9 February 2017
EMA/PRAC/243286/2017
Inspections, Human Medicines Pharmacovigilance and Committees Division

Pharmacovigilance Risk Assessment Committee (PRAC)

Minutes of the meeting on 9-12 January 2017

Chair: June Raine – Vice-Chair: Almath Spooner

Health and safety information

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

Disclaimers

Some of the information contained in this agenda 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, this agenda is a working document primarily designed for PRAC members and the work the Committee undertakes.

Note on access to documents

Some documents mentioned in the agenda 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).

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1. Introduction

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

The Chairperson opened the 9-12 January 2017 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 (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 Ana Sofia Diniz Martins, replacing Margarida Guimarães, as the new member for Portugal and Marcia Sofia Sanches de Castro Lopes Silva, replacing Leonor Chambel, as the new alternate for Portugal. The PRAC Chair also announced that Miroslava Matíková was to step down as PRAC alternate for Slovakia after the current PRAC plenary meeting. The PRAC thanked her for her contribution to the work of the Committee.

Finally, the PRAC welcomed the new Maltese presidency of the Council of the EU.

1.2. Adoption of agenda of the meeting of 9 - 12 January 2017

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

1.3. Adoption of the minutes of the previous meeting of 28 November - 1 December 2016

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 28 November-1 December 2016 were published on the EMA website on 10 April 2017 (EMA/PRAC/237221/2017).

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

2.1. Newly triggered procedures

None

2.2. Ongoing procedures

None

2.3. Procedures for finalisation

None

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. Human coagulation (plasma-derived) factor VIII: human coagulation factor VIII (antihemophilic factor A) (NAP); human coagulation factor VIII (inhibitor bypassing fraction) (NAP); human coagulation factor VIII, human von Willebrand factor - VONCENTO (CAP) Recombinant factor VIII: antihemophilic factor (recombinant) (NAP); moroctocog alfa – REFACTO AF (CAP) octocog alfa – ADVATE (CAP), HELIXATE NEXGEN (CAP), IBLIAS (CAP), KOGENATE (CAP), KOVALTRY (CAP) - EMEA/H/A-31/1448

Applicant: Baxter AG (Advate), Bayer Pharma AG (Helixate Nexgen, Iblias, Kogenate, Kovaltry), CSL Behring GmbH (Voncento), Pfizer Limited (Refacto AF), various

PRAC Rapporteur: Rafe Suvarna; PRAC Co-rapporteur: Brigitte Keller-Stanislawski

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

Background

A referral procedure under Article 31 of Directive 2001/83/EC is ongoing for the review of factor VIII-containing medicines indicated for the treatment of haemophilia A to assess the impact of the results of the SIPPET study by *Peyvandi et al*.[1] recently published in the New England Journal of Medicine, with further consideration of any potential for risk minimisation measures or other changes to the marketing authorisations of these medicinal products. For further background, see PRAC minutes July 2016 and PRAC minutes November 2016.

Summary of recommendation(s)/conclusions

The PRAC reviewed the list of experts for the ad-hoc expert group meeting scheduled on 22 February 2017. The final list is to be adopted at the February 2017 PRAC meeting. In

[1] F. Peyvandi et al. A randomized trial of factor VIII and neutralizing antibodies in hemophilia A. N. Eng.l J. Med. 2016 May 26;374(21):2054-64) (SIPPET study)

addition, the PRAC adopted a second list of questions (LoQ) to the authors of the SIPPET study.

3.2.2. Retinoids: acitretin (NAP); adapalene (NAP); alitretinoin - PANRETIN (CAP); bexarotene – TARGRETIN (CAP); isotretinoin (NAP); tazarotene (NAP); tretinoin (NAP) - EMEA/H/A-31/1446

Applicant: Eisai Ltd (Panretin, Targretin), various

PRAC Rapporteur: Ana Sofia Diniz Martins; PRAC Co-rapporteur: Julie Williams

Scope: Review of the benefit-risk balance following notification by the United Kingdom 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 retinoid-containing medicines (acitretin; adapalene; alitretinoin; bexarotene; isotretinoin; tazarotene; tretinoin) indicated for the treatment of several conditions mainly affecting the skin such as acne, severe chronic hand eczema unresponsive to corticosteroids, severe forms of psoriasis and keratinisation disorders[2] to evaluate measures currently in place for pregnancy prevention and the possible risk of neuropsychiatric disorders for oral and topical retinoids. For further background, see PRAC minutes July 2016, PRAC minutes September 2016, PRAC Minutes October 2016 and PRAC minutes December 2016.

Summary of recommendation(s)/conclusions

The PRAC adopted a second list of questions (LoQ) for the meeting with stakeholders entitled 'engagement with HCPs and patients targeted meeting' focussed on teratogenic effects scheduled on 3 March 2017.

3.3. Procedures for finalisation

None

3.4. Article 5(3) of Regulation (EC) No 726/2004 as amended: PRAC advice on CHMP request

None

3.5. Others

None

[2] Tretinoin may also be used to treat promyelocytic leukaemia

4. Signals assessment and prioritisation[3]

4.1. New signals detected from EU spontaneous reporting systems

See Annex I 14.1.

4.2. New signals detected from other sources

See Annex I 14.2.

4.3. Signals follow-up and prioritisation

4.3.1. Azacitidine – VIDAZA (CAP) - EMEA/H/C/000978/SDA/031

Applicant: Celgene Europe Limited

PRAC Rapporteur: Sabine Straus

Scope: Signal of pericarditis and pericardial effusion

EPITT 18733 – Follow-up to September 2016

Background

The MAH replied to the request for information on the signal of pericarditis and pericardial effusion and the responses were assessed by the Rapporteur. For background information, see PRAC minutes September 2016.

Discussion

Having considered the data submitted by the MAH of Vidaza (azacitine), the PRAC considered that despite the presence of confounding factors and taking into account the imbalance observed in the clinical trial database for reports of pericardial effusion, the available evidence suggests a possible causal association between azacitidine and pericardial effusion. Therefore, the PRAC agreed that the product information should be amended to reflect pericardial effusion as an undesirable effect.

Summary of recommendation(s)

- The MAH for Vidaza (azacitine) should submit to EMA, within 60 days, a variation[4] to amend the product information to add 'pericardial effusion' as an undesirable effect with a common frequency.

For the full PRAC recommendation, see EMA/PRAC/5653/2017 published on 06/02/2017 on the EMA website.

4.3.2. Darbepoetin alfa - ARANESP (CAP) - EMEA/H/C/000332/SDA/090

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Valerie Strassmann

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

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

Scope: Signal of incorrect use of device associated with adverse reactions including underdose, drug dose omission, accidental exposure to product and injection site reactions

EPITT 18718 – Follow-up to September 2016

Background

The MAH replied to the request for information on the signal of incorrect use of device associated with adverse reactions including underdose, drug dose omission, accidental exposure to product and injection site reactions and the responses were assessed by the Rapporteur. For background information, see PRAC minutes September 2016.

Discussion

Having considered the data submitted by the MAH of Aranesp (darbepoetin alfa), the PRAC agreed that, in light of the available evidence from the cumulative review of cases, the product information of Aranesp should be amended to reflect 'injection site bruising' and 'injection site haemorrhage' as undesirable effects and the user manual part of the package leaflet should be revised with further consideration of user testing results.

Summary of recommendation(s)

- The MAH for Aranesp (darbepoetin alfa) should submit to EMA, within 120 days, a variation[5] updating the product information to add 'injection site bruising' and 'injection site haemorrhage' as undesirable effects with an unknown frequency, and revise the user manual part of the package leaflet with further consideration of user testing results. The variation should also include a discussion on the need for inclusion of a warning regarding the importance of adequate instructions on device handling. Moreover, it should include results of further research on the effectiveness of training tools as well as a discussion on the need for additional risk minimisation. Finally, the MAH should provide a detailed review of the type of device malfunctions reported and their outcomes, including a discussion on the need for further risk minimisation regarding this issue.
- In the next PSUR, the MAH should closely monitor cases of use errors with pre-filled syringes and provide a detailed review of user errors with pre-filled syringe use (DLP: 31/10/2017).

For the full PRAC recommendation, see EMA/PRAC/5653/2017 published on 06/02/2017 on the EMA website.

4.3.3. Fluconazole (NAP)

Applicant: various

PRAC Rapporteur: Doris Stenver

Scope: Signal of spontaneous abortion and stillbirth

EPITT 18666 – Follow-up to May 2016

Background

The MAH replied to the request for information on the signal of spontaneous abortion and stillbirth and the responses were assessed by the Rapporteur. For background information, see PRAC minutes May 2016.

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

Discussion

Having considered the available evidence, including the review and assessment of the register-based cohort study[6] as well as the cumulative review of all available data from clinical trials, post-marketing data and literature publications concerning the risk following exposure to fluconazole during pregnancy, the PRAC agreed that further consideration is warranted before recommending updating of the product information of fluconazole-containing products in order to accurately reflect the available evidence on the risks of fluconazole in pregnancy. The PRAC acknowledged that the signal had been triggered by a well conducted observational study, but noted some limitations, in particular that there was insufficient evidence to support a dose relationship based on the study. The PRAC considered on the basis of the available evidence that there was insufficient justification for adding a new requirement for effective contraception and MAH's responses received in this respect.

Summary of recommendation(s)

- The MAH for the innovator fluconazole-containing product (Pfizer) should submit to EMA, within 15 days, a refined proposal for updating the product information.
- Further PRAC recommendation is planned in February 2017.

4.3.4. Lenalidomide – REVLIMID (CAP) - EMEA/H/C/000717/SDA/048

Applicant: Celgene Europe Limited

PRAC Rapporteur: Claire Ferard

Scope: Signal of hemophagocytic lymphohistiocytosis (HLH)

EPITT 18689 – Follow-up to September 2016

Background

The MAH replied to the request for information on the signal of hemophagocytic lymphohistiocytosis (HLH) and the responses were assessed by the Rapporteur. For background information, see PRAC minutes September 2016.

Discussion

Having considered the available evidence from the cumulative review of clinical data from all sources including spontaneous reports, clinical trials and relevant literature provided by the MAH for Revlimid (lenalidomide), the PRAC agreed that the likelihood of a causal relationship between the treatment with lenalidomide and hemophagocytic lymphohistiocytosis is not sufficiently strong to warrant changes to the product information at this stage.

Summary of recommendation(s)

- The MAH for Revlimid (lenalidomide) should continue to monitor these events as part of its routine safety surveillance activities. For the next PSUR, the MAH should review and present any emerging data of significance, including new studies and published literature.

For the full PRAC recommendation, see EMA/PRAC/5653/2017 published on 06/02/2017 on the EMA website.

[6] Mølgaard-Nielsen D et al. Association between use of oral fluconazole during pregnancy and risk of spontaneous abortion and stillbirth. JAMA 2016; 315(1); 58-67

4.3.5. Paracetamol (NAP)

Applicant: various

PRAC Rapporteur: Laurence de Fays

Scope: Signal of paracetamol use in pregnancy and child neurodevelopment

EPITT 17796 – Follow-up to October 2016

Background

Since the PRAC recommendation dated May 2014 on paracetamol and the signal on 'drug exposure in pregnancy' (see PRAC minutes May 2014), results of several epidemiological studies investigating the effect of exposure to paracetamol during pregnancy and neurodevelopmental outcomes in childhood have become available[7]. The Rapporteur further assessed the newly available data, taking into account the findings and limitations of the studies. For background information, see PRAC minutes October 2016.

Discussion

Having considered the Rapporteur's review of newly published epidemiological studies of the association between paracetamol use during pregnancy and neurodevelopmental outcomes in children, the PRAC agreed that a causal relationship between paracetamol exposure during pregnancy and neurodevelopmental outcomes could not be established.

Summary of recommendation(s)

- The PRAC considered that there was insufficient evidence provided by the studies due to their limitations including the heterogeneity of outcomes, the weak associations observed, the potential of confounding by indication and its severity, the potential role of genetic factors, and the potential of unmeasured and residual confounding (including determinants such as maternal psychiatric illness, family related stress, maternal smoking and alcohol consumption during pregnancy).
- The PRAC advice for paracetamol use in pregnancy remains unchanged (see PRAC minutes May 2014): paracetamol can be used during pregnancy if clinically needed, however, as with any medicine it should be used at the lowest effective dose for the shortest possible time.

For the full PRAC recommendation, see EMA/PRAC/5653/2017 published on 06/02/2017 on the EMA website.

4.3.6. Propofol (NAP); valproate (NAP)

Applicant: various

[7] Liew Z et al. Maternal use of acetaminophen during pregnancy and risk of autism spectrum disorders in childhood: A Danish national birth cohort study. Autism Res. 2016;9:951–958
Liew Z et al. Prenatal use of acetaminophen and child intelligence quotient (IQ): A Danish cohort study. Epidemiology. 2016 Nov;27(6):912-918.
Avella-Garcia C. et al. Acetaminophen use in pregnancy and neurodevelopment: attention function and autism spectrum symptoms. Int. J. Epidemiol. 2016 Jun 28. pii: dyw115.
Stergiakouli E., Thapar A., Smith G.D. Association of acetaminophen use during pregnancy with behavioural problems in childhood evidence against confounding. JAMA Pediatr. 2016 Aug 15. doi:10.1001/jamapediatrics.2016.1775
Thompson JM et al. Associations between acetaminophen use during pregnancy and attention deficit hyperactivity disorder (ADHD) symptoms measured at ages 7 and 11 years. PLoS One. 2014 Sep 24; 9(9): e108210.
Vlenterie R et al. Neurodevelopmental problems at 18 months among children exposed to paracetamol in utero: a propensity score matched cohort study. Int J Epidemiol. 2016, 1–11 doi: 10.1093/ije/dyw192

PRAC Rapporteur: Helga Haugom Olsen

Scope: Signal of drug interaction leading to a reduction in the required dose of propofol

EPITT 18696 – Follow-up to September 2016

Background

The MAH for the originator of propofol-containing medicinal product (Diprivan) replied to the request for information on the signal of drug interaction leading to a reduction in the dose of propofol needed for anaesthesia and the responses were assessed by the Rapporteur. For background information, see PRAC minutes September 2016.

Discussion

Having considered the available evidence from the literature on the drug interaction between propofol and valproate, the PRAC agreed that the product information of propofol-containing medicinal products should be updated in order to include advice that consideration of a dose reduction of propofol may be needed when administered concomitantly in patients taking valproate.

Summary of recommendation(s)

- The MAHs for propofol-containing medicinal products should submit to national competent authorities of the Member States, within 60 days, a variation[8] to update the product information in order to add the interaction observed between propofol and valproate and that consideration may be given to reduce the dose of propofol when concomitantly used with valproate.

For the full PRAC recommendation, see EMA/PRAC/5653/2017 published on 06/02/2017 on the EMA website.

4.3.7. Proton pump inhibitors (PPIs): dexlansoprazole (NAP); esomeprazole – NEXIUM CONTROL (CAP) NAP; lansoprazole (NAP); omeprazole (NAP); pantoprazole – CONTROLOC CONTROL (CAP) - EMEA/H/C/001097/SDA/016, PANTECTA CONTROL (CAP) - EMEA/H/C/001099/SDA/016, PANTOLOC CONTROL (CAP) - EMEA/H/C/001100/SDA/015, PANTOZOL CONTROL (CAP) - EMEA/H/C/001013/SDA/016, SOMAC CONTROL (CAP) - EMEA/H/C/001098/SDA/021, NAP; rabeprazole (NAP)

Applicants: Pfizer Consumer Healthcare Ltd (Nexium Control), Takeda GmbH (Controloc Control, Pantecta Control, Pantoloc Control, Pantozol Control, Somac Control), various

PRAC Rapporteur: Rafe Suvarna

Scope: Signal of incident chronic kidney disease (CKD) and progression to end stage renal disease (ESRD)

EPITT 18698 – Follow-up to September 2016

Background

The MAHs replied to the request for information on the signal of incident chronic kidney disease (CKD) and progression to end stage renal disease (ESRD) and the responses were

[8] Update of SmPC section 4.5

assessed by the Rapporteur. For background information, see PRAC minutes September 2016.

Discussion

Having considered the data from clinical trials with proton pump inhibitors (PPIs) provided by MAHs in their cumulative reviews, together with the evidence from observational studies, the PRAC concluded that in light of the current knowledge, there is insufficient evidence for a causal relationship between PPIs and incident CKD and progression to ESRD to warrant an update of the product information or any additional risk minimisation measure.

Summary of recommendation(s)

- The MAHs of PPI (dexlansoprazole-, esomeprazole-, lansoprazole-, omeprazole-, pantoprazole-, rabeprazole-) containing products should continue to monitor these events as part of their routine pharmacovigilance activities. In next PSURs, the MAHs should review and present any emerging data of significance, including new studies, and published literature.

For the full PRAC recommendation, see EMA/PRAC/5653/2017 published on 06/02/2017 on the EMA website.

5. Risk management plans (RMPs)

5.1. Medicines in the pre-authorisation phase

See also Annex I Medicines in the pre-authorisation phase15.1.

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

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

5.1.1. Glibenclamide - EMEA/H/C/004379, Orphan

Applicant: Pharma Services

Scope accelerated assessment: Treatment of neonatal diabetes

5.1.2. Meningococcal group B vaccine (recombinant, component, adsorbed) - EMEA/H/C/004051

Scope: Active immunisation of individuals of 10 to 40 years of age to prevent invasive meningococcal disease caused by *Neisseria meningitidis* serogroup B

5.1.3. Methotrexate – EMEA/H/C/003756

Scope: Treatment of rheumatological, dermatological and oncological diseases

5.1.4. Nusinersen - EMEA/H/C/004312, Orphan

Applicant: Biogen Idec Ltd

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

5.1.5. Tivozanib hydrochloride monohydrate - EMEA/H/C/004131, Orphan

Applicant: EUSA Pharma

Scope: Treatment of adult patients with advanced renal cell carcinoma (RCC)

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

See Annex I 15.2.

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

See Annex I 15.3.

6. Periodic safety update reports (PSURs)

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

See also Annex I 16.1.

6.1.1. Belatacept - NULOJIX (CAP) - PSUSA/00000311/201606 (with RMP)

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Background

Belatacept is a selective costimulation blocker indicated, in combination with corticosteroids and a mycophenolic acid (MPA), for prophylaxis of graft rejection in adults receiving a renal transplant.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Nulojix (belatacept) in the approved indication(s) remains unchanged.

- Nevertheless, the product information should be updated to reflect the reporting of a case of anaphylaxis during belatacept infusion. Therefore the current terms of the marketing authorisation(s) should be varied[9].
- The MAH should submit to EMA, within 60 days, a detailed review on the potential increased risk for allograft thrombosis when belatacept is co-administered with anti-thymocyte globulin. The MAH should also propose to update the product information and/or the RMP as applicable.
- In the next PSUR, the MAH should monitor 'venous thrombosis of the allograft' as a safety concern.

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

6.1.2. Cabazitaxel - JEVTANA (CAP) - PSUSA/00000476/201606

Applicant: Sanofi-Aventis Groupe

PRAC Rapporteur: Claire Ferard

Scope: Evaluation of a PSUSA procedure

Background

Cabazitaxel is an antineoplasic agent indicated in combination with prednisone or prednisolone for the treatment of adult patients with hormone refractory metastatic prostate cancer previously treated with a docetaxel-containing regime.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Jevtana, a centrally authorised medicine containing cabazitaxel, 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 risk-benefit balance of Jevtana (cabazitaxel) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add 'cystitis due to radiation recall phenomenon' as an undesirable effect with an uncommon frequency. Therefore the current terms of the marketing authorisation(s) should be varied[10].
- In the next PSUR, the MAH should closely monitor cases of hepatic failure, pulmonary fibrosis, cardiac arrhythmia as well as of medication errors. The MAH should provide a detailed analysis of all adverse events that occurred in patients with hepatic impairment. Moreover, the MAH should provide results of a further survey conducted in hospital pharmacies where preparation errors were identified, in order to analyse the impact of the product information modifications as well as of the DHPC distributed in 2014. Finally, with regard to the reconstitution method, the MAH should provide clarification on the

[9] Update of SmPC sections 4.2, 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion
[10] 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

updated product information, packaging and risk minimisation measures implemented worldwide.

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

6.1.3. Influenza vaccine (intranasal, live attenuated) - FLUENZ TETRA (CAP) - PSUSA/00001742/201606

Applicant: MedImmune LLC

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

Background

Influenza vaccine (intranasal, live attenuated) is a tetravalent influenza live attenuated vaccine containing antigens for four influenza virus strains, an A/(H1N1) strain, an A/(H3N2) strain, and two B strains (one from each lineage) and is indicated in the prophylaxis of influenza in children and adolescents from 24 months to less than 18 years of age.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Fluenz Tetra, a centrally authorised vaccine, 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 risk-benefit balance of Fluenz Tetra (influenza vaccine (intranasal, live attenuated)) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- The MAH should submit to EMA, within 30 days, a list of hypotheses to be investigated with regard to the lower vaccine effectiveness than expected against A/H1N1pdm09 and an action plan. Moreover, the MAH should provide a critical discussion on the methodologies applied to the listed observational studies.
- In the next PSUR, the MAH should provide an analysis of reports of narcolepsy per influenza season preferably according to the date of onset of the medical condition.

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 PSUR should be changed from 6-monthly to 8-monthly and the list of Union reference dates (EURD list) will be updated accordingly. The frequency of submission of the following PSURs should be changed to yearly as this reporting period would cover the period of the vaccination campaign and the period of influenza outbreaks in the Northern Hemisphere, allowing collection of sufficient data for a thorough assessment of the benefit/risk balance of the vaccine at the end of the flu season.

6.1.4. Nivolumab - OPDIVO (CAP) - PSUSA/00010379/201607

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

Background

Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody (HuMAb) indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults in monotherapy or in combination with ipilimumab as well as for the treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy in adults. Nivolumab is also indicated for the treatment of advanced renal cell carcinoma after prior therapy in adults as monotherapy.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Opdivo (nivolumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to refine the warning on 'other immune related adverse reactions' to reflect that cases of 'encephalitis' were reported in less than 1% of patients treated with nivolumab monotherapy in clinical trials across doses and tumour types. 'Encephalitis' should be also added as an undesirable effect with a rare frequency for nivolumab monotherapy and with an uncommon frequency for the combination of nivolumab with ipilimumab.
- Therefore the current terms of the marketing authorisation(s) should be varied[11].
- In the next PSUR, the MAH should comment on reported cases of haemolytic anaemia and autoimmune haemolytic anaemia and provide the corresponding cumulative review. In addition, the MAH should closely monitor the adverse events of special interest 'pancytopenia' and 'agranulocytosis'. Moreover, the MAH should provide a cumulative search and evaluation of all cases of possible cardiotoxic events other than myocarditis.

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. Secukinumab - COSENTYX (CAP) - PSUSA/00010341/201606

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

Background

Secukinumab is a human immunoglobulin (Ig)G1/κ monoclonal antibody indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy and for the treatment, alone or in combination with methotrexate (MTX), of active

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

psoriatic arthritis in adult patients when the response to previous disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate. It is also indicated for the treatment of active ankylosing spondylitis in adults who have responded inadequately to conventional therapy.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Cosentyx, a centrally authorised medicine containing secukinumab, 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 risk-benefit balance of Cosentyx (secukinumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include 'mucosal and cutaneous candidiasis (including oesophageal candidiasis)' as an undesirable effect with an unknown frequency. Therefore the current terms of the marketing authorisation(s) should be varied[12].
- The MAH should submit to EMA, within 60 days, an updated RMP to include the important potential risk of 'suicidal ideation and behaviour'. The MAH should include a review on feasible pharmacovigilance activities to be developed to address this risk.
- In the next PSUR, the MAH should closely monitor cases reporting central nervous system (CNS) infection and inflammation and provide more information on cases of serious systemic mycosis and pyelonephritis. The MAH should propose to update the product information as appropriate to better reflect the known information on infections (including pneumonia and other respiratory infections). Moreover, the MAH should include a review investigating the pattern of distribution of gastrointestinal cancers found in the treated population. Finally, the MAH should discuss the need to update the current warning on Crohn's disease in the product information, given the post-marketing cases reported in addition to Crohn's disease such as ulcerative colitis, inflammatory bowel disease and haemorrhagic diarrhoea.

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

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

See Annex I 16.2.

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

See also Annex I 16.3.

[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

6.3.1. Budesonide (NAP) - PSUSA/00000449/201604

Applicant: various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

Background

Budesonide is a corticosteroid agent indicated for the treatment of various diseases of the respiratory system, the intestine and the skin, and for seasonal or non-seasonal allergic rhinitis, vasomotor rhinitis and nasal polyps as well as for the treatment of asthma. Additionally, in some countries, budesonide-containing medicinal products are indicated for the symptomatic treatment of chronic obstructive pulmonary disease (COPD), for the treatment of Crohn's disease, collagenous colitis, ulcerative colitis (UC) and autoimmune hepatitis, for the treatment of corticosteroid-responsive dermopathies (e.g. seborrheic dermatitis, atopic dermatitis, allergic or irritative contact dermatitis, lichen planus, psoriasis, neurodermatitis) and for the symptomatic treatment of pruritus.
Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing budesonide, 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 risk-benefit balance of budesonide-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include a warning on visual disturbance associated with central serous chorioretinopathy and to add blurred vision as an undesirable effect with a rare frequency for enteral and intranasal formulations of budesonide-containing medicinal products, and with an uncommon frequency for inhaled and dermatologic formulations of budesonide-containing medicinal products. Therefore the current terms of the marketing authorisation(s) of all formulations should be varied[13].
- In the next PSUR, MAHs should monitor the safety issues of 'menstrual disturbance' and 'diabetes and hyperglycaemia', present all relevant evidence for the safety issue 'palpitations', as well as perform a cumulative review of the safety issue 'bone density decreased' with an appropriate discussion. MAHs of enteral formulations of budesonide-containing medicinal products should discuss the risk of adrenal suppression with those formulations, and those with the text 'atrophy of the adrenal cortex' included in their product information should discuss how adrenal atrophy can occur outside the context of adrenal suppression. If this is not the case, the term adrenal suppression should be added to the product information. Moreover, MAHs of enteral forms of budesonide-containing medicinal products should provide a cumulative review and discussion on the safety issue 'infections'. Finally, MAHs of inhaled forms of budesonide-containing medicinal products should review all data on the extent of reduction in initial growth velocity in children and final adult height in the scientific literature. As a consequence, MAHs should propose to update the product information as applicable.

[13] 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

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. Goserelin (NAP) - PSUSA/00001562/201605

Applicant: various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Goserelin is a gonadotropin-releasing hormone (GnrH) analogue indicated for the treatment of hormone-dependent breast and prostate cancer. Furthermore, goserelin is indicated for the management of uterine fibroids, the management of endometriosis as an endometrial thinning agent prior to endometrial ablation and for assisted reproduction.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing goserelin, 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 risk-benefit balance of goserelin-containing medicinal products in the approved indications remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAHs should closely monitor cases of 'thyroid disorder', 'vasculitis', 'biliary disease' and 'acute kidney injury' (AKI) and discuss the potential association of these adverse drug reactions with goserelin. Moreover, the MAHs should monitor cases of medication errors related to wrong administration techniques. In addition, the MAHs should provide detailed reviews of cases of pneumonia further to the required monitoring of the issue and of suicidal behaviour given the requested monitoring of events related to suicidal behaviour, and the implementation of specific patient follow-up forms for suicidal behaviour in order to obtain more information on such cases.

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. Human hemin (NAP) - PSUSA/00001629/201605

Applicant: various

PRAC Lead: Claire Ferard

Scope: Evaluation of a PSUSA procedure

Background

Human hemin is a haematological agent indicated for the treatment of acute attacks of hepatic porphyria (acute intermittent porphyria, porphyria variegata, hereditary coproporphyria).

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing human hemin, 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 risk-benefit balance of human hemin-containing medicinal products in the approved indications remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAH(s) should monitor the important identified risk of thrombosis. Moreover, MAH(s) should provide cumulative reviews of all fatal cases and of all cardiac events. Furthermore, the MAH should provide a safety review of all cases of serious disorders and potential organ toxicity disorders (hepatic, pulmonary, renal, myocardial disorders) following long-term use and multiple dosing (especially in the case of prophylactic treatment) or overdose with Normosang (human hemin). A special focus should be given to the development of fibrosis. The role of hemin overload and of iron overload should be assessed. In addition, the MAH should provide an exhaustive review of the organ toxicity caused by porphyrogenic precursors in hepatic porphyria and provide an assessment of the potential role of the underlying disease in the cases of organ disorders reported with Normosang (human hemin).

The frequency of PSUR submission should be revised from three-yearly to yearly and the next PSUR should be submitted to EMA within 70 days of the data lock point. The list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC is updated accordingly.

6.3.4. Misoprostol[14] (NAP) - PSUSA/00010353/201605

Applicant: various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

Background

Misoprostol is a synthetic prostaglandin E1 analogue indicated[15] for the induction of labour in women with an unfavourable cervix, from 36 weeks gestation, in whom induction is clinically indicated as well as for expansion of the non-pregnant uterine cervix before hysteroscopy or other gynaecological procedures requiring access to the uterine cavity.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing misoprostol, and issued a recommendation on their marketing authorisations for gynaecological indication, labour induction.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of misoprostol-containing medicinal products in the approved indications remains unchanged.

[14] For gynaecological indication, labour induction
[15] Misoprostol is also authorised in other indications that are outside the scope of the current PSUSA procedure

- The current terms of the marketing authorisation(s) for gynaecological indication, labour induction should be maintained for the medicinal products containing misoprostol as vaginal tablet formulation.
- Nevertheless, for the medicinal products containing misoprostol as a 200 microgram vaginal insert formulation, the product information should be updated to reinforce the warning about the risk of uterine tachysystole to emphasise that excessive uterine tachysystole may occur with use of the medicinal product(s) and therefore close monitoring is recommended to ensure adequate removal of the vaginal delivery system at onset of labour or if uterine contractions are excessive. Therefore, the current terms of the marketing authorisation(s) for gynaecological indications, labour induction, and for the medicinal products containing misoprostol in a 200 microgram vaginal insert formulation should be varied[16].
- In the next PSUR, the MAH Ferring should present a cumulative review of Moebius II syndrome related to use of misoprostol during pregnancy earlier than 36 weeks of pregnancy and the MAH Laboratorios Bial is requested to present a cumulative review of postpartum haemorrhage in connection with use of misoprostol based on post-marketing cases and the literature. Moreover, MAHs should present and discuss all cases of medication error.

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. Moxifloxacin[17] (NAP) - PSUSA/00009231/201605

Applicant: various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Moxifloxacin is a fluoroquinolone antibiotic indicated for the treatment of bacterial infections in adults susceptible to moxifloxacin (systemic use) as a second line treatment option.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing moxifloxacin (systemic use), 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 risk-benefit balance of moxifloxacin-containing medicinal products for systemic use in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to modify the warnings on hypersensitivity reactions to specify that moxifloxacin (systemic use) should be discontinued in case of clinical manifestations of severe hypersensitivity reactions and that patients under treatment with moxifloxacin should be advised to inform their

[16] Update of SmPC section 4.4. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position
[17] For systemic use

medical doctor prior to continuing treatment if they experience symptoms of neuropathy in order to prevent the development of an irreversible condition as well as to include vasculitis as an undesirable effect with a very rare frequency. Therefore the current terms of the marketing authorisation(s) should be varied[18].

- In the next PSUR, the MAH(s) should present data showing the effectiveness of the risk minimisation measures, especially with regard to the restriction of the indications to last line treatment, stratified by year for the last five years.

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. Nadifloxacin (NAP) - PSUSA/00002102/201605

Applicant: various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Nadifloxacin is a topical synthetic fluoroquinolone indicated for the treatment of mild to moderate inflammatory forms of acne vulgaris as well as for the treatment of various bacterial skin infections.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing nadifloxacin, 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 risk-benefit balance of nadifloxacin-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include 'application site burning' and 'rash' as undesirable effects with an uncommon frequency as well as to revise the frequency of 'erythema' to uncommon and the frequency of 'urticaria' to rare. Therefore the current terms of the marketing authorisation(s) should be varied[19].
- In the next PSUR, the MAH(s) should consider adding 'safety and efficacy in children under 14 years of age' and 'safety in pregnancy' as missing information as well as 'development of bacterial resistance to nadifloxacin' as an important potential risk. In addition, the MAH(s) should provide an update of all available data on bacterial resistance (including *Propionibacterium acnes*) to nadifloxacin in EU and should provide a cumulative review of reports of fever.

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.

[18] Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position
[19] 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

6.3.7. Nefopam (NAP) - PSUSA/00002131/201603

Applicant: various

PRAC Lead: Nikica Mirosevic Skvrce

Scope: Evaluation of a PSUSA procedure

Background

Nefopam is a centrally-acting non-opioid analgesic and anti-pyretic indicated, as a solution for injection, for the symptomatic treatment of acute painful conditions, whereas nefopam oral formulations are indicated for the relief of acute and chronic pain, including post-operative pain, dental pain, musculoskeletal pain, acute traumatic pain and cancer pain.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing nefopam, 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 risk-benefit balance of nefopam-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information of nefopam-containing medicinal products as parenteral formulations should be updated to add 'confusional state' and 'coma' as undesirable effects with a not known frequency as well to include 'coma' as the symptom of nefopam overdose. Therefore the current terms of the marketing authorisation(s) for parenteral formulations should be varied[20].
- Moreover, the product information of nefopam-containing medicinal products as oral formulations should be updated to revise the warning on nefopam use in patients with angle closure glaucoma, to include a warning on the occurrence of drug abuse and dependence associated with nefopam use, to add the undesirable effect 'coma' with a not known frequency and to include 'coma' as the symptom of nefopam overdose. Therefore the current terms of the marketing authorisation(s) for parenteral formulations should be varied[21].
- In the next PSUR, the MAHs for all formulations should provide a cumulative analysis of case reports including a discussion on the appropriateness of revising the product information with regard to effects on the blood, effects on the liver, severe cutaneous adverse reactions, effects on renal impairment and use in patients with renal impairment and underlying renal conditions, and finally, use in patients with underlying cardiac conditions. Moreover, the MAHs are requested to present a cumulative analysis of duration of use of nefopam. The MAH(s) for parenteral formulation should evaluate 'hypotension' (including orthostatic hypotension), 'paraesthesia', 'syncope', 'insomnia', 'tremor', 'rash', 'pruritus', 'erythema', and 'application site reactions' as signals with proposals for product information revision as a consequence, and should provide number of case reports (patients) reporting off-label use and product use issues with the clarification of those overlapping. Finally, the MAH(s) for oral formulations should

[20] 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
[21] Update of SmPC sections 4.4, 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

evaluate 'rash', 'pruritus', 'agitation', and 'malaise' as signals with a proposal for product information revision as a consequence.

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. Nicardipine (NAP) - PSUSA/00002149/201605

Applicant: various

PRAC Lead: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure

Background

Nicardipine is a dihydropyridine derivative, a selective calcium channel blocker indicated as oral formulation for the treatment of essential hypertension, prophylaxis and treatment of angina pectoris, prophylaxis and treatment of ischemia caused by cerebral infarction and its sequelae, prophylaxis of neurological impairment caused by cerebral vasospasm secondary to subarachnoid haemorrhage as well as the treatment of chronic congestive heart failure. Nicardipine as intravenous (IV) I.V. formulation is indicated for the treatment of acute hypertension in which immediate control of the blood pressure is essential, as well as the treatment of acute heart failure.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing nicardipine, 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 risk-benefit balance of nicardipine-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to add a warning on the interaction of nicardipine with systemic formulations of tacrolimus and sirolimus as concomitant administration results in elevated plasma cyclosporine, tacrolimus or sirolimus levels and consequently those levels should be monitored and the dosage of immunosuppressant and/or nicardipine should be reduced, if required. Therefore the current terms of the marketing authorisation(s) should be varied[22].
- In the next PSUR, MAHs should closely monitor the interaction between nicardipine and sirolimus. Moreover, the MAH Astellas Pharma Ltd is requested to include a detailed review of cases of medication errors (ME), to monitor cases of interaction between nicardipine with macrolide antibiotics and clarithromycin, and to provide a cumulative review of 'haematological disorders' including the description of any case considered clinically relevant. The MAH Teva Group should closely monitor events of 'haematological disorders'.

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

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

6.3.9. Sulprostone (NAP) - PSUSA/00002828/201604

Applicant: various

PRAC Lead: Caroline Laborde

Scope: Evaluation of a PSUSA procedure

Background

Sulprostone is an uterotonic analogue of prostaglandin E2 (PGE2) indicated for inducing medical abortion and termination of pregnancy after foetal death, for the treatment of severe atonic postpartum haemorrhage after vaginal delivery and for removal of the placenta in patients with retained placenta.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing sulprostone, 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 risk-benefit balance of sulsprostone-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to add a warning on hypertension and to include 'hypertension' as an undesirable effect with an unknown frequency. Therefore the current terms of the marketing authorisation(s) should be varied[23].
- In the next PSUR, the MAH(s) should monitor cases of 'hypersensitivity', 'disseminated intravascular coagulation', 'acute respiratory distress syndrome', 'cerebrovascular disorders and hypertension' and 'renal disorders', and provide a cumulative safety analysis of renal disorders. Moreover, the MAH(s) should provide a detailed review of cases of medication errors.

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.

6.3.10. Treprostinil (NAP) - PSUSA/00003013/201605

Applicant: various

PRAC Lead: Caroline Laborde

Scope: Evaluation of a PSUSA procedure

Background

[23] 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

Treprostinil is a prostacyclin analogue indicated for the treatment of primary pulmonary arterial hypertension (PAH) to improve exercise tolerance and symptoms of the disease in patients classified as New York Heart Association (NYHA) class III.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing treprostinil, 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 risk-benefit balance of treprostinil-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include arthralgia and myalgia as undesirable effects with a common frequency. Therefore the current terms of the marketing authorisation(s) should be varied[24].
- In the next PSUR, the MAH(s) should provide detailed reviews of cases of pancytopenia, cases reported in patients with underlying sickle cell anaemia, and cases of renal disorders including cases of deterioration of renal insufficiency after use of treprostinil in patients with renal dysfunction. In addition, the MAH(s) should provide a review of cases of pain in the extremities and propose to update the product information as applicable. Furthermore, the MAH(s) should provide further information on the practical measures put in place to verify that prescribers are familiar with existing warnings regarding co-administration of treprostinil with a CYP2C8[25] inhibitor or inducer. Finally, the MAH(s) should ensure that information is collected on the health status of infants after delivery following maternal treatment with treprostinil during pregnancy.

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

6.4. Follow-up to PSUR/PSUSA procedures

See Annex I 16.4.

7. Post-authorisation safety studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)[26]

See also Annex I 17.1.

7.1.1. Pomalidomide - IMNOVID (CAP) - EMEA/H/C/002682/PSA/S/0012

Applicant: Celgene Europe Limited

PRAC Rapporteur: Rafe Suvarna

[24] Update of SmPC sections 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position
[25] Cytochrome P450 2C8
[26] In accordance with Article 107n of Directive 2001/83/EC

Scope: Submission of a revised PASS protocol in order to amend the study milestones for the study CC-4047-MM015: a non-interventional post authorisation registry of patients treated with pomalidomide for relapsed and refractory multiple myeloma to monitor the incidence of adverse reactions and to monitor the implementation of and compliance with the Celgene pregnancy prevention programme and off label use the controlled distribution system on a country basis in agreement with relevant national competent authorities

Background

Pomalidomide has direct anti-myeloma tumoricidal activity, immunomodulatory activities and inhibits stromal cell support for multiple myeloma (MM) tumour cell growth. Imnovid is a centrally authorised medicine containing pomalidomide indicated in combination with dexamethasone in the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least two prior treatment regimens, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy.

In order to characterize and determine the incidence of important identified and potential risks as outlined in the risk management plan (RMP) among previously treated MM patients who are currently being treated with Immovid (pomalidomide) in a post-marketing setting, the MAH was requested to conduct and submit the results of a post-authorisation non-interventional registry according to an agreed protocol as a condition to the Marketing Authorization. The initial PASS protocol was endorsed by PRAC in December 2013.

Endorsement/Refusal of the protocol

- The PRAC, having considered the amended PASS protocol version 3.0 in accordance with Article 107n of Directive 2001/83/EC, objected to the substantial amendments for the above listed medicinal product(s), as the Committee considered that the design of the study did not fulfil the study objectives.
- The PRAC therefore recommended that key questions relating to study milestones (e.g. the discrepancy between the slow recruitment and the commercial uptake of pomalidomide, a higher than expected withdrawal rate, and clarification with regards to the targeted number of patients to be recruited) as well as the possibility of focussing the study analysis on further useful information, should be addressed by the MAH.
- The MAH should submit to EMA, within 60 days, a revised PASS protocol. A 60 days-assessment timetable will be applied.

7.2. Protocols of PASS non-imposed in the marketing authorisation(s)[27]

See Annex I 17.2.

7.3. Results of PASS imposed in the marketing authorisation(s)[28]

None

[27] 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
[28] In accordance with Article 107p-q of Directive 2001/83/EC

7.4. Results of PASS non-imposed in the marketing authorisation(s)[29]

See also Annex I 17.4.

7.4.1. Pioglitazone - ACTOS (CAP) - EMEA/H/C/000285/WS0991/0075; GLUSTIN (CAP) - EMEA/H/C/000286/WS0991/0073; Pioglitazone, glimepiride - TANDEMACT (CAP) - EMEA/H/C/000680/WS0991/0051 Pioglitazone, metformin - COMPETACT (CAP) - EMEA/H/C/000655/WS0991/0062; GLUBRAVA (CAP) - EMEA/H/C/000893/WS0991/0047

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Almath Spooner

Scope: Submission of the final study report for the Clinical Practice Research Datalink (CPRD) GOLD linkage study (Pioglitazone_5018) conducted to investigate a possible association of the use of pioglitazone with prostate cancer and data on the incidence of adjudicated prostate cancer in patients receiving pioglitazone in the long-term insulin resistance intervention after stroke (IRIS) trial

Background

Pioglitazone is a thiazolidinedione indicated alone or in combination with glimepiride, a sulfonylurea antidiabetic or with metformin, a biguanide, in the treatment of type 2 diabetes mellitus (T2DM) under certain conditions.

In order to further investigate a potential association between pioglitazone use and the risk of prostate cancer, the MAH for pioglitazone-containing products conducted a non-imposed PASS (a nested case-control study (study Pioglitazone_5018) using the CPRD GOLD database) as listed in the RMP. The study was specifically designed to evaluate the risk of prostate cancer with use of pioglitazone in male patients with type 2 diabetes mellitus (T2DM). The Rapporteur assessed the MAH's submission of the final study report for the CPRD GOLD linkage study (Pioglitazone_5018). Additionally, data on the incidence of adjudicated prostate cancer in patients receiving pioglitazone in the long-term Insulin Resistance Intervention after Stroke (IRIS) trial were reviewed as part of the assessment.

Summary of advice

- Based on the available data and the Rapporteur's review, the PRAC agreed that the results of the CPRD GOLD prostate cancer study and analysis of prostate cancer in the IRIS trial do not support a causal association of pioglitazone use with prostate cancer. The PRAC considered the results of the specifically designed CPRD GOLD study in the context of the original signal arising from an imbalance seen in the PROactive study and two recent observational pioglitazone malignancy studies (KPNC non-bladder malignancy study, and the PROactive extension study). The overall results of the CPRD GOLD study, the post-hoc analysis of the IRIS trial, the meta-analysis of clinical trial data previously provided by the MAH and the available non-clinical evidence do not support the association and on this basis, the PRAC considered that uncertainties remain in relation to any causal association between prostate cancer and pioglitazone therapy.

[29] 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

- The MAH for pioglitazone-containing products should continue to closely monitor this issue in upcoming PSURs, including relevant scientific publications and review and present this issue again should relevant data emerge.

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.

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 agenda.

9.3. Others

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

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

10.1. Safety related variations of the marketing authorisation

None

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

None

10.3. Other requests

10.3.1. Capecitabine - XELODA (CAP) - EMEA/H/C/000316/LEG 033

Applicant: Roche Registration Limited

PRAC Rapporteur: Martin Huber

Scope: Evaluation of MAH's submission addressing the proposal by a group of academic and clinical experts put forward to the CHMP and PRAC to review the SmPCs of fluoropyrimidines (Xeloda (capecitabine) and 5-fluorouracil (5FU)) and suggesting that screening for dihydropyriminidine dehydrogenase (DPYD) variants and relevant dose reduction in patients taking fluoropyrimidines could reduce the risk of toxicity in patients with dihydropyrimidine dehydrogenase deficiency

Background

Capecitabine is a non-cytotoxic fluoropyrimidine carbamate, precursor of the cytotoxic moiety 5-fluorouracil (5-FU). Xeloda is a centrally authorised medicine containing capecitabine and is indicated for the adjuvant treatment of patients following surgery of stage III (Dukes' stage C) colon cancer, for the treatment of metastatic colorectal cancer, and as a first-line treatment of advanced gastric cancer in combination with a platinum-based regimen. It is also indicated in combination with docetaxel for the treatment of patients with locally advanced or metastatic breast cancer after failure of cytotoxic chemotherapy as well as in monotherapy for the treatment of patients with locally advanced or metastatic breast cancer after failure of taxanes and an anthracycline-containing chemotherapy regimen or for whom further anthracycline therapy is not indicated.

Based on the work and proposal of a group of academic and clinical experts in the Netherlands[30] to conduct upfront genotyping for variants of the dihydropyrimidine dehydrogenase (DYPD) gene before initiation of 5-FU or capecitabine treatment and to reduce the initial starting dose in carriers of the heterozygous polymorphisms DPYD*2A or

[30] Professor Schellens et al, The Netherlands Cancer Institute, Amsterdam, The Netherlands

c.1679T>G to 50% of the standard dose, and in carriers of the heterozygous c.2846A>T or c.1236G>A/HapB3 to 75% of the standard dose for the first two cycles plus individual dose titration upwards and downwards, the PRAC discussed the assessment of the MAH's response to the literature article by *Hendricks et al.*[31] and further additional literature articles. The PRAC agreed to give advice to CHMP on this issue.

Summary of advice

- Based on the available data assessed relating to screening for DPYD variants and DPYD genotype-guided dose adjustments for patients taking capecitabine/5-FU, the PRAC agreed that at this stage, it is not possible to recommend any changes to the product information to request mandatory upfront genotyping.
- Nevertheless, the PRAC considered that this issue requires further consideration to better reflect available information to optimise patient treatment, taking into account newly generated and upcoming evidence. Therefore, the PRAC advised on the need to consult the Pharmacogenomics Working Party (PgWP)[32] to seek advice based on an in-depth review of the issue. The PRAC suggested that such a review could take into account experience within the EU Member States with genotype-guided dose adjustments, as well as the possible impact of upcoming data from on-going studies (e.g. NCT02324452[33]) and might also consider information from organisations in the field regarding the latest developments in dosing guidelines.

10.3.2. Human normal immunoglobulin – HYQVIA (CAP) - EMEA/H/C/002491/II/0032

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: PRAC consultation on a direct healthcare professional communication (DHPC) and proposed measures evaluated in the framework of a variation to update of section 4.2 and 4.8 of the SmPC in order to add information on infusion site leakage. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet and to bring the PI in line with the latest QRD template (version 10)

Background

Human normal immunoglobulin contains mainly immunoglobulin G (IgG) with a broad spectrum of opsonising and neutralizing antibodies against infectious agents. HyQvia is a centrally authorised medicine containing a human normal immunoglobulin and is indicated as a replacement therapy in adults, children and adolescents (0-18 years) in primary immunodeficiency syndromes with impaired antibody production, in hypogammaglobulinaemia and recurrent bacterial infections in patients with chronic lymphocytic leukaemia (CLL), in whom prophylactic antibiotics have failed or are contraindicated, hypogammaglobulinaemia and recurrent bacterial infections in multiple myeloma (MM) patients as well as in hypogammaglobulinaemia in patients pre- and post-allogeneic hematopoietic stem cell transplantation (HSCT).

[31] Henricks LM, Lunenburg CA, Meulendijks D, Gelderblom H, Cats A, Swen JJ, Schellens JH, Guchelaar HJ. Translating DPYD genotype into DPD phenotype: using the DPYD gene activity score. Pharmacogenomics. 2015;16(11):1277-86
[32] The LoQ is transmitted to the CHMP for agreement in advance of the PgWP consultation
[33] Safety, Feasibility and cost-effectiveness of genotype-directed individualized dosing of fluoropyrimidines (M14DPD). EudraCT number: 2014-005064-15. NCT02324452.

A type II variation was submitted in order to update the product information of HyQvia, (human normal immunoglobulin) with information on infusion site leakage. The appropriateness of a direct healthcare professional communication (DHPC) was to be discussed in order to communicate on suggested improvements in subcutaneous administration in case of infusion site leakage.

The CHMP requested PRAC advice on the need for a DHPC to communicate on suggested improvements in subcutaneous administration in case of infusion site leakage.

Summary of advice

- Based on the available data, the PRAC considered that infusion site leakage is also known to occur with other subcutaneous immunoglobulins and that healthcare professionals are aware of the measures to minimise the risk of infusion site leakage, by using for example a larger needle or by using different injection sites. Therefore, the PRAC advised that a DHPC was not necessary at this stage and suggested following up this concern in the next PSUR (data lock point (DLP): 31/05/2017).

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

11.1. Safety related variations of the marketing authorisation

None

11.2. Other requests

11.2.1. Sulfamethoxazole, trimethoprim (co-trimoxazole) (NAP)

Applicant: various

PRAC Lead: Željana Margan Koletić

Scope: PRAC consultation on an assessment from Croatia on prolongation of QT interval and torsade de pointes (TdP) and proposed wording for inclusion in the product information

Background

Co-trimoxazole is an antibacterial drug composed of two active substances, sulfamethoxazole and trimethoprim, indicated for the treatment of various infections caused by sensitive organisms, such as *Pneumocystis jiroveci* (*P. carinii*) pneumonitis, toxoplasmosis, acute uncomplicated urinary tract infections. In the EU, medicinal products containing co-trimoxazole are nationally approved.

Croatia, as the lead Member State (LMS) responsible for signal management activities for sulfamethoxazole[34], received a notification from EMA regarding the reclassification of the combination sulfamethoxazole/trimethoprim (co-trimoxazole) from the 'conditional list' to the 'drugs to avoid in patients with congenital Long QT list' in the CredibleMeds List (Woosley)[35]. Based on an ongoing systematic analysis of all available evidence,

[34] As per 'list of substances and products subject to worksharing for signal management'. LMS for trimethoprim has not yet been appointed
[35] CredibleMeds was a university-based, federally funded Center for Education and Research on Therapeutics (CERT) and since recently has been under a contract with the FDA's safe use initiative

CredibleMeds places drugs into broad categories based on whether they can cause QT prolongation or TdP. Given that in Croatia, the product information of marketed medicine containing co-trimoxazole does not contain any information about QT prolongation/torsade de pointes, Croatia conducted an analysis of the issue and requested PRAC advice on its assessment.

Summary of advice

- Based on the review of the available information including the known association of trimethoprim with hyperkalaemia, the PRAC considered that the available evidence does not support new changes to the product information of sulfamethoxazole/trimethoprim-containing medicinal products regarding QT prolongation and torsades de pointes.

12. Organisational, regulatory and methodological matters

12.1. Mandate and organisation of the PRAC

None

12.2. Coordination with EMA Scientific Committees or CMDh

12.2.1. Conditional marketing authorisation for medicinal product for human use – report on 10 years of experience

As a follow-up to the presentations made to PRAC in June 2015 (see PRAC minutes June 2015) and November 2015 (see PRAC minutes November 2015) on draft revised CHMP guideline on conditional marketing authorisation[36], the PRAC was presented at the current meeting with a report on ten years of experience with the conditional marketing authorisation regulatory tool. This report was prepared by EMA with data collected between July 2006 and June 2016, in response to public consultation comments on the CHMP Guideline[37] and also in view of the strategic importance of this regulatory provision, and its close link with other early access initiatives, such as PRIME.

Post-meeting note: EMA published on 23 January 2017, the 10-year report on its experience with conditional marketing authorisations, together with annexes and 10-year report highlights, see on the EMA website.

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

12.3.1. Advisory group on classification of post-authorisation studies (CPAS) - metrics

As a follow-up to the presentation at the January 2016 PRAC meeting (see PRAC minutes January 2016) of the newly established advisory group at EMA on classification of post-authorisation studies (CPAS), the EMA Secretariat presented to PRAC at the current meeting an analysis conducted on the classification of post-authorisation studies by the CPAS from

[36] Guideline on the scientific application and the practical arrangements necessary to implement Commission Regulation (EC) No 507/2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004

[37] Guideline on the scientific application and the practical arrangements necessary to implement Commission Regulation (EC) No 507/2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004. EMA/CHMP/509951/2006, Rev.1

February to December 2016. The PRAC requested EMA to explore possibilities to strengthen the collaboration with PRAC Rapporteurs in the CPAS activities and to consider drafting a guidance on the classification of studies when sufficient experience is gained as well as to clarify the process for handling interventional PASS-related procedures. Follow-up is planned in Q2 2017.

12.3.2. Working Party with Healthcare Professionals' Organisations (HCPWP) - work plan 2017

The PRAC endorsed on 19 January 2017 by written procedure the HCPWP work plan for 2017 and welcomed the opportunities for further dialogue and interaction with representatives of healthcare professionals, academia and learned societies.

12.3.3. Working Party with Patients' and Consumers' Organisations (PCWP) – work plan 2017

The PRAC endorsed on 19 January 2017 by written procedure the PCWP work plan for 2017 and fully endorsed the value of the strengthened involvement of patient and consumer organisations in a wide array of EMA activities, including PRAC activities where appropriate.

12.4. Cooperation within the EU regulatory network

12.4.1. Pharmacovigilance operation - EU training curriculum design document

As a follow-up to the discussion in December 2016 (for background, see PRAC minutes December 2016) on the draft EU training curriculum design, the PRAC reviewed and adopted the draft outline of the curriculum framework for training in operating pharmacovigilance by the EU network.

12.5. Cooperation with International Regulators

None

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

None

12.7. PRAC work plan

12.7.1. 2017 PRAC work plan – consolidation

The topic was deferred to the February 2017 PRAC meeting.

12.8. Planning and reporting

12.8.1. EU Pharmacovigilance system - PRAC work tracking including quarterly workload measures and performance indicators for the last three months - predictions

The EMA secretariat presented, at the organisational matters teleconference held on 26 January 2016, quarterly figures on the EMA pharmacovigilance system-related workload and

performance indicators, as well as some predictions in terms of workload by procedure type, when available, and per NCA for the upcoming months.

12.8.2. Marketing authorisation applications (MAA) - planned for 2017

The EMA Secretariat presented to the PRAC for information a quarterly updated report on marketing authorisation applications planned for submission (the business 'pipeline'). For further background, see PRAC minutes October 2016.

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

The PRAC was updated on the activities of the GPAG, focussing on harmonising and streamlining the EURD list, and welcomed the progress being made. A call for interest to join the GPAG was launched at PRAC to replace Margarida Guimaraes, who stepped down in December 2016 as PRAC member for Portugal. PRAC delegates were invited to send their expressions of interest by 24 January 2017.

12.10.3. PSURs repository

None

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

The PRAC endorsed the draft revised EURD list version January 2017 reflecting the PRAC's comments impacting on the 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 January 2017, the updated EURD list was adopted by the CHMP and CMDh at their January 2017 meetings and published on the EMA website on 30 January 2017, 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: Sabine Straus

The PRAC was updated on the outcome of the January 2017 SMART Working Group (SMART WG) work stream WS1. The WG WS1 reviewed an overview of the group's activities and achievements in 2016 and held a discussion on the impact of additional monitoring on pharmacovigilance performance with an ongoing project mandated by the legislation (article 23 of the Regulation (EU) No 726/2004 as amended) aiming to analyse the impact of the additional monitoring on the performance of pharmacovigilance. Clarification on how the project relates to the general initiative on measuring the impact of pharmacovigilance will be presented to PRAC in Q2 2017 with a protocol to be further developed. In addition, the WG WS1 discussed the timelines of the revision of the 'Good Pharmacovigilance Practice (GVP) module IX: signal management' and the further consultation steps with PRAC and other relevant stakeholders including the European Commission.

12.12. Adverse drug reactions reporting and additional reporting

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 23 January 2017 on the EMA website (see: Home>Human Regulatory>Human medicines>Pharmacovigilance>Signal management>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. Activities related to the confirmation of full functionality – EudraVigilance auditable requirement project update – Pharmacovigilance Adverse Drug Reaction Project

Following the last discussion on the EudraVigilance (EV) auditable requirement project (see PRAC minutes June 2016), the EMA secretariat presented a further update on the audit plan. Before the implementation of centralised reporting of adverse drug reactions (ADRs), the new EudraVigilance (EV) system has to undergo an independent audit as previously presented to PRAC. Assuming a positive outcome of the audit, the new functionalities of the EV system would be released to all stakeholders/partners in Q4 2017. The PRAC will be provided with a regular status update on the latest developments, activities and outcomes.

12.13.3. Guide on the interpretation of spontaneous case reports of suspected adverse reactions to medicines – draft revision 1

The PRAC adopted revision 1 of the existing 'Guide to the interpretation of spontaneous case reports of suspected adverse reactions to medicines'[38] (EMA/CHMP/PHVWP/646186/2010) providing guidance on how to interpret adverse drug reaction (ADR) data that are publically accessible[39]. The document also gives an overview of current pharmacovigilance systems put in place to monitor the safety of medicinal products and has been reviewed in anticipation of the enhanced 'European database of suspected drug reaction reports' website to be made available in Q4 2017.

12.14. Risk management plans and effectiveness of risk minimisations

12.14.1. Risk management systems

None

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

None

12.14.3. Good Pharmacovigilance Practice (GVP) Module V on risk management systems- draft revision 2

The topic was deferred to the March 2017 PRAC meeting.

12.14.4. Good Pharmacovigilance Practice (GVP) Module XVI on risk minimisation measures: selection of tools and effectiveness indicators – draft revision 2

The PRAC adopted Revision 2 of the Good Pharmacovigilance Practice (GVP) module XVI on 'Risk minimisation measures: selection of tools and effectiveness indicators' subject to minor changes with the specific objective to align its content with the major changes being implemented in revision 2 of GVP Module V on 'risk management systems'. In particular, the content referring to additional risk minimisation measures previously considered in GVP module V is solely reflected in the revised GVP module XVI.

[38] Available on the EMA web-portal and the Public Access to EudraVigilance web-portal (adrrerports.eu)
[39] via adrreports.eu web-portal

12.14.5. Risk management plan (RMP) template for industry - revision

The topic was deferred to the March 2017 PRAC meeting.

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

12.18.3. Results of PASS imposed in the marketing authorisation(s)[40] – communication strategy

The PRAC explored with the EMA Secretariat a communication strategy for the experience gained in the use of PASS as a tool for additional pharmacovigilance activities on the basis of completed assessments of the final results of imposed PASS. The PRAC agreed to adopt a step-wise approach and gather further experience with a range of products/therapeutic scenarios before communicating on lessons learnt with the use of PASS. However, as part of the procedures on the final results for imposed PASS for cyproterone/ethinylestradiol (see PRAC minutes December 2016), the Committee endorsed the publication of the full PRAC assessment reports on the following dedicated EMA webpage: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/general/general_content_001741.jsp&murl=menus/medicines/medicines.jsp&mid=WC0b01ac0580ad90f5.

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

12.19. Continuous pharmacovigilance

12.19.1. Incident management

None

12.20. Others

12.20.1. Serious cutaneous adverse reactions (SCARs) - regulatory perspective

PRAC lead: Sabine Straus, Herve Le Louet, Zane Neikena

The PRAC discussed the progress of a new initiative to strengthen assessment and to better reflect serious cutaneous adverse drug reactions (SCARs) in regulatory documents. The initiative is one of the key themes for the PRAC work plan 2017 and takes into consideration the definition of SCARs from a clinical and scientific perspective as a basis to develop a guide for pharmacovigilance assessors, including an assessors' checklist with minimum criteria to consider in relation to SCARs during assessments, as well as a regulatory rationale for warnings and guidance to patients and prescribers in the product information. A follow-up discussion is planned at PRAC in April 2017.

13. Any other business

None

14. Annex I – Signals assessment and prioritisation[41]

14.1. New signals detected from EU spontaneous reporting systems

As per agreed criteria under evaluation 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[42].

14.1.1. Amoxicillin (NAP)

Applicant: various

PRAC Rapporteur: Jan Neuhauser

Scope: Signal of drug rash eosinophilia systemic symptoms (DRESS) syndrome

EPITT 18802 – New signal

Lead Member State: AT

[41] 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

[42] 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. Sodium iodide [^{131}I] (NAP)

Applicant: various

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Signal of hyperparathyroidism and parathyroid adenomas

EPITT 18820 – New signal

Lead Member State: PT

14.2. New signals detected from other sources

14.2.1. Gabapentin (NAP)

Applicant: various

PRAC Rapporteur: Martin Huber

Scope: Signal of respiratory depression without concomitant opioid use

EPITT 18814 - New signal

Lead Member State: DE

14.2.2. Pembrolizumab – KEYTRUDA (CAP)

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Sabine Straus

Scope: Signal of sarcoidosis

EPITT 18806 – New signal

Lead Member State: NL

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. Tadalafil - EMEA/H/C/004666

Scope: Treatment of erectile dysfunction in adult males

15.1.2. Umeclidinium - EMEA/H/C/004654

Scope: Treatment of chronic obstructive pulmonary disease (COPD)

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

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. Albiglutide - EPERZAN (CAP) - EMEA/H/C/002735/II/0029/G

Applicant: GlaxoSmithKline Trading Services

PRAC Rapporteur: Julie Williams

Scope: Grouped variation to: 1) update the RMP to amend the category 3 study 201805: an observational study of the risk of common malignant neoplasms and malignant neoplasms of special interest (thyroid and pancreatic cancer) in subjects prescribed albiglutide compared to those prescribed other antidiabetic agents, in order to use a different database to study the risk of neoplasms in association with albiglutide exposure; 2) update the RMP to add a new category 3 study as an additional pharmacovigilance activity study 207351: an observational study to assess maternal and foetal outcomes following exposure to albiglutide during pregnancy

15.2.2. Darunavir - PREZISTA (CAP) - EMEA/H/C/000707/WS1059/0084; Darunavir, cobicistat - REZOLSTA (CAP) - EMEA/H/C/002819/WS1059/0015

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Menno van der Elst

Scope: Update of the RMP (version 3.1) in order to delete the category 3 study TMC114HIV3015: a single arm, open label trial to assess the pharmacokinetics of darunavir/ritonavir, darunavir/cobistat, etravirine and rilpivirine in human immunodeficiency virus (HIV)-1 infected pregnant women, and replace it by pharmacokinetics data in HIV-1 pregnant women

15.2.3. Denosumab - PROLIA (CAP) - EMEA/H/C/001120/II/0065

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of the RMP (version 18) to update the 'important potential risk: hypercalcemia following treatment discontinuation in patients with growing skeletons' to 'important potential risk: hypercalcemia following treatment discontinuation in patients with growing skeletons and the adult population'. The RMP is updated based on Amgen's updated safety assessment conducted in 2016. The MAH also took the opportunity to request the removal of the important potential risk of fracture healing complications as recommended in April 2016 by PRAC in procedure EMEA/H/C/PSUSA/00000954/201509. Furthermore, addition of study 20090601: a post-marketing active safety surveillance program for soliciting adverse events of special interest in the United States as a category 4 study pharmacovigilance activity

15.2.4. Denosumab - XGEVA (CAP) - EMEA/H/C/002173/II/0051

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of the RMP (version 23) to update the 'important potential risk: hypercalcemia following treatment discontinuation in patients with growing skeletons' with the new important potential risk: hypercalcemia following treatment discontinuation in patients other than those with growing skeletons'. The MAH also took the opportunity to include minor changes for correction and/or to add clarification

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

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

15.3.1. Abatacept - ORENCIA (CAP) - EMEA/H/C/000701/II/0105

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Kirsti Villikka

Scope: Extension of indication to include the treatment of psoriatic arthritis in adults. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet and RMP (version 21) are updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet

15.3.2. Amifampridine - FIRDAPSE (CAP) - EMEA/H/C/001032/II/0043

Applicant: BioMarin Europe Ltd

PRAC Rapporteur: Julie Williams

Scope: Update of sections 4.4 and 5.3 of the SmPC in order to delete the statement that amifampridine has not been fully tested in carcinogenicity models and to include the findings from the carcinogenicity reports as required in completed SOB 004 (carcinogenicity testing in an appropriate model). Annex II and the RMP (version 9) are updated accordingly

15.3.3. Ataluren - TRANSLARNA (CAP) - EMEA/H/C/002720/II/0027

Applicant: PTC Therapeutics International Limited

PRAC Rapporteur: Sabine Straus

Scope: Update of section 4.8 of the SmPC to add that the safety profile of ataluren in non-ambulatory patients is similar to the safety profile in ambulatory patients following the results of a 48-week open label extension study in patients with nonsense mutation Duchenne muscular dystrophy (nmDMD). The RMP (version 6.3) is updated accordingly

15.3.4. Cabozantinib - COMETRIQ (CAP) - EMEA/H/C/002640/II/0024

Applicant: Ipsen Pharma

PRAC Rapporteur: Sabine Straus

Scope: Update of section 5.3 of the SmPC to reflect the results of the non-clinical study (XL184-NC-036) assessing the carcinogenicity potential in rat. The RMP is updated

accordingly

15.3.5. Ceritinib - ZYKADIA (CAP) - EMEA/H/C/003819/II/0010

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of sections 4.8 and 5.1 of the SmPC to reflect the safety and efficacy findings of study A2303 (a phase III, multicentre, randomized, open label, study of oral *vs* standard chemotherapy in adult patients with anaplastic lymphoma kinase (ALK)-rearranged (ALK-positive) advanced non-small cell lung cancer (NSCLC) who have been treated previously with chemotherapy (platinum doublet) and crizotinib) to further confirm the efficacy of ceritinib in the treatment of patients previously treated with crizotinib. Annex II, the Package Leaflet, Labelling and the RMP (version 5) are updated accordingly

15.3.6. Empagliflozin, metformin - SYNJARDY (CAP) - EMEA/H/C/003770/II/0015

Applicant: Boehringer Ingelheim GmbH

PRAC Rapporteur: Dolores Montero Corominas

Scope: Modification of the indication for Synjardy to reflect new data on cardiovascular outcomes based on study 1245.25 (EMPA-REG OUTCOME). As a consequence the SmPC sections 4.1, 4.2, 4.4, 4.8, 5.1 have been updated. The Package Leaflet and RMP have been updated accordingly

15.3.7. Fampridine - FAMPYRA (CAP) - EMEA/H/C/002097/II/0036/G

Applicant: Biogen Idec Ltd

PRAC Rapporteur: Sabine Straus

Scope: Grouped variation to 1) update sections 4.2 and 5.1 of the SmPC, Annex II and the Package Leaflet based on the results of the clinical study ENHANCE: a multicentre, randomized, double blind, placebo controlled study to assess the long-term efficacy and safety of prolonged release fampridine 10 mg, administered twice daily in subjects with multiple sclerosis; 2) update of section 4.6 of the SmPC based on the data from pregnancy registry; 3) update of section 4.2 and 5.2 of the SmPC based on the core data sheet (CDS) and PRAC review of the Fampyra PSUR 03. The RMP (version 11) is updated accordingly. In addition, the MAH took the opportunity to bring the Product Information in line with the latest QRD template (version 10.0). Finally, a switch from a conditional to a standard marketing authorisation (MA) is assessed as part of this procedure

15.3.8. Fingolimod - GILENYA (CAP) - EMEA/H/C/002202/II/0040

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Claire Ferard

Scope: Update of section 4.6 of the SmPC to add information on the use of fingolimod in pregnancy. In addition, update of section 5.3 of the SmPC to include information about the dose correspondence between human and the species used for the preclinical tests of teratogenicity. The RMP (version 12.0) is updated accordingly. The MAH took the opportunity to introduce minor editorial changes in sections 4.4, 4.5, 4.6 and 5.2 of the

SmPC and in Annex II.D

15.3.9. Insulin degludec - TRESIBA (CAP) - EMEA/H/C/002498/II/0024/G

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Qun-Ying Yue

Scope: Grouped variation to update sections 4.2 and 5.1 of the SmPC in order to include updated information on the use of Tresiba in terms of transfer from other basal insulin regimens and the effects of Tresiba on hypoglycaemia following the completion of studies NN1250-3995 (SWITCH 1: a randomised, double blind, cross-over trial comparing the safety and efficacy of insulin degludec and insulin glargine, both with insulin aspart as mealtime insulin in subjects with type 1 diabetes) and NN1250-3998 (SWITCH 2:a randomised, double blind, cross-over trial comparing the safety and efficacy of insulin degludec and insulin glargine, with or without oral antidiabetic drugs in subjects with type 2 diabetes), comparing the safety and efficacy of Tresiba (insulin degludec) and insulin glargine U-100. The Package Leaflet, Labelling and RMP (version 7.0) are updated accordingly. The MAH took the opportunity to bring the Product Information in line with the latest QRD template (version 10.0). Finally, minor changes have been made to the SmPC section 4.2 and the corresponding section of the Package Leaflet to clarify the correct use of Tresiba (insulin degludec)

15.3.10. Lenalidomide - REVLIMID (CAP) - EMEA/H/C/000717/II/0089/G

Applicant: Celgene Europe Limited

PRAC Rapporteur: Claire Ferard

Scope: Grouped variation including: 1) extension of indication to add the treatment of adult patients with newly diagnosed multiple myeloma (NDMM) who have undergone autologous stem cell transplantation (ASCT). Sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC, the Package Leaflet and RMP are updated accordingly; 2) Introduction of a 7-day pack sizes for the 10 mg and 15 mg strengths with subsequent changes to the Product Information. The RMP (version 31.1) is updated accordingly

15.3.11. Lopinavir, ritonavir - KALETRA (CAP) - EMEA/H/C/000368/II/0161/G

Applicant: AbbVie Ltd.

PRAC Rapporteur: Claire Ferard

Scope: Grouped variation including: 1) extension of indication to include children aged 14 days and older in the treatment of human immunodeficiency virus (HIV)-1. As a consequence, sections 4.1, 4.2, 4.3, 4.8, 5.1 and 5.2 of the SmPC are updated. The studies provided in support of the paediatric indication are part of the agreed PIP decision P/0144/2012. In addition, the MAH further updated section 4.4 to add information regarding the use of Kaletra oral solution with feeding tubes. The Package Leaflet, Labelling and RMP (version 8) are updated accordingly; 2) addition of a new pack size of 120 mL in (2 x 60ml bottles) for Kaletra 80mg/ml and 20 mg/ml oral solution (EU/1/01/172/003); 3) addition of a new 2 ml oral dose syringe for the 120 mL presentation

15.3.12. Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/II/0017

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include treatment of recurrent or metastatic squamous cell cancer of the head and neck (SCCHN) after platinum-based therapy in adults. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 of the SmPC are updated in order to add the proposed new indication, add a warning that patients with a baseline performance score ≥ 2, untreated brain metastasis, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the SCCHN clinical trial and update the undesirable effect and safety information. The Labelling and RMP (version 6.0) are updated accordingly

15.3.13. Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/II/0024

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of section 5.1 of the SmPC in order to reflect the final overall survival and response data, including duration of response with longer follow-up, following completion of PAES CA209037: a randomized, open-label, phase 3 trial of nivolumab versus investigator's choice in advanced (unresectable or metastatic) melanoma patients progressing post anti-CTLA-4 therapy) and its addendum on predictability of efficacy with biomarkers. This fulfils ANX 001 (submission of CA209037 final study report) and 003.1 (submission of results relating to the exploration of the optimal cut-off for death-ligand 1 (PD-L1) positivity based on current assay method used to further elucidate its value as predictive of nivolumab efficacy as part of CA209037 results submission). Annex II and the RMP (version 5.5) are updated accordingly

15.3.14. Obinutuzumab - GAZYVARO (CAP) - EMEA/H/C/002799/II/0016

Applicant: Roche Registration Limited

PRAC Rapporteur: Julie Williams

Scope: Extension of indication to include a new indication for Gazyvaro (obinutuzumab) in combination with chemotherapy, followed by obinutuzumab maintenance therapy in patients achieving a response for the treatment of patients with previously untreated advanced follicular lymphoma. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8 and 5.1 of the SmPC, Package Leaflet and the RMP (version 3.0) are updated accordingly. In addition, the due date for provision of the final clinical study report for study BO21223/GALLIUM (multicentre, phase III, open label, randomized study in previously untreated patients with advanced indolent non-Hodgkin's lymphoma evaluating the benefit of obinutuzumab + chemotherapy compared to rituximab + chemotherapy followed by obinutuzumab or rituximab maintenance therapy in responders) listed in the RMP as a category 3 has been updated. Furthermore, the Product Information is brought in line with the missing information of QRD template version 9.1 regarding annex II C. In addition, clarification or editorial changes to the SmPC are proposed for accuracy and clarity

15.3.15. Pembrolizumab - KEYTRUDA (CAP) - EMEA/H/C/003820/II/0014

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Sabine Straus

Scope: Extension of indication to include the treatment of classical Hodgkin lymphoma (cHL) in adults who have refractory disease, or who have relapsed after greater than 3 prior lines of therapy, based on the results from study KEYNOTE-087, an open-label phase II trial of pembrolizumab in subjects with relapsed or refractory cHL and study KEYNOTE-013, a phase Ib multi-cohort trial of pembrolizumab in subjects with hematologic malignancies. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet and the RMP (version 5.0) are updated accordingly

15.3.16. Pembrolizumab - KEYTRUDA (CAP) - EMEA/H/C/003820/II/0018/G

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Sabine Straus

Scope: Grouped variation to update section 5.1 of the SmPC to reflect the data from the post-authorisation efficacy studies (PAES) in melanoma study P001 (phase I study of pembrolizumab alone in patients with progressive locally advanced or metastatic carcinoma, melanoma, and non-small cell lung carcinoma), study P002 (randomized, phase II study of pembrolizumab versus chemotherapy in patients with advanced melanoma) and study P006 (a multicentre, randomized, controlled, three-arm, phase III study to evaluate the safety and efficacy of two dosing schedules of pembrolizumab compared to ipilimumab in patients with advanced melanoma). Annex II and the RMP (version 6.0) are updated accordingly

15.3.17. Reslizumab - CINQAERO (CAP) - EMEA/H/C/003912/II/0005/G

Applicant: Teva Pharmaceuticals Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Grouped variation to 1) update section 4.2 of the SmPC in order to include a revised dosing regimen as a result of the new 25 mg vial presentation; 2) change of the pack size of the finished product and update of sections 6.5 and 6.6 of the SmPC. Annex II, Package Leaflet, Labelling and RMP (version 2.0) are updated accordingly

15.3.18. Safinamide - XADAGO (CAP) - EMEA/H/C/002396/II/0014

Applicant: Zambon SpA

PRAC Rapporteur: Almath Spooner

Scope: Submission of the final study report for the study VDD4193 (safinamide: in vitro metabolic stability in human cryopreserved hepatocytes, by fatty acid amide hydrolase enzyme (FAAH), recombinant human n-acylethanolamine acid amidase (NAAA) and recombinant human acid ceramidase (ASAHl)) conducted in order to identify specific substances blocking the amidases (inhibitors of amidases) involved in the metabolism of safinamide (MEA 001.2). The RMP is updated accordingly

15.3.19. Sevelamer - RENVELA (CAP) - EMEA/H/C/000993/WS0965/0035; SEVELAMER CARBONATE ZENTIVA (CAP) - EMEA/H/C/003971/WS0965/0007

Applicant: Genzyme Europe BV

PRAC Rapporteur: Laurence de Fays

Scope: Extension of indication to include the control of hyperphosphataemia in paediatric patients (>6 years of age and a body surface area (BSA) of >0.75 m^2) with chronic kidney disease. As a consequence, section 4.2 of the SmPC is updated to detail the posology in the paediatric patients. The Package Leaflet is updated accordingly. The RMP is updated accordingly

15.3.20. Sofosbuvir, velpatasvir - EPCLUSA (CAP) - EMEA/H/C/004210/WS1075/0006; HARVONI (CAP) - EMEA/H/C/003850/WS1075/0043; Sofosbuvir - SOVALDI (CAP) - EMEA/H/C/002798/WS1075/0037

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Submission of the final non-clinical study report PC-334-2035 assessing the potential for a pharmacokinetic interaction via transporter or enzyme based inhibition when sofosbuvir and other Direct Acting Antivirals (DAAs) are used concomitantly with amiodarone. The RMPs (version 1.0 (Epclusa), version 2.0 (Harvoni), version 5.0 (Sovaldi)) are updated accordingly

15.3.21. Sofosbuvir, ledipasvir - HARVONI (CAP) - EMEA/H/C/003850/II/0039

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Extension of indication to add treatment of chronic hepatitis C in adolescents aged 12 to <18 years. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated in order to add information on posology, warnings, safety, efficacy and pharmacokinetics. The Package Leaflet and RMP (version 2) are updated accordingly

15.3.22. Sonidegib - ODOMZO (CAP) - EMEA/H/C/002839/II/0007

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Julie Williams

Scope: Submission of the final study report from the category 3 nonclinical study 1070056 to perform an evaluation of a subset of tissues from the 6-month rat study using Ki-67 immunohistochemistry and to quantify cell proliferation

15.3.23. Sonidegib - ODOMZO (CAP) - EMEA/H/C/002839/II/0008/G

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Julie Williams

Scope: Submission of the final study report from the category 3 clinical pharmacology study CLDE225A2120, a relative bioavailability study to evaluate timing of meal relative to dose

and fast conditions and effect of light meal (low fat meal). The clinical study report (CSR) submission date for category 3 study X2116 is changed from Q1 2017 to Q4 2018. The clinical study report (CSR) due date for the category 3 CLDE225A2404 study (non-interventional PASS to further characterise long term efficacy) is changed from Q4 2024 to Q1 2025. The RMP (version 5.0) is updated accordingly

15.3.24. Sulphur hexafluoride - SONOVUE (CAP) - EMEA/H/C/000303/X/0034/G

Applicant: Bracco International B.V.

PRAC Rapporteur: Claire Ferard

Scope: Grouped variation including 1) extension application to introduce intravesical use as a new route of administration; 2) addition of a new indication to include use in ultrasonography of the excretory urinary tract in paediatric patients to detect or exclude vesicoureteral reflux. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 6 of the SmPC are updated. The Package Leaflet and the RMP (version 9.1) are updated accordingly. In addition, the MAH took the opportunity to bring Annex IIIA in line with the latest QRD template (version 10)

15.3.25. Trifluridine, tipiracil - LONSURF (CAP) - EMEA/H/C/003897/II/0002/G

Applicant: Les Laboratoires Servier

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Grouped variations to: 1) update of sections 4.2, 4.4 and 5.2 of the SmPC following availability of the final clinical study report for study TO-TAS-102-106: a phase I, open-label study evaluating the safety, tolerability, and pharmacokinetics of TAS-102 in patients with advanced solid tumours and varying degrees of hepatic impairment (requested in MEA 002). The RMP (version 5.0) is updated accordingly to remove the missing information 'use in patients with moderate to severe hepatic impairment' and to add 'hyperbilirubinaemia in patients with baseline moderate to severe hepatic impairment' as important potential risk; 2) update of sections 4.5 and 5.2 of the SmPC following availability of the results in vitro CYP induction study of tipiracil hydrochloride (TPI) using the appropriate concentration of TPI (requested in a recommendation). The RMP is updated accordingly; 3) update of section 4.2 of the SmPC in order to correct inconsistencies in the dose calculation according to body surface area. The package leaflet is updated to add 'interstitial lung disease'. Finally, the MAH took the opportunity to update Annex IIIA in accordance with the latest QRD template

15.3.26. Umeclidinium bromide, vilanterol - ANORO (CAP) - EMEA/H/C/002751/WS1031/0013; Umeclidinium, vilanterol - LAVENTAIR (CAP) - EMEA/H/C/003754/WS1031/0014

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Carmela Macchiarulo

Scope: Update of section 4.8 of the SmPC in order to add the adverse reactions 'vision blurred', 'intraocular pressure increased' and 'paradoxical bronchospasm' and to change the frequency of the adverse reaction 'glaucoma' from not known to rare. The Package Leaflet and the RMP (version 7.0) are updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet and to bring the Product Information in line with the latest QRD template (version 10)

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 procedures including centrally authorised products only

16.1.1. Afamelanotide - SCENESSE (CAP) - PSUSA/00010314/201606

Applicant: Clinuvel (UK) Limited

PRAC Rapporteur: Valerie Strassmann

Scope: Evaluation of a PSUSA procedure

16.1.2. Ambrisentan - VOLIBRIS (CAP) - PSUSA/00000129/201606

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

16.1.3. Asfotase alfa - STRENSIQ (CAP) - PSUSA/00010421/201607

Applicant: Alexion Europe SAS

PRAC Rapporteur: Almath Spooner

Scope: Evaluation of a PSUSA procedure

16.1.4. Avanafil - SPEDRA (CAP) - PSUSA/00010066/201606 (with RMP)

Applicant: Menarini International Operations Luxembourg S.A.

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

16.1.5. Brinzolamide, brimonidine tartrate - SIMBRINZA (CAP) - PSUSA/00010273/201606

Applicant: Alcon Laboratories (UK) Ltd

PRAC Rapporteur: Almath Spooner

Scope: Evaluation of a PSUSA procedure

16.1.6. Bromfenac - YELLOX (CAP) - PSUSA/00000436/201605

Applicant: PharmaSwiss Ceska Republika s.r.o

PRAC Rapporteur: Torbjorn Callreus

Scope: Evaluation of a PSUSA procedure

16.1.7. Canakinumab - ILARIS (CAP) - PSUSA/00000526/201606

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.8. Daclatasvir - DAKLINZA (CAP) - PSUSA/00010295/201607

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.1.9. Dasatinib - SPRYCEL (CAP) - PSUSA/00000935/201606

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Doris Stenver

Scope: Evaluation of a PSUSA procedure

16.1.10. Edoxaban - LIXIANA (CAP) - PSUSA/00010387/201606

Applicant: Daiichi Sankyo Europe GmbH

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.11. Elotuzumab - EMPLICITI (CAP) - PSUSA/00010500/201605

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.12. Fidaxomicin - DIFICLIR (CAP) - PSUSA/00001390/201605

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

16.1.13. Galsulfase - NAGLAZYME (CAP) - PSUSA/00001515/201605

Applicant: BioMarin Europe Ltd

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of a PSUSA procedure

16.1.14. Glycerol phenylbutyrate - RAVICTI (CAP) - PSUSA/00010454/201605

Applicant: Horizon Pharma Ireland Limited

PRAC Rapporteur: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure

16.1.15. Human fibrinogen, human thrombin - EVARREST (CAP); EVICEL (CAP); RAPLIXA (CAP); TACHOSIL (CAP) - PSUSA/00010297/201606

Applicant: Takeda Austria GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.16. Human papillomavirus vaccine (rDNA) (4-valent) - GARDASIL (CAP); SILGARD (CAP) - PSUSA/00001634/201605

Applicant: Sanofi Pasteur MSD SNC

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

16.1.17. Human papillomavirus 9-valent vaccine (recombinant, adsorbed) - GARDASIL 9 (CAP) - PSUSA/00010389/201606

Applicant: Sanofi Pasteur MSD

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.18. Human plasma protease C1 inhibitor - CINRYZE (CAP) - PSUSA/00010104/201606

Applicant: Shire Services BVBA

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.19. Hydroxycarbamide[43] - SIKLOS (CAP) - PSUSA/00001692/201606

Applicant: Addmedica

PRAC Rapporteur: Jean-Michel Dogné

[43] Indication in sickle cell syndrome

Scope: Evaluation of a PSUSA procedure

16.1.20. Lesinurad - ZURAMPIC (CAP) - PSUSA/00010470/201606

Applicant: Gruenenthal GmbH

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

16.1.21. Levofloxacin[44] - QUINSAIR (CAP) - PSUSA/00010429/201605

Applicant: Raptor Pharmaceuticals Europe BV

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

16.1.22. Lutetium (^{177}Lu) chloride - LUMARK (CAP) - PSUSA/00010391/201606

Applicant: I.D.B. Holland B.V.

PRAC Rapporteur: Almath Spooner

Scope: Evaluation of a PSUSA procedure

16.1.23. Matrix-applied characterised autologous cultured chondrocytes - MACI (CAP) - PSUSA/00010116/201606

Applicant: Vericel Denmark ApS

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of a PSUSA procedure

16.1.24. Mirabegron - BETMIGA (CAP) - PSUSA/00010031/201606

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

16.1.25. Mixture of polynuclear iron(III) oxyhydroxide, sucrose, starches - VELPHORO (CAP) - PSUSA/00010296/201605

Applicant: Vifor Fresenius Medical Care Renal Pharma France

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.26. Nepafenac - NEVANAC (CAP) - PSUSA/00002143/201605

Applicant: Alcon Laboratories (UK) Ltd

[44] Centrally authorised product only

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

16.1.27. Nonacog gamma - RIXUBIS (CAP) - PSUSA/00010320/201606

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.28. Olaparib - LYNPARZA (CAP) - PSUSA/00010322/201606

Applicant: AstraZeneca AB

PRAC Rapporteur: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure

16.1.29. Pertuzumab - PERJETA (CAP) - PSUSA/00010125/201606

Applicant: Roche Registration Limited

PRAC Rapporteur: Doris Stenver

Scope: Evaluation of a PSUSA procedure

16.1.30. Ponatinib - ICLUSIG (CAP) - PSUSA/00010128/201606

Applicant: Incyte Biosciences UK Ltd

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of a PSUSA procedure

16.1.31. Sacubitril, valsartan - ENTRESTO (CAP); NEPARVIS (CAP) - PSUSA/00010438/201607

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of a PSUSA procedure

16.1.32. Selexipag - UPTRAVI (CAP) - PSUSA/00010503/201606

Applicant: Actelion Registration Ltd.

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of a PSUSA procedure

16.1.33. Sofosbuvir - SOVALDI (CAP) - PSUSA/00010134/201606

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of a PSUSA procedure

16.1.34. Sonidegib - ODOMZO (CAP) - PSUSA/00010408/201606

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.35. Tasimelteon - HETLIOZ (CAP) - PSUSA/00010394/201607

Applicant: Vanda Pharmaceuticals Ltd.

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.36. Tedizolid phosphate - SIVEXTRO (CAP) - PSUSA/00010369/201606

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

16.1.37. Tolvaptan[45] - JINARC (CAP) - PSUSA/00010395/201605

Applicant: Otsuka Pharmaceutical Europe Ltd

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.38. Trametinib - MEKINIST (CAP) - PSUSA/00010262/201605

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.39. Umeclidinium bromide, vilanterol - ANORO (CAP); LAVENTAIR (CAP) - PSUSA/00010264/201606

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure

[45] Indications for autosomal dominant polycystic kidney disease (ADPKD) only

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

16.2.1. Capsaicin - QUTENZA (CAP); NAP - PSUSA/00000533/201605

Applicant: Astellas Pharma Europe B.V. (Qutenza), various

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.2.2. Human normal immunoglobulin - FLEBOGAMMA DIF (CAP); HIZENTRA (CAP); HYQVIA (CAP); KIOVIG (CAP); PRIVIGEN (CAP); NAP - PSUSA/00001633/201605

Applicant: Instituto Grifols, S.A. (Flebogamma DIF), Baxalta Innovations GmbH (HyQvia), Baxter AG (Kiovig), CSL Behring GmbH (Hizentra, Privigen), various

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.3. PSUR procedures including nationally approved products (NAPs) only

16.3.1. Bemiparin (NAP) - PSUSA/00000312/201604

Applicant: various

PRAC Lead: Eva Segovia

Scope: Evaluation of a PSUSA procedure

16.3.2. Benazepril, hydrochlorothiazide (NAP) - PSUSA/00000314/201605

Applicant: various

PRAC Lead: Caroline Laborde

Scope: Evaluation of a PSUSA procedure

16.3.3. Bismuth subcitrate potassium, metronidazole, tetracycline (NAP) - PSUSA/00010199/201605

Applicant: various

PRAC Lead: Nikica Mirosevic Skvrce

Scope: Evaluation of a PSUSA procedure

16.3.4. Clevidipine (NAP) - PSUSA/00010288/201605

Applicant: various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.3.5. Docosanol (NAP) - PSUSA/00010092/201604

Applicant: various

PRAC Lead: Nikica Mirosevic Skvrce

Scope: Evaluation of a PSUSA procedure

16.3.6. F(Ab')2 fragments of equine antirabies immunoglobulin (NAP) - PSUSA/00001348/201605

Applicant: various

PRAC Lead: Zane Neikena

Scope: Evaluation of a PSUSA procedure

16.3.7. Fusidic acid (NAP) - PSUSA/00010226/201605

Applicant: various

PRAC Lead: Julia Pallos

Scope: Evaluation of a PSUSA procedure

16.3.8. Human prothrombin complex (NAP) - PSUSA/00001638/201604

Applicant: various

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.3.9. Hydroxyzine chloride, hydroxyzine pamoate and all fixed combination, hydroxyzine (NAP) - PSUSA/00001696/201605

Applicant: various

PRAC Lead: Claire Ferard

Scope: Evaluation of a PSUSA procedure

16.3.10. Isoniazide, rifampicin (NAP) - PSUSA/00001792/201605

Applicant: various

PRAC Lead: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

16.3.11. Lactulose (NAP) - PSUSA/00001821/201605

Applicant: various

PRAC Lead: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.3.12. Latanoprost[46] (NAP) - PSUSA/00001832/201604

Applicant: various

PRAC Lead: Laurence de Fays

Scope: Evaluation of a PSUSA procedure

16.3.13. Loperamide (NAP) - PSUSA/00001903/201605

Applicant: various

PRAC Lead: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.3.14. Macrogol 3350 (NAP) - PSUSA/00001924/201605

Applicant: various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.3.15. Macrogol 4000 and combinations[47] (NAP) - PSUSA/00010392/201605

Applicant: various

PRAC Lead: Caroline Laborde

16.3.16. Moxifloxacin[48] (NAP) - PSUSA/00002094/201605

Applicant: various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.3.17. Tirofiban (NAP) - PSUSA/00002974/201605

Applicant: various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.4. Follow-up to PSUR procedures

16.4.1. Cinacalcet - MIMPARA (CAP) - EMEA/H/C/000570/LEG 029

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

[46] Except products with paediatric indication
[47] For systemic use
[48] For topical ophthalmic use

Scope: Submission of a safety assessment of all haemorrhagic events for cinacalcet events in all controlled clinical studies with cinacalcet, irrespective of indication as requested in the conclusions of EMEA/H/C/PSUSA/00000756/201602 adopted by the PRAC on 29 September 2016

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)[49]

17.1.1. Hydroxyethyl starch (NAP) - EMEA/H/N/PSA/S/0011

Applicant: B. Braun Melsungen AG

PRAC Rapporteur: Qun-Ying Yue

Scope: Submission of a revised PASS protocol for the retrospective drug utilisation study (ENCEPP/SDDP/12540) to investigate the routine use of hydroxyethyl starch (HES)-containing infusion solutions of B.Braun Melsungen AG in hospitals

17.1.2. Ketoconazole - KETOCONAZOLE HRA (CAP) - EMEA/H/C/003906/PSP/0040.2

Applicant: Laboratoire HRA Pharma

PRAC Rapporteur: Željana Margan Koletić

Scope: Submission of a revised PASS protocol for the prospective, multinational, observational registry to collect clinical information on patients with endogenous Cushing's syndrome exposed to ketoconazole (using the existing European Registry on Cushing's syndrome (ERCUSYN)), to assess drug utilisation pattern and to document the safety (e.g. hepatotoxicity, QT prolongation) and effectiveness of ketoconazole

17.1.3. Lesinurad - ZURAMPIC (CAP) - EMEA/H/C/003932/PSP/S/0050.1

Applicant: Gruenenthal GmbH

PRAC Rapporteur: Dolores Montero Corominas

Scope: Submission of a revised PASS protocol for an observational post-authorisation safety study of lesinurad patients (SATURATES) to further assess cardiovascular (CV) safety with a focus on major adverse cardiovascular events (MACE), and renal safety, in gout patients treated with Zurampic, lesinurad (LESU) in combination with xanthine oxidase inhibitors (XOI) (LESU+XOI cohort), compared to similar patients who are continuing treatment with XOI monotherapy (XOI mono cohort)

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

17.1.4. Thiocolchicoside (NAP) - EMEA/H/N/PSA/J/0010

Applicant: Sanofi

PRAC Rapporteur: Amelia Cupelli

Scope: Submission of a revised PASS protocol for the EUPAS1108, a drug utilisation study of thiocolchicoside (TCC) containing medicinal products for systemic use in France and Italy: an electronic medical record databases study

17.2. Protocols of PASS non-imposed in the marketing authorisation(s)[50]

17.2.1. Daclizumab - ZINBRYTA (CAP) - EMEA/H/C/003862/MEA 002

Applicant: Biogen Idec Ltd

PRAC Rapporteur: Eva Segovia

Scope: Submission of a PASS protocol for the category 3 Biogen multiple sclerosis (MS) pregnancy exposure registry 109MS402 to prospectively evaluate pregnancy outcomes in women with MS who were exposed to a registry-specified Biogen MS product during the eligibility window for that product

17.2.2. Emtricitabine, tenofovir disoproxil - TRUVADA (CAP) - EMEA/H/C/000594/MEA 045

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Julie Williams

Scope: Submission of a PASS protocol for a drug utilisation study (GS-EU-276-4027) to characterize: 1) prescribers' level of knowledge about the key risks of Truvada for a pre-exposure prophylaxis (PrEP) indication and assess the effectiveness of risk minimisation measures, 2) prescribing practices in routine clinical practice of Truvada for PrEP by describing the demographics of human immunodeficiency virus (HIV)-1 uninfected individuals who were prescribed Truvada for PrEP, and the prescribed dosing schedule for Truvada for PrEP as reported by the prescriber, as a result of variation II/0126 finalised at CHMP/PRAC in July 2016 to extend the indication to PrEP

17.2.3. Etanercept - ENBREL (CAP) - EMEA/H/C/000262/MEA 167.1

Applicant: Pfizer Limited

PRAC Rapporteur: Rafe Suvarna

Scope: Submission of a revised PASS protocol for study B1801396: an observational cohort study to evaluate the risk of adverse pregnancy outcomes in patients treated with etanercept compared to those not treated with etanercept or other biologics using merged data from Sweden, Denmark and Finland, as per the conclusions of variation II/184 further to the RSI adopted in July 2016

[50] 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

17.2.4. Fentanyl - IONSYS (CAP) - EMEA/H/C/002715/MEA 002

Applicant: Incline Therapeutics Europe Ltd

PRAC Rapporteur: Almath Spooner

Scope: Submission of a PASS protocol for the study MDCO-ION-16-03, a IONSYS prescriber survey to evaluate the effectiveness of the IONSYS EU RMP Healthcare Provider Educational Programme.

17.2.5. Lenalidomide - REVLIMID (CAP) - EMEA/H/C/000717/MEA 046

Applicant: Celgene Europe Limited

PRAC Rapporteur: Claire Ferard

Scope: Submission of a PASS protocol to further investigate and characterise the associations of lenalidomide and TFR (Tumour Flare Reaction)/high tumour burden following the extension of indication for the treatment of adult patients with relapsed and/ or refractory mantle cell lymphoma (RRMCL) (EMEA/H/C/000717/II/0079)

17.2.6. Ponatinib - ICLUSIG (CAP) - EMEA/H/C/002695/MEA 015

Applicant: Incyte Biosciences UK Ltd

PRAC Rapporteur: Rafe Suvarna

Scope: Submission of a PASS protocol for a post-marketing observational registry (AP24534-14-401) to evaluate the incidence of and risk factors for vascular occlusive events associated with Iclusig (ponatinib) in routine clinical practice in the US (OMNI)

17.3. Results of PASS imposed in the marketing authorisation(s)[51]

None

17.4. Results of PASS non-imposed in the marketing authorisation(s)[52]

17.4.1. Dexamethasone - OZURDEX (CAP) - EMEA/H/C/001140/II/0025

Applicant: Allergan Pharmaceuticals Ireland

PRAC Rapporteur: Julie Williams

Scope: Submission of the final report for PASS 206207-025: a prospective observational study to evaluate long-term safety in real-world clinical practice

17.4.2. Eltrombopag - REVOLADE (CAP) - EMEA/H/C/001110/II/0039

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Eva Segovia

Scope: Submission of final report of the drug utilisation study REVIEU (CETB115B2406): a

[51] In accordance with Article 107p-q of Directive 2001/83/EC
[52] 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

multinational, retrospective, observational drug utilisation study in selected countries in the European Union in fulfilment of MEA 21.1.

17.4.3. Eltrombopag - REVOLADE (CAP) - EMEA/H/C/001110/II/0040

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Eva Segovia

Scope: Submission of the final data from the nested eltrombopag HCV-TARGET cohort study: a prospective observational cohort study nested within the Hepatitis C Therapeutic Registry and Research Network (HCV- TARGET) to evaluate real world use of eltrombopag in adult patients with chronic hepatitis C virus infection who are unable to initiate or maintain optimal interferon based therapy due to thrombocytopenia. The RMP (version 44.0) is updated accordingly

17.4.4. Etanercept - ENBREL (CAP) - EMEA/H/C/000262/II/0198

Applicant: Pfizer Limited

PRAC Rapporteur: Rafe Suvarna

Scope: Submission of the final clinical study report for the BSPAR (British society for paediatric and adolescent rheumatology) etanercept registry, a cohort study (category 3 in the RMP)

17.4.5. Ivacaftor - KALYDECO (CAP) - EMEA/H/C/002494/II/0054

Applicant: Vertex Pharmaceuticals (Europe) Ltd.

PRAC Rapporteur: Dolores Montero Corominas

Scope: Submission of the final clinical study report (CSR) for study VX12-770-112: a rollover study to evaluate the long-term safety and efficacy of ivacaftor treatment in subjects ≥6 years of age with cystic fibrosis (CF) and a non-G551D mutation in the CFTR gene. The RMP (version 5.4) is updated accordingly

17.4.6. Ivacaftor - KALYDECO (CAP) - EMEA/H/C/002494/WS1047/0055; Lumacaftor, ivacaftor - ORKAMBI (CAP) - EMEA/H/C/003954/WS1047/0016

Applicant: Vertex Pharmaceuticals (Europe) Ltd.

PRAC Rapporteur: Dolores Montero Corominas

Scope: Submission of the final clinical study report (CSR) for study VX12-770-115: an ocular safety study of ivacaftor-treated paediatric patients 11 years of age or younger with cystic fibrosis (CF) as a follow up of Kalydeco MEA 023 and Orkambi MEA 004. The RMPs (version 5.3 (Kalydeco) and version 2.6 (Orkambi)) are updated accordingly

17.4.7. Liraglutide - SAXENDA (CAP) - EMEA/H/C/003780/WS0943/0009; VICTOZA (CAP) - EMEA/H/C/001026/WS0943/0041

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Menno van der Elst

Scope: Submission of the final results from a category 3 study: liraglutide safety and surveillance programme using the Optum research database study, and its sub-study on breast cancer

17.4.8. Saxagliptin, metformin hydrochloride - KOMBOGLYZE (CAP) - EMEA/H/C/002059/WS0960/0033/G; Saxagliptin - ONGLYZA (CAP) - EMEA/H/C/001039/WS0960/0040/G

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Group of variations consisting of final epidemiological study results for studies D1680R00011 (a cohort study comparing risk of major cardiovascular (CV) events between patients with type 2 diabetes mellitus (T2DM) who are new initiators of saxagliptin and those who are new initiators of oral antidiabetic drug (OAD) treatments in classes other than DPP-4 inhibitors), D1680R00012 (a cohort study comparing risk of hospitalization with acute liver failure between patients with T2DM exposed to saxagliptin and those exposed to other OAD treatments), D1680R00013 (a cohort study comparing risk of hospitalization with infections between patients with T2DM exposed to saxagliptin and those exposed to other OAD treatments), D1680R00014 (a cohort study comparing risk of hospitalization for severe hypersensitivity (including severe cutaneous reactions) between patients with T2DM exposed to saxagliptin and those exposed to other OAD treatments) and D1680R00015 (a cohort study comparing risk of hospitalization for acute kidney injury between patients with T2DM initiating saxagliptin and those initiating other OAD treatments), and consequent update of the RMP. As a consequence, the RMP (version 11) is updated accordingly. In addition, routine changes are made in parts III (pharmacovigilance plan, overview of planned pharmacovigilance actions) and IV. A safety review based on literature has also been included to investigate acute kidney injury associated with saxagliptin, saxagliptin and metformin at the PRAC request

17.4.9. Voriconazole - VFEND (CAP) - EMEA/H/C/000387/II/0121

Applicant: Pfizer Limited

PRAC Rapporteur: Sabine Straus

Scope: Submission of study A1501102 evaluating the effectiveness of additional risk minimisation measure that aim to reduce the risks of phototoxicity, squamous cell carcinoma (SCC) of the skin and hepatic toxicity in patients receiving Voriconazole in the European Union (EU). The RMP (version 5) is updated accordingly

17.5. Interim results of imposed and non-imposed PASS submitted before the entry into force of the revised variation regulation[53]

17.5.1. Agomelatine - THYMANAX (CAP) - EMEA/H/C/000916/MEA 023.2

Applicant: Servier (Ireland) Industries Ltd.

PRAC Rapporteur: Kristin Thorseng Kvande

[53] In line with the revised variations regulation for any submission before 4 August 2013

Scope: Submission of interim results report of the nested case-control analysis in two Spanish Populations and Germany of the category 3 PASS Study No. CLE-20098-094, a post-authorisation safety study of agomelatine and the risk of hospitalisation for acute liver injury further to variation II/18

17.5.2. Agomelatine - VALDOXAN (CAP) - EMEA/H/C/000915/MEA 023.2

Applicant: Les Laboratoires Servier

PRAC Rapporteur: Kristin Thorseng Kvande

Scope: Submission of interim results report of the nested case-control analysis in two Spanish Populations and Germany of the category 3 PASS Study No. CLE-20098-094, a post-authorisation safety study of agomelatine and the risk of hospitalisation for acute liver injury further to variation II/18

17.5.3. Bedaquiline - SIRTURO (CAP) - EMEA/H/C/002614/MEA 010

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Qun-Ying Yue

Scope: Submission of an interim results report for a category 3 study TMC207TBC4002: a multinational prospective multidrug resistant tuberculosis patient registry to monitor bedaquiline safety, utilisation, and emergence of resistance

17.5.4. Estrogens conjugated, bazedoxifene - DUAVIVE (CAP) - EMEA/H/C/002314/MEA 002.4

Applicant: Pfizer Limited

PRAC Rapporteur: Martin Huber

Scope: MAH's response to MEA 002.3: first interim analysis report for an US category 3, PASS (B2311060 study): active surveillance of conjugated estrogens (CE)/bazedoxifene acetate (BZA) using US healthcare data as per the request for supplementary information (RSI) adopted in June 2016

17.5.5. Micafungin - MYCAMINE (CAP) - EMEA/H/C/000734/MEA 013.3

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Martin Huber

Scope: Submission of MAH’s responses to MEA 13.2 [second annual interim report from an observational database-assisted comparative cohort study to investigate the risk of hepatotoxicity and hepatocellular carcinoma (protocol number: ISN 9463-CL-140) a multicentre cohort study of the short and long-term safety of micafungin and Other parenteral antifungal agents (MYCOS)] as per the request for supplementary information adopted in June 2016

17.5.6. Ospemifene - SENSHIO (CAP) - EMEA/H/C/002780/PSP/001.2

Applicant: Shionogi Limited

PRAC Rapporteur: Julie Williams

Scope: Submission of the first annual interim report of the five year PASS (ENCEPP/SDPP/8585) to assess the safety and incidence of side effects in a cohort of postmenopausal women prescribed ospemifene relative to patients diagnosed with but not treated for vulvar and vaginal atrophy (VVA) and patients on selective oestrogen receptor modulators (SERMs) for oestrogen-deficiency conditions or breast cancer prevention

17.5.7. Ponatinib - ICLUSIG (CAP) - EMEA/H/C/002695/MEA 012

Applicant: Incyte Biosciences UK Ltd

PRAC Rapporteur: Rafe Suvarna

Scope: Submission of the interim result report for the risk minimisation assessment survey and interim report for risk minimisation measures distribution to assess the effectiveness of two risk minimisation measures (DHPC and HCP brochure)

17.5.8. Turoctocog alfa - NOVOEIGHT (CAP) - EMEA/H/C/002719/MEA 004.1

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Submission of an interim report for the post-authorisation safety 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%)

17.6. Others

17.6.1. Canagliflozin - INVOKANA (CAP) - EMEA/H/C/002649/MEA 005.9

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Valerie Strassmann

Scope: MAH's responses to MEA 005.7: provision of data to address additional pharmacovigilance activity in the RMP: canagliflozin Independent Data Monitoring Committee (IDMC) status reports for studies DIA3008 (CANVAS: a randomized, multicentre, double-blind, parallel, placebo-controlled study of the effects of canagliflozin on cardiovascular outcomes in adult subjects with type 2 diabetes mellitus) and DIA4003 (CANVAS-R: a randomized, multicentre, double-blind, parallel, placebo-controlled study of the effects of canagliflozin on Renal endpoints in adult subjects with type 2 diabetes mellitus), as per the request for supplementary information (RSI) adopted in July 2016

17.6.2. Canagliflozin - INVOKANA (CAP) - EMEA/H/C/002649/MEA 005.10

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Valerie Strassmann

Scope: Provision of the fifth canagliflozin Independent Data Monitoring Committee (IDMC) status report for the DIA3008 (CANVAS) and DIA4003 (CANVAS-R) studies

17.6.3. Canagliflozin - INVOKANA (CAP) - EMEA/H/C/002649/MEA 006.6

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Valerie Strassmann

Scope: Bi-annual status reports for DNE3001/CREDENCE: a randomized, double-blind, event-driven, placebo-controlled, multicentre study of the effects of canagliflozin on renal and cardiovascular outcomes in subjects with type 2 diabetes mellitus and diabetic nephropathy) from the Independent Data Monitoring Committee (IDMC) (September 2016 status report)

17.6.4. Canagliflozin, metformin - VOKANAMET (CAP) - EMEA/H/C/002656/MEA 004.9

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Menno van der Elst

Scope: MAH's responses to MEA 004.7: provision of data to address additional pharmacovigilance activity in the RMP: Canagliflozin Independent Data Monitoring Committee (IDMC) status reports for studies DIA3008 (CANVAS: a randomized, multicentre, double-blind, parallel, placebo-controlled study of the effects of canagliflozin on cardiovascular outcomes in adult subjects with type 2 diabetes mellitus) and DIA4003 (CANVAS-R: a randomized, multicentre, double-blind, parallel, placebo-controlled study of the effects of canagliflozin on Renal endpoints in adult subjects with type 2 diabetes mellitus), as per the request for supplementary information (RSI) as adopted in July 2016

17.6.5. Canagliflozin, metformin - VOKANAMET (CAP) - EMEA/H/C/002656/MEA 004.10

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Menno van der Elst

Scope: Provision of a fifth Independent Data Monitoring Committee (IDMC) status report for the DIA 3008 (CANVAS) and DIA4003 (CANVAS-R) studies

17.6.6. Canagliflozin, metformin - VOKANAMET (CAP) - EMEA/H/C/002656/MEA 005.6

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Menno van der Elst

Scope: Bi-annual status reports for DNE3001/CREDENCE: a randomized, double-blind, event-driven, placebo-controlled, multicentre study of the effects of canagliflozin on renal and cardiovascular outcomes in subjects with type 2 diabetes mellitus and diabetic nephropathy) from the Independent Data Monitoring Committee (September 2016 status report)

17.6.7. Epoetin beta - NEORECORMON (CAP) - EMEA/H/C/000116/LEG 051.1

Applicant: Roche Registration Limited

PRAC Rapporteur: Valerie Strassmann

Scope: Submission of a summary of the results achieved with the LungSys II project (systems biology of lung cancer – dynamic properties of early metastasis and therapeutic

interventions) with focus on relevant results concerning the erythropoietin/erythropoietin receptor system and erythropoiesis stimulating agents (ESA)

17.6.8. Golimumab - SIMPONI (CAP) - EMEA/H/C/000992/MEA 008.3

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of MAH's responses to MEA 008.2 regarding the annual interim report on an i3 drug safety epidemiology study CNTO148ART4002: golimumab safety and surveillance programme using the Optum research database

17.6.9. Zoledronic acid - ACLASTA (CAP) - EMEA/H/C/000595/LEG 035

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of a summary report on data on the effectiveness of the patient reminder card (PRC) introduced as additional risk minimisation measure for the existing identified risk of osteonecrosis of the jaw (EMEA/H/C/000595/II/0056)

17.7. New Scientific Advice

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

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. Alipogene tiparvovec - GLYBERA (CAP) - EMEA/H/C/002145/S/0057 (without RMP)

Applicant: uniQure biopharma B.V.

PRAC Rapporteur: Julie Williams

Scope: Annual reassessment of the marketing authorisation

18.1.2. Canakinumab - ILARIS (CAP) - EMEA/H/C/001109/S/0047 (without RMP)

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Annual reassessment of the marketing authorisation

18.1.3. Cholic acid - ORPHACOL (CAP) - EMEA/H/C/001250/S/0016 (without RMP)

Applicant: Laboratoires CTRS - Boulogne Billancourt

PRAC Rapporteur: Rafe Suvarna

Scope: Annual reassessment of the marketing authorisation

18.1.4. Idebenone - RAXONE (CAP) - EMEA/H/C/003834/S/0005 (without RMP)

Applicant: Santhera Pharmaceuticals (Deutschland) GmbH

PRAC Rapporteur: Carmela Macchiarulo

Scope: Annual reassessment of the marketing authorisation

18.1.5. Tocofersolan - VEDROP (CAP) - EMEA/H/C/000920/S/0019 (without RMP)

Applicant: Orphan Europe S.A.R.L.

PRAC Rapporteur: Julie Williams

Scope: Annual reassessment of the marketing authorisation

18.2. Conditional renewals of the marketing authorisation

18.2.1. Bosutinib - BOSULIF (CAP) - EMEA/H/C/002373/R/0023 (without RMP)

Applicant: Pfizer Limited

PRAC Rapporteur: Martin Huber

Scope: Conditional renewal of the marketing authorisation

18.2.2. Ceritinib - ZYKADIA (CAP) - EMEA/H/C/003819/R/0009 (without RMP)

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Conditional renewal of the marketing authorisation

18.2.3. Delamanid - DELTYBA (CAP) - EMEA/H/C/002552/R/0017 (without RMP)

Applicant: Otsuka Novel Products GmbH

PRAC Rapporteur: Rafe Suvarna

Scope: Conditional renewal of the marketing authorisation

18.2.4. Pixantrone - PIXUVRI (CAP) - EMEA/H/C/002055/R/0034 (with RMP)

Applicant: CTI Life Sciences Limited

PRAC Rapporteur: Rafe Suvarna

Scope: Conditional renewal of the marketing authorisation

18.3. Renewals of the marketing authorisation

18.3.1. Hydroxycarbamide - SIKLOS (CAP) - EMEA/H/C/000689/R/0030 (with RMP)

Applicant: Addmedica

PRAC Rapporteur: Jean-Michel Dogné

Scope: 5-year renewal of the marketing authorisation

18.3.2. Imiquimod - ZYCLARA (CAP) - EMEA/H/C/002387/R/0012 (with RMP)

Applicant: Meda AB

PRAC Rapporteur: Rafe Suvarna

Scope: 5-year renewal of the marketing authorisation

18.3.3. Ivacaftor - KALYDECO (CAP) - EMEA/H/C/002494/R/0052 (with RMP)

Applicant: Vertex Pharmaceuticals (Europe) Ltd.

PRAC Rapporteur: Dolores Montero Corominas

Scope: 5-year renewal of the marketing authorisation

18.3.4. Linagliptin, metformin - JENTADUETO (CAP) - EMEA/H/C/002279/R/0036 (with RMP)

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Menno van der Elst

Scope: 5-year renewal of the marketing authorisation

18.3.5. Perampanel - FYCOMPA (CAP) - EMEA/H/C/002434/R/0035 (without RMP)

Applicant: Eisai Europe Ltd.

PRAC Rapporteur: Julie Williams

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 9-12 January 2017 meeting.

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
June Munro Raine	Chair	United Kingdom	No interests declared	Full involvement
Jan Neuhauser	Member - via telephone*	Austria	No interests declared	Full involvement
Jean-Michel Dogné	Member	Belgium	No restrictions applicable to this meeting	Full involvement
Laurence Defays	Alternate	Belgium	No interests declared	Full involvement
Yuliyan Eftimov	Alternate	Bulgaria	No interests declared	Full involvement
Nikica Mirošević Skvrce	Member - via telephone*	Croatia	No interests declared	Full involvement
Željana Margan Koletić	Alternate	Croatia	No interests declared	Full involvement
Eva Jirsovà	Alternate	Czech Republic	No interests declared	Full involvement
Doris Stenver	Member	Denmark	No interests declared	Full involvement
Torbjörn Callreus	Alternate	Denmark	No interests declared	Full involvement
Maia Uusküla	Member	Estonia	No interests declared	Full involvement
Kirsti Villikka	Member	Finland	No interests declared	Full involvement
Claire Ferard	Member	France	No interests declared	Full involvement
Caroline Laborde	Alternate	France	No interests declared	Full involvement
Martin Huber	Member - via telephone*	Germany	No interests declared	Full involvement
Valerie Strassmann	Alternate	Germany	No interests declared	Full involvement
Julia Pallos	Member	Hungary	No interests declared	Full involvement
Guðrún Kristín Steingrímsdóttir	Member	Iceland	No interests declared	Full involvement
Almath Spooner	Member (Vice-Chair)	Ireland	No interests declared	Full involvement
Carmela Macchiarulo	Member	Italy	No interests declared	Full involvement
Amelia Cupelli	Alternate	Italy	No interests	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			declared	
Zane Neikena	Member	Latvia	No interests declared	Full involvement
Zane Stade	Alternate	Latvia	No interests declared	Full involvement
Jolanta Gulbinovic	Member	Lithuania	No interests declared	Full involvement
Marcel Bruch	Member	Luxembourg	No interests declared	Full involvement
John Joseph Borg	Alternate	Malta	No interests declared	Full involvement
Sabine Straus	Member	Netherlands	No interests declared	Full involvement
Menno van der Elst	Alternate	Netherlands	No interests declared	Full involvement
Helga Haugom Olsen	Member	Norway	No interests declared	Full involvement
Kristin Thorseng Kvande	Alternate	Norway	No interests declared	Full involvement
Adam Przybylkowski	Member	Poland	No interests declared	Full involvement
Ana Sofia Diniz Martins	Member	Portugal	No interests declared	Full involvement
Roxana Stefania Stroe	Member	Romania	No interests declared	Full involvement
Miroslava Matíková	Alternate	Slovakia	No restrictions applicable to this meeting	Full involvement
Milena Radoha-Bergoč	Member	Slovenia	No restrictions applicable to this meeting	Full involvement
Dolores Montero Corominas	Member	Spain	No interests declared	Full involvement
Eva Segovia	Alternate	Spain	No interests declared	Full involvement
Ulla Wändel Liminga	Member	Sweden	No interests declared	Full involvement
Qun-Ying Yue	Alternate	Sweden	No interests declared	Full involvement
Julie Williams	Member	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
Rafe Suvarna	Alternate	United Kingdom	No interests declared	Full involvement
Stephen J. W. Evans	Member	Independent scientific expert	No interests declared	Full involvement
Brigitte Keller-Stanislawski	Member	Independent scientific expert	No interests declared	Full involvement
Herve Le Louet	Member	Independent scientific expert	No restrictions applicable to this meeting	Full involvement
Lennart Waldenlind	Member	Independent scientific expert	No interests declared	Full involvement
Raymond Anderson	Member	Healthcare Professionals' Representative	No restrictions applicable to this meeting	Full involvement
Kirsten Myhr	Alternate	Healthcare Professionals' Representative	No interests declared	Full involvement
Albert van der Zeijden	Alternate	Patients' Organisation Representative	No restrictions applicable to this meeting	Full involvement
Christelle Bizimungu	Expert - via telephone*	Belgium	No restrictions applicable to this meeting	Full involvement
Jamila Hamdani	Expert - via telephone*	Belgium	No interests declared	Full involvement
Françoise Wuillaume	Expert - via telephone*	Belgium	No interests declared	Full involvement
Predrag Tadinac	Expert - in person*	Croatia	No restrictions applicable to this meeting	Full involvement
Pernille Lynge Gammelgaard	Expert - via telephone*	Denmark	No interests declared	Full involvement
Janne Lehmann Knudsen	Expert - in person*	Denmark	No interests declared	Full involvement
Martin Erik Nyeland	Expert - in person*	Denmark	No restrictions applicable to this meeting	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Helle Gerda Olsen	Expert - in person*	Denmark	No interests declared	Full involvement
Thomas Senderovitz	Expert - in person*	Denmark	No restrictions applicable to this meeting	Full involvement
Mette Georgi Willesen	Expert - via telephone*	Denmark	No interests declared	Full involvement
Pauline Dayani	Expert - via telephone*	France	No restrictions applicable to this meeting	Full involvement
Pierre Demolis	Expert - in person*	France	No interests declared	Full involvement
Sara Franco	Expert - in person*	France	No interests declared	Full involvement
Sara Miranda	Expert - via telephone*	France	No interests declared	Full involvement
Alexandre Moreau	Expert - in person*	France	No interests declared	Full involvement
Thomas Grüger	Expert - via telephone*	Germany	No interests declared	Full involvement
Nils Lilienthal	Expert - via telephone*	Germany	No interests declared	Full involvement
Eleanor Carey	Expert - in person*	Ireland	No interests declared	Full involvement
Ronan Grimes	Expert - in person*	Ireland	No interests declared	Full involvement
Lourens Bloem	Expert - in person*	Netherlands	No restrictions applicable to this meeting	Full involvement
Charlotte Backman	Expert - in person*	Sweden	No interests declared	Full involvement
Yi-Fang Cheng	Expert - via telephone*	Sweden	No interests declared	Full involvement
Anders Lignell	Expert - in person*	Sweden	No interests declared	Full involvement
Dag Nilsson	Expert - via telephone*	Sweden	No restrictions applicable to this meeting	Full involvement
Patrick Batty	Expert - in	United Kingdom	No interests	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
	person*		declared	
Philip Bryan	Expert - via telephone*	United Kingdom	No interests declared	Full involvement
Max Lagnado	Expert - via telephone*	United Kingdom	No interests declared	Full involvement
A representative from the European Commission attended the meeting				
Meeting run with support from relevant EMA staff				

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

20. Annex III - List of acronyms and abbreviations

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

21. Explanatory notes

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

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

(Items 2 and 3 of the PRAC minutes)

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

Signals assessment and prioritisation

(Item 4 of the PRAC minutes)

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

be necessary and this usually takes the form of an update of the summary of product characteristics and the package leaflet.

Risk Management Plans (RMPs)

(Item 5 of the PRAC minutes)

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

Assessment of Periodic Safety Update Reports (PSURs)

(Item 6 of the PRAC minutes)

A PSUR is a report providing an evaluation of the benefit-risk balance of a medicine, which is submitted by marketing authorisation holders at defined time points following a medicine's authorisation. PSURs summarises data on the benefits and risks of a medicine and includes the results of all studies carried out with this medicine (in the authorised and unauthorised indications).

Post-authorisation Safety Studies (PASS)

(Item 7 of the PRAC minutes)

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

Product related pharmacovigilance inspections

(Item 9 of the PRAC minutes)

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

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