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Pharmacovigilance Risk Assessment Committee (PRAC) Minutes of the meeting on 6-9 February 2017

Chair: June Raine – Vice-Chair: Almath Spooner

Health and safety information

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

Disclaimers

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

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

Note on access to documents

Some documents mentioned in the minutes cannot be released at present following a request for access to documents within the framework of Regulation (EC) No 1049/2001 as they are subject to ongoing 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 6-9 February 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 (see Annex II – List of participants). No new or additional conflicts were declared.

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

The PRAC Chairperson welcomed Andri Andreou as the new member for Cyprus, replacing Nectaroula Cooper, and noted that Ioannis Kkolos is the new alternate for Cyprus. The PRAC Chairperson also announced that Rafe Suvarna was to step down as PRAC alternate for the United Kingdom after the current PRAC plenary meeting. The PRAC thanked him for his contribution to the work of the Committee.

1.2. Agenda of the meeting on 6-9 February 2017

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

1.3. Minutes of the previous meeting on 9-12 January 2017

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 9-12 January 2017 were published on the EMA website on 11 April 2017 ([EMA/PRAC/243286/2017](#)).

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

- 3.1.1. Fluoroquinolones for systemic and inhalation use: ciprofloxacin (NAP); enoxacin (NAP); flumequine (NAP); levofloxacin – QUINSAIR (CAP), NAP; lomefloxacin (NAP); moxifloxacin (NAP); norfloxacin (NAP); ofloxacin (NAP); pefloxacin (NAP); prulifloxacin (NAP); rufloxacin (NAP)
Quinolones for systemic and inhalation use: cinoxacin (NAP); nalidixic acid (NAP); pipemidic acid (NAP)

Applicant: Raptor Pharmaceuticals Europe BV (Quinsair), various

PRAC Rapporteur: Eva Jirsová; PRAC Co-rapporteur: Martin Huber

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

Background

Fluoroquinolone- and quinolone-containing medicines for systemic and inhalation use (cinoxacin; ciprofloxacin; enoxacin; flumequin; levofloxacin (Quinsair); lomefloxacin; moxifloxacin; nalidixic acid; norfloxacin; ofloxacin; pefloxacin; pipemidic acid; prulifloxacin; rufloxacin) are a class of broad spectrum antibiotics active against gram-negative and gram-positive bacteria indicated for the treatment of bacterial infections, in particular those which are serious and life-threatening.

The German Federal Institute for Drugs and Medical Devices ([BfArM](#)) sent a letter of [notification](#) dated 1 February 2017 of a referral under Article 31 of Directive 2001/83/EC for the review of quinolone- and fluoroquinolone-containing medicines for systemic and inhalation use to assess the persistence of side effects known to occur with quinolone and fluoroquinolone antibiotics, following reports of long-lasting side effects mainly affecting musculoskeletal and nervous systems. Quinolone- and fluoroquinolone-containing medicines are widely prescribed in the EU and represent important options for treating serious and life-threatening bacterial infections. Taking into account that the specific safety concern of disabling and potentially permanent side effects mainly affecting muscles, joints and the nervous system has not yet been systematically evaluated for all relevant medicinal

products within previous EU regulatory procedures, while the side effects themselves are included in the product information of most of the medicinal products, BfArM considered a review of this safety issue necessary in the interest of the European Union. This review will assess the need for adequate and consistent risk minimisation measures and the impact of this safety concern if confirmed on the overall benefit risk balance of quinolones and fluoroquinolones for systemic and inhalation use especially in authorised indications which are related to treatment of non-serious/non severe infections.

Discussion

The PRAC noted the notification letter from the BfArM and discussed a list of questions (LoQ) to be addressed by the MAHs of fluoroquinolone- and quinolone-containing medicines for systemic and inhalation use as well as a timetable for conducting the review.

The PRAC appointed Eva Jirsová as Rapporteur and Martin Huber as Co-Rapporteur for the procedure.

Summary of recommendation(s)/conclusions

The Committee adopted a LoQ to the MAHs ([EMA/PRAC/38617/2017](#)) and a timetable for the procedure ([EMA/PRAC/38618/2017](#)).

The PRAC discussed the option to conduct a public hearing in the context of the procedure on quinolone- and fluoroquinolone-containing medicines for systemic and inhalation use under Article 31 of Directive 2001/83/EC, according to the pre-defined criteria set out in the rules of procedure¹ ([EMA/363479/2015](#)). It was agreed by the Committee that at this stage in the assessment, in light of the currently available data and the need to determine the appropriate approach to stakeholder engagement, a public hearing would not be appropriate. The PRAC can come back to reconsider this at a later stage of the procedure as needed.

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

¹ Rules of procedure on the organisation and conduct of public hearings at the PRAC

impact of the results of the SIPPET study by *Peyvandi et al.*² 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](#), [PRAC minutes November 2016](#) and [PRAC minutes January 2017](#).

Summary of recommendation(s)/conclusions

At the current meeting, the authors of the SIPPET study presented their findings to the PRAC. The PRAC also adopted a list of experts (LoE) for the ad-hoc expert group meeting scheduled on 22 February 2017. In addition, the PRAC adopted a second list of outstanding issues (LoOI) to the MAHs in accordance with a revised timetable for the procedure ([EMA/PRAC/4751536/2016 rev.2](#)).

3.2.2. Paracetamol³ (NAP) - EMEA/H/A-31/1445

Applicant: GlaxoSmithKline Consumer Healthcare AB (Alvedon, 665 mg modified-release tablet), various

PRAC Rapporteur: Laurence de Fays; PRAC Co-rapporteur: Ulla Wändel Liminga

Scope: Review of the benefit-risk balance of paracetamol modified release following notification by Sweden 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 modified- and prolonged-release paracetamol-containing medicines, following the recent publication by *Salmonson H et al.*⁴ of a retrospective pharmacokinetic (PK) and clinical analysis, in order to assess ways to minimise possible harm in cases of overdosing and to consider whether the recommendations to manage such cases can be further improved. In addition, the procedure includes a review of measures to minimise the risk associated with poisoning with modified- and prolonged-release formulations taking into account the benefit-risk balance for all indications of such modified- and prolonged-release formulations. For further background, see [PRAC minutes July 2016](#) and [PRAC minutes November 2016](#).

Summary of recommendation(s)/conclusions

The PRAC adopted a list of experts (LoE) for the ad-hoc expert group meeting scheduled on 28 February 2017.

3.3. Procedures for finalisation

- 3.3.1. Sodium-glucose co-transporter 2 (SGLT2) inhibitors:
Canagliflozin – INVOKANA (CAP); canagliflozin, metformin – VOKANAMET (CAP);
dapagliflozin – EDISTRIDE (CAP), FORXIGA (CAP); dapagliflozin, metformin –

² F. Peyvandi et al. A randomized trial of factor VIII and neutralizing antibodies in hemophilia A. N. Eng. J. Med. 2016 May 26;374(21):2054-64 (SIPPET study)

³ Modified release formulations

⁴ Salmonson H, et al.: The standard treatment protocol is inadequate following overdose of extended release paracetamol: a pharmacokinetic and clinical analysis of 53 cases. Clin Toxicol 2016;54:424 (Abstract 124)

Applicant: Janssen-Cilag International N.V. (Invokana, Vokanamet); AstraZeneca AB (Edistride, Forxiga, Xigduo, Ebymect); Boehringer Ingelheim International GmbH (Jardiance; Synjardy)

PRAC Rapporteur: Valerie Strassmann; PRAC Co-rapporteur: Menno van der Elst

Scope: Review of the benefit-risk balance of sodium-glucose co-transporter-2 (SGLT2) inhibitors following notification by the European Commission of a referral under Article 20 of Regulation (EC) No 726/2004, based on pharmacovigilance data

Background

A referral procedure under Article 20 of Regulation (EC) 726/2004 is to be concluded for sodium-glucose co-transporter-2 (SGLT2)-containing medicines for type 2 diabetes mellitus reviewing the potential increased risk of lower limb amputation (primarily of the toe), following observation of such an increased risk in ongoing clinical trials⁵ with canagliflozin, assessing ways to minimise this risk and evaluating its impact on the benefit-risk balance of SGLT2-containing medicines. For further background, see [PRAC minutes April 2016](#), [PRAC minutes June 2016](#), [PRAC minutes July 2016](#) and [PRAC minutes November 2016](#).

Discussion

The PRAC reviewed the totality of the data submitted by the MAHs as well as the available data on amputation from the CANVAS and CANVAS-R ongoing clinical trials⁵ and discussed the conclusion reached by the Rapporteurs. The PRAC considered that the available data on amputation in the CANVAS and CANVAS-R trials confirm that treatment with canagliflozin may contribute to an increased risk of amputation of the lower limb, primarily of the toe. Furthermore, given that a mechanism of action is still unclear, that the data on lower limb amputation for dapagliflozin and empagliflozin are either not available to the same extent as for canagliflozin or there were some limitations in the data collection of these events, taking also into account that currently it is not possible to identify an underlying cause for the observed imbalances in amputation risk that would be specifically attributable to canagliflozin-containing medicines and not to the other substances of the class, the PRAC considered that the risk may constitute a possible class effect.

Consequently, the PRAC was of the view that in order to address the risk of lower limb amputation a warning should be included in the product information of all SGLT2-containing medicines highlighting to healthcare professionals and patients the importance of routine preventive foot care. The warning for canagliflozin also includes information that, in patients developing amputation preceding events, consideration may be given to discontinue treatment. For canagliflozin-containing medicines, 'lower limb amputations (mainly of the toe)' should also be added to the product information as an undesirable effect with an uncommon frequency. Because no specific risk factors could be identified apart from general amputation risk factors potentially contributing to the events, the PRAC recommended that patients should be advised on routine preventive foot care and maintaining adequate hydration as general advice to minimise the risk of amputation.

⁵ CANVAS: randomised, multicentre, double-blind, parallel, placebo-controlled study of the effects of canagliflozin on cardiovascular outcomes in adult subjects with type 2 diabetes mellitus; CANVAS-R: Randomized, multicentre, double-blind, parallel, placebo-controlled study of the effects of canagliflozin on renal endpoints in adult subjects with type 2 diabetes mellitus

Moreover, the PRAC considered that additional information on amputation events should be collected through appropriate case report forms (CRFs) for clinical trials, follow-up questionnaires for post-marketing cases, use of common MedDRA⁶ preferred term (PT) lists for events preceding amputation, and appropriate meta-analyses of large studies including cardiovascular outcome studies. All RMPs should be updated accordingly via an appropriate variation to be submitted to EMA no later than 30 days after the European Commission Decision.

Summary of recommendation(s)/conclusions

The PRAC adopted a recommendation to vary the terms of the marketing authorisations for SGLT2-containing medicines (canagliflozin (Invokana), canagliflozin/metformin (Vokanamet), dapagliflozin (Edistride, Forxiga), dapagliflozin/metformin (Xigduo, Ebymect), empagliflozin (Jardiance), and empagliflozin/metformin (Synjardy) and adopted a recommendation to be considered by CHMP for an opinion. See press release ([EMA/76661/2017](#)) entitled 'PRAC concludes that diabetes medicine canagliflozin may contribute to risk of toe amputation'.

Post-meeting note: the press release entitled 'SGLT2 inhibitors: information on potential risk of toe amputation to be included in prescribing information' ([EMA/118223/2017](#)) representing the opinion adopted by the CHMP was published on the EMA website on 24 February 2017.

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

None

3.5. Others

None

4. Signals assessment and prioritisation⁷

4.1. New signals detected from EU spontaneous reporting systems

None

4.2. New signals detected from other sources

4.2.1. Dabigatran – PRADAXA (CAP); lovastatin (NAP); simvastatin (NAP)

Applicant: Boehringer Ingelheim International GmbH (Pradaxa), various

⁶ Medical dictionary for regulatory activities

⁷ 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

PRAC Rapporteur: Torbjorn Callreus

Scope: Signal of major haemorrhage following dabigatran interaction with simvastatin or lovastatin

EPITT 18819 – New signal

Lead Member State: DK

Background

Dabigatran is a direct thrombin inhibitor indicated for the primary prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery, the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF) under certain conditions and the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.

The exposure for Pradaxa, a centrally authorised medicine containing dabigatran, is estimated to have been 6,478,207 patient-years worldwide, in the period from first authorisation in 2008 until 31 August 2016.

Following the publication by *Antoniou et al.*⁸, a signal of major haemorrhage following dabigatran interaction with simvastatin or lovastatin was identified by EMA. Denmark confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

Based on the available evidence from the literature and in particular the biologically plausible mechanism proposed by the authors, the PRAC considered it necessary to investigate the signal further, taking into consideration that the use of statins among users of dabigatran is prevalent and the new evidence from this study, if confirmed, might potentially question the use of simvastatin and lovastatin in patients taking dabigatran-containing medicine. Therefore the PRAC agreed that the MAH for Pradaxa (dabigatran) should provide a review of the published literature on potential interaction between dabigatran and statins, and relevant analyses of data from clinical trials on the risk of haemorrhagic events in patients with/without statin treatments. In addition, based on the above, the MAH should discuss the impact of the patients' risk factors and the underlying mechanism for the interaction, provide a proposal to investigate the potential interaction between dabigatran and concomitantly used relevant statins, and discuss the need for any potential amendment to the product information and/or the RMP.

The PRAC appointed Torbjorn Callreus as Rapporteur for the signal.

Summary of recommendation(s)

- The MAH for Pradaxa (dabigatran) should submit to EMA, within 60 days, a review of cases of major haemorrhage following the concomitant administration of Pradaxa (dabigatran) and statins, including a discussion on possible mechanisms, impact of patients' risk factors, approaches for further investigation, and a proposal for amending the product information as well as a proposal for appropriate risk minimisation measures as applicable.

⁸ Antoniou T, et al. Association between statin use and ischemic stroke or major hemorrhage in patients taking dabigatran for atrial fibrillation. J CMAJ. 2016 Oct 21

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

4.2.2. Darbepoetin alfa – ARANESP (CAP); epoetin alfa – ABSEAMED (CAP), BINOCRIT (CAP), EPOETIN ALFA HEXAL (CAP), NAP; epoetin beta – NEORECORMON (CAP); epoetin theta – BIOPOIN (CAP), EPORATIO (CAP); epoetin zeta – RETACRIT (CAP), SILAPO (CAP), Methoxy polyethylene glycol-epoetin beta – MIRCERA (CAP); NAPs

Applicants: Amgen Europe B.V. (Aranesp), Hexal AG (Epoetin Alfa Hexal), Hospira UK Limited (Retacrit), Medice Arzneimittel Pütter GmbH & Co. KG (Abseamed), Roche Registration Limited (Neorecormon, Mircera), Ratiopharm GmbH (Eporatio), Sandoz GmbH (Binocrit), Stada Arzneimittel AG (Silapo), Teva GmbH (Biopoin); various

PRAC Rapporteur: Valerie Strassmann

Scope: Signal of severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)

EPITT 18846 – New signal

Lead Member State: DE

Background

Erythropoietin is an essential hormone for red blood cell production. Recombinant human erythropoietins (darbepoetin alfa, epoetin alfa, epoetin beta, epoetin theta, epoetin zeta and methoxy polyethylene glycol-epoetin beta) are anti-anaemic preparations indicated for the treatment of symptomatic anaemia associated with chronic renal failure (CRF) under certain conditions. Darbepoetin alfa, epoetin alfa, epoetin beta, and epoetin theta are also indicated for the treatment of symptomatic anaemia in adult patients receiving chemotherapy according to certain conditions. In addition, some erythropoietin products are indicated for increasing the yield of autologous blood from patients in a pre-donation programme and/or to reduce exposure to allogeneic blood transfusions in adult non-iron deficient patients prior to major elective orthopaedic surgery, having a high perceived risk for transfusion complications.

Following reports of occurrence of severe cutaneous adverse reactions (in particular Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)) a signal of severe cutaneous adverse reactions (SCARs) including SJS and TEN was identified by Germany. Subsequently, Germany confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

Having considered preliminary data provided by the MAH of Aranesp (darbepoetin alfa) and the data from EudraVigilance, the PRAC considered that further evaluation of the association between epoetins and SCARs was warranted. The PRAC also noted that SJS and TEN were already included in the product information of Mircera (methoxy polyethylene glycol-epoetin beta). The PRAC recommended that the MAHs of erythropoietin-containing medicines should submit supplementary information to EMA in order to assess this signal.

The PRAC appointed Valerie Strassmann as Rapporteur for the signal.

Summary of recommendation(s)

- The MAHs for Aranesp (darbepoetin alfa); Abseamed, Binocrit, Epoetin Alfa Hexal, Eprex, Erypo, Erypo FS (epoetin alfa); NeoRecormon (epoetin beta); Biopoin, Eporatio (epoetin theta); Retacrit, Silapo (epoetin zeta) and Mircera (methoxy polyethylene glycol-epoetin beta) should submit to EMA, within 60 days, a detailed review of cases related to SCARs, an analysis of the underlying mechanism and outcome of the events as well as a discussion in the context of exposure data. Moreover, the MAHs should perform a cumulative literature review. The MAHs should also provide a discussion on the possible biological mechanisms for the occurrence of SCARs in association with epoetin treatment and, depending on the outcome of the discussion, a proposal for amending the product information as well as a proposal for a direct healthcare professional communication (DHPC) together with a communication plan.
- A 90-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.2.3. Levonorgestrel⁹ (NAP)

Applicant: various

PRAC Rapporteur: Martin Huber

Scope: Signal of anxiety, panic attacks, mood changes, sleep disorders and restlessness

EPITT 18849 – New signal

Lead Member State: DE

Background

Levonorgestrel is a progestogen indicated as an intrauterine device (IUD) for contraception and treatment of menorrhagia.

Following the publication of a petition by a German patient organisation requesting the inclusion of further undesirable effects in the product information of levonorgestrel intrauterine device (IUD) that may be associated with the use of IUD-containing levonorgestrel medicines, a signal of anxiety, panic attacks, mood changes, sleep disorders and restlessness was identified by Germany. Germany confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

Considering the results of a search performed in the German national database of adverse drug reactions (ADRs), the information available from the literature¹⁰, and taking into account that mood changes are part of the spectrum of depression and depressive/depressed mood (reactions already included in the product information of Mirena, Jaydess and Luadei (levonorgestrel) nationally authorised products), the PRAC agreed that further evaluation of the association between levonorgestrel IUD and psychiatric disorders including panic attacks, anxiety, sleep disorders and restlessness is warranted. The PRAC recommended that the MAHs should submit supplementary information to EMA in order to further assess this signal.

The PRAC appointed Martin Huber as Rapporteur for the signal.

⁹ Intrauterine device (IUD)

¹⁰ Mitteilungen: Arzneimittelkommission der deutschen Ärzteschaft 'Aus der UAW-Datenbank' Psychiatrische Erkrankungen als unerwünschte Arzneimittelwirkung von Mirena'; Dtsch Arztebl International 2009; (8); 5: 234; DAE64623

Summary of recommendation(s)

- The MAHs for levonorgestrel-containing IUD should submit to EMA, within 60 days, a cumulative review of the signal, including an analysis of cases related to panic attacks, anxiety, sleep disorders and restlessness. The MAHs should also provide any additional evidence regarding psychiatric reactions, including data from studies and information available from the published literature, as well as a review and discussion on whether there is also a possible association with psychiatric adverse reactions other than the already labelled depression and depressive/depressed mood, namely panic attacks, anxiety, sleep disorders and restlessness. Depending on the outcome of the discussion, MAHs should provide a proposal for amending the product information as well as a proposal for a direct healthcare professional communication (DHPC) and a communication plan.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.2.4. Selexipag - UPTRAVI (CAP)

Applicant: Actelion Registration Ltd.

PRAC Rapporteur: Rafe Suvarna

Scope: Signal of fatal cases in patients with pulmonary arterial hypertension (PAH)

EPITT 18833 – New signal

Lead Member State: UK

Background

Selexipag is a selective prostacyclin (IP) receptor agonist indicated for the long-term treatment of pulmonary arterial hypertension (PAH) in adult patients with WHO¹¹ functional class (FC) II–III, either as combination therapy in patients insufficiently controlled with an endothelin receptor antagonist (ERA) and/or a phosphodiesterase type 5 (PDE-5) inhibitor, or as monotherapy in patients who are not candidates for these therapies.

A signal of fatal cases in patients with pulmonary arterial hypertension (PAH) was identified by France. Following the recent occurrence of five fatal cases in the weeks following initiation of a treatment with Uptravi (selexipag), on 24 January 2017 the French National Competent Authority ([ANSM](#)) recommended as a precautionary measure not to initiate any new treatment with Uptravi (selexipag) before further assessment is performed. The United Kingdom confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

Taking into account the available evidence from the five index case reports in France together with data from clinical trials, published literature, as well as the preliminary data submitted by the MAH, the PRAC considered that further evaluation of the signal of fatal cases in patients with PAH was warranted. The PRAC recommended that the MAH should submit supplementary information to EMA.

The PRAC appointed Rafe Suvarna as Rapporteur for the signal.

¹¹ World Health Organization

Summary of recommendation(s)

- The MAH for Uptravi (selexipag) should submit to EMA, within 30 days, a comparison of the cases associated with selexipag and those associated with other medicines currently used to treat PAH with WHO FC II–III, a proposed plan to provide further long-term follow-up data, a thorough discussion comparing the exclusion criteria of the pivotal clinical trial with the consequent warnings and contraindications in the product information as well as the potential consequences of non-adherence to the existing warnings and contraindications in terms of the risk of adverse drug reactions (ADRs). In addition, the MAH should propose further routine risk minimisation or additional risk minimisation measures and provide a discussion on the need to amend the product information as applicable.
- A 30-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.2.5. Tick-borne encephalitis vaccine (inactivated) (NAP)

Applicant: various

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Signal of potential vaccination failure in children

EPITT 18825 – New signal

Lead Member State: DE

Background

Tick-borne encephalitis (TBE) is a viral infectious disease involving the central nervous system. Tick-borne encephalitis vaccine containing inactivated tick-borne encephalitis virus is indicated for the prevention of TBE.

Following a national review in Austria by the Institute of Virology (Medical University, Vienna), a signal of potential vaccination failure in children was identified by Austria. Germany confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

Taking into account the available evidence from vaccination failure case reports in children in Austria, the PRAC considered that further evaluation of the signal of vaccination failure was warranted. The PRAC recommended that the MAHs should submit supplementary information to EMA.

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

Summary of recommendation(s)

- The MAHs of tick-borne encephalitis vaccines (inactivated) should submit to EMA, within 60 days, a cumulative review of the signal, including an analysis of all case reports of vaccination failure associated with TBE vaccine and related terms, together with consideration of inclusion of other relevant terms within the MedDRA SOC¹² 'injury, poisoning and procedural complications'. In addition, the MAHs should provide the estimated exposure per EU Member State where TBE vaccine is marketed, from 1990 to

¹² Medical dictionary for regulatory activities – System organ class

2016, by age category and completeness of vaccination schedules, an overview of efficacy/effectiveness data for the vaccine according to different age categories as well as an overview of ongoing immunogenicity studies in children by age group. The MAHs should comment on the findings of a potential decreased effectiveness of TBE vaccination since 2002 and the potential underlying cause. Moreover, the MAHs should comment on possible activities to minimize vaccination failure and provide a proposal to amend the product information as applicable.

- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.
- The PRAC adopted a list of questions (LoQ) to the CHMP Vaccine Working Party ([VWP](#))¹³.

4.3. Signals follow-up and prioritisation

4.3.1. Dexlansoprazole (NAP); lansoprazole (NAP)

Applicant: various

PRAC Rapporteur: Kirsti Villikka

Scope: Signal of unexpected histopathological findings from a juvenile rat toxicity study

EPITT 18645 – Follow-up to October 2016

Background

The MAH replied to the request for information on the signal of unexpected histopathological findings from a juvenile rat toxicity study and the responses were assessed by the Rapporteur. For background information, see [PRAC minutes October 2016](#).

Discussion

Having considered the data submitted by the MAH, including the additional data on testosterone metabolism, the PRAC agreed that no definitive mechanism explaining the recent histopathological findings in the juvenile rats could be found. Considering the lack of any safety signal in humans relevant to these findings, the PRAC considered plausible that the effects observed in animals might be species-specific, rats belonging to the most sensitive species. Nevertheless, the PRAC noted the absence of clinical data in children with regard to effects on testosterone synthesis. Therefore, the PRAC agreed that no amendment to the product information was warranted at this stage and that the MAHs of lansoprazole- and dexlansoprazole-containing products should continue to monitor the issue through routine pharmacovigilance and report any new data when they become available.

Summary of recommendation(s)

- The MAHs of lansoprazole- and dexlansoprazole-containing products should continue to monitor the issue through routine pharmacovigilance and report any new data when they become available.

¹³ The LoQ is transmitted to the CHMP for agreement in advance of the VWP consultation

4.3.2. Exenatide - BYDUREON (CAP) - EMEA/H/C/002020/SDA/023; BYETTA (CAP) - EMEA/H/C/000698/SDA/043

Applicant: AstraZeneca AB

PRAC Rapporteur: Qun-Ying Yue

Scope: Signal of incorrect use of device associated with (serious) adverse reactions including hyperglycaemia and hypoglycaemia

EPITT 18688 – Follow-up to July 2016

Background

The MAH replied to the request for information on the signal of incorrect use of device associated with (serious) adverse reactions, including hyperglycaemia and hypoglycaemia, and the responses were assessed by the Rapporteur. For background information, see [PRAC minutes July 2016](#).

Discussion

Taking into account the data submitted by the MAH, the PRAC considered that the available evidence suggested that the majority of reported events were in fact non-serious and relatively 'expected'. Nevertheless, given the large number of events of incorrect use of the device associated with a root cause of non-compliance with instructions for use in the Package Leaflet (PL), the PRAC considered it relevant for the MAH to review and make efforts to improve the instructions for use (IFU) for exenatide-containing products, in order to reduce the risk of patients' non-compliance.

Summary of recommendation(s)

- The MAH for exenatide-containing medicinal products should submit to EMA, within 60 days, a review of the IFU for the exenatide-containing products, and a proposal to update them to better instruct patients on how to prepare and self-inject these medicinal products. The latter should include a proposal for testing to ensure readability and comprehension in the appropriate patient population, via human factors study(ies). Additionally, the MAH should provide plans and timelines for developing a device programme to minimise incorrect use of device such as the implementation of a 'dummy device' and also consider other suitable options.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

Post-meeting note: on 3 March 2017, the PRAC agreed with the MAH's request to extend the timeframe for submitting responses to EMA to 90 days (instead of 60).

4.3.3. Fluconazole (NAP)

Applicant: various

PRAC Rapporteur: Doris Stenver

Scope: Signal of spontaneous abortion and stillbirth

EPITT 18666 – Follow-up to January 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 January 2016](#).

Discussion

The PRAC considered the available evidence, including the review and assessment of the register-based cohort study by *Mølgaard-Nielsen et al.*¹⁴, the cumulative review of all available data from clinical trials, post-marketing data and literature publications concerning the risk of spontaneous abortion and stillbirth following exposure to fluconazole during pregnancy, as well as the proposal of the MAH of the innovator product containing fluconazole to update the product information. The PRAC considered that although the evidence of an increased risk of spontaneous abortion in women treated with fluconazole during the first pregnancy trimester had some limitations, it was sufficient to update the product information of fluconazole-containing products and to delete inconsistent information. Nonetheless, the PRAC considered there was insufficient justification for adding a requirement for effective contraception.

Summary of recommendation(s)

- The MAHs for fluconazole-containing products should submit to the national competent authorities of the Member States, within 60 days, a variation to amend the product information¹⁵.
- The MAHs of fluconazole-containing medicinal products with an RMP in place should update it accordingly at the next regulatory opportunity.

For the full PRAC recommendation, see [EMA/PRAC/68642/2017](#) published on 06/03/2017 on the EMA website.

4.3.4. Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/SDA/014

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Signal of pemphigoid

EPITT 18759 – Follow-up to October 2016

Background

The MAH replied to the request for information on the signal of pemphigoid and the responses were assessed by the Rapporteur. For background information, see [PRAC Minutes October 2016](#).

Discussion

Having reviewed the available evidence from EudraVigilance and the published literature, the PRAC agreed that an association between medicines in the class and pemphigoid cannot be excluded. Taking into account that pemphigoid is already listed in the product information of Keytruda (pembrolizumab), another anti-programmed death-1 (PD-1) receptor, the PRAC recommended that the product information of Opdivo (nivolumab) is

¹⁴ 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

¹⁵ Update of SmPC section 4.6 for fluconazole-containing medicinal products

amended to include 'pemphigoid' among undesirable effects related to skin rash, with a very common frequency. The PRAC also recommended that a review of cases of pemphigoid should be conducted for Yervoy (ipilimumab), an immune checkpoint inhibitor that blocks T-cell inhibitory signals induced by the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) pathway.

Summary of recommendation(s)

- The MAH for Opdivo (nivolumab) should submit to EMA, within 60 days, a variation to amend the product information¹⁶.
- The MAH for Yervoy (ipilimumab) should include a cumulative review of cases of pemphigoid within the next PSUR (DLP: 24/03/2017).

For the full PRAC recommendation, see [EMA/PRAC/68642/2017](https://www.ema.europa.eu/en/PRAC/68642/2017) published on 06/03/2017 on the EMA website.

5. Risk management plans (RMPs)

5.1. Medicines in the pre-authorisation phase

See also Annex I 15.1.

5.1.1. Cariprazine - EMEA/H/C/002770

Scope: Treatment of schizophrenia

5.1.2. Cenegermin - EMEA/H/C/004209, Orphan

Applicant: Dompe Farmaceutici S.p.A.

Scope, accelerated assessment: Treatment of neurotrophic keratitis

5.1.3. Dimethyl fumarate - EMEA/H/C/002157

Scope: Treatment of moderate to severe plaque psoriasis in adults in need of systemic drug therapy, treatment of plaque psoriasis

5.1.4. Etanercept - EMEA/H/C/004192

Scope: Treatment of rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, axial spondyloarthritis, ankylosing spondylitis (AS), non-radiographic axial spondyloarthritis, plaque psoriasis and paediatric plaque psoriasis

¹⁶ Update of SmPC section 4.8. The Package Leaflet is to be updated accordingly

5.1.5. Expanded human allogeneic mesenchymal adult stem cells extracted from adipose tissue- EMEA/H/C/004258, Orphan

Applicant: Tigenix, S.A.U., ATMP¹⁷

Scope: Treatment of complex perianal fistula(s)

5.1.6. Iloperidone - EMEA/H/C/004149

Scope: Treatment of schizophrenia

5.1.7. Inotuzumab ozogamicin - EMEA/H/C/004119, Orphan

Applicant: Pfizer Limited

Scope: Treatment of B-cell precursor acute lymphoblastic leukaemia (ALL)

5.1.8. Masitinib - EMEA/H/C/004159, Orphan

Applicant: AB Science

Scope: Treatment of mastocytosis

5.1.9. Patiromer sorbitex calcium - EMEA/H/C/004180

Scope: Treatment of hyperkalaemia

5.1.10. Rituximab - EMEA/H/C/003903

Scope: Treatment of non-Hodgkin's lymphoma (NHL), chronic lymphocytic leukaemia (CLL), rheumatoid arthritis and granulomatosis with polyangiitis and microscopic polyangiitis

5.1.11. Rituximab - EMEA/H/C/004729

Scope: Treatment of non-Hodgkin's lymphoma (NHL), chronic lymphocytic leukaemia (CLL), rheumatoid arthritis and granulomatosis with polyangiitis and microscopic polyangiitis

5.1.12. Sarilumab - EMEA/H/C/004254

Scope: Treatment of active rheumatoid arthritis

5.1.13. Spheroids of human autologous matrix-associated chondrocytes - EMEA/H/C/002736

ATMP¹⁸

Scope: Treatment of cartilage defects

¹⁷ Advanced therapy medicinal product

¹⁸ Advance therapy medicinal product

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

See Annex I 15.2.

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

See also Annex I 15.3.

5.3.1. Fluticasone furoate, vilanterol - RELVAR ELLIPTA (CAP) - EMA/H/C/002673/WS1101/0029; REVINTY ELLIPTA (CAP) - EMA/H/C/002745/WS1101/0025

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Dolores Montero Corominas

Scope: Update of section 5.1 of the SmPC in order to update the safety information with the results of HZC115151 study: a 12-month, open label, randomised, effectiveness study to evaluate fluticasone furoate/vilanterol inhalation powder delivered once daily via a novel dry powder inhaler (NDPI) compared with the existing chronic obstructive pulmonary disease (COPD) maintenance therapy alone in subjects with COPD (Annex II condition) of the Relvar Ellipta and Revinty Ellipta (92/22mcg strength only). The RMP (version 8.3) is updated accordingly

Background

Fluticasone furoate is a synthetic corticosteroid and vilanterol, a selective, long-acting beta₂-receptor agonist. In combination, fluticasone furoate/vilanterol is indicated for the regular treatment of asthma in adults and adolescents aged 12 years and older where use of a combination medicinal product (long-acting beta₂-agonists and inhaled corticosteroid) is appropriate. Fluticasone furoate/vilanterol is also indicated for the symptomatic treatment of adults with chronic obstructive pulmonary disease (COPD) with a FEV₁¹⁹ < 70% predicted normal (post-bronchodilator) with an exacerbation history despite regular bronchodilator therapy.

The CHMP is evaluating a worksharing variation procedure for Relvar Ellipta/Revinty Ellipta, centrally authorised products containing fluticasone furoate/vilanterol, following the submission of the final clinical report for an interventional PASS²⁰ investigating the risk of pneumonia with fluticasone furoate/vilanterol compared with other inhaled corticosteroids (ICS)/long acting β₂-adrenoceptor agonist (LABA) fixed dose combinations (FDCs) in the treatment of COPD and asthma as requested in Annex II of the marketing authorisations. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this worksharing variation. For further background on the PRAC consultation of the study protocol, see [PRAC minutes February 2014](#) and [PRAC minutes May 2014](#).

Summary of advice

- The RMP version 8.3 for Relvar Ellipta and Revinty Ellipta (fluticasone furoate/vilanterol) in the context of the variation under evaluation by the CHMP could be

¹⁹ Forced expiratory volume in 1 second

²⁰ Salford Study (COPD) (HZC115151): a 12-month, open label, randomised, effectiveness study to evaluate fluticasone furoate (FF, GW685698)/vilanterol (VI, GW642444) inhalation powder delivered once daily via a novel dry powder inhaler (NDPI) compared with the existing chronic obstructive pulmonary disease (COPD) maintenance therapy alone in subjects with COPD

considered acceptable provided that satisfactory responses to a request for supplementary information (RSI) are submitted by the MAH.

- Based on the final clinical report of the PASS, the PRAC agreed that the results are consistent with the conclusions of the completed referral procedure dated 2016 ([EMEA/H/A-31/1415](#)) with regard to the risk of pneumonia and the safety profile of fluticasone furoate/vilanterol combination remains unchanged. In terms of pharmacovigilance plan, the MAH should provide further information on the current status of several studies addressing the risk of 'asthma-related intubations and deaths' within the next PSUR (DLP: 09/05/2017).

5.3.2. Liraglutide - SAXENDA (CAP) - EMEA/H/C/003780/II/0011

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Menno van der Elst

Scope: Update of sections 4.4 and 5.1 of the SmPC in order to reflect the clinical study results of the LEADER study (EX2211-3748, category 3 study): liraglutide effect on and action in diabetes - evaluation of cardiovascular outcome results to specifically address the important potential risk of cardiovascular disorders in patients with type 2 diabetes mellitus (T2DM)). The Package Leaflet, Labelling and RMP (version 27) are updated accordingly. This variation application fulfils two post-approval commitments in relation to the cardiovascular outcomes trial (MEA 002), as well as providing additional information on the breast cancer cases reported in the LEADER study (MEA 005). Finally, the MAH took the opportunity to implement minor editorial changes throughout the product information

Background

Liraglutide is an acylated human glucagon-like peptide-1 (GLP-1) analogue indicated as an adjunct to a reduced-calorie diet and increased physical activity for weight management in adult patients with an initial body mass index (BMI) of ≥ 30 kg/m² (obese), or ≥ 27 kg/m² to < 30 kg/m² (overweight) in the presence of at least one weight-related comorbidity such as dysglycaemia (pre-diabetes or type 2 diabetes mellitus), hypertension, dyslipidaemia or obstructive sleep apnoea.

The CHMP is evaluating a type II variation procedure for Saxenda, a centrally authorised product containing liraglutide, to update the product information based on the results of the LEADER study entitled 'liraglutide effect and action in diabetes: evaluation of cardiovascular outcome results to specifically address the important potential risk of cardiovascular disorders in patients with type 2 diabetes mellitus (T2DM)'. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this type II variation.

Summary of advice

- The RMP version 27.0 for Saxenda (liraglutide) in the context of the variation under evaluation by the CHMP could be considered acceptable provided that satisfactory responses to a request for supplementary information (RSI) are submitted by the MAH.
- The PRAC supported removing 'pancreatitis' as an important identified risk and 'cardiovascular disorders' as an important potential risk from the RMP. In addition, the PRAC considered that 'neoplasms (including melanoma)' and 'pancreatic cancer' should remain in the safety specifications as important potential risks, as the results of the

LEADER study point towards a higher risk of pancreatic cancer in the liraglutide group compared to the placebo group. Such a numerical imbalance was also observed with other neoplasms, especially melanoma. Finally, the MAH should justify keeping the inclusion of 'patients with severe renal impairment' as missing information in the RMP.

5.3.3. Liraglutide - VICTOZA (CAP) - EMEA/H/C/001026/II/0042

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to include the prevention of major adverse cardiovascular events (MACE) in adults with type 2 diabetes mellitus (T2DM) at high cardiovascular risk and as an adjunct to standard of care therapy in section 4.1 of the SmPC implementing the clinical study results of the LEADER study (EX2211-3748): liraglutide effect on and action in diabetes, evaluation of cardiovascular outcome results (category 3 study: to specifically address the important potential risk of cardiovascular disorders in patients with T2DM). As a consequence, sections 4.2, 4.4, 4.7, 4.8, 5.1 and 6.5 of the SmPC, the Package Leaflet, Labelling and RMP (version 27) are updated accordingly

Background

Liraglutide is an acylated human glucagon-like peptide-1 (GLP-1) analogue indicated for the treatment of adults with type 2 diabetes mellitus to achieve glycaemic control, in monotherapy when diet and exercise alone do not provide adequate glycaemic control in patients for whom use of metformin is considered inappropriate due to intolerance or contraindications, or in combination with oral glucose-lowering medicinal products and/or basal insulin when these, together with diet and exercise, do not provide adequate glycaemic control.

The CHMP is evaluating a type II variation procedure for Victoza, a centrally authorised product containing liraglutide, to update the product information based on the results of the LEADER study entitled 'liraglutide effect and action in diabetes: evaluation of cardiovascular outcome results to specifically address the important potential risk of cardiovascular disorders in patients with type 2 diabetes mellitus (T2DM)'. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this type II variation.

Summary of advice

- The RMP version 27.0 for Victoza (liraglutide) in the context of the variation under evaluation by the CHMP could be considered acceptable provided that satisfactory responses to a request for supplementary information (RSI) are submitted by the MAH.
- The PRAC supported removing 'pancreatitis' as an important identified risk and 'cardiovascular disorders' as an important potential risk from the RMP. In addition, the PRAC considered that 'neoplasms (including melanoma)' and 'pancreatic cancer' should remain in the safety specifications as important potential risks, as the results of the LEADER study point towards a higher risk of pancreatic cancer in the liraglutide group compared to the placebo group. Such a numerical imbalance was also observed with other neoplasms, especially melanoma. Finally, the PRAC considered that 'mild and moderate hepatic impaired patients' should remain as missing information in the RMP, as no information on the hepatic status of patients included in the LEADER study was

provided. Therefore, the MAH should provide information to justify the deletion of these patient groups as missing information.

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. Atazanavir, cobicistat - EVOTAZ (CAP) - PSUSA/00010404/201607 (with RMP)

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Claire Ferard

Scope: Evaluation of a PSUSA procedure

Background

Atazanavir is an azapeptide human immunodeficiency virus (HIV)-1 protease inhibitor (PI) and cobicistat a selective, mechanism-based inhibitor of cytochromes P450 of the CYP3A²¹ subfamily enhancing the systemic exposure of CYP3A substrates. The combination of atazanavir boosted with cobicistat as a pharmacokinetic enhancer is indicated in combination with other antiretroviral medicinal products for the treatment of HIV-1 infected adults without known mutations associated with resistance to atazanavir.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Evotaz, a centrally authorised fixed-dose combination medicine containing atazanavir/cobicistat, 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 Evotaz (atazanavir/cobicistat) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include information that atazanavir is detected in human milk. Therefore the current terms of the marketing authorisation(s) should be varied²².
- In the next PSUR, the MAH should gather, via the antiretroviral pregnancy registry (APR), the number of pregnancy cases with in utero exposure to an atazanavir- and cobicistat-containing antiretroviral regimen and the number of birth defects if any.

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.

²¹ Cytochrome P450, family 3, subfamily A

²² Update of SmPC section 4.6. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

6.1.2. Brivaracetam - BRIVIACT (CAP) - PSUSA/00010447/201607

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

Background

Brivaracetam is an antiepileptic indicated as adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalisation in adult and adolescent patients from 16 years of age with epilepsy.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Briviact, a centrally authorised medicine containing brivaracetam, 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 Briviact (brivaracetam) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include safety information regarding the risk of type I hypersensitivity and add clarification on the third brivaracetam metabolite (hydroxy acid). Therefore the current terms of the marketing authorisation(s) should be varied²³.
- In the next PSUR, the MAH should provide detailed analyses of cases of rhabdomyolysis, acute kidney injury, encephalopathy and interstitial nephritis. In addition, the MAH should provide clarifications with regard to the risk for medication errors arising from names' similarity between Briviact (brivaracetam) and Brivirac (brivudine) as well as proposed actions to prevent such medication errors. Finally, the MAH should provide a cumulative review of all reported overdoses and associated symptoms.

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

6.1.3. Ingenol mebutate - PICATO (CAP) - PSUSA/00010035/201607

Applicant: Leo Pharma A/S

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

Background

Ingenol mebutate induces local lesion cell death and promotes an inflammatory response characterised by local production of pro-inflammatory cytokines and chemokines and infiltration of immunocompetent cells. It is indicated for the cutaneous treatment of non-hyperkeratotic, non-hypertrophic actinic keratosis in adults.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Picato,

²³ Update of SmPC sections 4.8 and 5.2. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

a centrally authorised medicine containing ingenol mebutate, 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 Picato (ingenol mebutate) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning on keratoacanthoma as well as information on the high incidence of keratoacanthoma observed in a clinical trial²⁴ (large treatment area). Therefore the current terms of the marketing authorisation(s) should be varied²⁵.
- In the next PSUR, the MAH should discuss cumulative data on squamous cell carcinoma (SCC) and other skin tumours in ongoing clinical trials (CT), provide a table summarising the local skin response-related preferred terms (PTs) reported with 'application site haemorrhage' events, and discuss the need to update the product information accordingly to make the possibility of bleeding at the application site clearer to the patients. In addition, the MAH should discuss the possibility of a further non-interventional study to gather follow-up information on patients who recently completed participation to clinical trials (retrospective data/clinical records).

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

6.1.4. Rotavirus vaccine monovalent (live, oral) - ROTARIX (CAP) - PSUSA/00002665/201607

Applicant: GlaxoSmithKline Biologicals S.A.

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

Background

Rotarix, a centrally authorised medicine, is a rotavirus vaccine indicated for the active immunisation of infants aged 6 to 24 weeks for prevention of gastroenteritis due to rotavirus infection.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Rotarix (rotavirus vaccine monovalent (live, oral)), 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 Rotarix (rotavirus vaccine monovalent (live, oral)) in the approved indication(s) remains unchanged.

²⁴ LP0105-1020, Efficacy and safety of ingenol mebutate gel 0.06% when applied once daily for 2, 3 or 4 consecutive days to a treatment area of approximately 250 cm² on trunk and extremities in subjects with actinic keratosis. NCT 01998984

²⁵ Update of SmPC sections 4.4 and 5.1. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

- Nevertheless, the product information should be updated to accurately reflect the known risk of intussusception following results of a European study by *Stowe et al.*²⁶. Therefore the current terms of the marketing authorisation(s) should be varied²⁷.
- In the next PSUR, the MAH should closely monitor the risk of intussusception, elaborate on the incidence of non-rotavirus gastroenteritis in the rotavirus vaccinated population, comment on publications related to Rotarix vaccination impact and update the cumulative review concerning the influence of breastfeeding.
- The MAH should be requested to collaborate with EU NCAs upon their request to communicate the updated information on the known risk of intussusception, and its early diagnosis and management.

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

6.2. PSUR 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.

6.3.1. Ibuprofen, pseudoephedrine (NAP) - PSUSA/00001711/201607

Applicant: various

PRAC Lead: Caroline Laborde

Scope: Evaluation of a PSUSA procedure

Background

Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID) with anti-inflammatory, analgesic and antipyretic activities. Pseudoephedrine is a natural stereoisomer of ephedrine and triprolidine is a competitive histamine H1 antagonist. The combination ibuprofen/pseudoephedrine is indicated for the symptomatic relief of nasal/sinus congestion with headache, fever and pain associated with the common cold and flu in adults and adolescents under certain conditions.

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

Summary of recommendation(s) and conclusions

²⁶ Stowe J, Andrews N, Ladhani S, Miller E. The risk of intussusception following monovalent rotavirus vaccination in England: A self-controlled case-series evaluation. *Vaccine*. 2016;34(32):3684-9

²⁷ 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

- Based on the review of the data on safety and efficacy, the risk-benefit balance of ibuprofen/pseudoephedrine-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 the maternal exposition by ibuprofen/pseudoephedrine during the first 6 months of pregnancy and cases of ischaemic colitis. Moreover, acute generalised exanthematous pustulosis (AGEP) and all severe cutaneous adverse reactions (SCARs) should be closely monitored. In addition, AGEP should be considered an important identified risk in the summary of safety concerns.

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

6.4. 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)²⁸

See also Annex I 17.1.

7.1.1. Cidofovir (NAP) - EMEA/H/N/PSP/S/0052

Applicant: Emcure Pharma UK Ltd (Cidofovir Emcure Pharma)

PRAC Rapporteur: Julie Williams

Scope: Protocol (version 1.0) for a non-interventional, prospective, exposure (safety outcome) registry study of cidofovir to further elucidate the characteristics of the different patient populations for cidofovir use, gather details of adverse events and patient outcome following treatment in a specified indication

Background

Cidofovir is an antiviral for systemic use indicated for the treatment of cytomegalovirus (CMV) retinitis in adults with acquired immunodeficiency syndrome (AIDS) and without renal dysfunction.

To address the identified important potential risk of off-label use including intraocular administration, the MAH for Cidofovir Emcure Pharma was requested to implement a registry as an additional pharmacovigilance measure to collect data relating to any exposure to cidofovir in any indications for which the medicinal product is used (on or off-label) and to characterise the impact of off-label use. The protocol version 1.0 was reviewed by the PRAC.

²⁸ In accordance with Article 107n of Directive 2001/83/EC

Endorsement/Refusal of the protocol

- The PRAC, having considered the draft protocol version 1.0 in accordance with Article 107n of Directive 2001/83/EC, as set out in the appended assessment report, objected to the draft protocol for the above listed medicinal product(s), as the Committee considered that the design of the study does not fulfil the study objectives.
- The MAH should consider the effect of small numbers of exposed/enrolled patients and the impact this might have on conducting statistical tests. The MAH should also conduct a power analysis to calculate the minimum sample size required to be reasonably certain of detecting an effect of a given size. In addition, the MAH should consider the proportion of prescriptions which are likely to be for an off-label indication and use this data in the sample size calculation to provide an indication as to approximately how long the study may be anticipated to run. Finally, additional revisions to the study design and timelines should be considered by the MAH.
- The MAH should submit a revised PASS protocol to EMA within 30 days. A 30 days-assessment timetable will be applied.

7.2. Protocols of PASS non-imposed in the marketing authorisation(s)²⁹

See Annex I 17.2.

7.3. Results of PASS imposed in the marketing authorisation(s)³⁰

None

7.4. Results of PASS non-imposed in the marketing authorisation(s)³¹

See Annex I 17.4.

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

See Annex I 17.5.

7.6. Others

See Annex I 17.6.

7.7. New Scientific Advice

None

²⁹ 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

³⁰ In accordance with Article 107p-q of Directive 2001/83/EC

³¹ In accordance with Article 61a (6) of Regulation (EC) No 726/2004, in line with the revised variations regulation for any submission as of 4 August 2013

7.8. Ongoing Scientific Advice

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 minutes.

9.3. Others

None

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

10.1. Safety related variations of the marketing authorisation

10.1.1. Parecoxib – DYNASTAT (CAP) - EMEA/H/C/000381/II/0068/G

Applicant: Pfizer Limited

PRAC Rapporteur: Almath Spooner

Scope: PRAC consultation on a grouped variation to: 1) update of section 4.4 of the SmPC in order to update the safety information related to cardiovascular risk information, 2) update of section 4.4 of the SmPC in order to update the safety information related to alcohol use and gastrointestinal (GI) risk, 3) update of section 4.6 of the SmPC in order to update the safety information related to oligohydramnios if the product is used during the second or third trimester of pregnancy. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet, to bring the Product Information in line with the latest QRD template (version 10.0)

Background

Parecoxib is a non-steroidal anti-inflammatory drug (NSAID). Dynastat, a centrally authorised product containing parecoxib, is indicated for the short-term treatment of postoperative pain.

The cardiovascular risk of NSAIDs is well established and warnings relating to this risk are currently reflected in the product information (PI) of Dynastat (parecoxib). In December 2016, the MAH for Dynastat (parecoxib) submitted a variation to further update the PI to include additional information relating to this risk. This proposal follows an FDA review and finalisation of labelling updates to prescription NSAIDs in May 2016. The type II variation proposing to update the PI for Dynastat (parecoxib) is under evaluation at the CHMP. The PRAC was requested to provide advice on this variation.

Summary of advice

- Based on the review of the available information, the PRAC considered that there was insufficient evidence to conclude that the relative risk of cardiovascular (CV) events is similar in patients with or without known CV disease or CV risk factors, and that the MAH's proposed updates do not improve the clinical advice already included in the Dynastat (parecoxib) product information, which is currently consistent with the outcomes of previous referral procedures completed in 2004 (CPMP/1747/04) and in 2005 (CHMP/323166/05). As a consequence, the PRAC did not support the MAH's proposal to amend the existing warning on cardiovascular risks in patients receiving Dynastat (parecoxib).

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

None

10.3. Other requests

None

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

11.1. Safety related variations of the marketing authorisation

11.1.1. Finasteride (NAP) - SE/H/xxx/WS/139

Applicant: Merck Sharp & Dohme Limited (Propecia, Proscar)

PRAC Lead: Ulla Wändel Liminga

Scope: PRAC consultation on a variation procedure for Propecia, Proscar (finasteride) (SE/H/xxx/WS/139) exploring the possible causal relationship between finasteride 1 mg for the treatment of alopecia and the risk of depression

Background

Finasteride, a synthetic 4-azasteroid compound, is a specific inhibitor of type II 5 alpha-reductase, an intracellular enzyme that metabolizes the androgen testosterone to dihydrotestosterone (DHT). It is indicated for the treatment and control of benign prostatic hyperplasia (BPH), for the prevention of urologic events under certain conditions, and for the treatment of men with male pattern hair loss (androgenetic alopecia) to increase hair growth and prevent further hair loss.

Based on the assessment of the PSUR(s) for finasteride-containing medicines (PSUSA/00001392/201508, PSUSA procedure concluded at PRAC in April 2016), the PRAC agreed that MAHs should be requested to submit to EU National Competent Authorities an additional cumulative review of all events relating to depression or suicidality associated with the use of finasteride for male pattern hair loss for the approved 1 mg dose and provide a review of cases where higher doses have been used for the treatment of this condition. The MAHs were also requested to make proposals to update their product information as applicable. For further background, see [PRAC minutes April 2016](#).

In the context of the evaluation of this review, assessed in the context of a worksharing type II variation procedure, Sweden requested PRAC advice on its assessment.

Summary of advice

- Based on the review of the available information, the PRAC acknowledged that the evidence supporting a causal relationship between finasteride 1 mg and depression was relatively limited. This was due to the difficulties reviewing the spontaneously reported cases, as well as in light of the target population, which may be more prone to psychiatric distress than the general population. Nevertheless, taking into account a possible mechanistic explanation, and the available spontaneously reported cases, the PRAC considered that there was sufficient supportive evidence to conclude on at least a possible relationship between depression and finasteride 1 mg use. Therefore the

Committee recommended adding 'depression' in the product information as an undesirable effect with an unknown frequency³².

- Given that the indication for use is not a 'serious' condition, the PRAC considered it of importance that healthcare professionals and subjects to be treated should be fully aware of the possibility that finasteride 1 mg may be associated with depression, and therefore also recommended the inclusion of a warning statement in product information³³. This warning should reflect that cases of depression, mood alterations and suicidal ideation have been reported. It was also recommended that patients should be monitored for psychiatric symptoms, and should a subject experience such symptoms, the treatment should be discontinued and medical advice sought.
- The PRAC did not find it necessary to implement further EU-level communication activities beyond updating the product information. Nevertheless, a need for healthcare professionals' communications may be considered further at a national level. Furthermore, the PRAC did not consider it warranted for the MAHs to be requested to undertake further pharmacovigilance activities (i.e. further studies).

11.1.2. Racecadotril (NAP) - SE/H/1342/01-03/II/44

Applicant: Bioprojet Europe Ltd (Hidrasec)

PRAC Lead: Qun-Ying Yue

Scope: PRAC consultation on a variation procedure for Hidrasec (racecadotril) (SE/H/1342/01-03/II/44) with regard to interaction with angiotensin converting enzyme (ACE) inhibitors and angioedema occurrence

Background

Racecadotril is a peripheral acting enkephalinase inhibitor indicated for the symptomatic treatment of acute diarrhoea in adults under certain conditions.

In the framework of a renewal procedure for Hidrasec (SE/H/1342/01-03/R/02 finalised in May 2016), the Swedish National Competent Authority (MPA) noted that an interaction between racecadotril and angiotensin-converting-enzyme inhibitor (ACE)-inhibitors leading to angioedema had been added to the French guide on interactions published on the French National Competent Authority (ANSM) website in April 2015. The MAH had submitted a variation in France for its nationally approved product Tiorfan (racecadotril). In the context of the evaluation of a type II variation procedure (SE/H/1342/01-03/II/44) on Hidrasec (racecadotril) to update the product information to reflect the interaction between racecadotril and ACE inhibitors, Sweden requested PRAC advice on its assessment. The PRAC agreed that, at the national level within variation SE/H/1342/01-03/II/44, the MAH should provide further justification for a contraindication and submit supporting data in line with the request for supplementary information (RSI) of the on-going variation procedure. For further background, see [PRAC minutes October 2016](#).

In the context of the evaluation of the MAH's answers to the RSI, Sweden requested PRAC advice on its assessment.

Summary of advice

³² Update of SmPC section 4.8. The package leaflet is to be updated accordingly

³³ Update of SmPC section 4.4. The package leaflet is to be updated accordingly

- Based on the review of the available information, further to the discussion of the potential increased risk of angioedema in patients who previously experienced angioedema with angiotensin-converting enzyme inhibitors (ACE-I), and even though the PRAC recognised that the active metabolite of racecadotril, thiorfan, has an inhibitory effect on neutral endopeptidase (NEP) in the metabolism of bradykinin, the Committee considered that the increase in bradykinin was not of the same magnitude as the effect ACE-I have on bradykinin. Therefore, the PRAC did not consider that the use of racecadotril in patients with a history of angioedema taking ACE-I treatment, in patients with a history of hereditary angioedema, or the use of of racecadotril in patients taking concomitantly ACE-I would require a contraindication.
- The PRAC also noted that in pre-clinical models, definitive conclusions cannot be drawn on the additive effect of racecadotril and ACE inhibitors on angioedema risk due to limitations in study design and conflicting results. Nevertheless, based on the involvement of the enzymes in bradykinin breakdown as well as the clinical findings with case reports, the PRAC agreed that concomitant use of racecadotril and ACE-inhibitors may increase the risk of angioedema, and the benefit-risk needs to be considered before initiating treatment with racecadotril in patients on ACE-I. The PRAC also supported the warning proposed by the MAH that patients with a history of angioedema unrelated to racecadotril therapy may be at increased risk of angioedema.
- The PRAC supported updating the product information as proposed by the MAH and further amended by Sweden.

11.2. Other requests

11.2.1. Bendamustine (NAP) - DE/H/1250/001/R/001

Applicant: Astellas Pharma GmbH (Levact)

PRAC Lead: Martin Huber

Scope: PRAC consultation on a renewal procedure for Levact (bendamustine) with regard to the safety profile of bendamustine, strengthening warnings and precautionary measures regarding infections, cardiac disorders, and submission of a direct healthcare professional communication (DHPC) addressing mainly the issue of increased mortality associated with off-label use of bendamustine and the strengthened warnings on opportunistic infections

Background

Bendamustine hydrochloride is an alkylating antitumour agent with an anti-neoplastic and cytotoxic effect indicated for first-line treatment of chronic lymphocytic leukaemia (CLL; Binet stage B or C) in patients for whom fludarabine combination chemotherapy is not appropriate, for the treatment of indolent and/or low grade non-Hodgkin's lymphoma (NHL) as monotherapy in patients who have progressed during or within 6 months following treatment with rituximab or a rituximab containing regimen, and as a first line treatment of multiple myeloma (MM; Durie-Salmon stage II with progress or stage III) in combination with prednisone for patients older than 65 years who are not eligible for autologous stem cell transplantation (AutoSCT) and who have clinical neuropathy at the time of diagnosis, precluding the use of thalidomide or bortezomib containing treatment.

Levact (bendamustine) marketing authorisation (MA) was granted via a decentralised

procedure with Germany acting as Reference Member State. As a condition to the MA, the MAH was requested to perform, as a post-authorisation commitment, a comparative randomised multicentre phase 3 trial to investigate the efficacy of bendamustine in the treatment of patients with indolent non-Hodgkin's lymphoma refractory to rituximab. The recruitment of the imposed study is planned to be completed in 2020. Consequently, Germany proposed an additional 5-year renewal based on pharmacovigilance grounds.

Additionally, based on the assessment of the PSUR(s) for bendamustine-containing medicines (PSUSA/00003162/201601, PSUSA procedure concluded at PRAC in September 2016), the PRAC recommended that the MAH performs a cumulative review of cardiac failure and myocardial infarction including causality assessment as per WHO-UMC³⁴ as well as provide data on the outcome of opportunistic infections separately for clinical trials and post-marketing cases (in particular herpes zoster, *Pneumocystis jiroveci* pneumonia (PJP) and cytomegalovirus (CMV)) and discuss the need for a direct healthcare professional communication (DHPC) as appropriate. For further background, see [PRAC minutes September 2016](#).

In the context of the evaluation of a renewal procedure, the Reference Member State (Germany) proposes strengthening warnings and precautionary measures regarding infections, cardiac disorders and a number of other amendments. The distribution of a DHPC is also proposed in order to communicate on the issue of increased mortality if bendamustine is used outside the terms of the MA as well as the proposed strengthened warnings on opportunistic infections. Germany requested PRAC advice on its assessment.

Summary of advice

- Based on the review of the available information, the PRAC agreed that a DHPC was needed to inform HCPs about the results of recent clinical studies and post-marketing data showing increased mortality when used off-label and an increased frequency of opportunistic infections with bendamustine respectively. The PRAC agreed with the proposed communication plan.
- Moreover, the PRAC supported to review the need for any further changes to the product information in the framework of the ongoing renewal procedure of the MA for Levact (bendamustine).

12. Organisational, regulatory and methodological matters

12.1. Mandate and organisation of the PRAC

12.1.1. PRAC working group - best practice guide – update on the implementation goals

PRAC lead: Martin Huber, Rafe Suvarna, Ulla Wändel Liminga

Following the adoption at PRAC of the 'best practice guidance (BPG) on using PRAC plenary time efficiently and effectively' (see [PRAC minutes May 2016](#)) and of the implementation plan for the BPG including goals to measure compliance with the recommendations (see [PRAC minutes June 2016](#)), the PRAC was updated at the organisational matters teleconference held

³⁴ World Health Organization - Uppsala Monitoring Centre

on 23 February 2017 on quantitative measures collected for the last 2016 quarter of PRAC meetings as well as cumulatively since July 2016. For previous update, see [PRAC minutes November 2016](#).

12.2. Coordination with EMA Scientific Committees or CMDh

12.2.1. Joint Paediatric Committee (PDCO)-PRAC Working Group – report from extraordinary meeting held on 2 December 2016

At the organisational matters teleconference held on 23 February 2017, the EMA secretariat updated the PRAC on the outcome of the extraordinary meeting of the joint PDCO-PRAC working group held on 2 December 2016 to maximise synergies between paediatric development and pharmacovigilance (see [PRAC minutes November 2016](#)). The Committee representatives discussed the opportunities and steps further to the development of the draft Good Pharmacovigilance Practices (GVP) chapter for special populations with a special focus on the paediatric population, in particular the section on post-authorisation safety studies (PASS), as well as the guidance and actions to further integrate paediatric development and pharmacovigilance processes such as the alignment of [paediatric investigation plans](#) (PIP) and RMPs.

12.2.2. EMA Scientific Co-ordination Board (SciCoBo) - update

PRAC lead: June Raine

The PRAC chair provided feedback from the last Scientific Co-ordination Board (SciCoBo) meeting held on 31 January 2017. See also under 12.7.1.

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

12.3.1. Guideline on safety and efficacy follow-up – risk management plan of advanced therapy medicinal products (ATMP) – revision

As a follow-up to the last PRAC discussions on the exercise to revise the 'Guideline on safety and efficacy follow-up – risk management plan of advanced therapy medicinal products (ATMPs)' ([EMEA/149995/2008](#)) (see [PRAC minutes January 2016](#) and [PRAC minutes April 2016](#) and [PRAC minutes July 2016](#)), the PRAC was updated by the EMA Secretariat of the revisions performed by the drafting group, composed of CAT, CHMP, PRAC and EMA members. Members were invited to provide comments on the draft guideline by 1 March 2017. An updated version of the guideline will be presented for discussion in April 2017 with a view to adopt the final guidance in June/July 2017.

12.3.2. Post-authorisation efficacy studies (PAES) – review of experience

The EMA Secretariat reported to PRAC on the experience of imposition of PAES in accordance with the Commission delegated Regulation (EU) No 357/2014 since its entry into force in April 2014. The numbers of PAES imposed per therapeutic area, PAES imposed per type of procedure and the related criteria of the regulation fulfilled were presented. It was noted that

PAES have been mainly imposed in the oncology area and that in the majority of cases, only one PAES had been imposed for a specific product, however in limited cases, several PAES have been imposed at different times during the product-life cycle.

12.3.3. PRIority MEdicines (PRIME) - update

The EMA Secretariat presented an update on the [PRIME](#) scheme designed to facilitate the development and accelerated assessment of innovative medicines of major public health interest, in particular from the viewpoint of therapeutic innovation and unmet medical need. Clarification on the role of PRAC representatives at PRIME kick-off meetings and feedback on experience to date were provided.

12.4. Cooperation within the EU regulatory network

None

12.5. Cooperation with International Regulators

None

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

None

12.7. PRAC work plan

12.7.1. PRAC work plan for 2017

At the organisational matters teleconference on 23 February 2017, the EMA Secretariat presented to the PRAC the draft PRAC work plan for 2017 for consolidation. PRAC members provided further input. An updated version of the draft PRAC work plan for 2017 will be presented in March 2017 for adoption.

12.8. Planning and reporting

12.8.1. PRAC workload statistics

The EMA secretariat presented, at the organisational matters teleconference held on 23 February 2017, quarterly figures to estimate the evolution of the workload of the PRAC, by reflecting the number of procedures and agenda items covered at each PRAC plenary meeting.

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. Further to the call for interest to join the GPAG launched at January 2017 PRAC meeting (see [PRAC minutes January 2017](#)) to replace Margarida Guimaraes, who stepped down in December 2016 as PRAC member for Portugal, the appointment of Charlotte Backman (SE) and Maia Uuskula (EE) was endorsed by the PRAC. The PRAC adopted the 'Granularity and Periodicity Advisory Group: 2017 Work Programme' with 3 long term objectives: the development of guidance and criteria to set the periodicity of single assessment procedures, the agreement on the scientific scope of single assessment procedures defined in the EURD list to ensure the use of a clear terminology in the EURD list, and the estimation of the workload-related to single-assessment procedures as well as monitoring the capacity of the network.

12.10.3. PSURs repository

None

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

The PRAC endorsed the draft revised EURD list version February 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 of February 2017, the updated EURD list was adopted by the CHMP and CMDh at their February 2017 meetings and published on the EMA website on 28/02/2017, 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 February 2017 SMART Working Group (SMART WG) work stream WS1. Further to the discussion in the December 2016 SMART WG WS1 of the pilot for the adoption of signal recommendations without an initial discussion at the plenary meeting, SMART reviewed the metrics collected and agreed on a 6-month extension of the pilot in order to gather more information on signals not discussed during plenary PRAC meetings, since the current review period was considered too short to draw any conclusions. In addition, the WG WS1 reviewed the overview of the MAHs' compliance with implementing the PRAC recommendations for updates to the product information for centrally authorised products (CAP) resulting from signals.

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 – impact on pharmacovigilance performance

Further to the [implementation of the Pharmacovigilance legislation](#) in 2012, the [additional monitoring](#) has been introduced for medicines that are being monitored particularly closely by regulatory authorities. These medicines have an inverted black triangle printed on the product information. In this context, at the organisational matters teleconference held on 23 February 2017, the EMA Secretariat updated the PRAC on an ongoing project to analyse experience with the black triangle in the context of pharmacovigilance performance in the EEA countries. The collection of data and analysis will start in May 2017 for a report expected by end of 2017/beginning of 2018.

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 22 February 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. EudraVigilance – Annual report 2016

At the organisational matters teleconference held on 23 February 2017, the EMA secretariat presented to the PRAC the 2016 EudraVigilance annual report for the European Parliament, the Council and the Commission. Following the next EMA Management Board meeting in March 2017, the report will be submitted to the EU institutions and published on the EMA website in Q1 2017.

Post-meeting note: On 16 March 2017, the EudraVigilance annual report 2016 ([EMA/9942/2017](#)) was published on the EMA website.

12.14. Risk management plans and effectiveness of risk minimisations

12.14.1. Risk management systems

None

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

None

12.15. Post-authorisation safety studies (PASS)

12.15.1. Post-authorisation Safety Studies – imposed PASS

None

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

None

12.16. Community procedures

12.16.1. Referral procedures for safety reasons

None

12.17. Renewals, conditional renewals, annual reassessments

None

12.18. Risk communication and transparency

12.18.1. Public participation in pharmacovigilance

None

12.18.2. Safety communication

None

12.19. Continuous pharmacovigilance

12.19.1. Incident management

None

12.20. Others

12.20.1. EMA Committees – findings of survey to members 2016

Further to the consultation of the Committee members launched in July 2016 to gauge the quality of the service offered by the EMA Secretariat, the PRAC welcomed the high participation across committees as well as the satisfaction of the service provided by Secretariat. The PRAC was informed that areas where improvement action is deemed necessary will be addressed and once done, a second survey will gauge the satisfaction level.

13. Any other business

None

14. Annex I – Signals assessment and prioritisation³⁵

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 timetables³⁶.

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. Carglumic acid - EMEA/H/C/004019

Scope: Treatment of hyperammonemia

15.1.2. Emtricitabine, tenofovir disoproxil – EMEA/H/C/004686

Scope: Treatment of human immunodeficiency virus (HIV)-1 infection

15.1.3. Febuxostat - EMEA/H/C/004374

Scope: Treatment of hyperuricaemia

15.1.4. Parathyroid hormone - EMEA/H/C/003861, Orphan

Applicant: NPS Pharma Holdings Limited

Scope: Treatment of hypoparathyroidism

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

³⁵ 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

³⁶ 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

mentioned medicine(s).

15.2.1. Albiglutide - EPERZAN (CAP) - EMEA/H/C/002735/II/0028/G

Applicant: GlaxoSmithKline Trading Services

PRAC Rapporteur: Julie Williams

Scope: Grouped variation to update the RMP in order to: 1) introduce additional risk minimisation measures addressing the important potential risk of medication errors. Annex II of the product information is updated accordingly; 2) add a new category 3 study as an additional pharmacovigilance activity: study 204879: a randomized, open-label, active-controlled, parallel-group, exploratory study on the effects of repeated doses of albiglutide compared to exenatide on gastric myoelectrical activity and gastric emptying in subjects with type 2 diabetes mellitus (T2DM); 3) add a new category 3 study as an additional pharmacovigilance activity – study 201840: an exploratory randomized, 2-part, single-blind, 2-period crossover study comparing the effect of albiglutide with exenatide on regional brain activity related to nausea in healthy volunteers; 4) add a new category 3 study as an additional pharmacovigilance activity: cross-sectional survey to assess the effectiveness of the proposed additional educational materials using patient connect

15.2.2. Antithrombin alfa - ATRYN (CAP) - EMEA/H/C/000587/II/0027

Applicant: GTC Biotherapeutics UK Limited

PRAC Rapporteur: Claire Ferard

Scope: Introduction of a RMP (version 1) as requested in the sixth annual re-assessment (EMEA/H/C/000587/S/0021) and second five-year renewal (EMEA/H/C/000587/R/0024)

15.2.3. Eribulin - HALAVEN (CAP) - EMEA/H/C/002084/II/0033

Applicant: Eisai Europe Ltd.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of the RMP (version 4.2) following the revision of the protocol for a post-authorisation study (PAS) to capture data on the frequency of resolution and time to resolution of eribulin-induced or aggravated peripheral neuropathy from a phase 3 study, E7389-A001-303 (ACCRU: a randomized phase 3 trial of eribulin compared to standard weekly paclitaxel as first- or second-line therapy for locally recurrent or metastatic breast cancer) to an observational post authorisation, single-arm, prospective multicentre cohort study E7389-M044-504 (IRENE). The submission of the corresponding study report to the EMA/PRAC remains unchanged and is planned in 2019

15.2.4. Exenatide - BYDUREON (CAP) - EMEA/H/C/002020/II/0042

Applicant: AstraZeneca AB

PRAC Rapporteur: Qun-Ying Yue

Scope: Update of the RMP (version 25) following closure and final summary of the exenatide pregnancy registry (a prospective, observational study conducted in the United States that

actively collected information on exposure to antidiabetic medication during pregnancy and the associated pregnancy outcomes in patients with type 2 diabetes mellitus (T2CM)). Moreover, the MAH included additional minor updates to the RMP

15.2.5. [Retigabine - TROBALT \(CAP\) - EMEA/H/C/001245/II/0045](#)

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Doris Stenver

Scope: Update of the RMP (version 18) in order to remove a post-authorisation study (PASS) RTG116158: an open label study evaluating the effects of retigabine added to existing anti-epileptic drug(s) on urinary voiding function in subjects with partial onset seizures

15.2.6. [Riociguat - ADEMPAS \(CAP\) - EMEA/H/C/002737/II/0014, Orphan](#)

Applicant: Bayer Pharma AG

PRAC Rapporteur: Julie Williams

Scope: Update of the RMP (version 6.1) in order to add off-label use in patients with idiopathic pulmonary pneumonia, with or without pulmonary hypertension as an important identified risk

15.2.7. [Thyrotropin alfa - THYROGEN \(CAP\) - EMEA/H/C/000220/II/0088](#)

Applicant: Genzyme Europe BV

PRAC Rapporteur: Almath Spooner

Scope: Update of the RMP (version 9.0) to bring it in line with the latest RMP template. As a consequence, 'gastrointestinal symptoms', 'constitutional symptoms' and 'injection site reactions' are deleted resulting from their downgrade to identified risks as not categorized as important any longer. In addition, 'perceived lower thyroid-stimulating hormone (TSH) elevation after thyrotropin alfa administration' is deleted from the list of important potential risks as it does not correspond to a safety risk for patients treated with Thyrogen. Finally, the study results and completion date for the T4 study (collection of data about remnant ablation in patients originally diagnosed with T4 thyroid cancer) are added and as a consequence, use of Thyrogen for remnant ablation in patients originally diagnosed with T4N0-1M0-1 thyroid cancer' is removed as missing information

15.2.8. [Vildagliptin - GALVUS \(CAP\) - EMEA/H/C/000771/WS1088/0048; JALRA \(CAP\) - EMEA/H/C/001048/WS1088/0048; XILIARX \(CAP\) - EMEA/H/C/001051/WS1088/0047](#) [Vildagliptin, metformin hydrochloride - EUCREAS \(CAP\) - EMEA/H/C/000807/WS1088/0057; ICANDRA \(CAP\) - EMEA/H/C/001050/WS1088/0058; ZOMARIST \(CAP\) - EMEA/H/C/001049/WS1088/0058](#)

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Qun-Ying Yue

Scope: Update of the RMPs for Galvus, Jalra, Xiliarx, Eucreas, Icandra and Zomarist in order to reflect the outcome of the recently finalised procedure for metformin-containing products under Article 31 of Directive 2001/83/EC (EMEA/H/A-31/1432) in order to implement a targeted questionnaire for cases of lactic acidosis

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. Belatacept - NULOJIX (CAP) - EMEA/H/C/002098/II/0038

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of sections 4.8 and 5.1 of the SmPC following the completion of the post-authorisation efficacy studies: IM103-008 (belatacept evaluation of nephro-protection and efficacy as first-line immunosuppression trial (BENEFIT) and IM103-027 (belatacept evaluation of nephro-protection and efficacy as first-line immunosuppression trial - extended criteria donors (BENEFIT-EXT)). The Package Leaflet and the RMP (version 12) are updated accordingly

15.3.2. Belimumab - BENLYSTA (CAP) - EMEA/H/C/002015/X/0046/G

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Grouped application including: 1) line extension to introduce a new pharmaceutical form (solution for injection), a new strength (200 mg) and a new route of administration (subcutaneous use); 2) update of sections 4.2, 4.8, 5.1 and 5.2 for the authorised presentations (Benlysta powder for concentrate for solution for infusion) as a consequence of the data package submitted to support the new proposed solution for injection subcutaneous. The RMP (version 21) is updated accordingly

15.3.3. Brentuximab vedotin - ADCETRIS (CAP) - EMEA/H/C/002455/II/0043, Orphan

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Sabine Straus

Scope: Update of sections 4.8 and 5.1 of the SmPC in order to add data from study C25007: a single-arm study of brentuximab vedotin in patients with relapsed or refractory Hodgkin lymphoma who are not suitable for stem cell transplantation or multi-agent chemotherapy. The submission of the clinical study report fulfils SOB 011 of the conditional marketing authorisation for Adcetris. The RMP (version 8.0) is updated accordingly

15.3.4. Daratumumab - DARZALEX (CAP) - EMEA/H/C/004077/II/0002, Orphan

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Extension of indication to add the treatment of adult patients with multiple myeloma who have received at least one prior therapy. As a consequence, sections 4.2, 4.4, 4.5, 5.1 and 5.2 of the SmPC are updated. A new warning is introduced in section 4.4 regarding neutropenia/thrombocytopenia induced by background therapy. Annex II is also updated to remove all the specific obligations following submissions of the final results of studies MMY3003 (a phase 3 randomised study investigating lenalidomide and dexamethasone with or without daratumumab in patients with previously treated multiple myeloma) and MMY3004 (a phase 3 randomised study investigating bortezomib and dexamethasone with or without daratumumab in patients with previously treated multiple myeloma). The Package Leaflet and RMP (version 2) are updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet

15.3.5. Deferasirox - EXJADE (CAP) - EMEA/H/C/000670/X/0054, Orphan

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Claire Ferard

Scope: Extension application for a new pharmaceutical form (Exjade 90, 180 and 360 mg granules). The RMP (version 15.0) is updated accordingly

15.3.6. Dimethyl fumarate - TECFIDERA (CAP) - EMEA/H/C/002601/II/0035

Applicant: Biogen Idec Ltd

PRAC Rapporteur: Martin Huber

Scope: Update of section 4.8 of the SmPC to include 'liver function abnormalities' as an adverse event observed in the post-marketing setting and to clarify events not observed in placebo-controlled studies. The Package Leaflet and the RMP (version 8) are updated accordingly. The MAH has also taken the opportunity to make minor administrative changes in the Package Leaflet

15.3.7. Efmoroctocog alfa - ELOCTA (CAP) - EMEA/H/C/003964/II/0010

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Rafe Suvarna

Scope: Submission of the final clinical study report (CSR) for study 997HA307 (RMP category 3) to investigate the pharmacokinetics (PK) of recombinant Factor VIII Fc fusion protein (rFVIIIFc) at two vial strengths (1000 and 3000IU) and evaluate the safety of rFVIIIFc. The RMP (version 1.5) is updated accordingly

15.3.8. Empagliflozin - JARDIANCE (CAP) - EMEA/H/C/002677/II/0026

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Dolores Montero Corominas

Scope: Submission of the final results of a non-clinical study on the effect of empagliflozin

on blood ketone level at refeeding after a fasting period, comparison between refeeding with glucose or fat in order to fulfil MEA 010. The RMP (version 11.0) is updated accordingly

15.3.9. Emtricitabine, tenofovir disoproxil - TRUVADA (CAP) - EMEA/H/C/000594/II/0131

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Julie Williams

Scope: Extension of indication to include treatment of human immunodeficiency virus (HIV)-1 infected adolescents, with nucleoside reverse transcriptase inhibitors (NRTI) resistance or toxicities precluding the use of first line agents, aged 12 to <18 years for Truvada. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet and the RMP (version 13) are updated accordingly

15.3.10. Fluticasone furoate, vilanterol - RELVAR ELLIPTA (CAP) - EMEA/H/C/002673/WS0992/0022/G;REVINTY ELLIPTA (CAP) - EMEA/H/C/002745/WS0992/0017/G

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Dolores Montero Corominas

Scope: Grouped variations to update sections 4.4, 4.8 and 5.1 of the SmPC in order to include data from study HZC113782 (SUMMIT): clinical outcomes study comparing the effect of fluticasone furoate/vilanterol inhalation powder 100/25mcg with placebo on survival in subjects with moderate chronic obstructive pulmonary disease (COPD) and a history of or at increased risk for cardiovascular disease. In addition, section 4.8 of the SmPC is updated to add 'paradoxical bronchospasm' to the list of adverse reactions as well as section 5.1 of the SmPC to correct an error identified in the pharmacodynamic section. The Package Leaflet, Labelling and RMP (version 8.1) are updated accordingly

15.3.11. Fulvestrant - FASLODEX (CAP) - EMEA/H/C/000540/II/0057

Applicant: AstraZeneca UK Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension of indication to include the treatment of postmenopausal women with locally advanced or metastatic breast cancer who have not received prior endocrine therapy for Faslodex. As a consequence, sections 4.1, 4.8 and 5.1 of the SmPC are updated in order to update the safety and pharmacodynamics information. The Package Leaflet and the RMP (version 10) are updated accordingly. In addition, the MAH took the opportunity to introduce clarifications in the SmPC

15.3.12. Gefitinib - IRESSA (CAP) - EMEA/H/C/001016/II/0026

Applicant: AstraZeneca AB

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of the final study report for the IMPRESS study (D791LC00001): a phase 3 randomised, double blind, placebo controlled, parallel, multicentre study to assess the

efficacy and safety of continuing Iressa 250 mg in addition to chemotherapy versus chemotherapy alone in patients who have epidermal growth factor receptor (EGFR) mutation positive locally advanced or metastatic non-small cell lung cancer (NSCLC) and have progressed on first line Iressa. In addition, the procedure includes a discussion in line with the conclusions of PSUSA procedure (EMA/H/C/PSUSA/00001518/201507) concluded in January 2016. No change to the Product Information and RMP is proposed

15.3.13. [Human fibrinogen, human thrombin - EVARREST \(CAP\) - EMEA/H/C/002515/II/0027/G](#)

Applicant: Omrix Biopharmaceuticals N. V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Grouped variations consisting of: 1) submission of the final results for study BIOS-13-005 (a phase 3, randomized, controlled, superiority study evaluating Evarrest fibrin sealant patch versus standard of care treatment in controlling parenchymal bleeding during hepatic surgery) updating the efficacy and safety information; 2) submission of the final results for study BIOS-13-004 (a single-blinded, randomized, controlled, comparative phase 3 study evaluating the safety and effectiveness of Evarrest fibrin sealant patch as an adjunct to haemostasis during cardiovascular surgery) updating the efficacy and safety information; 3) submission of the final results for study 400-12-002 (a randomized, controlled, comparative phase II study evaluating the safety and effectiveness of Evarrest fibrin sealant patch as an adjunct to haemostasis during cardiovascular surgery) updating the efficacy and safety information; 4) submission of the final results for study 400-12-005 (a non-investigational post-market trial using Evarrest fibrin sealant patch as an adjunct to haemostasis in soft tissue bleeding during intra-abdominal, retroperitoneal, pelvic and non-cardiac thoracic surgery) updating the safety information; 5) update of section 5.1 of the SmPC to include further information on main existing efficacy studies. As a consequence, sections 4.8, 5.1 of the SmPC are also updated. In addition, the product information (PI) is brought in line with the latest QRD template (version 10) and Guideline on core SmPC for plasma-derived fibrin/sealant/haemostatic products (EMA/CHMP/BPWP/598816/2010 rev.1). Furthermore, section 4.2 is updated regarding the paediatric information for children under the age of 1 month, according to the EMA waiver. The RMP (version 3) is updated accordingly, including consequential and routine changes

15.3.14. [Ibrutinib - IMBRUVICA \(CAP\) - EMEA/H/C/003791/II/0025, Orphan](#)

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Julie Williams

Scope: Update of section 4.4 of the SmPC to remove the warning and precaution regarding the effect of ibrutinib on the QT interval and section 5.1 to provide additional information regarding the pharmacodynamic effect of ibrutinib on QT/QTc intervals and cardiac electrophysiology. The RMP (version 6.1) is updated accordingly

15.3.15. [Idebenone - RAXONE \(CAP\) - EMEA/H/C/003834/II/0003, Orphan](#)

Applicant: Santhera Pharmaceuticals (Deutschland) GmbH

PRAC Rapporteur: Carmela Macchiarulo

Scope: Extension of indication to include treatment of patients with Duchenne muscular dystrophy in whom respiratory function has started to decline and who are currently not taking concomitant glucocorticoids. The RMP (version 2.0) is updated accordingly

15.3.16. Insulin detemir - LEVEMIR (CAP) - EMEA/H/C/000528/II/0084

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Doris Stenver

Scope: Submission of the summary analysis report on the incidence of neoplasms with the combination of liraglutide and insulin detemir from the cardiovascular outcome trial for Victoza (liraglutide): study EX2211-3748 (LEADER: liraglutide effect and action in diabetes): a long-term, multicentre, international, randomised double-blind, placebo-controlled trial to determine liraglutide effects on cardiovascular events. The RMP (version 18) is updated accordingly to delete the important potential risk 'potential risk of malignant neoplasms following combination treatment with insulin detemir + liraglutide + metformin'

15.3.17. Lumacaftor, ivacaftor - ORKAMBI (CAP) - EMEA/H/C/003954/II/0017

Applicant: Vertex Pharmaceuticals (Europe) Ltd.

PRAC Rapporteur: Almath Spooner

Scope: Update of sections 4.8 and 5.1 of the SmPC in order to reflect the long-term safety and efficacy data from study VX12 809 105: a phase 3, rollover study to evaluate the safety and efficacy of long term treatment with lumacaftor/ivacaftor in subjects aged 12 years and older with cystic fibrosis, homozygous or heterozygous for the F508del cystic fibrosis transmembrane conductance regulator (CFTR) mutation (MEA 001). The RMP (version 2.7) is updated accordingly. In addition, the MAH took the opportunity to bring the Product Information in line with the latest QRD template (version 10)

15.3.18. Maraviroc - CELSENTRI (CAP) - EMEA/H/C/000811/X/0046/G

Applicant: ViiV Healthcare UK Limited

PRAC Rapporteur: Qun-Ying Yue

Scope: Line extension to introduce a new pharmaceutical form (20mg/ml oral solution) and two new strengths of film-coated tablets (25mg and 75mg) to the currently approved presentations for Celsentri, grouped with an extension of indication to include paediatric use (2 to 18 years). As a consequence, sections 4.2 and 4.4 of the SmPC are updated to detail posology in paediatric patients and to update the safety information respectively. The Package Leaflet, Labelling and RMP (version 11) are updated accordingly. Furthermore, the product information is brought in line with the latest QRD template (version 10)

15.3.19. Mecasermin - INCRELEX (CAP) - EMEA/H/C/000704/II/0044/G, Orphan

Applicant: Ipsen Pharma

PRAC Rapporteur: Kirsti Villikka

Scope: Update of section 4.4 of the SmPC in order to amend the warning regarding

antibody response to injected insulin-like growth factor 1 (IGF-1). The RMP (version 9) is updated accordingly, including changes to the educational materials and changes to the instructions for antibody testing

15.3.20. Peginterferon alfa-2a - PEGASYS (CAP) - EMEA/H/C/000395/II/0091

Applicant: Roche Registration Limited

PRAC Rapporteur: Qun-Ying Yue

Scope: Extension of indication to include paediatric patients from 3 to less than 18 years of age with chronic hepatitis B in the immune-active phase for Pegasys. 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 efficacy and safety information from study YV25718: a phase 3b parallel group, open label study of pegylated interferon alfa-2a monotherapy compared to untreated control in children with HBeAg positive chronic hepatitis B. The Package Leaflet and the RMP (version 8.0) are updated accordingly

15.3.21. Pirfenidone - ESBRIET (CAP) - EMEA/H/C/002154/X/0035/G, Orphan

Applicant: Roche Registration Limited

PRAC Rapporteur: Julie Williams

Scope: Line extension to introduce a new pharmaceutical form associated with 3 new strengths (267 mg, 534 mg and 801 mg film-coated tablets). In addition, manufacturing sites are also introduced for the currently approved 267 mg hard capsules presentations (EU/1/11/667/001-003). The RMP (version 8.0) is updated accordingly

15.3.22. Pertuzumab - PERJETA (CAP) - EMEA/H/C/002547/II/0028

Applicant: Roche Registration Limited

PRAC Rapporteur: Doris Stenver

Scope: Final clinical study report for the TRYPHAENA study (BO22280): a randomised, multicentre, multinational phase II study to evaluate pertuzumab in combination with trastuzumab, given either concomitantly or sequentially with standard anthracycline based chemotherapy or concomitantly with a non-anthracycline-based chemotherapy regimen, as neoadjuvant therapy for patients with locally advanced, inflammatory or early stage HER2-positive breast cancer. The RMP (version 8) is updated accordingly

15.3.23. Regorafenib - STIVARGA (CAP) - EMEA/H/C/002573/II/0020

Applicant: Bayer Pharma AG

PRAC Rapporteur: Sabine Straus

Scope: Extension of indication to include the treatment of adult patients with hepatocellular carcinoma (HCC) who have been previously treated with one systemic therapy. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The package leaflet and RMP (version 5.0) are updated accordingly. Furthermore, the Product Information is brought in line with the latest QRD template (version 10)

15.3.24. Sofosbuvir - SOVALDI (CAP) - EMEA/H/C/002798/II/0036

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Rafe Suvarna

Scope: Extension of indication to add the 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 the RMP (version 5.0) are updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. Furthermore, the Product Information is brought in line with the latest QRD template (version 10)

15.3.25. Sofosbuvir, velpatasvir - EPCLUSA (CAP) - EMEA/H/C/004210/II/0003

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Update of sections 4.4, 4.5 and 5.1 of the SmPC in order to reflect on emerging clinical data from study GS-US-342-1202 (a phase 3, open-label study to investigate the efficacy and safety of sofosbuvir/velpatasvir fixed dose combination for 12 weeks in subjects with chronic hepatitis C virus (HCV) and human immunodeficiency virus (HIV)-1 coinfection). The RMP (version 1.0) is updated accordingly. In addition, minor administrative changes are implemented throughout the Product Information

15.3.26. Trametinib - MEKINIST (CAP) - EMEA/H/C/002643/WS0996/0018; Dabrafenib - TAFINLAR (CAP) - EMEA/H/C/002604/WS0996/0022

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension of indication to include the combination treatment with trametinib and dabrafenib of adult patients with advanced non-small cell lung cancer (NSCLC) with a BRAF V600 mutation. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 5.3 of the Mekinist and Tafinlar SmPC are updated. The Package Leaflet and RMPs are updated accordingly. In addition, the Worksharing applicant (WSA) took the opportunity to align the SmPCs of Mekinist and Tafinlar. Furthermore, the Product Information is brought in line with the latest QRD template (version 10)

15.3.27. Temsirolimus - TORISEL (CAP) - EMEA/H/C/000799/II/0063, Orphan

Applicant: Pfizer Limited

PRAC Rapporteur: Martin Huber

Scope: Final results from study 3066K1-4438-WW (B1771007) entitled 'a randomized phase 4 study comparing two intravenous temsirolimus (TEMSR) regimens in subjects with relapsed, refractory mantle cell lymphoma' and fulfilment of obligation to conduct post authorisation measure ANX 027.2. In addition, submission of the toxic effects of interest (e.g. bleeding, infection- and mucositis-related events) for study 3066K1-4438-WW (post-

marketing commitment MEA 028) together with a review discussing potential new safety concerns arising from the results. The RMP (version 3.0) is updated accordingly to add myocardial infarction and cardiovascular events in patient with coexisting cardiovascular conditions as important potential risks, and anaemia, thrombocytopenia, hypercholesterolemia, and hypertriglyceridemia as important identified risks. Furthermore, the MAH took the opportunity to update the list of local representatives in the Package Leaflet

15.3.28. Vismodegib - ERIVEDGE (CAP) - EMEA/H/C/002602/II/0032

Applicant: Roche Registration Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of section 5.3 of the SmPC in order to reflect non-clinical carcinogenicity studies (MEA 003): 1) study 13-0322: a 26-week oral gavage carcinogenicity study with vismodegib in hemizygous CByB6F1-Tg(HRAS)^{2Jic} mice; 2) study 13-0323: a 104-week and 52-week with a 12-week recovery phase oral gavage carcinogenicity study with vismodegib in Sprague Dawley rats. The RMP (version 12.0) is updated accordingly. Furthermore, additional routine changes (including some resulting from the assessment of RMP version 11) have been introduced

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. Aclidinium bromide - BRETARIS GENUAIR (CAP); EKLIRA GENUAIR (CAP) - PSUSA/00009005/201607

Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.2. Aflibercept³⁷ - ZALTRAP (CAP) - PSUSA/00010019/201608 (with RMP)

Applicant: Sanofi-Aventis Groupe

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.3. Antithrombin alpha - ATRYN (CAP) - PSUSA/00000224/201607

Applicant: GTC Biotherapeutics UK Limited

PRAC Rapporteur: Claire Ferard

Scope: Evaluation of a PSUSA procedure

16.1.4. Asparaginase³⁸ - SPECTRILA (CAP) - PSUSA/00010445/201607

Applicant: Medac Gesellschaft für klinische Spezialpräparate GmbH

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.5. Ataluren - TRANSLARNA (CAP) - PSUSA/00010274/201607

Applicant: PTC Therapeutics International Limited

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUSA procedure

16.1.6. Birch bark extract³⁹ - EPISALVAN (CAP) - PSUSA/00010446/201607

Applicant: Birken AG

PRAC Rapporteur: Zane Neikena

Scope: Evaluation of a PSUSA procedure

16.1.7. Carfilzomib - KYPROLIS (CAP) - PSUSA/00010448/201607

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

16.1.8. Catridecacog - NOVOTHIRTEEN (CAP) - PSUSA/00010034/201607

Applicant: Novo Nordisk A/S

³⁷ Oncology indication(s) only

³⁸ Centrally authorised product(s) only

³⁹ Centrally authorised product(s) only

PRAC Rapporteur: Claire Ferard

Scope: Evaluation of a PSUSA procedure

16.1.9. Dapagliflozin, metformin - EBYMECT (CAP); XIGDUO (CAP) - PSUSA/00010294/201607

Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.10. Dasabuvir - EXVIERA (CAP) - PSUSA/00010363/201607

Applicant: AbbVie Ltd.

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

16.1.11. Dolutegravir – TIVICAY (CAP); dolutegravir, abacavir, lamivudine - TRIUMEQ (CAP) - PSUSA/00010075/201607

Applicant: ViiV Healthcare UK Limited

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.12. Etanercept⁴⁰ - BENEPAI (CAP) - PSUSA/00010452/201607

Applicant: Samsung Bioepis UK Limited (SBUK)

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of a PSUSA procedure

16.1.13. Evolocumab - REPATHA (CAP) - PSUSA/00010405/201607

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

16.1.14. Idursulfase - ELAPRASE (CAP) - PSUSA/00001722/201607

Applicant: Shire Human Genetic Therapies AB

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of a PSUSA procedure

⁴⁰ Etanercept - Benepali centrally authorised product only

16.1.15. Icatibant - FIRAZYR (CAP) - PSUSA/00001714/201607

Applicant: Shire Orphan Therapies GmbH

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

16.1.16. Idelalisib - ZYDELIG (CAP) - PSUSA/00010303/201607

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of a PSUSA procedure

16.1.17. Lipegfilgrastim - LONQUEx (CAP) - PSUSA/00010111/201607

Applicant: Sicor Biotech UAB

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.18. Lomitapide - LOJUXTA (CAP) - PSUSA/00010112/201607

Applicant: Aegerion Pharmaceuticals Limited

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.19. Modified vaccinia Ankara virus - IMVANEX (CAP) - PSUSA/00010119/201607

Applicant: Bavarian Nordic A/S

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of a PSUSA procedure

16.1.20. Ombitasvir, paritaprevir , ritonavir - VIEKIRAX (CAP) - PSUSA/00010367/201607

Applicant: AbbVie Ltd.

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

16.1.21. Pegaspargase⁴¹ - ONCASPAR (CAP) - PSUSA/00010457/201607

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Julie Williams

⁴¹ Centrally authorised product(s) only

Scope: Evaluation of a PSUSA procedure

16.1.22. Peginterferon beta-1A - PLEGRIDY (CAP) - PSUSA/00010275/201607

Applicant: Biogen Idec Ltd

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.23. Perampanel - FYCOMPA (CAP) - PSUSA/00009255/201607

Applicant: Eisai Europe Ltd.

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.24. Phenylephrine, ketorolac - OMIDRIA (CAP) - PSUSA/00010419/201607

Applicant: Omeros London Limited

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.25. Romiplostim - NPLATE (CAP) - PSUSA/00002660/201607

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

16.1.26. Simoctocog alfa - NUWIQ (CAP) - PSUSA/00010276/201607

Applicant: Octapharma AB

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.27. Stavudine - ZERIT (CAP) - PSUSA/00002787/201606 (with RMP)

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

16.1.28. Tocofersolan - VEDROP (CAP) - PSUSA/00002981/201607

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

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.29. Vorapaxar - ZONTIVITY (CAP) - PSUSA/00010357/201607

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure

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

16.2.1. Aripiprazole - ABILIFY (CAP); ABILIFY MAINTENA (CAP); ARIPIPRAZOLE SANDOZ (CAP); NAP - PSUSA/00000234/201607

Applicant: Otsuka Pharmaceutical Europe Ltd (Abilify, Abilify Maintena), Sandoz GmbH (Aripiprazole Sandoz), various

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.2.2. Nitric oxide - INOMAX (CAP); NAP - PSUSA/00002172/201606

Applicant: Linde Healthcare AB (INOmax), various

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

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

16.3.1. Dienogest, estradiol⁴² (NAP)- PSUSA/00010443/201606

Applicant: various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.3.2. Ganciclovir (NAP) - PSUSA/00001516/201606

Applicant: various

PRAC Lead: Sabine Straus

Scope: Evaluation of a PSUSA procedure

⁴² Hormone replacement therapy (HRT) indication(s) only

16.3.3. Levonorgestrel, ethinylestradiol; ethinylestradiol⁴³ (NAP) - PSUSA/00010442/201607

Applicant: various

PRAC Lead: Claire Ferard

Scope: Evaluation of a PSUSA procedure

16.3.4. Midodrine (NAP) - PSUSA/00003178/201606

Applicant: various

PRAC Lead: Roxana Stefania Stroe

Scope: Evaluation of a PSUSA procedure

16.3.5. Misoprostol⁴⁴ (NAP) - PSUSA/00010291/201606

Applicant: various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

16.4. Follow-up to PSUR procedures

16.4.1. Trastuzumab - HERCEPTIN (CAP) - EMEA/H/C/000278/LEG 098.1

Applicant: Roche Registration Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: MAH's response to LEG 098 [submission of a proposal for a DHPC to treating oncologists and/or oncologists to ensure awareness of the need to follow the current guidance on cardiac monitoring during and after completion of treatment with Herceptin and to highlight the need for cardiac monitoring during handover of patient management to other physicians as requested in the conclusions of EMEA/H/C/PSUSA/00003010/201509 adopted in April 2016] as per the request for supplementary information (RSI) adopted by PRAC in October 2016

16.4.2. Ulipristal acetate - ESMYA (CAP) - EMEA/H/C/002041/LEG 017

Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of a detailed review on arterial and venous thromboembolic events (ATE/VTE) including a discussion on the biological plausibility based on the mechanism of action of ulipristal acetate, focusing on the role of oestrogen and progesterone as requested in the conclusions of PSUSA/00009325/201602 adopted by PRAC and CHMP in September

⁴³ Combination pack

⁴⁴ Gastrointestinal indication(s) only

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)⁴⁵

17.1.1. Ferric citrate coordination complex - FEXERIC (CAP) - EMEA/H/C/003776/PSP/S/0038.1

Applicant: Keryx Biopharma UK Ltd.

PRAC Rapporteur: Julie Williams

Scope: Revised protocol (KRX-0502-401, version 1.0) for an imposed non-interventional observational post-authorisation study to assess the safety of Fexeric as a phosphate binder in routine clinical practice as per the conclusions of procedure EMEA/H/C/PSP/0038 adopted by PRAC in March 2016

17.1.2. Ethinylestradiol (NAP); levonorgestrel, ethinylestradiol (NAP); - EMEA/H/C/PSP/0037.2

Applicant: Teva Pharma B.V.

PRAC Rapporteur: Claire Ferard

Scope: Revised protocol (version 5.0) for an imposed non-interventional post-authorisation study to assess the risk of venous thromboembolic events (VTE) in women exposed to Seasonique as per the conclusion of the procedure EMEA/H/C/PSP/0037.1 adopted by PRAC in September 2016

17.1.3. Roflumilast - DALIRESP (CAP); DAXAS (CAP); LIBERTEK (CAP) - EMEA/H/C/PSA/J/0014

Applicant: AstraZeneca AB

PRAC Rapporteur: Dolores Montero Corominas

Scope: Revised protocol following substantial amendments to the previously agreed protocol in October 2011 by CHMP for a PASS study (D7120R00003, previously RO-2455-403-RD): a long-term comparative observational safety study to evaluate mortality rate, including cardiovascular, suicide and cancer death rates and incidence rate of hospitalisations in treated chronic obstructive pulmonary disease (COPD) patients compared to match COPD patients not treated with roflumilast

⁴⁵ In accordance with Article 107n of Directive 2001/83/EC

17.1.4. Teicoplanin (NAP) EMEA/H/C/PSA/S/0013

Applicant: Sanofi-aventis (Targocid)

PRAC Rapporteur: Valerie Strassmann

Scope: Revised protocol following substantial amendments to the previously agreed protocol in June 2015 for a PASS study: a prospective, observational cohort, evaluating the incidence of nephrotoxicity and other adverse events of interest in patients treated with the higher recommended teicoplanin loading dose (12mg/kg twice a day), and comparison with external historical comparator data

17.2. Protocols of PASS non-imposed in the marketing authorisation(s)⁴⁶

17.2.1. Alemtuzumab - LEMTRADA (CAP) - EMEA/H/C/003718/MEA 006.2

Applicant: Genzyme Therapeutics Ltd

PRAC Rapporteur: Torbjorn Callreus

Scope: MAH's response to MEA 06.1 [Submission of a revised protocol for a pregnancy registry study OBS13436: an international Lemtrada pregnancy exposure cohort in multiple sclerosis] as per the request for supplementary information (RSI) adopted by PRAC in September 2016

Action: For adoption of advice to CHMP

17.2.2. Alirocumab - PRALUENT (CAP) - EMEA/H/C/003882/MEA 017.1

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: MAH's response to MEA 017 [PASS protocol for study ALIROC07997: 'monitoring of the safety of alirocumab in human immunodeficiency virus (HIV)-infected patients, using healthcare databases'] as per the request for supplementary information (RSI) adopted by PRAC in November 2016

17.2.3. Collagenase clostridium histolyticum - XIAPEX (CAP) - EMEA/H/C/002048/MEA 030

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Martin Huber

Scope: Protocol for study Sobi.Xiapex-PASS02: a non-interventional post-authorisation safety study (PASS) measuring the effectiveness of Xiapex educational material for healthcare professional in the treatment of Dupuytren's contracture (as per the conclusions of variation II/59)

Action: For adoption of advice to CHMP

⁴⁶ 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. Dapagliflozin - EDISTRIDE (CAP) - EMEA/H/C/004161/MEA 003.1

Applicant: AstraZeneca AB

PRAC Rapporteur: Qun-Ying Yue

Scope: MAH's responses to MEA 003: revised PASS protocol to evaluate the incidence of diabetic ketoacidosis (DKA) in sodium-dependent glucose cotransporters (SGLT)-2 inhibitors as an outcome of the Article 20 referral on sodium-dependent glucose cotransporters (SGLT)-2 inhibitors (EMA/H/A-20/1419), as per request for supplementary information (RSI) adopted in September 2016

17.2.5. Dapagliflozin - FORXIGA (CAP) - EMEA/H/C/002322/MEA 020.1

Applicant: AstraZeneca AB

PRAC Rapporteur: Qun-Ying Yue

Scope: MAH's responses to MEA 020: revised PASS protocol to evaluate the incidence of diabetic ketoacidosis (DKA) in sodium-dependent glucose cotransporters (SGLT)-2 inhibitors as an outcome of the Article 20 referral on sodium-dependent glucose cotransporters (SGLT)-2 inhibitors (EMA/H/A-20/1419), as per request for supplementary information (RSI) adopted in September 2016

17.2.6. Dapagliflozin, metformin - EBYMECT (CAP) - EMEA/H/C/004162/MEA 003.1

Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

Scope: MAH's response to MEA 003: revised PASS protocol to evaluate the incidence of diabetic ketoacidosis (DKA) in sodium-dependent glucose cotransporters (SGLT)-2-inhibitors as an outcome of the Article 20 referral on SGLT-2 inhibitors (EMA/H/A-20/1419), as per request for supplementary information (RSI) adopted in September 2016

17.2.7. Dapagliflozin, metformin - XIGDUO (CAP) - EMEA/H/C/002672/MEA 006.1

Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

Scope: MAH's response to MEA 006: revised PASS protocol to evaluate the incidence of diabetic ketoacidosis (DKA) in sodium-dependent glucose cotransporters (SGLT)-2-inhibitors as an outcome of the Article 20 referral on SGLT-2 inhibitors (EMA/H/A-20/1419), as per request for supplementary information (RSI) adopted in September 2016

17.2.8. Rivastigmine - EXELON (CAP) - EMEA/H/C/000169/MEA 034.2

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Claire Ferard

Scope: Revised protocol (version 02) for study CENA713D2409: a drug utilisation study (DUS) in patients treated with Exelon/Prometax (rivastigmine) transdermal patch, as per

the request for supplementary information (RSI) adopted in April 2014

17.2.9. Rivastigmine - PROMETAX (CAP) - EMEA/H/C/000255/MEA 035.1

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Claire Ferard

Scope: Revised protocol (version 02) for study CENA713D2409: a drug utilisation study (DUS) in patients treated with Exelon/Prometax (rivastigmine) transdermal patch, as per the request for supplementary information (RSI) adopted in April 2014

17.2.10. Safinamide - XADAGO (CAP) - EMEA/H/C/002396/MEA 004.2

Applicant: Zambon SpA

PRAC Rapporteur: Almath Spooner

Scope: MAH's response to MEA 004.1 [revised protocol for study Z7219N02: a drug utilisation study (DUS): observational European multicentre retrospective-prospective cohort study to observe Safinamide safety profile and pattern of use in clinical practice during the first post-commercialisation phase] as per request for supplementary information (RSI) adopted in September 2016

17.2.11. Selexipag - UPTRAVI (CAP) - EMEA/H/C/003774/MEA 001.1

Applicant: Actelion Registration Ltd.

PRAC Rapporteur: Rafe Suvarna

Scope: MAH's response to MEA 001 [protocol for a non-interventional non-imposed PASS: observational cohort study of pulmonary arterial hypertension (PAH) patients exposed and unexposed to selexipag in routine clinical practice] as per request for supplementary information (RSI) adopted in October 2016

17.2.12. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/MEA 024.9

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Julie Williams

Scope: MAH's response to MEA 024.8 [revised protocol (CNT01275PSO4007) and sixth interim report for the pregnancy research initiative study] as per request for supplementary information (RSI) adopted in July 2016

17.2.13. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/MEA 044.2

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Julie Williams

Scope: MAH's response to MEA 044.1 [revised protocol for an adolescent registry: an observational PASS of ustekinumab in the treatment of pediatric patients aged 12 years and older with moderate to severe plaque psoriasis] as per the request for supplementary

information (RSI) adopted in September 2016

17.3. Results of PASS imposed in the marketing authorisation(s)⁴⁷

None

17.4. Results of PASS non-imposed in the marketing authorisation(s)⁴⁸

17.4.1. Afibercept - ZALTRAP (CAP) - EMEA/H/C/002532/II/0034

Applicant: Sanofi-Aventis Groupe

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of the final results of the drug utilisation study monitoring the use of Zaltrap in cancer patients including potential off-label use and evaluating the potential for intravitreal use. This fulfils the post authorisation commitment MEA 03

17.4.2. Empagliflozin - JARDIANCE (CAP) - EMEA/H/C/002677/II/0025

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Dolores Montero Corominas

Scope: Submission of the final results for a non-interventional study 1245.122 exploring the characteristics of patients initiating empagliflozin or other noninsulin glucose lowering drugs in the United Kingdom in order to fulfil MEA 009. The RMP (version 11.0) is updated accordingly

17.4.3. Infliximab - REMICADE (CAP) - EMEA/H/C/000240/II/0201/G

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Grouped variation including the submission of the clinical study reports (CSR) for studies C0168T45 (safety under long term study: multicentre international observational study of the long-term safety of infliximab) and C0168T62 (safety under long-term study in ulcerative colitis (UC): multicentre international study of the long-term safety of infliximab in UC) together with an overall summary and evaluation of the complete long term safety follow-up programmes for Remicade (as per MEA 79). The RMP (version 14.0) is updated accordingly

17.4.4. Paliperidone - XEPLION (CAP) - EMEA/H/C/002105/II/0031

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Qun-Ying Yue

⁴⁷ In accordance with Article 107p-q of Directive 2001/83/EC

⁴⁸ In accordance with Article 61a (6) of Regulation (EC) No 726/2004, in line with the revised variations regulation for any submission as of 4 August 2013

Scope: Submission of the final study report for a PASS using European Union databases to assess the risk of cardiovascular and cerebrovascular adverse events in elderly patients treated with paliperidone palmitate, paliperidone prolonged-release, and other antipsychotics. No change in the Product Information is proposed

17.5. Interim results of imposed and non-imposed PASS submitted before the entry into force of the revised variation regulation⁴⁹

17.5.1. Apixaban - ELIQUIS (CAP) - EMEA/H/C/002148/MEA 021.3

Applicant: Bristol-Myers Squibb, Pfizer EEIG

PRAC Rapporteur: Menno van der Elst

Scope: Interim study report of study CV185-365: evaluation of the effectiveness of Eliquis (apixaban) risk minimisation tools in the European Economic Area (EEA) countries

17.5.2. Human normal immunoglobulin - PRIVIGEN (CAP) - EMEA/H/C/000831/MEA 022.5

Applicant: CSL Behring GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Second interim report for study IgPro10_5003: an observational hospital-based cohort study in the US on `Privigen use and haemolytic anaemia in adults and children and Privigen safety profile in children with chronic inflammatory demyelinating polyneuropathy (CIDP) (as per the conclusions of renewal procedure R/65 and variation II/63)

17.5.3. Meningococcal group B vaccine (rDNA, component, adsorbed) - BEXSERO (CAP) - EMEA/H/C/002333/MEA 017.2

Applicant: GSK Vaccines S.r.l

PRAC Rapporteur: Qun-Ying Yue

Scope: Second interim report for study V72_360B: an observational safety study after meningococcal B vaccine 4CMenB (Bexsero) vaccination in routine UK care

17.5.4. Mixture of polynuclear iron(III)-oxyhydroxide, sucrose and starches - VELPHORO (CAP) - EMEA/H/C/002705/MEA 002.3

Applicant: Vifor Fresenius Medical Care Renal Pharma France

PRAC Rapporteur: Julie Williams

Scope: Interim results of the VERIFIE study (VFMCRP-MEAF-PA21-01-EU): a non-interventional study to investigate the short and long-term real-life safety, effectiveness, and adherence of Velphoro in patients with hyperphosphataemia undergoing haemodialysis or peritoneal dialysis (PD)

⁴⁹ In line with the revised variations regulation for any submission before 4 August 2013

17.5.5. Strontium ranelate - OSSEOR (CAP) - EMEA/H/C/561/ANX 039.1

Applicant: Les Laboratoires Servier

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Second annual report for an imposed non-interventional safety study to evaluate the effectiveness of the applied risk minimisation measures, including a description of the treated patient population in everyday clinical practice

17.5.6. Strontium ranelate - PROTELOS (CAP) - EMEA/H/C/560/ANX 039.1

Applicant: Les Laboratoires Servier

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Second annual report for an imposed non-interventional safety study to evaluate the effectiveness of the applied risk minimisation measures, including a description of the treated patient population in everyday clinical practice

17.6. Others

17.6.1. Palonosetron - PALONOSETRON ACCORD (CAP) - EMEA/H/C/004129/LEG 002

Applicant: Accord Healthcare Ltd

PRAC Rapporteur: Almath Spooner

Scope: Submission of a six-monthly cumulative review of cases of injection site reactions classified as an important potential risk (1 April-30 September 2016) as requested at the time of the opinion for marketing authorisation(s) for Palonosetron Accord 250 micrograms solution for injection until further market experience is acquired

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., ATMP⁵⁰

PRAC Rapporteur: Julie Williams

Scope: Annual reassessment of the marketing authorisation

18.1.2. Lomitapide - LOJUXTA (CAP) - EMEA/H/C/002578/S/0023 (without RMP)

Applicant: Aegerion Pharmaceuticals Limited

PRAC Rapporteur: Menno van der Elst

Scope: Annual reassessment of the marketing authorisation

18.1.3. Mecasermin - INCRELEX (CAP) - EMEA/H/C/000704/S/0041 (without RMP)

Applicant: Ipsen Pharma

PRAC Rapporteur: Kirsti Villikka

Scope: Annual reassessment of the marketing authorisation

18.1.4. Susoctocog alfa - OBIZUR (CAP) - EMEA/H/C/002792/S/0006 (with RMP)

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Annual reassessment of the marketing authorisation

18.2. Conditional renewals of the marketing authorisation

18.2.1. Daratumumab - DARZALEX (CAP) - EMEA/H/C/004077/R/0003 (without RMP)

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: 1-year conditional renewal of the marketing authorisation

18.2.2. Pandemic influenza vaccine (H5N1) (live attenuated, nasal) - PANDEMIC INFLUENZA VACCINE H5N1 MEDIMMUNE (CAP) - EMEA/H/C/003963/R/0003 (without RMP)

Applicant: MedImmune LLC

PRAC Rapporteur: Jan Neuhauser

⁵⁰ Advanced therapy medicinal product

Scope: 1-year conditional renewal of the marketing authorisation

18.3. Renewals of the marketing authorisation

18.3.1. Acridinium bromide - BRETARIS GENUAIR (CAP) - EMEA/H/C/002706/R/0031 (with RMP)

Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

Scope: 5-year renewal of the marketing authorisation

18.3.2. Acridinium bromide - EKLIRA GENUAIR (CAP) - EMEA/H/C/002211/R/0031 (with RMP)

Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

Scope: 5-year renewal of the marketing authorisation

18.3.3. Aliskiren - RASILEZ (CAP) - EMEA/H/C/000780/R/0112 (without RMP)

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Carmela Macchiarulo

Scope: 5-year renewal of the marketing authorisation

18.3.4. Ceftaroline fosamil - ZINFORO (CAP) - EMEA/H/C/002252/R/0031 (without RMP)

Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

Scope: 5-year renewal of the marketing authorisation

18.3.5. Follitropin alfa, lutropin alfa - PERGOVERIS (CAP) - EMEA/H/C/000714/R/0050 (without RMP)

Applicant: Merck Serono Europe Limited

PRAC Rapporteur: Julie Williams

Scope: 5-year renewal of the marketing authorisation

18.3.6. Human normal immunoglobulin - FLEBOGAMMA DIF (CAP) - EMEA/H/C/000781/R/0048 (with RMP)

Applicant: Instituto Grifols, S.A.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: 5-year renewal of the marketing authorisation

18.3.7. 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

18.3.8. 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

18.3.9. Mecasermin - INCRELEX (CAP) - EMEA/H/C/000704/R/0042 (without RMP)

Applicant: Ipsen Pharma

PRAC Rapporteur: Kirsti Villikka

Scope: 5-year renewal of the marketing authorisation

18.3.10. Nelarabine - ATRIANCE (CAP) - EMEA/H/C/000752/R/0037 (without RMP)

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Torbjorn Callreus

Scope: 5-year renewal of the marketing authorisation

18.3.11. Orlistat - ALLI (CAP) - EMEA/H/C/000854/R/0054 (with RMP)

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Rafe Suvarna

Scope: 5-year renewal of the marketing authorisation

18.3.12. Ruxolitinib - JAKAVI (CAP) - EMEA/H/C/002464/R/0032 (with RMP)

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: 5-year renewal of the marketing authorisation

18.3.13. Zoledronic acid - ZOLEDRONIC ACID MEDAC (CAP) - EMEA/H/C/002359/R/0018 (without RMP)

Applicant: Medac Gesellschaft für klinische Spezialpräparate GmbH

PRAC Rapporteur: Doris Stenver

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 6-9 February 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	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
Željana Margan Koletić	Alternate	Croatia	No interests declared	Full involvement
Andri Andreou	Member	Cyprus	No restrictions applicable to this meeting	Full involvement
Jana Mladá	Member	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
Kimmo Jaakkola	Alternate	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	Germany	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Valerie Strassmann	Alternate	Germany	No interests declared	Full involvement
Agni Kapou	Alternate	Greece	No interests declared	Full involvement
Julia Pallos	Member	Hungary	No interests declared	Full involvement
Guðrún Kristín Steingrimsdóttir	Member	Iceland	No interests declared	Full involvement
Almath Spooner	Member (Vice-Chair)	Ireland	No interests declared	Full involvement
Ruchika Sharma	Alternate - via telephone*	Ireland	No participation in final deliberations and voting on:	4.3.4. Nivolumab - OPDIVO (CAP); 5.3.1. Belatacept - NULOJIX (CAP); 6.1.6. Atazanavir/cobicistat - EVOTAZ (CAP); 6.1.31. Stavudine - ZERIT (CAP); 7.5.1. Apixaban - ELIQUIS (CAP)
Carmela Macchiarulo	Member	Italy	No interests declared	Full involvement
Zane Neikena	Member	Latvia	No interests declared	Full involvement
Jolanta Gulbinovic	Member	Lithuania	No interests declared	Full involvement
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
Ana Sofia Diniz Martins	Member	Portugal	No interests declared	Full involvement
Marcia Sofia Sanches	Alternate	Portugal	No interests	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
de Castro Lopes Silva			declared	
Roxana Stefania Stroe	Member	Romania	No interests declared	Full involvement
Gabriela Jazbec	Alternate	Slovenia	No interests declared	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
Rafe Suvarna	Alternate	United Kingdom	No interests declared	Full involvement
Marie Louise (Marieke) De Bruin	Member	Independent scientific expert	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 interests declared	Full involvement
Marco Greco	Member	Patients' Organisation 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

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Francoise Wuillaume	Expert - via telephone*	Belgium	No interests declared	Full involvement
Radim Tobolka	Expert - via telephone*	Czech Republic	No interests declared	Full involvement
Daniel Pilsgaard Henriksen	Expert - via telephone*	Denmark	No interests declared	Full involvement
Tiina Jaakkola	Expert - via telephone*	Finland	No interests declared	Full involvement
Thomas Grüger	Expert - via telephone*	Germany	No interests declared	Full involvement
Benjamin Hofner	Expert - via telephone*	Germany	No restrictions applicable to this meeting	Full involvement
Tania Meier	Expert - via telephone*	Germany	No interests declared	Full involvement
Clemens Mittmann	Expert - via telephone*	Germany	No interests declared	Full involvement
Susanne Müller	Expert - via telephone*	Germany	No interests declared	Full involvement
Ellen Pantke	Expert - via telephone*	Germany	No restrictions applicable to this meeting	Full involvement
Rhea Fitzgerald	Expert - in person*	Ireland	No restrictions applicable to this meeting	Full involvement
Negar Babae	Expert - via telephone*	Netherlands	No interests declared	Full involvement
Inge Zomerdijk	Expert - in person*	Netherlands	No interests declared	Full involvement
Joanna Plichta	Expert - in person*	Poland	No interests declared	Full involvement
Veronica Arthurson	Expert - in person*	Sweden	No interests declared	Full involvement
Charlotte Backman	Expert - in person*	Sweden	No interests declared	Full involvement
Arzu Günes Granberg	Expert - in person*	Sweden	No interests declared	Full involvement
Lena Hedman	Expert - via telephone*	Sweden	No interests declared	Full involvement
Bengt Ljungberg	Expert - via	Sweden	No interests	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
	telephone*		declared	
Eva Macri	Expert - via telephone*	Sweden	No interests declared	Full involvement
Anna Schölin	Expert - via telephone*	Sweden	No interests declared	Full involvement
Miriam Taekema	Expert - via telephone*	Sweden	No interests declared	Full involvement
Karolina Törneke	Expert - in person*	Sweden	No interests declared	Full involvement
Phillip Bryan	Expert - in person*	United Kingdom	No interests declared	Full involvement
Jo Lyn Chooi	Expert - in person*	United Kingdom	No interests declared	Full involvement
Claire Davies	Expert - in person*	United Kingdom	No interests declared	Full involvement
Katherine Donegan	Expert - in person*	United Kingdom	No interests declared	Full involvement
Andrew Ruddick	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=W00b01ac05800240d0

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/