as well as internal MAH's guidelines based on information from literature, health authority and working group guidelines. Furthermore, the MAH took the opportunity to update details of the local representatives and introduced minor editorial changes in the package leaflet. The RMP (version 10) is updated accordingly

15.3.25. 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

15.3.26. 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 (FIGO[46] stage III-IV) ovarian cancer following first line platinum based chemotherapy. The package leaflet and the RMP (version 17) are updated accordingly

15.3.27. Palbociclib - IBRANCE (CAP) - EMEA/H/C/003853/II/0017/G

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Doris Stenver

Scope: Grouped variations consisting of an update of section 5.3 of the SmPC in order to include information from two completed non-clinical studies: a 6-month carcinogenicity study in mice (20084764), and a 2-year carcinogenicity study in rats (20066483). Furthermore, the MAH submitted the final report from the non-clinical study 20084675: a pre- and postnatal developmental toxicity study in rats. The RMP (version 1.5) is updated accordingly. The MAH took the opportunity to introduce minor editorial changes throughout the product information

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

Applicant: Biogen Netherlands B.V.

[46] International Federation of Gynaecology and Obstetrics

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Grouped variations consisting of: 1) update of sections 4.3 and and 4.6 of the SmPC in order to add information on pregnancy and update the statement regarding breast-feeding following the completion of the European interferon beta (IFN-β) pregnancy registry (eighth annual and final report) and the final clinical study report (CSR) of the register-based study in the Nordic countries (EUPAS13054: multiple sclerosis pregnancy study - pregnancy outcomes in multiple sclerosis populations exposed and unexposed to interferon beta - a register-based study in the Nordic countries); 2) update of section 4.6 of the SmPC in order to update the statement regarding breast-feeding following a review of studies, case reports and literature articles. The package leaflet has been updated accordingly (fulfilment of MEA 8.2 and 002). The RMP (version 4.1) is updated accordingly, including the deletion of the important potential risk 'pregnancy outcomes'. The RMP is also updated to bring it in line with revision 2 of the guidance on the format of RMP in the EU (template)

15.3.29. Plasmodium falciparum and hepatitis B vaccine (recombinant, adjuvanted) - MOSQUIRIX (Art 58[47]) - EMEA/H/W/002300/II/0036

Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Jean-Michel Dogné

Scope: Update of section 4.4 of the SmPC in order to modify the warning on 'protection against *Plasmodium falciparum* malaria' over time. This update is based on the final results from study MALARIA-076 (listed as a category 3 study in the RMP): an open extension to phase 3, multicentre study MALARIA-055 PRI (110021) to evaluate long-term efficacy, safety and immunogenicity of Mosquirix (plasmodium falciparum and hepatitis B vaccine (recombinant, adjuvanted)) malaria vaccine in infants and children. The RMP (version 4.1) is updated accordingly

15.3.30. Prepandemic influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) - AFLUNOV (CAP) - EMEA/H/C/002094/II/0044/G

Applicant: Seqirus S.r.l

PRAC Rapporteur: Amelia Cupelli

Scope: Grouped variations consisting of an update of sections 4.4, 4.6, 4.8 and 5.1 of the SmPC following the completion of clinical study reports for 1) study V87_25: a phase 3, prospective, controlled, observer-blind, multicentre study to evaluate the safety, tolerability and immunogenicity of two doses of a monovalent A/H5N1 influenza vaccine adjuvanted with MF59 when administered to subjects with and without underlying medical conditions; 2) study V87_26: a phase 3, prospective, controlled, observer-blind, multicentre study to evaluate the safety, tolerability and immunogenicity of two doses of a monovalent A/H5N1 influenza vaccine adjuvanted with MF59 when administered to adults and elderly subjects with immunosuppressive disorders. The package leaflet, labelling and RMP (version 3.0) are updated accordingly. In addition, the MAH took the opportunity to implement some amendments to the product information and introduce some additional minor editorial corrections

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

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

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ulla Wändel Liminga

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

15.3.32. Selexipag - UPTRAVI (CAP) - EMEA/H/C/003774/II/0022

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Adrien Inoubli

Scope: Update of Sections 4.2, 4.4 and 4.5 of the SmPC in order to update the safety information based on the final results from study AC-065-117 (listed as a category 3 study in the RMP): clinical pharmacology drug-drug interaction (DDI) study evaluating the effect of clopidogrel a moderate inhibitor of CYP2C8[48], on the pharmacokinetics of selexipag and its active metabolite ACT-333679. The package leaflet and the RMP (version 6.1) are updated accordingly. In addition, the MAH took the opportunity to correct minor discrepancies in the SmPC

15.3.33. Talimogene laherparepvec - IMLYGIC (CAP) - EMEA/H/C/002771/II/0029

Applicant: Amgen Europe B.V., ATMP[49]

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of section 5.2 of the SmPC in order to amend the pharmacokinetic properties information based on the final results from study 20120324: a phase 2, multicentre, single-arm trial to evaluate the biodistribution and shedding of talimogene laherparepvec in subjects with unresected, stage IIIB to stage IVM1c melanoma. This submission fulfils MEA 006.1. In addition, the MAH took the opportunity to update Annex II as per the outcome of the assessment of ANX 001 procedure concluded in October 2018

15.3.34. 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,

[48] Cytochrome P450 2C8
[49] Advanced therapy medicinal product

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

15.3.35. Trastuzumab - ONTRUZANT (CAP) - EMEA/H/C/004323/II/0016

Applicant: Samsung Bioepis NL B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Addition of a new presentation with a new fill weight (420 mg) of a sterile single dose partial use parenteral medicinal product for Ontruzant (trastuzumab). The RMP (version 3.0) is updated accordingly. In addition, the MAH took the opportunity to introduce editorial changes in the product information in line with the originator product

15.3.36. Vandetanib - CAPRELSA (CAP) - EMEA/H/C/002315/II/0028

Applicant: Genzyme Europe BV

PRAC Rapporteur: Ghania Chamouni

Scope: Update of sections 4.1, 4.4 and 5.1 of the SmPC in order to delete the information regarding rearranged during transfection (RET) mutation. The application fulfils SOB 001 and includes a proposal to revert from conditional marketing authorisation to standard marketing authorisation. Annex II, the package leaflet and the RMP (version 12.2) are updated accordingly. In addition, the MAH took the opportunity to bring the product information in line with the latest QRD template (version 10)

15.3.37. Venetoclax - VENCLYXTO (CAP) - EMEA/H/C/004106/II/0020, Orphan

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Eva Jirsova

Scope: Update of sections 4.2 and 5.2 of the SmPC in order to include that a 50% dose reduction of venetoclax is recommended in patients with severe hepatic impairment, based on the final results from study M15-342 (listed as a category 3 study in the RMP): a study to evaluate the safety and pharmacokinetics of a single dose of ventoclax in female subjects with mild, moderate, or severe hepatic impairment. The package leaflet and the RMP (version 3.4) are updated accordingly

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

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

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

2001/83/EC and published on the European medicines web-portal, unless changes apply as stated in the outcome of the relevant PSUR/PSUSA procedure(s).

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

16.1.1. Aclidinium bromide - BRETARIS GENUAIR (CAP); EKLIRA GENUAIR (CAP) - PSUSA/00009005/201807

Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.2. Aflibercept[50] - ZALTRAP (CAP) - PSUSA/00010019/201808

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

16.1.3. Albutrepenonacog alfa - IDELVION (CAP) - PSUSA/00010497/201807

Applicant: CSL Behring GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.4. Alirocumab - PRALUENT (CAP) - PSUSA/00010423/201807

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.5. Antithrombin alfa - ATRYN (CAP) - PSUSA/00000224/201807

Applicant: Laboratoire Francais du Fractionnement et des Biotechnologies

PRAC Rapporteur: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

16.1.6. Ataluren - TRANSLARNA (CAP) - PSUSA/00010274/201807

Applicant: PTC Therapeutics International Limited

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

[50] Oncology indication(s) only

16.1.7. Atazanavir, cobicistat - EVOTAZ (CAP) - PSUSA/00010404/201807

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

16.1.8. Beclometasone, formoterol, glycopyrronium bromide - RIARIFY (CAP); TRIMBOW (CAP); TRYDONIS (CAP) - PSUSA/00010617/201807

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.1.9. Bictegravir, emtricitabine, tenofovir alafenamide - BIKTARVY (CAP) - PSUSA/00010695/201808

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.10. Birch bark extract[51] - EPISALVAN (CAP) - PSUSA/00010446/201807

Applicant: Amryt AG

PRAC Rapporteur: Zane Neikena

Scope: Evaluation of a PSUSA procedure

16.1.11. Brivaracetam - BRIVIACT (CAP) - PSUSA/00010447/201807

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.12. Brodalumab - KYNTHEUM (CAP) - PSUSA/00010616/201807

Applicant: LEO Pharma A/S

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

16.1.13. Catridecacog - NOVOTHIRTEEN (CAP) - PSUSA/00010034/201807

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Ghania Chamouni

[51] Centrally authorised product(s) only

Scope: Evaluation of a PSUSA procedure

16.1.14. Efavirenz, emtricitabine, tenofovir - ATRIPLA (CAP) - PSUSA/00001201/201807

Applicant: Bristol-Myers Squibb and Gilead Sciences Ltd.

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.15. Elbasvir, grazoprevir - ZEPATIER (CAP) - PSUSA/00010519/201807

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.1.16. Etanercept[52] - BENEPALI (CAP); ERELZI (CAP) - PSUSA/00010452/201807

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

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

16.1.17. Gefitinib - IRESSA (CAP) - PSUSA/00001518/201807

Applicant: AstraZeneca AB

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

16.1.18. Guselkumab - TREMFYA (CAP) - PSUSA/00010652/201807

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.19. Hydrocortisone[53] - ALKINDI (CAP) - PSUSA/00010674/201808

Applicant: Diurnal Europe BV

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.20. Ibandronic acid – BONDRONAT (CAP); BONVIVA (CAP) - PSUSA/00001702/201806

Applicant: Atnahs Pharma UK Limited

[52] Biosimilar products only
[53] Centrally authorised product(s) for adrenal insufficiency, paediatric use only

PRAC Rapporteur: Doris Stenver

Scope: Evaluation of a PSUSA procedure

16.1.21. Idelalisib - ZYDELIG (CAP) - PSUSA/00010303/201807

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

16.1.22. Idursulfase - ELAPRASE (CAP) - PSUSA/00001722/201807

Applicant: Shire Human Genetic Therapies AB

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

16.1.23. Lomitapide - LOJUXTA (CAP) - PSUSA/00010112/201807

Applicant: Amryt Pharmaceuticals DAC

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.24. Mercaptamine[54] - CYSTADROPS (CAP) - PSUSA/00010574/201807

Applicant: Orphan Europe SARL

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

16.1.25. Modified vaccinia Ankara virus - IMVANEX (CAP) - PSUSA/00010119/201807

Applicant: Bavarian Nordic A/S

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.26. Palbociclib - IBRANCE (CAP) - PSUSA/00010544/201808

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Doris Stenver

Scope: Evaluation of a PSUSA procedure

[54] For treatment of corneal cystine crystal deposits only

16.1.27. Paliperidone - INVEGA (CAP); paliperidone palmitate - TREVICTA (CAP); XEPLION (CAP) - PSUSA/00002266/201806

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.28. Pegaptanib - MACUGEN (CAP) - PSUSA/00002324/201806

Applicant: PharmaSwiss Ceska Republika s.r.o

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

16.1.29. Peginterferon beta-1A - PLEGRIDY (CAP) - PSUSA/00010275/201807

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.30. Perampanel - FYCOMPA (CAP) - PSUSA/00009255/201807

Applicant: Eisai GmbH

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.31. Phenylephrine, ketorolac - OMIDRIA (CAP) - PSUSA/00010419/201807

Applicant: Omeros London Limited

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.32. Sacubitril, valsartan - ENTRESTO (CAP); NEPARVIS (CAP) - PSUSA/00010438/201807

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.33. Sarilumab - KEVZARA (CAP) - PSUSA/00010609/201807

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

16.1.34. Saxagliptin, dapagliflozin - QTERN (CAP) - PSUSA/00010520/201807

Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.35. Sofosbuvir, velpatasvir, voxilaprevir - VOSEVI (CAP) - PSUSA/00010619/201807

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.1.36. Stavudine - ZERIT (CAP) - PSUSA/00002787/201806

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.37. Telithromycin - KETEK (CAP) - PSUSA/00002881/201807

Applicant: Aventis Pharma S.A.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.38. Tobramycin[55] - TOBI PODHALER (CAP) - PSUSA/00009315/201806

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.39. Tocofersolan - VEDROP (CAP) - PSUSA/00002981/201807

Applicant: Orphan Europe SARL

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

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

None

[55] Inhalation powder, capsules only

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

16.3.1. Aciclovir (NAP) – PSUSA/00000048/201806

Applicant(s): various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

16.3.2. Calcitonin salmon (NAP); synthetic analogue of eel calcitonin (NAP) - PSUSA/00000494/201806

Applicant(s): various

PRAC Lead: Eva Segovia

Scope: Evaluation of a PSUSA procedure

16.3.3. Cefepime (NAP) - PSUSA/00000593/201806

Applicant(s): various

PRAC Lead: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.3.4. Dexchlorpheniramine (NAP) - PSUSA/00000989/201806

Applicant(s): various

PRAC Lead: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.3.5. Dihydroergocryptine (NAP) - PSUSA/00001074/201807

Applicant(s): various

PRAC Lead: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.3.6. Fosinopril (NAP); fosinopril, hydrochlorothiazide (NAP) - PSUSA/00010463/201807

Applicant(s): various

PRAC Lead: Eva Segovia

Scope: Evaluation of a PSUSA procedure

16.3.7. Glibenclamide, metformin hydrochloride (NAP) - PSUSA/00002002/201806

Applicant(s): various

PRAC Lead: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

16.3.8. Human fibrinogen (NAP) - PSUSA/00001624/201806

Applicant(s): various

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.3.9. Levonorgestrel, ethinylestradiol; ethinylestradiol (NAP)[56] - PSUSA/00010442/201807

Applicant(s): various

PRAC Lead: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

16.3.10. Lidocaine hydrochloride, phenylephrine hydrochloride, tropicamide (NAP) - PSUSA/00010390/201807

Applicant(s): various

PRAC Lead: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

16.3.11. Misoprostol[57] (NAP) - PSUSA/00010291/201806

Applicant(s): various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

16.3.12. Nilutamide (NAP) - PSUSA/00002163/201807

Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.3.13. Nimesulide[58] (NAP) - PSUSA/00009236/201806

Applicant(s): various

PRAC Lead: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

[56] Combination pack only
[57] For gastrointestinal indication(s) only
[58] Systemic formulations only

16.3.14. Nimesulide[59] (NAP) - PSUSA/00002165/201806

Applicant(s): various

PRAC Lead: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.3.15. Phenylpropanolamine (NAP) - PSUSA/00010483/201806

Applicant(s): various

PRAC Lead: Eva Jirsova

Scope: Evaluation of a PSUSA procedure

16.3.16. Pipobroman (NAP) - PSUSA/00002427/201806

Applicant(s): various

PRAC Lead: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

16.3.17. Pitavastatin (NAP) - PSUSA/00010502/201807

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.3.18. Rizatriptan (NAP) - PSUSA/00002655/201806

Applicant(s): various

PRAC Lead: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

16.3.19. Solifenacin, tamsolusin (NAP) - PSUSA/00010285/201807

Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.3.20. Thiocolchicoside (NAP); paracetamol, thiocolchicoside (NAP) - PSUSA/00010464/201807

Applicant(s): various

PRAC Lead: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

[59] Topical formulations only

16.3.21. Tiagabine (NAP) - PSUSA/00002942/201806

Applicant(s): various

PRAC Lead: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

16.3.22. Urapidil (NAP) - PSUSA/00003078/201807

Applicant(s): various

PRAC Lead: Eva Jirsova

Scope: Evaluation of a PSUSA procedure

16.4. Follow-up to PSUR/PSUSA procedures

16.4.1. Ticagrelor - BRILIQUE (CAP) - EMEA/H/C/001241/LEG 024

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Review on the risk of interaction between morphine and Brilique (ticagrelor) as requested in the conclusions of PSUSA/00002499/201802 for prasugrel adopted in September 2018 for other $P2Y_{12}$ inhibitors, agents of the same class as prasugrel

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)[60]

17.1.1. Velmanase alfa - LAMZEDE (CAP) - EMEA/H/C/PSP/S/0060.2

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Jan Neuhauser

Scope: MAH's response to PSP/S/060.1 [protocol for the alfa-mannosidosis registry: a multicentre, multi-country, non-interventional, prospective cohort, in alfa-mannosidosis patients to evaluate the long-term effectiveness and safety profile of treatment with Lamzede (velmanase alfa) under conditions of routine clinical care and to characterize the entire alfa-mannosidosis population, including variability of clinical manifestation, progression and natural history] as per the request for supplementary information (RSI) adopted in October 2018

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

17.2. Protocols of PASS non-imposed in the marketing authorisation(s)[61]

17.2.1. Aflibercept - EYLEA (CAP) - EMEA/H/C/002392/MEA 016.1

Applicant: Bayer AG

PRAC Rapporteur: Ghania Chamouni

Scope: MAH's response to MEA 016 [Protocol for a follow-up survey measuring the effectiveness of the updated educational material for healthcare professionals (HCPs): a survey to investigate whether physicians have received the revised educational materials, measuring physician knowledge and understanding of the key information in the revised educational materials, and whether physicians have provided the patient booklet to their patients [result due date expected within 6 months after completion of the survey] as per the request for supplementary information (RSI) adopted in September 2018

17.2.2. Alectinib - ALECENSA (CAP) - EMEA/H/C/004164/MEA 002.1

Applicant: Roche Registration GmbH

PRAC Rapporteur: Patrick Batty

Scope: MAH's response to MEA 002 [protocol for study BO40643: a survey measuring the effectiveness of the risk minimisation activities to prescribers: correct implementation of Alecensa (alectinib) label guidance by prescribers of the following important identified risks: interstitial lung disease (ILD)/pneumonitis, hepatotoxicity, photosensitivity, bradycardia, severe myalgia and creatine phosphokinase (CPK) elevations] as per the request for supplementary information (RSI) adopted in September 2018

17.2.3. Benralizumab - FASENRA (CAP) - EMEA/H/C/004433/MEA 004.1

Applicant: AstraZeneca AB

PRAC Rapporteur: David Olsen

Scope: MAH's response to MEA 004 [protocol for study D3250R00042: a descriptive study of the incidence of malignancy in patients with severe asthma overall and among those receiving benralizumab and other therapies in real-world settings] as per the request for supplementary information (RSI) adopted in September 2018

17.2.4. Ciclosporin - VERKAZIA (CAP) - EMEA/H/C/004411/MEA 001

Applicant: Santen Oy

PRAC Rapporteur: Jan Neuhauser

Scope: Protocol and feasibility study for a case-control study linked to existing cancer registries to understand the data sources and analytic methods available to quantify the risk of periocular skin cancer, conjunctival or corneal neoplasia in children treated with Verkazia (ciclosporin) (from initial opinion/MA)

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

17.2.5. Guselkumab - TREMFYA (CAP) - EMEA/H/C/004271/MEA 004.1

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: MAH's response to MEA 004 [Protocol for study CSIMM000265: a retrospective cohort study using health administrative claims databases to assess adverse pregnancy and infant outcomes in women with psoriasis who were exposed to guselkumab versus other biologic therapies during pregnancy] as per the request for supplementary information (RSI) adopted in November 2018

17.2.6. Naltrexone hydrochloride, bupropion hydrochloride - MYSIMBA (CAP) - EMEA/H/C/003687/MEA 003.6

Applicant: Orexigen Therapeutics Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: MAH's response to MEA 003.5 [protocol for study NB-451: a protocol synopsis for an observational retrospective database study based on secondary data analysis using existing databases, as suitable] as per the request for supplementary information (RSI) adopted in September 2018

17.2.7. Patisiran - ONPATTRO (CAP) - EMEA/H/C/004699/MEA 002

Applicant: Alnylam Netherlands B.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Protocol for study ALN-TTR02-0009: a prospective observational study to monitor and assess the safety of Onpattro (patisiran) in a real-world cohort of hereditary transthyretin amyloidosis (hATTR) patients

17.2.8. Tezacaftor, ivacaftor - SYMKEVI (CAP) - EMEA/H/C/004682/MEA 002

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Protocol for study VX17-661-117 (listed as a category 3 study in the RMP): an observational cohort study on utilisation patterns and real-world effects of tezacaftor and ivacaftor combination therapy (TEZ/IVA) in patients with cystic fibrosis (CF) [final report expected: December 2023]

17.2.9. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/MEA 008.1

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: MAH's response to MEA 008 [protocol for study A3921312 (listed as a category 3 study in the RMP): a prospective non-interventional comparative active surveillance PASS of serious infection, malignancy, cardiovascular and other adverse event rates among patients treated with Xeljanz (tofacitinib) for moderately to severely active rheumatoid arthritis (RA) within the British Society for Rheumatology Biologics Register-Rheumatoid Arthritis

(BSRBR-RA)] as per the request for supplementary information (RSI) adopted in September 2018

17.2.10. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/MEA 009.1

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: MAH's response to MEA 009 [protocol for study A3921314 (listed as a category 3 study in the RMP): a prospective non-interventional comparative active surveillance PASS of serious infection, malignancy, cardiovascular and other adverse event rates among patients treated with Xeljanz (tofacitinib) for moderately to severely active rheumatoid arthritis (RA) within the Swedish (ARTIS) register] as per the request for supplementary information (RSI) adopted in September 2018

17.2.11. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/MEA 010.1

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: MAH's response to MEA 010 [protocol for study A3921316 (listed as a category 3 study in the RMP): a prospective non-interventional comparative active surveillance PASS of serious infection, malignancy, cardiovascular and other adverse event rates among patients treated with Xeljanz (tofacitinib) for moderately to severely active rheumatoid arthritis (RA) within the Spanish registry of adverse events of biological therapies and biosimilars in rheumatoid diseases (BIOBADASER)] as per the request for supplementary information (RSI) adopted in September 2018

17.2.12. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/MEA 011.1

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: MAH's response to MEA 008 [Protocol for study A3921317 (listed as a category 3 study in the RMP): a prospective non-interventional comparative active surveillance PASS of serious infection, malignancy, cardiovascular and other adverse event rates among patients treated with Xeljanz (tofacitinib) for moderately to severely active rheumatoid arthritis (RA) within the German registry Rheumatoide Arthritis: Beobachtung der Biologika-Therapie (RABBIT)] as per the request for supplementary information (RSI) adopted in September 2018

17.2.13. Turoctocog alfa - NOVOEIGHT (CAP) - EMEA/H/C/002719/MEA 004.4

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Additional Interim Report for study NN7008-3553: a multicentre non-interventional study of safety and efficacy of turoctocog alfa (recombinant factor VIII (rFVIII)) during long-term treatment of severe and moderately severe haemophilia A (FVIII ≤2%) [final clinical study report (CSR): Q4 2021]

17.3. Results of PASS imposed in the marketing authorisation(s)[62]

None

17.4. Results of PASS non-imposed in the marketing authorisation(s)[63]

17.4.1. Belatacept - NULOJIX (CAP) - EMEA/H/C/002098/II/0050/G

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of the final report from studies (listed as category 3 studies in the RMP), namely: 1) study IM103074: an observational study designed to assess the pattern of use of belatacept in US transplant recipients in routine clinical practice; 2) study IM103077: an observational study designed to assess the patterns of use of belatacept in renal transplantation using the collaborative transplant study. The RMP is updated accordingly (version 16.0). In addition, the MAH took the opportunity to update the RMP 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) and also to reflect minor editorial changes and the earlier completion dates for two remaining studies (listed as category 3 studies in the RMP), namely study IM103075: a study to assess the association between the use of belatacept and the risk of post-transplant lymphoproliferative disease (PTLD) in US renal transplant recipients; and study IM103076: evaluation of Nulojix (belatacept) long term safety in transplant (ENLiST) registry in order to estimate the incidence rates (IRs) of confirmed PTLD and central nervous system (CNS) PTLD in adult renal transplant recipients treated with belatacept in the US

17.4.2. Colistimethate sodium - COLOBREATHE (CAP) - EMEA/H/C/001225/II/0039

Applicant: Teva B.V.

PRAC Rapporteur: Julie Williams

Scope: Submission of the final report from study CLB-MD-08 (listed as a category 3 study in the RMP): a non-interventional PASS cross-sectional survey study to evaluate the effectiveness of Colobreathe (colistimethate sodium) risk minimisation educational programme among healthcare professionals and patients. This submission fulfils MEA 012.1

17.4.3. Collagenase clostridium histolyticum - XIAPEX (CAP) - EMEA/H/C/002048/II/0106

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Martin Huber

Scope: Submission of the final report from a non-interventional PASS (listed as a category 3 study in the RMP): effectiveness of the educational material for healthcare professionals of Xiapex (collagenase clostridium histolyticum) in the treatment of Peyronie's disease

[62] In accordance with Article 107p-q of Directive 2001/83/EC
[63] 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

17.4.4. Emtricitabine, tenofovir disoproxil - TRUVADA (CAP) - EMEA/H/C/000594/II/0159

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Submission of the final study report for the non-interventional study GS-EU-276-4027 (listed as a category 3 study in the RMP): a cross-sectional post-authorisation safety study to assess healthcare providers' level of awareness of risk minimisation materials for Truvada (emtricitabine/tenofovir disoproxil) for pre-exposure prophylaxis (PrEP) in the European Union. This submission fulfils MEA 045.7

17.4.5. 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)

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

Applicant: Pierre Fabre Dermatologie

PRAC Rapporteur: Eva Segovia

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

17.4.7. Teriparatide - FORSTEO (CAP) - EMEA/H/C/000425/II/0050/G

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Adrien Inoubli

Scope: Grouped variations consisting of the submission of the final study reports of the European Union (EU) components of two PASS; namely study B3DMC-GHBX (2.2) and study B3D-MC-GHBX (2.3b) both US population-based comparative cohort studies undertaken to evaluate a potential association between teriparatide and adult osteosarcoma. The RMP (version 7.0) is updated accordingly

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

17.5.1. Ataluren - TRANSLARNA (CAP) - EMEA/H/C/002720/MEA 002.4

Applicant: PTC Therapeutics International Limited

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: MAH's response to MEA 002.3 [three year interim report for study PTC124-GD-025o-DMD (listed as a category 3 study in the RMP): a post-approval registry observational study exploring the long-term of ataluren safety and effectiveness in usual care setting [final clinical study report (CSR) expected in: April 2023]] as per the request for supplementary information (RSI) adopted in September 2018

17.5.2. Deferasirox - EXJADE (CAP) - EMEA/H/C/000670/ANX 038.10

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ghania Chamouni

Scope: Fifth annual interim report for study CICL670E2422: an observational, multicentre cohort study to evaluate the long term exposure and safety of deferasirox in the treatment of paediatric non-transfusion dependent thalassaemia patients over 10 years old for whom deferoxamine is contraindicated or inadequate

17.5.3. Filgrastim - NIVESTIM (CAP) - EMEA/H/C/001142/MEA 015.3

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Kirsti Villikka

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

17.5.4. Golimumab - SIMPONI (CAP) - EMEA/H/C/000992/MEA 027.6

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Annual progress report of the ENEIDA registry (study MK-8259-042): a long-term, non-interventional observational study of patients with inflammatory bowel disease (IBD) in Spain to evaluate whether the use of golimumab is associated with a risk of colectomy for intractable disease, advanced neoplasia (colorectal cancer or high grade dysplasia), and

hepatosplenic T-cell lymphoma (HSTCL) in patients with ulcerative colitis (UC) as compared with alternative therapies for similar severity of disease [final clinical study report (CSR) expected: March 2023]

17.5.5. Imatinib - GLIVEC (CAP) - EMEA/H/C/000406/ANX 191.7

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Eva Segovia

Scope: Fifth progress report for study CSTI571I2201: a European observational registry collecting efficacy and safety data in newly diagnosed paediatric Philadelphia positive (Ph+) acute lymphoblastic leukaemia (ALL) patients treated with chemotherapy + imatinib ± haematopoietic stem cell treatment (±HSCT)

17.5.6. Infliximab - INFLECTRA (CAP) - EMEA/H/C/002778/MEA 007.4

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Patrick Batty

Scope: MAH's response to MEA 007.3 [annual interim safety and efficacy report for registry CT-P13 4.2: an observational, prospective cohort study to evaluate safety and efficacy of Inflectra (infliximab) in patients with rheumatoid arthritis (EU and Korea) [final report expected: May 2026]] as per the request for supplementary information (RSI) adopted in September 2018

17.5.7. Infliximab - INFLECTRA (CAP) - EMEA/H/C/002778/MEA 010.4

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Patrick Batty

Scope: MAH's response to MEA 010.3 [annual interim safety and efficacy report for registry CT-P13 4.3: an observational, prospective cohort study to evaluate the safety and efficacy of Inflectra (infliximab) in patients with Crohn's disease (CD), and ulcerative colitis (UC) (EU and Korea) [final report expected: May 2026]] as per the request for supplementary information (RSI) adopted in September 2018

17.5.8. Infliximab - REMSIMA (CAP) - EMEA/H/C/002576/MEA 007.4

Applicant: Celltrion Healthcare Hungary Kft.

PRAC Rapporteur: Patrick Batty

Scope: MAH's response to MEA 007.3 [annual interim safety and efficacy report for registry CT-P13 4.2: an observational, prospective cohort study to evaluate safety and efficacy of Inflectra (infliximab) in patients with rheumatoid arthritis (EU and Korea) [final clinical study report (CSR) expected: May 2026]] as per the request for supplementary information (RSI) adopted in September 2018

17.5.9. Infliximab - REMSIMA (CAP) - EMEA/H/C/002576/MEA 010.4

Applicant: Celltrion Healthcare Hungary Kft.

PRAC Rapporteur: Patrick Batty

Scope: MAH's response to MEA 010.3 [annual interim safety and efficacy report for registry CT-P13 4.3: an observational, prospective cohort study to evaluate the safety and efficacy of Inflectra (infliximab) in patients with Crohn's disease (CD), and ulcerative colitis (UC) (EU and Korea) [final report expected: May 2026]] as per the request for supplementary information (RSI) adopted in September 2018

17.5.10. Liraglutide - SAXENDA (CAP) - EMEA/H/C/003780/MEA 015.3

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to MEA 015.2 [interim results for study NN8022-4246: a drug utilisation study (DUS) in the UK using UK clinical practice research datalink (CPRD) database evaluating if liraglutide (Saxenda) is used according to approved indication and posology and if liraglutide (Victoza) is used for weight management] as per the request for supplementary information (RSI) adopted in September 2018

17.5.11. Lumacaftor, ivacaftor - ORKAMBI (CAP) - EMEA/H/C/003954/ANX 003.2

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Annual report for study VX14 809 108: an observational study to evaluate the utilisation patterns and long-term effects of lumacaftor/ivacaftor therapy in patients with cystic fibrosis (CF) [final report expected: December 2021]

17.5.12. Naloxegol - MOVENTIG (CAP) - EMEA/H/C/002810/MEA 002.4

Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Ronan Grimes

Scope: Annual progress report for PASS D3820R00006: a post-marketing observational drug utilisation study (DUS) of Moventig (naloxegol) conducted in selected European populations in order to describe demographic, clinical, and treatment characteristics in the baseline of patients treated with naloxegol as well as to describe treatment pattern characteristics of naloxegol utilisation at initiation and follow-up

17.5.13. Naloxegol - MOVENTIG (CAP) - EMEA/H/C/002810/MEA 006.7

Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Ronan Grimes

Scope: Annual progress report for study D3820R00009: an observational PASS of Moventig (naloxegol) among patients aged 18 years and older treated with opioids chronically

17.5.14. Rituximab - RIXATHON (CAP) - EMEA/H/C/003903/MEA 005

Applicant: Sandoz GmbH

PRAC Rapporteur: Doris Stenver

Scope: First interim report for a category 3 study in the RMP from the British Society for Rheumatology Biologicals Register (BSRBR), Register for Antirheumatic Therapies in Sweden (ARTIS) and German Register for Rheumatoid Arthritis Observation of Biologic Therapy (RABBIT) (from initial opinion/MA) [final report expected: December 2022]

17.5.15. Rituximab - RIXIMYO (CAP) - EMEA/H/C/004729/MEA 005

Applicant: Sandoz GmbH

PRAC Rapporteur: Doris Stenver

Scope: First interim report for a category 3 study in the RMP from the British Society for Rheumatology Biologicals Register (BSRBR), Register for Antirheumatic Therapies in Sweden (ARTIS) and German Register for Rheumatoid Arthritis Observation of Biologic Therapy (RABBIT) (from initial opinion/MA) [final report expected: December 2022]

17.5.16. Sebelipase alfa - KANUMA (CAP) - EMEA/H/C/004004/ANX 001.2

Applicant: Alexion Europe SAS

PRAC Rapporteur: Ulla Wändel Liminga

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

17.5.17. Simoctocog alfa - NUWIQ (CAP) - EMEA/H/C/002813/MEA 004.4

Applicant: Octapharma AB

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Study progress report for study GENA-99: a prospective, multinational, non-interventional post-authorisation study to document the long-term immunogenicity, safety, and efficacy of simoctocog alfa in patients with haemophilia A treated in routine clinical practice [final report due date expected: 2020]

17.5.18. Simoctocog alfa - VIHUMA (CAP) - EMEA/H/C/004459/MEA 004.3

Applicant: Octapharma AB

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Study progress report for study GENA-99: a prospective, multinational, non-interventional post-authorisation study to document the long-term immunogenicity, safety, and efficacy of simoctocog alfa in patients with haemophilia A treated in routine clinical practice [final report due date expected: 2020]

17.5.19. Teriflunomide - AUBAGIO (CAP) - EMEA/H/C/002514/MEA 005

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Martin Huber

Scope: Annual progress report 2018 for study OBS13499 (US/CA): teriflunomide pregnancy outcome exposure registry: a 'teratology information specialists (OTIS)' autoimmune diseases in pregnancy project and study OBS12751 (international): an international pregnancy exposure registry of women with multiple sclerosis (MS) exposed to Aubagio (teriflunomide)

17.5.20. Teriflunomide - AUBAGIO (CAP) - EMEA/H/C/002514/MEA 006

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Martin Huber

Scope: Annual progress report 2018 for study OBS12753: a prospective cohort study of long-term safety of Aubagio (teriflunomide) in multiple sclerosis (MS) patients in Europe

17.6. Others

17.6.1. Estrogens conjugated, bazedoxifene - DUAVIVE (CAP) - EMEA/H/C/002314/MEA 002.10

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Martin Huber

Scope: MAH's feasibility analyses to add a second/third US healthcare claim data sources to the ongoing US non-interventional PASS (B2311060 study, listed as category 3 study in the RMP): an active surveillance of conjugated oestrogens (CE)/bazedoxifene acetate (BZA) using US healthcare data

17.6.2. Reslizumab - CINQAERO (CAP) - EMEA/H/C/003912/MEA 005.4

Applicant: Teva B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: MAH's response to MEA 005.3 [feasibility assessment conducted in US healthcare databases as per the agreed protocol (final version dated 25 May 2017) for study C38072-AS-50027 (listed as category 3 study in the RMP): a long-term non-interventional cohort study comparing the risk of malignancy in severe asthma patients treated with reslizumab and patients not treated with reslizumab using secondary administrative healthcare data [final clinical study report (CSR) expected: January 2020]]

17.7. New Scientific Advice

None

17.8. Ongoing Scientific Advice

None

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

None

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. Galsulfase - NAGLAZYME (CAP) - EMEA/H/C/000640/S/0073 (without RMP)

Applicant: BioMarin International Limited

PRAC Rapporteur: Patrick Batty

Scope: Annual reassessment of the marketing authorisation

18.1.2. Idebenone - RAXONE (CAP) - EMEA/H/C/003834/S/0012 (without RMP)

Applicant: Santhera Pharmaceuticals (Deutschland) GmbH

PRAC Rapporteur: Amelia Cupelli

Scope: Annual reassessment of the marketing authorisation

18.1.3. Mecasermin - INCRELEX (CAP) - EMEA/H/C/000704/S/0055 (with RMP)

Applicant: Ipsen Pharma

PRAC Rapporteur: Kirsti Villikka

Scope: Annual reassessment of the marketing authorisation

18.1.4. Susoctocog alfa - OBIZUR (CAP) - EMEA/H/C/002792/S/0023 (without RMP)

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Annual reassessment of the marketing authorisation

18.1.5. Tocofersolan - VEDROP (CAP) - EMEA/H/C/000920/S/0031 (without RMP)

Applicant: Orphan Europe SARL

PRAC Rapporteur: Melinda Palfi

Scope: Annual reassessment of the marketing authorisation

18.2. Conditional renewals of the marketing authorisation

18.2.1. Parathyroid hormone - NATPAR (CAP) - EMEA/H/C/003861/R/0016 (without RMP)

Applicant: Shire Pharmaceuticals Ireland Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Annual renewal of the conditional marketing authorisation

18.3. Renewals of the marketing authorisation

18.3.1. Dolutegravir, abacavir, lamivudine - TRIUMEQ (CAP) - EMEA/H/C/002754/R/0063 (with RMP)

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Martin Huber

Scope: 5-year renewal of the marketing authorisation

18.3.2. Idelalisib - ZYDELIG (CAP) - EMEA/H/C/003843/R/0043 (with RMP)

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Patrick Batty

Scope: 5-year renewal of the marketing authorisation

18.3.3. Pandemic influenza vaccine (H5N1) (live attenuated, nasal) - PANDEMIC INFLUENZA VACCINE H5N1 ASTRAZENECA (CAP) - EMEA/H/C/003963/R/0019 (with RMP)

Applicant: AstraZeneca AB

PRAC Rapporteur: Daniela Philadelphy

Scope: 5-year renewal of the marketing authorisation

18.3.4. Simoctocog alfa - NUWIQ (CAP) - EMEA/H/C/002813/R/0027 (without RMP)

Applicant: Octapharma AB

PRAC Rapporteur: Ulla Wändel Liminga

Scope: 5-year renewal of the marketing authorisation

19. Annex II – List of participants

including any restrictions with respect to involvement of members / alternates / experts following evaluation of declared interests for the 11-14 February 2019 meeting.

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Sabine Straus	Chair	The Netherlands	No interests declared	Full involvement
Jan Neuhauser	Member	Austria	No interests declared	Full involvement
Jean-Michel Dogné	Member	Belgium	No interests declared	Full involvement
Laurence de Fays	Alternate	Belgium	No interests declared	Full involvement
Nikica Mirošević Skvrce	Member	Croatia	No interests declared	Full involvement
Željana Margan Koletić	Alternate	Croatia	No interests declared	Full involvement
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 Kirstine Stark	Alternate	Denmark	No restrictions applicable to this meeting	Full involvement
Maia Uusküla	Member	Estonia	No interests declared	Full involvement
Katrin Kiisk	Alternate	Estonia	No interests declared	Full involvement
Kirsti Villikka	Member	Finland	No interests declared	Full involvement
Kimmo Jaakkola	Alternate	Finland	No interests declared	Full involvement
Ghania Chamouni	Member	France	No participation in discussion, final deliberations and voting on:	17.4.2. Colistimethate sodium - COLOBREATHE (CAP)
Adrien Inoubli	Alternate	France	No interests declared	Full involvement
Martin Huber	Member (Vice-Chair)	Germany	No interests declared	Full involvement
Brigitte Keller-Stanislawski	Alternate	Germany	No interests declared	Full involvement
Sophia Trantza	Alternate	Greece	No participation in discussion, final deliberations and voting on:	4.2.3. Olanzapine - OLANZAPINE APOTEX (CAP), OLANZAPINE GLENMARK (CAP), OLANZAPINE

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				GLENMARK EUROPE (CAP), OLANZAPINE MYLAN (CAP), OLANZAPINE TEVA (CAP), OLAZAX (CAP), OLAZAX DISPERZI (CAP), ZALASTA (CAP), ZYPADHERA (CAP), ZYPREXA (CAP), ZYPREXA VELOTAB (CAP); NAP 4.3.1. Olanzapine – OLANZAPINE APOTEX (CAP), OLANZAPINE GLENMARK (CAP), OLANZAPINE GLENMARK EUROPE (CAP), OLANZAPINE MYLAN (CAP), OLANZAPINE TEVA (CAP), OLAZAX (CAP), OLAZAX DISPERZI (CAP), ZALASTA (CAP) - EMEA/H/C/000792/SDA/007, ZYPADHERA (CAP) - EMEA/H/C/000890/SDA/029, ZYPREXA (CAP), NAP 11.2.1. Atorvastatin (NAP)
Julia Pallos	Member	Hungary	No interests declared	Full involvement
Guðrún Stefánsdóttir	Member	Iceland	No participation in discussion, final deliberations and voting on:	11.1.1. Leuprorelin (NAP) 16.3.20. Solifenacin, tamsolusin (NAP)

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
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
Rugile Pilviniene	Member	Lithuania	No interests declared	Full involvement
Marcel Bruch	Member	Luxembourg	No interests declared	Full involvement
John Joseph Borg	Member	Malta	No interests declared	Full involvement
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 discussion, final deliberations and voting on:	6.3.5. Paracetamol, pseudoephedrine (NAP) 6.3.6. Pseudoephedrine (CAP); acetylsalicylic acid, pseudoephedrine (NAP) 7.1.2. Damoctocog alfa pegol - JIVI (CAP) 17.2.1. Aflibercept - EYLEA (CAP) 15.3.18. Interferon beta-1b - BETAFERON (CAP) 16.3.4. Dexchlorpheniramine (NAP)
Karen Pernille Harg	Alternate	Norway	No interests declared	Full involvement
Katarzyna Ziolkowska	Alternate	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

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Roxana Stefania Stroe	Member	Romania	No interests declared	Full involvement
Alexandra - Maria Spurni	Alternate	Romania	No interests declared	Full involvement
Michal Radik	Member	Slovakia	No restrictions applicable to this meeting	Full involvement
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 restrictions applicable to this meeting	Full involvement
Livia Puljak	Member	Independent scientific expert	No interests declared	Full involvement
Raymond Anderson	Member	Healthcare Professionals' Representative	No interests declared	Full involvement
Marco Greco	Member	Patients' Organisation Representative	No interests declared	Full involvement
Fabrice Moore	Expert - via telephone*	Belgium	No interests declared	Full involvement
Françoise Wuillaume	Expert - via telephone*	Belgium	No interests declared	Full involvement
Benjamin Burrus	Expert - via telephone*	France	No interests declared	Full involvement
Marie-Caroline Pesquidous	Expert - in person*	France	No restrictions applicable to	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			this meeting	
Christine Diesinger	Expert - via telephone*	Germany	No interests declared	Full involvement
Maxim Frizler	Expert - via telephone*	Germany	No interests declared	Full involvement
Claudia Kayser	Expert - via telephone*	Germany	No interests declared	Full involvement
Anne Kleinau	Expert - via telephone*	Germany	No interests declared	Full involvement
Kerstin Loschcke	Expert - via telephone*	Germany	No interests declared	Full involvement
Jens Rotthauwe	Expert - via telephone*	Germany	No interests declared	Full involvement
Wiebke Seemann	Expert - via telephone*	Germany	No interests declared	Full involvement
Karin Seifert	Expert - in person*	Germany	No interests declared	Full involvement
Valerie Strassmann	Expert - in person*	Germany	No interests declared	Full involvement
Odoardo Maria Olimpieri	Expert - in person*	Italy	No interests declared	Full involvement
Marloes Bazelier	Expert - via telephone*	Netherlands	No interests declared	Full involvement
Rune Kjeken	Expert - in person*	Norway	No restrictions applicable to this meeting	Full involvement
Dolores Montero Corominas	Expert - in person*	Spain	No interests declared	Full involvement
Laura Oliveira Santamaria	Expert - via telephone*	Spain	No restrictions applicable to this meeting	Full involvement
Katarina Andersson	Expert - via telephone*	Sweden	No interests declared	Full involvement
Charlotte Backman	Expert - in person*	Sweden	No interests declared	Full involvement
Karl-Mikael Kälkner	Expert - via telephone*	Sweden	No interests declared	Full involvement
Helena Tidlund	Expert - via telephone*	Sweden	No interests declared	Full involvement
Jo Lyn Chooi	Expert - in person*	United Kingdom	No interests declared	Full involvement
Nourieh Hoveyda	Expert - in	United Kingdom	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
	person*			
Andrew Ruddick	Expert - in person*	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/