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Pharmacovigilance Risk Assessment Committee (PRAC) Minutes of the meeting on the meeting on 29-31 October 2018

Chair: Sabine Straus – Vice-Chair: Martin Huber

Health and safety information

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

Disclaimers

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

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

Note on access to documents

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



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1. Introduction

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

The Chairperson opened the 29-31 October 2018 meeting by welcoming all participants.

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

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

1.2. Agenda of the meeting on 29-31 October 2018

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

1.3. Minutes of the previous meeting on 01-04 October 2018

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

Post-meeting note: the PRAC minutes of the meeting held on 01-04 October 2018 were published on the EMA website on 29 November 2018 ([EMA/PRAC/752056/2018](https://www.ema.europa.eu/en/press-room/news/2018/11/29/ema-prac-752056-2018)).

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

2.1. Newly triggered procedures

None

2.2. Ongoing procedures

None

2.3. Procedures for finalisation

None

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

3.1. Newly triggered procedures

None

3.2. Ongoing procedures

None

3.3. Procedures for finalisation

None

3.4. Re-examination procedures¹

None

3.5. Others

None

4. Signals assessment and prioritisation²

4.1. New signals detected from EU spontaneous reporting systems

See Annex I 14.1.

4.2. New signals detected from other sources

See also Annex I 14.2.

4.2.1. Rivaroxaban – XARELTO (CAP)

Applicant(s): Bayer AG

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of recurrent thrombosis in patients with antiphospholipid syndrome

EPITT 19320 – New signal

Lead Member State(s): SE

Background

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

² Each signal refers to a substance or therapeutic class. The route of marketing authorisation is indicated in brackets (CAP for Centrally Authorised Products; NAP for Nationally Authorised Products including products authorised via Mutual Recognition Procedures and Decentralised Procedure). Product names are listed for reference Centrally Authorised Products (CAP) only. PRAC recommendations will specify the products concerned in case of any regulatory action required

Xarelto is a centrally authorised product containing rivaroxaban, a direct factor Xa inhibitor. Xarelto (rivaroxaban) is indicated for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers when co-administered with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine and for the prevention of atherothrombotic events in adult patients with coronary artery disease (CAD) or symptomatic peripheral artery disease (PAD) at high risk of ischaemic events when co-administered with ASA. Xarelto (rivaroxaban) is also indicated for the prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery, for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), as well as for the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors, such as congestive heart failure, hypertension, age \geq 75 years, diabetes mellitus, prior stroke or transient ischaemic attack and prevention of recurrent DVT and PE in adults.

The exposure for Xarelto (rivaroxaban) is estimated to have been more than 16.9 million person-years worldwide, in the period from first authorisation in 2008 to 2017.

Following the publication of an article by *Pengo et al.*³ in *Blood*, a signal of recurrent thrombosis in patients with antiphospholipid syndrome treated with rivaroxaban was identified by Sweden. Sweden confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

Having considered the evidence from clinical trials, the PRAC agreed that the signal should be extended to the whole class of direct oral anticoagulants (DOAC). The MAHs for Xarelto (rivaroxaban), Eliquis (apixaban), Lixiana (edoxaban) and Pradaxa (dabigatran) should submit a comprehensive review of the risk of recurrent thrombosis in patients with antiphospholipid syndrome treated with these respective medicinal products.

The PRAC appointed Ulla Wändel Liminga as Rapporteur for the signal.

Summary of recommendation(s)

- The MAHs Bayer AG, Bristol-Myers Squibb, Daiichi Sankyo Europe GmbH, Boehringer Ingelheim International GmbH for Xarelto (rivaroxaban), Eliquis (apixaban), Lixiana (edoxaban) and Pradaxa (dabigatran) respectively should submit to the EMA, within 60 days, a comprehensive review of the risk of recurrent thrombosis in patients with antiphospholipid syndrome treated with these respective medicinal products. The review should focus on data from ongoing and finalised randomised clinical trials (RCTs) in antiphospholipid syndrome patients but should also include relevant data from any other source. The MAHs should comment on the biological plausibility of this association and should discuss possible mechanisms for potential inferior effects of the respective direct oral anticoagulants DOAC compared with warfarin/other vitamin K antagonists (VKAs) in patients with antiphospholipid antibody syndrome (APS), taking all available data into account, including the *Pengo et al.* and *Dufrost et al.*⁴ publications.

³ Pengo et al. Rivaroxaban vs warfarin in high-risk patients with antiphospholipid syndrome. *Blood*. 2018 Sep 27;132(13):1365-1371

⁴ Dufrost et al. Increased risk of thrombosis in antiphospholipid syndrome patients treated with direct oral anticoagulants. Results from an international patient-level data meta-analysis. 2018 Oct;17(10):1011-1021

- The MAHs should also discuss the need for any potential amendment to the product information and/or the risk management plan and make a proposal accordingly for the changes to the relevant sections.
- A 90-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.3. Signals follow-up and prioritisation

- 4.3.1. Clomipramine (NAP);
 Serotonin and noradrenaline reuptake inhibitors (SNRI)⁵: desvenlafaxine (NAP); duloxetine - CYMBALTA (CAP), DULOXETINE LILLY (CAP), DULOXETINE MYLAN (CAP), DULOXETINE ZENTIVA (CAP), XERISTAR (CAP), YENTREVE (CAP); milnacipran (NAP); venlafaxine (NAP);
 Selective serotonin reuptake inhibitors (SSRI)⁶: citalopram (NAP); escitalopram (NAP); fluoxetine (NAP); fluvoxamine (NAP); paroxetine (NAP); sertraline (NAP); Vortioxetine – BRINTELLIX (CAP)
-

Applicant(s): Eli Lilly Nederland B.V. (Cymbalta, Duloxetine Lilly, Xeristar, Yentreve), Generics UK Limited (Duloxetine Mylan), H. Lundbeck A/S (Brintellix), Zentiva k.s. (Duloxetine Zentiva), various

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Signal of persistent sexual dysfunction after drug withdrawal

EPITT 19277 – Follow-up to September 2018

Background

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

Following the further investigation performed on the signal of persistent sexual dysfunction after drug withdrawal by the Lead Member States (LMS) and EMA, the consolidated review was assessed by the Rapporteur.

Discussion

Having considered the available evidence, the PRAC agreed that the MAHs should provide a cumulative review of the signal of persistent sexual dysfunction. This cumulative review should include data from all sources including non-clinical data, clinical data (e.g. withdrawal trials if available), spontaneous post-marketing cases as well as any relevant literature that was not yet evaluated in the assessment report. The review of any non-clinical data should include a discussion on the relevance for humans. To allow a meaningful assessment of post-marketing spontaneous data, the MAHs of originator-containing products are requested to include in the cumulative review only the cases that contain sufficient clinical details for causality assessment. Furthermore, the MAHs should discuss the most frequently reported symptoms of sexual dysfunction in descending order, provide the percentage of cases with each of the reported indications for each substance with which the treatment was initiated, provide the median duration of treatment with the considered substance (with interquartile range), the median duration of persistence of sexual dysfunction (with interquartile range), determine if there is any correlation between the dosage of a considered substance and the

⁵ Indicated in the treatment of major depressive disorder (MDD)

⁶ Indicated in the treatment of major depressive disorder (MDD)

duration of persistence of sexual dysfunction, determine if there is any correlation between the indication for which treatment was initiated with the considered substance and the duration of persistence of sexual dysfunction after discontinuation, determine if there is any correlation between the duration of treatment with the considered substance and the duration of persistence of sexual dysfunction after discontinuation.

The EMA will provide an analysis of data available in EudraVigilance including reporting trend analysis.

Summary of recommendation(s)

- The MAHs Eli Lilly for Cymbalta (duloxetine) and fluoxetine-containing product, Lundbeck for citalopram-containing product, escitalopram-containing product and Brintellix (vortioxetine), Mylan for fluvoxamine-containing product, Pfizer for sertraline- and desvenlafaxine-containing products, GSK for paroxetine-containing product, Almirall for venlafaxine-containing product, and Pierre-Fabre for milnacipram-containing product as well as Alfasigma for clomipramine-containing product should submit to EMA, within 60 days, a cumulative review of the signal of persistent sexual dysfunction, including data from all sources including non-clinical data, clinical data (e.g. withdrawal trials if available), and spontaneous post-marketing cases as well as any relevant literature not yet evaluated in the assessment report.
- Based on all the requested analyses, the MAHs are requested to evaluate and discuss the causality assessment of the post-marketing spontaneous reports on a cumulative level. Furthermore, the MAHs are requested to discuss the relationship between depression and sexual dysfunction as well as provide the available data regarding the prevalence of the most commonly reported symptoms (from the MAHs' cumulative analyses) in the general population. In addition, the MAHs are requested to discuss the possible mechanisms which may underlie the persistent sexual dysfunction events in humans. Based on all available data and analyses, the MAHs should discuss the need for any potential amendment to the product information and/or risk management plan.
- A 90-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.3.2. Paracetamol (NAP)

Applicant(s): various

PRAC Rapporteur: Laurence de Fays

Scope: Signal of paracetamol use in pregnancy and child neurodevelopment and effects on the urogenital apparatus

EPITT 17796 – Follow-up to February 2018

Background

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

The Safety Working Party ([SWP](#)) replied to the PRAC list of questions on the signal of paracetamol use in pregnancy and child neurodevelopment and effects on the urogenital apparatus and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence from literature, including non-clinical and epidemiological studies, regarding the signal of prenatal exposure to paracetamol and the impact on the urogenital apparatus or neurodevelopmental disorders in offspring, the PRAC agreed that the product information of paracetamol-containing medicinal products should be amended in order to reflect the current state of scientific knowledge regarding this signal, namely that the non-clinical data and epidemiological studies in children exposed to paracetamol in utero show conflicting results on the impact of prenatal exposure to paracetamol on the urogenital apparatus or neurodevelopmental disorders in offspring. Therefore, the MAHs should comment on the amendments proposed to update the product information accordingly.

Summary of recommendation(s)

- The MAHs Teva, GlaxoSmithKline, Bristol-Myers Squibb, Aurobindo, Stada, Fresenius, PanPharma, Novartis, Sanofi and Johnson & Johnson should submit to EMA, within 60 days comments on the proposal to amend the product information⁷.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.3.3. Tacrolimus⁸ – ADVAGRAF (CAP), ENVARSUS (CAP), MODIGRAF (CAP), TACFORIUS (CAP), NAP

Applicant(s): Astellas Pharma Europe B.V. (Advagraf, Modigraf), Chiesi Farmaceutici S.p.A. (Envarsus), Teva B.V. (Tacforius); various

PRAC Rapporteur: Rhea Fitzgerald

Scope: Signal of hepatitis E infection

EPITT 19246 – Follow-up to June 2018

Background

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

The MAH replied to the request for information on the signal of hepatitis E infection and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence from EudraVigilance and the literature as well as the cumulative review submitted by Astellas (MAH for originator tacrolimus-containing medicinal products), the PRAC agreed that the MAHs for tacrolimus systemic formulation should amend their product information to include special warnings and precautions for use about the increased risk of infections with viral hepatitis for patients under treatment and the consequent need for prevention and management in accordance with appropriate clinical guidance. No changes to the package leaflet are considered necessary in view of the existing warning on infections.

Summary of recommendation(s)

⁷ Update of SmPC sections 4.6 and 5.3. The package leaflet is proposed to be updated accordingly

⁸ Systemic formulations only

- The MAHs for systemic formulation of tacrolimus-containing medical products should submit to EMA, within 90 days, a variation to amend their product information⁹.

For the full PRAC recommendation, see [EMA/PRAC/758152/2018](#) published on 26/11/2018 on the EMA website.

4.3.4. Xylometazoline (NAP)

Applicant(s): various

PRAC Rapporteur: Zane Neikena

Scope: Signal of serious ventricular arrhythmia in patients with long QT syndrome

EPITT 19242 – Follow-up to June 2018

Background

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

The MAH replied to the request for information on the signal of serious ventricular arrhythmia in patients with long QT syndrome and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence in EudraVigilance and in the literature, the PRAC agreed that the MAH(s) of xylometazoline-containing medicinal products should submit the product information as applicable (taking into account the already existing wording in some nationally authorised products) to include special warnings and precautions for use in patients with long QT syndrome that may be at increased risk of serious ventricular arrhythmias.

Summary of recommendation(s)

- The MAHs for xylometazoline-containing medicinal products should submit to the relevant national competent authorities of the MSs, within 90 days, a variation to amend the product information¹⁰

For the full PRAC recommendation, see [EMA/PRAC/758152/2018](#) published on 26/11/2018 on the EMA website

5. Risk management plans (RMPs)

5.1. Medicines in the pre-authorisation phase

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

⁹ Update of SmPC section 4.4. The package leaflet is not to be updated in view of the existing warning on infections

¹⁰ Update of SmPC section 4.4. The package leaflet is to be updated accordingly

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

See also Annex I 15.1.

5.1.1. Buprenorphine - EMEA/H/C/004743

Scope: Substitution treatment for opioid drug dependence

5.1.2. Canakinumab - EMEA/H/C/004754

Scope: Treatment for the prevention of major cardiovascular events

5.1.3. Cannabidiol - EMEA/H/C/004675, Orphan

Applicant: GW Research Ltd

Scope: Adjunctive therapy of seizures associated with Lennox-Gastaut syndrome (LGS) or Dravet syndrome (DS)

5.1.4. Dacomitinib - EMEA/H/C/004779

Scope: First-line treatment of adults with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR)-activating mutations

5.1.5. Fremanezumab - EMEA/H/C/004833

Scope: Prevention of episodic and chronic migraine

5.1.6. Hydroxycarbamide - EMEA/H/C/004837

Scope: Prevention of complications of Sickle cell disease

5.1.7. Sotagliflozin - EMEA/H/C/004889

Scope: Adjunct treatment to insulin therapy to improve glycaemic control in adults with type 1 diabetes mellitus (T1DM)

5.1.8. Turoctocog alfa pegol - EMEA/H/C/004883, Orphan

Applicant: Novo Nordisk A/S

Scope: Treatment and prophylaxis of bleeding in patients with haemophilia A

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

See also Annex I 15.2.

5.2.1. Certolizumab pegol - CIMZIA (CAP) - EMEA/H/C/001037/II/0072

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of the RMP (version 14.0) in order to revise the distribution list of educational materials (addition of dermatologists) and to revise the RMP in line with revision 2 of GVP module V on 'Risk management systems' and revision 2 of the guidance on the format of RMP in the EU (template), including the update of the important identified risks and important potential risks. The PASS protocol for study UP0038 designed to assess the effectiveness of the educational material is updated to add dermatologists to the healthcare professional study population, to remove Italy and Spain from the study participation and to make additional administrative changes. In addition, the MAH took the opportunity to introduce some administrative changes in the RMP

Background

Certolizumab pegol is a tumour necrosis factor alfa (TNF α) inhibitor indicated, as Cimzia, for the treatment of rheumatoid arthritis (RA), axial spondyloarthritis, including ankylosing spondylitis (AS) and axial spondyloarthritis without radiographic evidence of AS, psoriatic arthritis as well as for the treatment of plaque psoriasis under certain conditions.

The PRAC is evaluating a type II variation procedure for Cimzia, a centrally authorised medicine containing certolizumab pegol, to update the RMP in order to revise the distribution's list of educational materials by adding dermatologists and to bring it in line with revision 2 of GVP module V. In addition, the PASS protocol for study UP0038 designed to assess the effectiveness of the educational material is updated to add dermatologists to the healthcare professional study population. The PRAC is responsible for producing an assessment report to be further considered at the level of the CHMP, responsible for adopting an opinion on this variation.

Summary of advice

- The RMP for Cimzia (certolizumab pegol) in the context of the variation under evaluation could be considered acceptable provided that an update to RMP version 14.0 and satisfactory responses to the request for supplementary information (RSI) are submitted.
- The MAH should provide a further review of the list of safety specification considering removing some specific safety concerns based on the data generated so far. In addition, the PRAC supported the discontinuation of the requirement for the 'prescriber guide' as an additional risk minimisation measure (aRMM) as the knowledge gathered over the years amongst healthcare professionals prescribing this class of medicines is considered sufficient to mitigate the relevant risk in clinical practice. Furthermore, the MAH should rename the 'patient alert card' (PAC) to 'patient reminder card' (PRC) and this PRC will continue to be distributed to all new patients across indications. The RMP and Annex II of the product information should be revised accordingly.

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

See also Annex I 15.3.

5.3.1. Sodium oxybate - XYREM (CAP) - EMEA/H/C/000593/II/0076

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Extension of indication to include adolescents and children older than 7 years to the existing indication of treatment of narcolepsy with cataplexy in adults. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The package leaflet and the RMP (version 9.0) are updated accordingly

Background

Sodium oxybate is a central nervous system depressant indicated, as Xyrem, for the treatment of narcolepsy with cataplexy in adult patients.

The CHMP is evaluating an extension of the therapeutic indication for Xyrem, a centrally authorised medicine containing sodium oxybate, to amend the existing indication to include adolescents and children older than 7 years. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this extension of indication.

Summary of advice

- The RMP for Xyrem (sodium oxybate) in the context of the variation procedure under evaluation by the CHMP could be considered acceptable provided that an update to RMP version 9 and satisfactory responses to the request for supplementary information (RSI) are submitted.
- In terms of pharmacovigilance plan, the PRAC considered that the currently planned follow up of up to two years for JAZZ paediatric study 13-005¹¹ (part 2) is insufficient to address Xyrem (sodium oxybate) safety concerns in the pediatric population. Therefore, the MAH should be requested to extend the follow up period and explore the possibility to embed data on neurodevelopmental problems (i.e. cognition, attention and learning abilities). The MAH should also guarantee that a sufficient number of patients are followed up to ensure meaningful results are obtained. Therefore, the MAH should provide a feasibility assessment, taking into account confounding factors due to the underlying disease and the possibility to include an active comparator group. The PRAC also suggested further investigating the matter in the non-clinical setting. In addition, the MAH should explore the possibility of setting up or joining an already existing disease registry on narcolepsy. With regard to additional risk minimisation measures (aRMM) proposed for paediatric patients and their caregivers, the MAH should submit a proposal for measuring their effectiveness. Furthermore, the PRAC endorsed the MAH's proposal for educational materials targeting pediatric patients and their caregivers, some adjustments should be introduced to the 'guide for pediatric patients and their caregivers'. Finally, the safety specification should be brought in line with revision 2 of GVP module V on 'Risk management systems'.

6. Periodic safety update reports (PSURs)

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

See also Annex I 16.1.

¹¹ A multicentre study of the efficacy and safety of Xyrem with an open-label pharmacokinetic evaluation and safety extension in paediatric subjects with narcolepsy with cataplexy

6.1.1. Irinotecan¹² - ONIVYDE (CAP) - PSUSA/00010534/201804

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: David Olsen

Scope: Evaluation of a PSUSA procedure

Background

Irinotecan is an antineoplastic agent. Onivyde (irinotecan) is indicated for the treatment of metastatic adenocarcinoma of the pancreas, in combination with 5-fluorouracil (5-FU) and leucovorin (LV), in adult patients who have progressed following gemcitabine based therapy.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Onivyde, a centrally authorised medicine containing irinotecan¹³, and issued a recommendation on its marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Onivyde (irinotecan) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add a warning on the risk of vascular disorders. Therefore, the current terms of the marketing authorisation(s) should be varied¹⁴.
- In the next PSUR, the MAH should closely monitor fungal and viral infections, and should discuss the potential lack of efficacy in study 331501¹⁵.

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

6.1.2. Parathyroid hormone - NATPAR (CAP) - PSUSA/00010591/201804

Applicant: Shire Pharmaceuticals Ireland Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

Background

Parathyroid hormone is a calcium homeostasis substance. Natpar (parathyroid hormone) is indicated as an adjunctive treatment of adult patients with chronic hypoparathyroidism who cannot be adequately controlled with standard therapy alone.

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

¹² Liposomal formulations only

¹³ Liposomal formulations only

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

¹⁵ A phase 2 randomized study of BAX2398 in combination with 5-fluorouracil and calcium levofolinate in Japanese patients with metastatic pancreatic cancer, which progressed or recurred after prior gemcitabine-based therapy. NCT02697058

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Natpar (parathyroid hormone) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add a warning on urolithiasis. Therefore, the current terms of the marketing authorisation(s) should be varied¹⁶.
- In the next PSUR, the MAH should present the key safety findings and study conclusions for study PAR-C10-008¹⁷, study SHP634-102¹⁸ and study SHP634-103¹⁹. In addition, the MAH should clarify its search strategy for the important potential risk of 'medication errors' and justify if it differs to that in the RMP, follow up the outcome of all cases of exposure in pregnant women and further clarify and justify the search strategy to identify cases of Natpar (parathyroid hormone) use in patients with severe renal and hepatic disease.

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. Propranolol²⁰ - HEMANGIOL (CAP) - PSUSA/00010250/201804

Applicant: Pierre Fabre Dermatologie

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

Background

Propranolol is a non-selective beta-blocking agent. Hemangioliol (propranolol) is indicated in the treatment of proliferating infantile haemangioma requiring systemic therapy: life- or function-threatening haemangioma, ulcerated haemangioma with pain and/or lack of response to simple wound care measures as well as haemangioma with a risk of permanent scars or disfigurement.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Hemangioliol, a centrally authorised medicine containing propranolol²¹ and issued a recommendation on its marketing authorisation(s).

Summary of recommendation(s) and conclusions

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

¹⁷ A long-term open-label study investigating the safety and tolerability of NPSP558, a recombinant human parathyroid hormone (rhPTH[1-84]), for the treatment of adults with hypoparathyroidism - a clinical extension study (RACE). NCT01297309

¹⁸ A phase 1, open-label, randomized, cross-over study to evaluate the pharmacokinetics, safety, and tolerability of a single dose of rhPTH[1-84] administered subcutaneously in Japanese healthy subjects compared with matched non-Hispanic, Caucasian healthy adult subjects and to assess dose proportionality of 3 doses of rhPTH [1-84] in the Japanese subjects. NCT03150108

¹⁹ A randomized, open-label, single-dose, two-treatment, two-period crossover study to determine the bioequivalence of rhPTH[1-84] administered subcutaneously with the Haselmeier and Scandinavian Health Ltd (SHL) injector pens in healthy volunteers

²⁰ Centrally authorised product(s) only

²¹ Centrally authorised product(s) only

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Hemangirol (propranolol) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include the undesirable effects dermatitis psoriasiform and dermatitis diaper with frequencies 'not known' and 'common' respectively. Therefore, the current terms of the marketing authorisation(s) should be varied²².
- In the next PSUR, the MAH should keep open the signal of 'sudden infant death syndrome (SIDS)' through routine pharmacovigilance activities, including a literature search on SIDS mechanism. In addition, the MAH should address the background incidence of neurodevelopmental abnormalities and strabismus in the general population and should also further evaluate the effectiveness of risk minimisation measures by including a discussion on the mean rate of educational guide per patient not reached in Spain.

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. Tocilizumab - ROACTEMRA (CAP) - PSUSA/00002980/201804

Applicant: Roche Registration GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

Background

Tocilizumab is an immunosuppressant, interleukin inhibitor. Roactemra (tocilizumab) is indicated in combination with methotrexate (MTX) for the treatment of severe, active and progressive rheumatoid arthritis (RA) in adults not previously treated with MTX, and for the treatment of moderate to severe active RA in adult patients who have either responded inadequately to, or who were intolerant to, previous therapy with one or more disease modifying anti-rheumatic drugs (DMARDs) or tumour necrosis factor (TNF) antagonists. Roactemra (tocilizumab) is also indicated for the treatment of active systemic juvenile idiopathic arthritis (sJIA) in patients 2 years of age and older, who have responded inadequately to previous therapy with nonsteroidal anti-inflammatory drugs (NSAIDs) and systemic corticosteroids, for the treatment of chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome (CRS) in adults and paediatric patients 2 years of age and older, and in combination with MTX for the treatment of juvenile idiopathic polyarthritis in patients 2 years of age and older, who have responded inadequately to previous therapy with MTX.

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

Summary of recommendation(s) and conclusions

²² Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Roactemra (tocilizumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add the undesirable effect hypofibrinogenaemia with a frequency 'common' and to include the information that during clinical studies with tocilizumab rapid decrease in fibrinogen was observed. Therefore, the current terms of the marketing authorisation(s) should be varied²³.
- In the next PSUR, the MAH should further review the signal of acute pancreatitis.
- In addition, the MAH should submit to EMA, within 60 days, the final cumulative hepatotoxicity drug safety reports (DSR). The MAH should also submit, within 30 days, a cumulative review of cases of psoriasis and psoriasis-related as well as provide a detailed analysis of whether the cases of hypofibrinogenaemia observed in tocilizumab-exposed patients are related to a disorder of liver protein synthesis performance.

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

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

See also Annex I 16.2.

6.2.1. Bimatoprost - LUMIGAN (CAP); NAP - PSUSA/00000413/201803

Applicants: Allergan Pharmaceuticals Ireland (Lumigan), various

PRAC Rapporteur: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

Background

Bimatoprost is an ophthalmological prostaglandin analogue. Lumigan (bimatoprost) is indicated for the reduction of elevated intraocular pressure in chronic open-angle glaucoma and ocular hypertension in adults (as monotherapy or as adjunctive therapy to beta-blockers).

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

Summary of recommendation(s) and conclusions

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

²³ Update of SmPC sections 4.8 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 for bimatoprost 0.1 mg/mL eye drops, solution (0.01%) should be updated to add the undesirable effects dizziness, hypertension, photophobia, ocular discomfort and skin discoloration (periocular) with a frequency 'not known'. Therefore, the current terms of the marketing authorisations should be varied²⁴.
- Moreover, the product information for bimatoprost 0.3 mg/mL eye drops, solution (0.03%), should be updated to add the undesirable effects ocular discomfort and skin discoloration (periocular) with a frequency 'not known'. Therefore, the current terms of the marketing authorisations should be varied²⁵.
- Finally, the product information for bimatoprost 0.3 mg/mL eye drops, solution in a single-dose container (0.03% preservative-free (PF)), should be updated to add the undesirable effects dizziness, eye discharge, ocular discomfort, hypertension and skin discoloration (periocular) with a frequency 'not known'. Therefore, the current terms of the marketing authorisations should be varied²⁶.
- In the next PSUR, the MAHs should provide a cumulative review (all sources) on prostaglandin-associated periorbitopathy (PAP)-related adverse events with bimatoprost treatment as well as a cumulative review of cases of myalgia and arthralgia (pre and post-marketing as well as literature reports and potential mechanisms) in association with exposure to bimatoprost, together with a discussion on the consequent need to update the product information (PI) and relevant proposal including the estimation of corresponding frequencies. The MAHs Allergan, OmniVision and Pharmathen should provide an analysis of actual use, including post-authorisation use in special populations (i.e. paediatric population, elderly population, pregnant or lactating women, patients with hepatic and/or renal impairment) and other post-authorisation use (patterns of use, such as evidence of overdose, abuse, misuse and off-label use). The MAH Omnivision should present a full evaluation of the signals of macular detachment, choroidal detachment and audible blink, blepharothorevia. The MAH Allergan is requested to review the discontinuation rates and any lack of efficacy in relation to benzalkonium chloride (BAK) content in the bimatoprost products (all formulations), discuss the corresponding need to update the product information(s) and provide if deemed necessary the appropriate proposals to update the PI.

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

6.2.2. Dexmedetomidine - DEXDOR (CAP); NAP - PSUSA/00000998/201803

Applicants: Orion Corporation (Dexdor), various

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

Background

²⁴ 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

²⁵ 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

²⁶ 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

Dexmedetomidine is a psycholeptic. Dexdor (dexmedetomidine) is indicated for the sedation of adult intensive care unit (ICU) patients requiring a sedation level not deeper than arousal in response to verbal stimulation (corresponding to Richmond Agitation-Sedation Scale (RASS) 0 to -3) and for the sedation of non-intubated adult patients prior to and/or during diagnostic or surgical procedures requiring sedation, i.e. procedural/awake sedation.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of dexmedetomidine-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add a warning on hyperthermia and to include hypertension and respiratory depression as symptoms of overdose. Therefore, the current terms of the marketing authorisations should be varied²⁷.
- In the next PSUR, the MAH(s) should provide a cumulative review of medication error and a cumulative review of reports concerning off-label use during labour and post-parturition.

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

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

See also Annex I 16.3.

6.3.1. Bacillus Calmette-Guerin (BCG) vaccine²⁸ (NAP) - PSUSA/00000304/201803

Applicant(s): various

PRAC Lead: Roxana Stefania Stroe

Scope: Evaluation of a PSUSA procedure

Background

Bacillus Calmette Guerin (BCG) vaccine manufactured by AJ Vaccines A/S is a live, freeze dried vaccine, manufactured from an attenuated strain of *Mycobacterium bovis* (*M. bovis*), designated Danish strain 1331 and indicated for the prevention of tuberculosis in humans.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicinal BCG vaccine(s) (freeze-dried) and issued a recommendation on their marketing authorisation(s).

²⁷ Update of SmPC sections 4.4 and 4.9. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

²⁸ Freeze-dried only

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of BCG vaccine(s) (freeze-dried) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add a warning on the reported cases of immune reconstitution inflammatory syndrome. Therefore, the current terms of the marketing authorisation(s) should be varied²⁹.
- In the next PSUR, the MAH(s) should monitor data on sensitivity of the BCG Danish strain 1331 and resistance to anti-tuberculous agents, take appropriate action, if necessary and provide a detailed analysis of the issue. In addition, the MAH(s) should monitor cases with BCG reactivation related adverse events after administration of other scheduled vaccines and should provide a cumulative analysis. Moreover, MAH(s) should provide a review of any new data in relation to the signal of 'confusion between BCG vaccine and BCG culture' after implementation of the name change for BCG Culture AJV in South Africa. Finally, the MAH(s) should provide a cumulative review of cases with localized and systemic infection with *M. bovis* and cumulative reviews of cases with allergic reactions including allergic reactions related terms and of cases with drug ineffective.

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

6.3.2. Cabergoline (NAP) - PSUSA/00000477/201803

Applicant(s): various

PRAC Lead: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

Background

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

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

Summary of recommendation(s) and conclusions

²⁹ Update of SmPC section 4.4. No update to the package leaflet is necessary. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

- Based on the review of the data on safety and efficacy, the benefit-risk balance of cabergoline-containing medicinal products in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAH(s) should monitor cases of suicidal ideation/suicide with a particular reference to those occurring in patients with impulse control disorders and monitor cases reporting the occurrence of brain neoplasms. The MAH(s) should also include a critical discussion on the available evidence documenting the effectiveness of the current risk minimisation measures (RMMs) applied to minimise and manage the risk of cardiac dysfunction/valvulopathy. With regards to the safety concern of cardiovascular adverse events, the MAH(s) should include an analysis of all available safety data (from clinical trials, pharmacoepidemiological studies, published literature and spontaneous reporting, including discussion on causality) relevant for the indication in inhibition or suppression of physiological lactation, with a specific discussion on all fatal outcomes and a discussion on the influence of treatment dose and duration in the occurrence of these events. In addition, a discussion and a proposal for further measures to minimise the risks of serious cardiovascular (CV) events with cabergoline-containing medicinal products authorised in the inhibition or suppression of physiological lactation should be provided.

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

6.3.3. Fenspiride (NAP) - PSUSA/00001368/201804

Applicant(s): various

PRAC Lead: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

Background

Fenspiride is a bronchodilator indicated for the symptomatic treatment of cough and expectoration in the course of inflammatory diseases of the bronchi and lungs.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of fenspiride-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include the undesirable effects dysgeusia, headache, dyspnoea, and increased blood pressure with a frequency

'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied³⁰.

- In the next PSUR, the MAH(s) should provide a complete safety review of cases of anxiety and panic attack and revise the important safety concern of Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) as a potential risk including other severe cutaneous reactions.
- Finally, further consideration is to be given on hERG channel binding study³¹ with fenspiride.

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

6.3.4. Fluorodopa (¹⁸F) (NAP) - PSUSA/00010002/201803

Applicant(s): various

PRAC Lead: John Joseph Borg

Scope: Evaluation of a PSUSA procedure

Background

Fluorodopa (¹⁸F) is a diagnostic radiopharmaceutical for tumour detection, intended for diagnostic use only, and indicated for use with positron emission (PET).

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing fluorodopa (¹⁸F) and issued a recommendation on their marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of fluorodopa (¹⁸F)-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include the undesirable effect burning sensation with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied³².

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

6.3.5. Influenza vaccine (surface antigen, inactivated) (NAP) - PSUSA/00001744/201803

Applicant(s): various

PRAC Lead: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

³⁰ Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

³¹ Study results are to be submitted to the relevant Competent Authorities by January 2019

³² Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

Background

Influenza vaccine (surface antigen, inactivated) is indicated for the prophylaxis of influenza in adults, especially in those who are at an increased risk of associated complications.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised influenza vaccine(s) (surface antigen, inactivated) and issued a recommendation on their marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of influenza vaccine (surface antigen, inactivated) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAHs Seqirus and Abbott/Mylan are requested to follow-up and review the signals of 'brachial neuritis' and 'facial paresis/paralysis'. This review should include observed versus expected analyses using background incidence rates from reviewed literature, and if available from published epidemiological studies. A cumulative review of febrile and non-febrile convulsions should be provided and cases of diplopia should be monitored.

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

6.3.6. Nitrofurantoin, nifurtoinol (NAP) - PSUSA/00002174/201802

Applicant(s): various

PRAC Lead: Jolanta Gulbinovic

Scope: Evaluation of a PSUSA procedure

Background

Nitrofurantoin and nifurtoinol are urinary antibacterial agents indicated for the treatment and prophylaxis of acute or recurrent uncomplicated urinary tract infections. Some countries have specific restrictions in some products.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of nitrofurantoin/nifurtoinol-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to specify the cut-off level of estimated glomerular filtration rate (eGFR) to < 45mL/min for the contraindication pertaining to renal impairment, to include a warning on autoimmune hepatitis, and to add the undesirable effects autoimmune hepatitis, interstitial nephritis and cutaneous

vasculitis with a frequency 'unknown'. Therefore, the current terms of the marketing authorisation(s) should be varied³³.

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

6.4.1. Apixaban - ELIQUIS (CAP) - EMEA/H/C/002148/LEG 028.1

Applicant: Bristol-Myers Squibb / Pfizer EEIG

PRAC Rapporteur: Menno van der Elst

Scope: MAH's responses to LEG 028 [cumulative review of cases of liver injury from all available sources (post marketing cases, clinical trial data and literature) as requested in the conclusions of PSUSA/00000226/201705 adopted at the December 2017 PRAC] as per the request for supplementary information (RSI) adopted in May 2018

Background

Eliquis is a centrally authorised medicine containing apixaban, a direct factor Xa inhibitor. Eliquis (apixaban) is indicated for the prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective hip or knee replacement surgery, the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAf), with one or more risk factors, the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and the prevention of recurrent DVT and PE in adults.

Following the evaluation of the most recently submitted PSURs for the above mentioned medicine(s), the PRAC requested the MAH to submit further data (for background, see [PRAC minutes May 2018](#)). The responses were assessed by the Rapporteur for further PRAC advice.

Summary of advice/conclusion(s)

- The PRAC discussed the PRAC Rapporteur's assessment conclusions as well as the Member State(s) comments received. The PRAC concluded that there is currently insufficient evidence to establish a causal relationship between the use of apixaban and liver injury and agreed that there is no need at present to update the product information. The PRAC supported requesting the MAH to continue monitoring serious liver injury cases in future PSURs.

6.4.2. Ledipasvir, sofosbuvir - HARVONI (CAP) - EMEA/H/C/003850/LEG 020

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Justification for not submitting a variation to implement cardiac arrhythmias associated with co-administration of sofosbuvir-containing regimens and amiodarone as a warning and to include Stevens-Johnson syndrome (SJS) as an undesirable effect in the

³³ Update of SmPC sections 4.3, 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

product information as requested in the conclusions of the PSUSA procedure for sofosbuvir (PSUSA/00010134/201712) adopted in June 2018

Background

Harvoni is a centrally authorised medicinal product containing a combination of ledipasvir and sofosbuvir, direct-acting antivirals, and is indicated for the treatment of chronic hepatitis C (CHC) in adults and in adolescents aged 12 to < 18 years.

Following the evaluation of the most recently submitted PSURs for the above mentioned medicine(s), the PRAC requested the MAH to submit further data (for background, see [PRAC minutes June 2018](#)). The responses were assessed by the Rapporteur for further PRAC advice.

Summary of advice/conclusion(s)

- The MAH disagreement with the recommendation of the PSUSA procedure for sofosbuvir (EMA/H/C/PSUSA/00010134/201712) to update the product information³⁴ of sofosbuvir-containing medicinal products (Eplclusa, Harvoni and Vosevi) with the adverse event of Steven-Johnson syndrome (SJS) is not endorsed.
- As previously proposed in PSUSA procedure for sofosbuvir (EMA/H/C/PSUSA/00010134/201712), the product information for sofosbuvir-containing medicinal products should be updated to include the undesirable effect SJS with a frequency 'not known' in accordance with the principles of the EU Guideline on summary of product characteristics (SmPC)³⁵ and with the very strong evidence of a causal role of sofosbuvir in the SJS reaction, including positive re-challenge to sofosbuvir demonstrated by the case in the published literature from *Verma et al. 2017*³⁶.
- The MAH of Harvoni (ledipasvir/sofosbuvir) should submit to EMA, within 60 day a variation to update the product information accordingly³⁷.

6.4.3. Sofosbuvir, velpatasvir - EPCLUSA (CAP) - EMA/H/C/004210/LEG 011

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Justification for not submitting a variation to implement cardiac arrhythmias associated with co-administration of sofosbuvir-containing regimens and amiodarone as a warning and to include Stevens-Johnson syndrome (SJS) as an undesirable effect in the product information as requested in the conclusions of the PSUSA procedure for sofosbuvir (PSUSA/00010134/201712) adopted in June 2018

Background

Eplclusa is a centrally authorised medicinal product containing a combination of sofosbuvir and velpatasvir, direct-acting antivirals, and is indicated for treatment of chronic hepatitis C virus (HCV) infection in adult.

³⁴ Update of SmPC section 4.8. The package leaflet is updated accordingly

³⁵ Volume 2C Notice to Applicants

³⁶ Verma N, Singh S, Sawatkar G, Singh V. BRIEF REPORT: sofosbuvir induced Steven Johnson syndrome in a patient with hepatitis c virus-related cirrhosis. *Hepatology Communications* 2017

³⁷ Update of SmPC section 4.8. The package leaflet is to be updated accordingly

Following the evaluation of the most recently submitted PSURs for the above mentioned medicine(s), the PRAC requested the MAH to submit further data (for background, see [PRAC minutes June 2018](#)). The responses were assessed by the Rapporteur for further PRAC advice.

Summary of advice/conclusion(s)

- The MAH disagreement with the recommendation of the PSUSA procedure for sofosbuvir (EMA/H/C/PSUSA/00010134/201712) to update the product information³⁸ of sofosbuvir-containing medicinal products (Eplclusa, Harvoni and Vosevi) with the adverse event of Steven-Johnson syndrome (SJS) is not endorsed.
- As previously proposed in PSUSA procedure for sofosbuvir (EMA/H/C/PSUSA/00010134/201712), the product information for sofosbuvir-containing medicinal products should be updated to include the undesirable effect SJS with a frequency 'not known' in accordance with the principles of the EU Guideline on summary of product characteristics (SmPC)³⁹ and with the very strong evidence of a causal role of sofosbuvir in the SJS reaction, including positive re-challenge to sofosbuvir demonstrated by the case in the published literature from *Verma et al. 2017*⁴⁰.
- The MAH of Eplclusa (sofosbuvir/velpatasvir) should submit to EMA, within 60 day a variation to update the product information accordingly⁴¹.

6.4.4. Sofosbuvir, velpatasvir, voxilaprevir - VOSEVI (CAP) - EMA/H/C/004350/LEG 005

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Justification for not submitting a variation to implement cardiac arrhythmias associated with co-administration of sofosbuvir-containing regimens and amiodarone as a warning and to include Stevens-Johnson syndrome (SJS) as an undesirable effect in the product information as requested in the conclusions of the PSUSA procedure for sofosbuvir (PSUSA/00010134/201712) adopted in June 2018

Background

Vosevi is a centrally authorised medicinal product containing a combination of sofosbuvir, velpatasvir and voxilaprevir, direct-acting antivirals, and is indicated for treatment of chronic hepatitis C virus (HCV) infection in adult.

Following the evaluation of the most recently submitted PSURs for the above mentioned medicine(s), the PRAC requested the MAH to submit further data (for background, see [PRAC minutes June 2018](#)). The responses were assessed by the Rapporteur for further PRAC advice.

Summary of advice/conclusion(s)

³⁸ Update of SmPC section 4.8. The package leaflet is updated accordingly

³⁹ Volume 2C Notice to Applicants

⁴⁰ Verma N, Singh S, Sawatkar G, Singh V. Brief report: sofosbuvir induced Steven Johnson syndrome in a patient with hepatitis c virus-related cirrhosis. *Hepatology Communications* 2017

⁴¹ Update of SmPC section 4.8. the package leaflet is to be updated accordingly

- The MAH disagreement with the recommendation of the PSUSA procedure for sofosbuvir (EMA/H/C/PSUSA/00010134/201712) to update the product information⁴² of sofosbuvir-containing medicinal products (Epclusa, Harvoni and Vosevi) with the adverse event of Steven-Johnson syndrome (SJS) is not endorsed.
- As previously proposed in PSUSA procedure for sofosbuvir (EMA/H/C/PSUSA/00010134/201712), the product information for sofosbuvir-containing medicinal products should be updated to include the undesirable effect SJS with a frequency 'not known' in accordance with the principles of the EU Guideline on summary of product characteristics (SmPC)⁴³ and with the very strong evidence of a causal role of sofosbuvir in the SJS reaction, including positive re-challenge to sofosbuvir demonstrated by the case in the published literature from *Verma et al. 2017*⁴⁴.
- The MAH of Vosevi (sofosbuvir/velpatasvir/voxilaprevir) should submit to EMA, within 60 day a variation to update the product information accordingly⁴⁵.

7. Post-authorisation safety studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)⁴⁶

See Annex I 17.1.

7.2. Protocols of PASS non-imposed in the marketing authorisation(s)⁴⁷

See also Annex I 17.2.

7.2.1. Cobimetinib - COTELLIC (CAP) - EMA/H/C/003960/MEA 003.3

Applicant: Roche Registration GmbH

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to MEA 003.2 [protocol for study ML39302 (COVENIS) (listed as a category 3 study in the RMP): a non-interventional study to investigate the effectiveness, safety and utilisation of cobimetinib and vemurafenib in patients with and without brain metastases with BRAF V600 mutant melanoma under real world conditions (final clinical study report (CSR) due date: December 2022)] as per the request for supplementary information (RSI) adopted in July 2018

Background

Cobimetinib is a reversible, selective, allosteric inhibitor that blocks the mitogen-activated protein kinase (MAPK) pathway. Cotellic (cobimetinib) is indicated for oral use for the

⁴² Update of SmPC section 4.8. The package leaflet is updated accordingly

⁴³ Volume 2C Notice to Applicants

⁴⁴ Verma N, Singh S, Sawatkar G, Singh V. BRIEF REPORT: Sofosbuvir Induced Steven Johnson Syndrome in a Patient With Hepatitis C Virus-Related Cirrhosis. *Hepatology Communications* 2017

⁴⁵ Update of SmPC section 4.8. The package leaflet is updated accordingly

⁴⁶ In accordance with Article 107n of Directive 2001/83/EC

⁴⁷ 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

treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation in combination with vemurafenib.

As part of the RMP for Cotellic (cobimetinib) the MAH was required to conduct a category 3 study ML29155 (a phase 2 study of cobimetinib in combination with vemurafenib in active melanoma brain metastases (coBRIM-B)) in order to determine the safety and efficacy of Cotellic in combination with vemurafenib, in patients with active melanoma brain metastases. Further to its discontinuation, the ML29155 study was replaced by an alternative ML39302 study (a non-interventional study to investigate the effectiveness, safety and utilization of cobimetinib and vemurafenib in patients with and without brain metastasis with BRAF V600 mutant melanoma under real world conditions) in the updated EU RMP version 3.2 for Cotellic (cobimetinib) during PSUSA procedure PSUSA/00010450/201608 (see [PRAC minutes March 2017](#)) to address the safety concern 'safety and efficacy of patients with central nervous system (CNS) involvement'. Further to the PRAC recommendation adopted at the March 2017 PRAC meeting, the MAH submitted ML39302 PASS protocol (version 2.0, dated 20 August 2018) which was assessed by the PRAC Rapporteur and CHMP Rapporteur. For further background, see [PRAC minutes July 2017](#), [PRAC minutes February 2018](#) and [PRAC minutes July 2018](#).

Summary of advice

- The study protocol for Cotellic (cobimetinib) could be acceptable provided that an updated protocol is submitted to EMA within 60 days to remove all parts regarding efficacy and limit the safety concern: missing information to 'safety in patients with CNS involvement'. Moreover, the MAH is requested to continue the study as planned and report back according to the milestones set.

7.3. Results of PASS imposed in the marketing authorisation(s)⁴⁸

See Annex I 17.3.

7.4. Results of PASS non-imposed in the marketing authorisation(s)⁴⁹

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

⁴⁸ In accordance with Article 107p-q of Directive 2001/83/EC

⁴⁹ In accordance with Article 61a (6) of Regulation (EC) No 726/2004, in line with the revised variations regulation for any submission as of 4 August 2013

7.8. Ongoing Scientific Advice

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

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

None

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

8.1. Annual reassessments of the marketing authorisation

See Annex I 18.1.

8.2. Conditional renewals of the marketing authorisation

See Annex I 18.2.

8.3. Renewals of the marketing authorisation

See Annex I 18.3.

9. Product related pharmacovigilance inspections

9.1. List of planned pharmacovigilance inspections

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

None

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

None

10.3. Other requests

None

10.4. Scientific Advice

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

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

11.1. Safety related variations of the marketing authorisation

None

11.2. Other requests

11.2.1. Roflumilast - DE/H/5807/001/DC, DE/H/5808/001/DC, DE/H/5811/001/DC, DE/H/5805/001/DC, DE/H/5806/001/DC

PRAC Lead: Martin Huber

Scope: PRAC consultation on the evaluation of initial marketing authorisation application(s) under the decentralised procedure for generic roflumilast-containing medicinal products on request of Germany

Background

Roflumilast is a selective phosphodiesterase type 4 (PDE4) inhibitor and approved for use in the EU Member States in as maintenance treatment of severe chronic obstructive pulmonary disease (COPD) (forced expiratory volume in 1 second [FEV₁] post-bronchodilator less than 50% predicted) associated with chronic bronchitis in adult patients with a history of frequent exacerbations as add on to bronchodilator treatment.

In the context of the evaluation by [BfArM](#) of a decentralised application under evaluation in accordance with Article 10(1) of Directive 2001/83/EC based on the centrally authorised product Daxas (roflumilast) 500 micrograms film-coated tablets as the reference medicinal product, Germany requested PRAC advice on its assessment.

Summary of advice

- The PRAC fully supported the assessment of the pharmacovigilance plan and risk minimisation measures as detailed in the assessment report from the RMS (Germany) and agreed that there is no need to impose an additional separate PASS as a condition to the marketing authorisation for generic applications containing roflumilast.

- Furthermore, as a principle for marketing authorisation applications in accordance with Article 10(1) of Directive 2001/83/EC, the PRAC agreed that risk minimisation measures should be aligned with the originator's risk minimisation measures. Therefore, educational materials (EM) should be implemented for generic applications of roflumilast.
- Lastly, the PRAC considered the option to have a wider reflection on the continuous need for additional risk minimisation for roflumilast-containing medicinal products in general in an appropriate procedure.

12. Organisational, regulatory and methodological matters

12.1. Mandate and organisation of the PRAC

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

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

In line with the adopted PRAC best practice guidance (BPG) on Committee efficiency (see [PRAC minutes May 2016](#) and [PRAC minutes June 2018](#)) and the adopted implementation plan for the BPG including goals to measure compliance with the recommendations (see [PRAC minutes June 2016](#) and [PRAC minutes June 2018](#)), the PRAC was updated at the organisational matters teleconference held on 15 November 2018 on quantitative measures collected for the third 2018 quarter of PRAC meetings. For previous update, see [PRAC minutes July 2018](#).

12.2. Coordination with EMA Scientific Committees or CMDh-v

None

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

None

12.4. Cooperation within the EU regulatory network

12.4.1. Heads of Medicines Agencies (HMA)-EMA joint big data taskforce

At the organisational matters teleconference held on 15 November 2018, the EMA Secretariat presented to PRAC the recommendations from the Heads of Medicines Agency (HMA)-EMA joint big data taskforce that includes PRAC input as per the [PRAC work plan 2018](#). The taskforce was formed in March 2017 with a mandate to provide a set of recommendations and a road map for 'big data' in the context of regulatory decision making. The recommendations will be presented to the HMA Management Board at the end of November 2018.

12.5. Cooperation with International Regulators

None

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

None

12.7. PRAC work plan

12.7.1. PRAC work plan 2019 – preparation

PRAC lead: Sabine Straus, Martin Huber

At the organisational matters teleconference held on 15 November 2018, the EMA Secretariat presented to PRAC the priorities for the work plan 2019 taking into account the Brexit preparedness business continuity plan including Committees' operational preparedness activities in view of the withdrawal of the UK from the European Union. Further discussion will take place in December 2018.

12.8. Planning and reporting

12.8.1. EU Pharmacovigilance system – quarterly workload measures and performance indicators – Q3 2018 and predictions

At the organisational matters teleconference held on 15 November 2018, the EMA Secretariat presented quarterly figures on the EMA pharmacovigilance system-related workload and performance indicators, as well as some predictions in terms of workload by procedure type, where available, and per EU National Competent Authority (NCA) for the upcoming months. For previous update, see [PRAC minutes July 2018](#).

12.8.2. PRAC workload statistics – Q3 2018

The EMA secretariat presented, at the organisational matters teleconference held on 15 November 2018, quarterly and cumulative figures to estimate the evolution of the workload of the PRAC, by reflecting on the number of procedures and agenda items covered at each PRAC plenary meeting. See previous update, [PRAC minutes July 2018](#).

12.9. Pharmacovigilance audits and inspections

12.9.1. Pharmacovigilance systems and their quality systems

None

12.9.2. Pharmacovigilance inspections

None

12.9.3. Pharmacovigilance audits - Working Group of Quality Managers (WGQM) - report to PRAC

PRAC lead: Jan Neuhauser

The PRAC welcomed the report from the Working Group of Quality Managers (WGQM) Chair on the ongoing work of the WGQM to update the ex-Pharmacovigilance Audit Facilitation Group (PAFG) documents. For further background, see [PRAC minutes October 2017](#). In addition, the draft of the revised 'Guide to network risk rating of pharmacovigilance process areas in order to support NCAs in the risk assessment required for risk-based audits' was circulated to PRAC for comments.

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

12.10.1. Periodic safety update reports

None

12.10.2. Granularity and Periodicity Advisory Group (GPAG)

PRAC lead: Menno van der Elst, Maia Uusküla

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

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

Post-meeting note: following the PRAC meeting November 2018 (29-31 October 2018), the updated EURD list was adopted by the CHMP and CMDh at their November 2018 meetings and published on the EMA website on 27/11/2018, see:

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

12.11. Signal management

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

None

12.12. Adverse drug reactions reporting and additional monitoring

12.12.1. Management and reporting of adverse reactions to medicinal products

None

12.12.2. Additional monitoring

None

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

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

Post-meeting note: The updated additional monitoring list was published on 28/11/2018 on the EMA website (see: [Home>Human Regulatory>Post-authorisation>Pharmacovigilance>Medicines under additional monitoring>List of medicines under additional monitoring](#)).

12.13. EudraVigilance database

12.13.1. Activities related to the confirmation of full functionality

None

12.14. Risk management plans and effectiveness of risk minimisations

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

Following the presentation to the Committee at the PRAC meeting October 2018 (see [PRAC minutes October 2018](#)), and in line with the [PRAC work plan 2018](#), the PRAC adopted the revision 2.01 of the guidance on the format of RMP in the EU (template), previously adopted as revision 2 in 2017 (see [PRAC minutes March 2017](#)).

12.14.2. Risk management systems

None

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

None

12.15. Post-authorisation safety studies (PASS)

12.15.1. Post-authorisation Safety Studies – imposed PASS

None

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

None

12.16. Community procedures

12.16.1. Referral procedures for safety reasons

None

12.17. Renewals, conditional renewals, annual reassessments

None

12.18. Risk communication and transparency

12.18.1. Public participation in pharmacovigilance

None

12.18.2. Safety communication

None

12.19. Continuous pharmacovigilance

12.19.1. Incident management

None

12.20. Others

12.20.1. Strategy on measuring the impact of pharmacovigilance - PRAC interest group (IG) Impact work plan status update

At the organisational matters teleconference held on 15 November 2018, the PRAC was provided with a status update on the PRAC interest group (IG) Impact 2018 work plan deliverables with the aim to develop a new work plan for 2019-2020. The Committee supported the proposed high level deliverables and mandated the PRAC IG impact to develop a detailed work plan. Follow-up discussion will be scheduled in January 2019.

13. Any other business

None

14. Annex I – Signals assessment and prioritisation⁵⁰

14.1. New signals detected from EU spontaneous reporting systems

As per agreed criteria for new signal(s), the PRAC adopted without further plenary discussion the recommendation of the Rapporteur to request MAH(s) to submit a cumulative review following standard timetables⁵¹.

14.1.1. Peramivir – ALPIVAB (CAP)

Applicant(s): Biocryst UK Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of hepatic failure

EPITT 19314 – New signal

Lead Member State(s): SE

14.2. New signals detected from other sources

14.2.1. Dabigatran – PRADAXA (CAP)

Applicant(s): Boehringer Ingelheim

PRAC Rapporteur: Anette Kristine Stark

Scope: Signal of hallucinations

EPITT 19298 – New signal

Lead Member State(s): DK

14.2.2. Mepolizumab – NUCALA (CAP)

Applicant(s): GlaxoSmithKline Trading

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Signal of hypertensive crisis and hypertension

EPITT 19301 – New signal

Lead Member State(s): DE

14.2.3. Niraparib – ZEJULA (CAP)

Applicant(s): Tesaro UK Limited

⁵⁰ 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

⁵¹ 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

PRAC Rapporteur: Patrick Batty

Scope: Signal of sepsis

EPITT 19311 – New signal

Lead Member State(s): UK

14.2.4. Nivolumab – OPDIVO (CAP)

Applicant(s): Bristol-Myers Squibb Pharma

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Signal of hypoparathyroidism

EPITT 19310 – New signal

Lead Member State(s): DE

14.2.5. Paracetamol (NAP)

Applicant(s): various

PRAC Rapporteur: To be appointed

Scope: Signal of maternal paracetamol use during pregnancy and premature ductus arteriosus closure in offspring

EPITT 19297 – New signal

Lead Member State(s): BE, FR

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. Adalimumab - EMEA/H/C/004475

Scope: Treatment of rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis

15.1.2. Adalimumab - EMEA/H/C/005158

Scope: Treatment of rheumatoid arthritis

15.1.3. Atazanavir - EMEA/H/C/004859

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

15.1.4. Bevacizumab - EMEA/H/C/004697

Scope: Treatment of adult patients with metastatic carcinoma of the colon or rectum, metastatic breast cancer, unresectable advanced, metastatic or recurrent non-small cell lung cancer, advanced and/or metastatic renal cell cancer, persistent, recurrent, or metastatic carcinoma of the cervix

15.1.5. Miglustat - EMEA/H/C/004904

Scope: Treatment of adult patients with mild to moderate type 1 Gaucher disease and only in the treatment of patients for whom enzyme replacement therapy is unsuitable

15.1.6. Silodosin - EMEA/H/C/004964

Scope: Treatment of prostatic hyperplasia (BPH)

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

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

15.2.1. Adalimumab - HUMIRA (CAP) - EMEA/H/C/000481/II/0182

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of the RMP (version 14.0) in order to include a review of the currently specified safety concerns and recently assessed safety concerns and to bring it in line with revision 2 of GVP module V on 'Risk management systems'

15.2.2. Apremilast - OTEZLA (CAP) - EMEA/H/C/003746/II/0023

Applicant: Celgene Europe BV

PRAC Rapporteur: Eva Segovia

Scope: Update of the RMP (version 11.0) in order to reclassify and/or rename the known safety concerns associated with the use of Otezla (apremilast) in line with revision 2 of GVP module V on 'Risk management systems' and revision 2 of the guidance on the format of RMP in the EU (template)

15.2.3. Fidaxomicin - DIFICLIR (CAP) - EMEA/H/C/002087/II/0033

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of the RMP (version 10) in order to reflect the final outcome (Year 5) of study AG2012-3459 (ClosER study: *Clostridium difficile* European Resistance surveillance study) (listed as a category 3 study in the RMP (MEA 002.4)): a prospective, longitudinal, pan-European, in vitro sentinel surveillance study of susceptibility of *Clostridium difficile* to

fidaxomicin and other antibiotics

15.2.4. Micafungin - MYCAMINE (CAP) - EMEA/H/C/000734/II/0038

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Martin Huber

Scope: Update of the RMP (version 20.0) in order to streamline and improve the educational programme and communication to prescribing physicians as requested in variation II/0035 concluded in June 2018

15.2.5. Osimertinib - TAGRISSO (CAP) - EMEA/H/C/004124/II/0026

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Update of the RMP (version 12.0) following the completion of study D6030C00001 (BLOOM study): a phase 1, open-label, multicentre study to assess the safety, tolerability, pharmacokinetics and preliminary anti-tumour activity of osimertinib (AZD9291) in patients with epidermal growth factor receptor (EGFR) mutation positive advanced stage non-small cell lung cancer (NSCLC) in order to remove 'use in patients with Eastern Cooperative Oncology Group (ECOG) performance status ≥ 2 ' and 'use in patients with symptomatic brain metastases' as missing information

15.2.6. Paclitaxel - ABRAXANE (CAP) - EMEA/H/C/000778/II/0092

Applicant: Celgene Europe BV

PRAC Rapporteur: Menno van der Elst

Scope: Update of the RMP (version 17.0) in order to propose the reclassification and/or renaming of known safety concerns associated with the use of Abraxane (paclitaxel) in line with revision 2 of GVP module V on 'Risk management systems'

15.2.7. Pипeraquine tetraphosphate, arteminol - EURARTESIM (CAP) - EMEA/H/C/001199/II/0032

Applicant: Alfasigma S.p.A.

PRAC Rapporteur: Julie Williams

Scope: Update of the RMP (version 15.2) to close the pregnancy registry in line with revision 2 of the guidance on the format of RMP in the EU (template). In addition, the MAH took the opportunity to include the 'distribution of a new version of the educational material', to add 'delayed haemolytic anaemia' and 'severe cutaneous adverse reactions' such as Stevens-Johnson syndrome and toxic epidermal necrolysis as important potential risks, to limit the reproductive risk to the first trimester of pregnancy; to update on several studies, to include Eurartesim (piperaquine tetraphosphate/arteminol) into the WHO⁵² list of essential medicines and to update the details of the MAH

⁵² World Health Organization

15.2.8. Rituximab - MABTHERA (CAP) - EMEA/H/C/000165/II/0144

Applicant: Roche Registration GmbH

PRAC Rapporteur: Doris Stenver

Scope: Update of the RMP (version 16.0) to remove the additional risk minimisation measure of educational outreaches for the important identified risk of 'infusion related reactions' and 'acute infusion related reactions' (IRR)

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

Applicant: Meda AB

PRAC Rapporteur: Rhea Fitzgerald

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

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

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

15.3.1. Ambrisentan - VOLIBRIS (CAP) - EMEA/H/C/000839/II/0054

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Eva Segovia

Scope: Update of sections 4.2 and 5.2 of the SmPC based on results of GSK1325760 study: a juvenile nonclinical toxicology study to further investigate the respiratory function following oral dosing from postnatal days 7 through 36, including an assessment of recovery. The RMP (version 7.5) is updated accordingly. In addition, the MAH took the opportunity to correct typographical errors including the frequency of the adverse drug reaction 'rash' in section 4.8 of the SmPC as well as the date of renewal. The MAH also proposed to introduce a minor update in the Braille section. Moreover, the MAH took the opportunity to propose a combined version of the SmPCs for the different authorised strengths

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

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of section 4.4 of the SmPC in order to update the safety information with inclusion of a statement on bedaquiline resistance in line with the outcome of the PSUSA procedure (EMEA/H/C/PSUSA/00010074/201709) finalised in April 2018 (LEG 011). The

RMP (version 3.0) is updated based on the data triggering the SmPC update and to reflect completion of studies which were assessed in previous procedures. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet

15.3.3. Deferiprone - FERRIPROX (CAP) - EMEA/H/C/000236/II/0126/G

Applicant: Apotex Europe BV

PRAC Rapporteur: Ghania Chamouni

Scope: Grouped variations consisting of an update of sections 4.2, 4.4 and 5.2 of the SmPC in order to update safety information on the use of Ferriprox (deferiprone) in patients with renal or hepatic impairment, based on the final results of two clinical studies (listed as category 3 studies in the RMP): 1) study LA39-0412: an open-label study to compare the pharmacokinetic profiles of a single dose of Ferriprox (deferiprone) in subjects with impaired renal function and healthy volunteers); 2) study LA40-0412: an open-label study to compare the pharmacokinetic profiles of a single dose of Ferriprox in subjects with impaired hepatic function and healthy volunteers. The package leaflet and labelling are updated accordingly. The RMP (version 13.1) is updated accordingly and in line with revision 2 of the guidance on the format of RMP in the EU (template). In addition, the MAH took the opportunity to introduce minor edits in the product information

15.3.4. Dupilumab - DUPIXENT (CAP) - EMEA/H/C/004390/X/0004/G

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Kimmo Jaakkola

Scope: Grouped applications consisting of: 1) extension application to add a new strength of 200 mg solution for injection in pre-filled syringe with safety system (PFS-S) and pre-filled pen (PFP); 2) extensions of indication to add as indications: 'add-on maintenance treatment in patients with moderate-to-severe asthma aged 12 years and older, who are inadequately controlled with medium-to-high dose inhaled corticosteroids (ICS) plus another medicinal product for maintenance treatment, including those with or without an eosinophilic phenotype', 'maintenance therapy to improve lung function' and 'maintenance therapy to reduce oral steroid use and improve lung function in steroid-dependent asthma patients' based on pivotal studies, namely: study DRI12544: a randomized, double-blind, placebo-controlled, dose-ranging study to evaluate dupilumab in patients with moderate to severe uncontrolled asthma; study LIBERTY ASTHMA QUEST: a randomized, double blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of dupilumab in patients with persistent asthma; and study VENTURE: a randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of dupilumab in patients with severe steroid dependent asthma. As a consequence, SmPC sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 are updated. The package leaflet and the RMP (version 2.0) are updated accordingly. In addition, the MAH proposed to merge the SmPCs for the 200 mg and 300 mg strengths

15.3.5. Eltrombopag, eltrombopag olamine - REVOLADE (CAP) - EMEA/H/C/001110/II/0049

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Eva Segovia

Scope: Extension of indication to include first line treatment of adult and paediatric patients aged 2 years and older with severe aplastic anaemia. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 50.0) are updated accordingly

15.3.6. Erlotinib - TARCEVA (CAP) - EMEA/H/C/000618/II/0058

Applicant: Roche Registration GmbH

PRAC Rapporteur: Doris Stenver

Scope: Update of sections 4.2, and 5.1 of the SmPC based on phase 3 clinical study MO22162 (CURRENTS) comparing a higher dose of Tarceva (erlotinib) (300 mg) over the recommended daily dose (150 mg) in current smokers with locally advanced or metastatic non-small cell lung cancer (NSCLC) in the second-line setting after failure of chemotherapy. The package leaflet and the RMP (version 7.0) are updated accordingly. In addition, the MAH took the opportunity to introduce minor editorial changes in sections 4.4, 4.5, 4.6, 4.7, 4.8 and 5.2 of the SmPC

15.3.7. Insulin aspart - NOVOMIX (CAP) - EMEA/H/C/000308/II/0095

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Annika Folin

Scope: Update of sections 4.2, 4.5 and 5.1 of the SmPC to include data on the use of NovoMix 30 combination use with glucagon-like peptide 1 (GLP-1) receptor agonists. The package leaflet and the RMP (version 3) are updated accordingly

15.3.8. Insulin glargine - TOUJEO (CAP) - EMEA/H/C/000309/II/0106

Applicant: Sanofi-Aventis Deutschland GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Submission of the final report from study EFC13799: a randomised phase 3b study, open-label, 2-arm, parallel-group, multicentre, 26-week study assessing the safety and efficacy of Toujeo (insulin glargine, HOE901-U300) versus Lantus (insulin glargine 100 U/mL) in patients \geq 65 years with treatment of type 2 diabetes mellitus (T2DM) inadequately controlled on antidiabetic regimens either including no insulin, or with basal insulin as their only insulin. The RMP is updated accordingly (version 5)

15.3.9. Lenalidomide - REVLIMID (CAP) - EMEA/H/C/000717/II/0102/G, Orphan

Applicant: Celgene Europe BV

PRAC Rapporteur: Ghania Chamouni

Scope: Grouped applications consisting of: 1) extension of indication to include the treatment in combination with bortezomib and dexamethasone of adult patients with previously untreated multiple myeloma; 2) addition of 7-capsule pack sizes for the 7.5 mg, 20 mg and 25 mg strengths of Revlimid (lenalidomide) to support the proposed posology and lenalidomide dose modification. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 6.5 and 8 of the SmPC are updated. The package leaflet and the RMP (version 36.1) are

updated accordingly. Additionally, minor editorial changes are introduced throughout the product information and Annex II-D 'conditions or restrictions with regard to the safe and effective use of the medicinal product' on key elements of the risk minimisation measures (RMM) to include information on timing of blood and semen donation in line with SmPC section 4.4

15.3.10. Lumacaftor, ivacaftor - ORKAMBI (CAP) - EMEA/H/C/003954/X/0034/G

Applicant: Vertex Pharmaceuticals (Europe) Ltd.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Grouped variations consisting of: 1) extension application to introduce a new pharmaceutical form (granules) in 2 strengths (100/125 mg and 150/188 mg) for paediatric use from 2 to 5 years. The RMP (version 4.0) is updated accordingly; 2) update of sections 4.1, 4.2, 4.5, 4.8 and 5.3 of the SmPC of the tablet formulations to bring it in line with the proposed paediatric 2-5 year old extension application

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

Applicant: Orexigen Therapeutics Ireland Limited

PRAC Rapporteur: Martin Huber

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

15.3.12. Nintedanib - OFEV (CAP) - EMEA/H/C/003821/II/0021, Orphan

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Update of section 4.8 of the SmPC in order to include 'myocardial infarction' as a new adverse drug reaction with a frequency 'uncommon' in order to fulfil LEG 004.1 in line with the outcome of the PSUSA procedure (PSUSA/00010319/201704) finalised at the November 2017 PRAC meeting. The package leaflet and the RMP (version 6.0) are updated accordingly and in line with revision 2 of the guidance on the format of RMP in the EU (template)

15.3.13. [Nivolumab - OPDIVO \(CAP\) - EMEA/H/C/003985/WS1278/0042;](#) [Ipilimumab - YERVOY \(CAP\) - EMEA/H/C/002213/WS1278/0053](#)

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope (re-examination procedure): Extension of indication to include the combination treatment with nivolumab and ipilimumab of adult patients with intermediate/poor-risk advanced renal cell carcinoma. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of Opdivo and Yervoy SmPCs are updated. The package leaflet and the RMP (version 19.0 for Yervoy and version 13.0 for Opdivo) are updated accordingly. In addition, the MAH took the opportunity to introduce some editorial changes throughout the Yervoy (ipilimumab) and Opdivo (nivolumab) product information

15.3.14. [Ocrelizumab - OCREVUS \(CAP\) - EMEA/H/C/004043/II/0002](#)

Applicant: Roche Registration GmbH

PRAC Rapporteur: Julie Williams

Scope: Update of sections 4.4 and 4.5 of the SmPC in order to include information on vaccination based on interim results from study BN29739 (listed as a category 3 study in the RMP): a phase 3b, multicentre, randomised, parallel-group, open-label study to evaluate the effects of ocrelizumab on immune response in patients with relapsing forms of multiple sclerosis (MS). The package leaflet and the RMP (version 2.0) are updated accordingly

15.3.15. [Oseltamivir - TAMIFLU \(CAP\) - EMEA/H/C/000402/II/0136](#)

Applicant: Roche Registration GmbH

PRAC Rapporteur: Kirsti Villikka

Scope: Update of sections 4.2, 4.8, 5.1 and 5.2 to guide prescribers on the use of Tamiflu (oseltamivir) for treatment in immunocompromised (IC) patients based on results from study NV20234: a phase 3, double-blind, randomized, stratified, multicentre study of conventional and double dose oseltamivir for the treatment of influenza in IC patients. The package leaflet and RMP (version 18) are updated accordingly. In addition, the MAH took the opportunity to correct some minor errors

15.3.16. [Pembrolizumab - KEYTRUDA \(CAP\) - EMEA/H/C/003820/II/0060](#)

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to include, in combination with carboplatin and either paclitaxel or nab-paclitaxel, for the first-line treatment of metastatic squamous non-small cell lung cancer (NSCLC) in adults. As a consequence, sections 4.1, 4.2 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 20.1) are updated accordingly. Additionally, the MAH took the opportunity to introduce some editorial corrections to section 5.1 of the SmPC in line with the outcome of variation EMEA/H/C/003820/II/0052 finalised in May 2018

15.3.17. Plasmodium falciparum and hepatitis B vaccine (recombinant, adjuvanted) - MOSQUIRIX (Art 58⁵³) - EMEA/H/W/002300/II/0036

Applicant: GlaxoSmithKline Biologicals SA

PRAC Rapporteur: Jean-Michel Dogné

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

15.3.18. Ramucirumab - CYRAMZA (CAP) - EMEA/H/C/002829/II/0027

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include Cyramza (ramucirumab) as monotherapy for the treatment of adult patients with hepatocellular carcinoma who have an alpha fetoprotein (AFP) of ≥ 400 ng/mL, after prior sorafenib therapy. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated in accordance. The package leaflet and the RMP (version 8.1) are updated accordingly

15.3.19. Ribociclib - KISQALI (CAP) - EMEA/H/C/004213/II/0004

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Doris Stenver

Scope: Extension of indication to include treatment of patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer in combination with an aromatase inhibitor or fulvestrant. In pre- or perimenopausal women, the endocrine therapy should be combined with a luteinizing hormone-releasing hormone (LHRH) agonist for Kisqali (ribociclib). This is based on data from: 1) study CLEE011E2301: a phase 3 randomized, double-blind, placebo-controlled study of ribociclib (LEE011) or placebo in combination with tamoxifen and goserelin or a non-steroidal aromatase inhibitor (NSAI) and goserelin for the treatment of premenopausal women with hormone receptor positive, HER2- negative, advanced breast cancer; 2) study CLEE011F2301: a randomized double-blind, placebo-controlled study of ribociclib in combination with fulvestrant for the treatment of men and postmenopausal women with hormone receptor positive, HER2 negative, advanced breast cancer who have received no or only one line of prior endocrine treatment. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5.1, 5.2 and 5.3 of the SmPC are updated. The package leaflet and the RMP (version 2.0) are updated accordingly. In addition, the MAH took the opportunity to introduce some editorial changes in the SmPC and to make an administrative update to the

⁵³ Article 58 of Regulation (EC) No 726/2004 allows the Committee for Medicinal Products for Human Use (CHMP) to give opinions, in co-operation with the World Health Organisation (WHO) on medicinal products for human use that are intended exclusively for markets outside of the European Union (EU)

Estonian and Latvian local representatives addresses in the package leaflet

15.3.20. Rituximab - MABTHERA (CAP) - EMEA/H/C/000165/II/0149

Applicant: Roche Registration GmbH

PRAC Rapporteur: Doris Stenver

Scope: Extension of indication to include the maintenance of remission of granulomatosis with polyangiitis (GPA) (Wegener's) and microscopic polyangiitis (MPA). As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 17.0) are updated accordingly. In addition, the MAH took the opportunity to implement a terminology change in Annex II

15.3.21. Rituximab - MABTHERA (CAP) - EMEA/H/C/000165/II/0150

Applicant: Roche Registration GmbH

PRAC Rapporteur: Doris Stenver

Scope: Extension of indication to include the treatment of patients with moderate to severe pemphigus vulgaris (PV). As a consequence, sections 4.1, 4.2, 4.3, 4.4, 4.8 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 17.0) are updated accordingly

15.3.22. Rolapitant - VARUBY (CAP) - EMEA/H/C/004196/II/0007/G

Applicant: Tesaro UK Limited

PRAC Rapporteur: Adam Przybylkowski

Scope: Grouped variations consisting of: 1) update of section 4.5 of the SmPC regarding interaction with organic cation transporter 1 (OCT1) substrates to reflect the results from non-clinical study 17TESAP2R1: an *in vitro* evaluation of the substrate and inhibitor potential of rolapitant for efflux and update of transporters; 2) update of section 4.5 of the SmPC regarding interaction with UDP-glucuronosyltransferase (UGT) substrates following the submission of the results from non-clinical studies, namely: study 170594: evaluation of potential UGT inhibition by rolapitant in cryopreserved human hepatocytes; and study TSRP/REP/07CRD75486/2017: evaluation of potential rolapitant metabolism by recombinantly expressed human UGT enzymes; 3) update of section 4.5 of the SmPC following the submission of the results from study 1000-01-001: an open-label, single-dose study to assess the effects of rolapitant (oral) on the pharmacokinetics of caffeine (CYP1A2⁵⁴) in healthy subjects. The RMP is updated accordingly (version 1.2)

15.3.23. Ticagrelor - BRILIQUE (CAP) - EMEA/H/C/001241/II/0042

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Update of sections 4.2, 4.9 and 5.2 of the SmPC in order to update the safety information in relation to renal impairment based on the final results from study D5130L00067: a single dose, randomized, open label, parallel group study conducted to

⁵⁴ Cytochrome P450 1A2

compare the pharmacokinetics (PK), pharmacodynamics (PD), safety and tolerability of ticagrelor in haemodialysis patients to subjects with normal renal function. The RMP is updated accordingly (version 11)

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

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

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

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

16.1.1. Alogliptin - VIPIDIA (CAP); alogliptin, metformin - VIPDOMET (CAP); alogliptin, pioglitazone - INCRESYNC (CAP) - PSUSA/00010061/201804

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.2. Bezlotoxumab - ZINPLAVA (CAP) - PSUSA/00010576/201804

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.3. Cariprazine - REAGILA (CAP) - PSUSA/00010623/201804

Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.1.4. Chenodeoxycholic acid - CHENODEOXYCHOLIC ACID LEADIANT (CAP) - PSUSA/00010590/201804

Applicant: Leadiant GmbH

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.5. Colesevelam - CHOLESTAGEL (CAP) - PSUSA/00000864/201803

Applicant: Genzyme Europe BV

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.6. Defibrotide - DEFITELIO (CAP) - PSUSA/00010086/201804

Applicant: Gentium S.r.l.

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.7. Diphtheria, tetanus, pertussis antigens (pertussis toxoid, filamentous haemagglutinin) (acellular, component), hepatitis B (rDNA), poliomyelitis (inactivated), haemophilus type b conjugate vaccines (adsorbed) - HEXACIMA (CAP); HEXAXIM (Art 58⁵⁵); HEXYON (CAP) - PSUSA/00010091/201804

Applicants: Sanofi Pasteur (Hexacima, Hexaxim), Sanofi Pasteur Europe (Hexyon)

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.8. Edoxaban - LIXIANA (CAP); ROTEAS (CAP) - PSUSA/00010387/201804 (with RMP)

Applicant: Daiichi Sankyo Europe GmbH

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.9. Empagliflozin - JARDIANCE (CAP); empagliflozin, metformin - SYNJARDY (CAP) - PSUSA/00010388/201804

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

16.1.10. Emtricitabine - EMTRIVA (CAP) - PSUSA/00001209/201804

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

⁵⁵ Article 58 of Regulation (EC) No 726/2004 allows the Committee for Medicinal Products for Human Use (CHMP) to give opinions, in co-operation with the World Health Organisation (WHO) on medicinal products for human use that are intended exclusively for markets outside of the European Union (EU)

16.1.11. Emtricitabine, tenofovir alafenamide - DESCOVY (CAP) - PSUSA/00010515/201804

Applicant: Gilead Sciences Ireland UC
PRAC Rapporteur: Ana Sofia Diniz Martins
Scope: Evaluation of a PSUSA procedure

16.1.12. Emtricitabine, tenofovir disoproxil - TRUVADA (CAP) - PSUSA/00001210/201804

Applicant: Gilead Sciences Ireland UC
PRAC Rapporteur: Julie Williams
Scope: Evaluation of a PSUSA procedure

16.1.13. Everolimus⁵⁶ - VOTUBIA (CAP) - PSUSA/00001343/201803

Applicant: Novartis Europharm Limited
PRAC Rapporteur: Martin Huber
Scope: Evaluation of a PSUSA procedure

16.1.14. Exenatide - BYDUREON (CAP); BYETTA (CAP) - PSUSA/00009147/201803

Applicant: AstraZeneca AB
PRAC Rapporteur: Annika Folin
Scope: Evaluation of a PSUSA procedure

16.1.15. Febuxostat - ADENURIC (CAP) - PSUSA/00001353/201804

Applicant: Menarini International Operations Luxembourg S.A.
PRAC Rapporteur: Jan Neuhauser
Scope: Evaluation of a PSUSA procedure

16.1.16. Fenofibrate, pravastatin - PRAVAFENIX (CAP) - PSUSA/00001363/201804

Applicant: Laboratoires SMB s.a.
PRAC Rapporteur: Adrien Inoubli
Scope: Evaluation of a PSUSA procedure

16.1.17. Florbetapir (¹⁸F) - AMYVID (CAP) - PSUSA/00010032/201804

Applicant: Eli Lilly Nederland B.V.
PRAC Rapporteur: Martin Huber
Scope: Evaluation of a PSUSA procedure

⁵⁶ Indicated in the treatment of astrocytoma

16.1.18. Herpes zoster vaccine (recombinant, adjuvanted) - SHINGRIX (CAP) - PSUSA/00010678/201804

Applicant: GlaxoSmithKline Biologicals SA

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.19. Histamine⁵⁷ - CEPLENE (CAP) - PSUSA/00001610/201804

Applicant: Noventia Pharma Srl

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

16.1.20. Idarucizumab - PRAXBIND (CAP) - PSUSA/00010435/201804

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.21. Insulin glargine - ABASAGLAR (CAP); LANTUS (CAP); LUSDUNA (CAP); SEMGLEE (CAP); TOUJEO (CAP) - PSUSA/00001751/201804

Applicants: Eli Lilly Nederland B.V. (Abasaglar), Sanofi-Aventis Deutschland GmbH (Lantus, Toujeo), Merck Sharp & Dohme B.V. (Lusduna), Mylan S.A.S (Semglee)

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.22. Insulin glulisine - APIDRA (CAP) - PSUSA/00001752/201804

Applicant: Sanofi-Aventis Deutschland GmbH

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.23. Japanese encephalitis vaccine (inactivated) - IXIARO (CAP) - PSUSA/00001801/201803

Applicant: Valneva Austria GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

⁵⁷ Indicated in the treatment of acute myeloid leukaemia

16.1.24. Mannitol⁵⁸ - BRONCHITOL (CAP) - PSUSA/00009226/201804

Applicant: Pharmaxis Pharmaceuticals Limited

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.25. Meningococcal group A, C, W-135, Y conjugate vaccines (conjugated to tetanus toxoid carrier protein) - NIMENRIX (CAP) - PSUSA/00010044/201804

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.26. Netupitant, palonosetron - AKYNZEO (CAP) - PSUSA/00010393/201804

Applicant: Helsinn Birex Pharmaceuticals Limited

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.1.27. Oestrogens conjugated, bazedoxifene - DUAVIVE (CAP) - PSUSA/00010321/201804

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.28. Olaratumab - LARTRUVO (CAP) - PSUSA/00010541/201804

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.29. Patiromer - VELTASSA (CAP) - PSUSA/00010618/201804

Applicant: Vifor Fresenius Medical Care Renal Pharma France

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

16.1.30. Pitolisant - WAKIX (CAP) - PSUSA/00010490/201803

Applicant: Bioprojet Pharma

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

⁵⁸ Indicated in the treatment of cystic fibrosis

16.1.31. Ramucirumab - CYRAMZA (CAP) - PSUSA/00010323/201804 (with RMP)

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.32. Regadenoson - RAPISCAN (CAP) - PSUSA/00002616/201804

Applicant: GE Healthcare AS

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

16.1.33. Siltuximab - SYLVANT (CAP) - PSUSA/00010254/201804

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.34. Temsirolimus - TORISEL (CAP) - PSUSA/00002887/201803

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.35. Thiotepa⁵⁹ - TEPADINA (CAP) - PSUSA/00002932/201803

Applicant: Adienne S.r.l.

PRAC Rapporteur: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

16.1.36. Vandetanib - CAPRELSA (CAP) - PSUSA/00009327/201804

Applicant: Genzyme Europe BV

PRAC Rapporteur: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

⁵⁹ Centrally authorised product(s) only

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

16.2.1. Cladribine⁶⁰ - LITAK (CAP); NAP - PSUSA/00000787/201802

Applicants: Lipomed GmbH (Litak), various

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

16.2.2. Hepatitis B vaccine (rDNA) - HBVAXPRO (CAP); NAP - PSUSA/00001597/201802

Applicants: MSD Vaccins (HBVAXPRO), various

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.2.3. Tenofovir disoproxil - TENOFOVIR DISOPROXIL MYLAN (CAP); TENOFOVIR DISOPROXIL ZENTIVA (CAP); VIREAD (CAP); NAP - PSUSA/00002892/201803

Applicants: Mylan S.A.S (Tenofovir Disoproxil Mylan), Zentiva k.s. (Tenofovir Disoproxil Zentiva), Gilead Sciences Ireland UC (Viread), various

PRAC Rapporteur: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

16.2.4. Zonisamide - ZONEGRAN (CAP); NAP - PSUSA/00003152/201803

Applicants: Eisai GmbH (Zonegran), various

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

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

16.3.1. Allergen for therapy: dermatophagoides pteronyssinus, dermatophagoides farina^{61 62} (NAP) - PSUSA/00010582/201803

Applicant(s): various

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

⁶⁰ All indications except multiple sclerosis

⁶¹ Oromucosal use only

⁶² Products authorised via mutually recognition procedure (MRP) and decentralised procedure (CP) only

16.3.2. Ampicillin, sulbactam (NAP) - PSUSA/00000197/201802

Applicant(s): various

PRAC Lead: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.3.3. Aprotinin (NAP) - PSUSA/00000230/201802

Applicant(s): various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

16.3.4. Bacillus Calmette-Guerin⁶³ (BCG) (NAP) - PSUSA/00000303/201803

Applicant(s): various

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.3.5. Citrulline malate (NAP) - PSUSA/00010579/201803

Applicant(s): various

PRAC Lead: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

16.3.6. Dienogest, ethinylestradiol (NAP) - PSUSA/00001057/201803

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.3.7. Dobutamine (NAP) - PSUSA/00001151/201803

Applicant(s): various

PRAC Lead: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

16.3.8. Enoxaparin⁶⁴ (NAP) - PSUSA/00010560/201804

Applicant(s): various

PRAC Lead: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

⁶³ For immunotherapy only

⁶⁴ All products except biosimilar(s)

16.3.9. Germanium (⁶⁸Ge) chloride, gallium (⁶⁸Ga) chloride (NAP) - PSUSA/00010364/201803

Applicant(s): various

PRAC Lead: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

16.3.10. Influenza vaccine (split virion, inactivated)⁶⁵ (NAP) - PSUSA/00010298/201803

Applicant(s): various

PRAC Lead: Brigitte Keller-Stanislowski

Scope: Evaluation of a PSUSA procedure

16.3.11. Influenza vaccine (split virion, inactivated, prepared in cell cultures) (NAP) - PSUSA/00010299/201803

Applicant(s): various

PRAC Lead: Brigitte Keller-Stanislowski

Scope: Evaluation of a PSUSA procedure

16.3.12. Influenza vaccine (surface antigen, inactivated, adjuvanted) (NAP) - PSUSA/00010300/201803

Applicant(s): various

PRAC Lead: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.3.13. Ioxaglic acid (NAP) - PSUSA/00001777/201802

Applicant(s): various

PRAC Lead: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.3.14. Latanoprost⁶⁶ (NAP) - PSUSA/00001834/201804

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

⁶⁵ All products except centrally authorised products

⁶⁶ Paediatric indication only

16.3.15. Meningococcal group A, C, W135, Y polysaccharide vaccine (NAP) - PSUSA/00010602/201803

Applicant(s): various

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.3.16. Nitrazepam (NAP) - PSUSA/00002170/201803

Applicant(s): various

PRAC Lead: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

16.3.17. Ondansetron (NAP) - PSUSA/00002217/201802

Applicant(s): various

PRAC Lead: Gabriela Jazbec

Scope: Evaluation of a PSUSA procedure

16.3.18. Pimecrolimus (NAP) - PSUSA/00002411/201803

Applicant(s): various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

16.3.19. Promestriene⁶⁷ (NAP) - PSUSA/00009271/201803

Applicant(s): various

PRAC Lead: Roxana Stefania Stroe

Scope: Evaluation of a PSUSA procedure

16.3.20. Spironolactone (NAP) - PSUSA/00002780/201803

Applicant(s): various

PRAC Lead: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

16.3.21. Tenoxicam (NAP) - PSUSA/00002893/201802

Applicant(s): various

PRAC Lead: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

⁶⁷ Cream and vaginal capsules only

16.4. Follow-up to PSUR/PSUSA procedures

None

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)⁶⁸

17.1.1. Cerliponase alfa – BRINEURA (CAP) - EMEA/H/C/PSP/S/0063.1

Applicant: BioMarin International Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: MAH's response to PSP/S/0063 [protocol for study 190-504 (replacing study 190-501): a non-interventional PASS (observational drug study) in order to evaluate the long-term safety of cerliponase alfa, including the occurrence of serious hypersensitivity reactions and anaphylaxis in patients with neuronal ceroid lipofuscinosis type 2 (CLN2)] as per the request for supplementary information (RSI) adopted in June 2018

17.1.2. Cidofovir (NAP) - EMEA/H/N/PSP/S/0052.3

Applicant: Emcure Pharma UK Ltd (Cidofovir Emcure Pharma)

PRAC Rapporteur: Julie Williams

Scope: MAH's response to PSP/S/0052.2 [protocol for cidofovir exposure registry study: 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] as per the request for supplementary information (RSI) adopted in May 2018

17.1.3. Prasterone – INTRAROSA (CAP) - EMEA/H/C/PSP/S/0061.1

Applicant: Endoceutics Limited

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to PSP/S/0061 [protocol for a non-interventional PASS: a drug utilisation study (DUS) to describe the baseline characteristics and utilisation patterns of EU postmenopausal women initiating treatment with Intrarosa (prasterone) and to assess whether EU prescribers abide by the contraindications stated in the EU SmPC] as per the request for supplementary information (RSI) adopted in June 2018

⁶⁸ In accordance with Article 107n of Directive 2001/83/EC

17.1.4. Susoctocog alfa – OBIZUR (CAP) - EMEA/H/C/PSA/S/0033

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Protocol for a prospective and retrospective non-interventional study to evaluate the safety, utilisation and effectiveness of Obizur (susoctocog alfa) in the treatment of bleeding episodes in real-life clinical practice in Europe and in the US

17.2. Protocols of PASS non-imposed in the marketing authorisation(s)⁶⁹

17.2.1. Apremilast - OTEZLA (CAP) - EMEA/H/C/003746/MEA 005.4

Applicant: Celgene Europe BV

PRAC Rapporteur: Eva Segovia

Scope: MAH's response to MEA 005.3 [MAH's response to MEA005.2 [PASS protocol in order to collect long-term data using the British Society of Rheumatology Biologics Register for Rheumatoid Arthritis (BSRBR) psoriatic arthritis (PsA) registry 'BSRBR PsA registry': a disease registry in the EU for PsA and psoriasis] as per the request for supplementary information (RSI) adopted in June 2018

17.2.2. Atezolizumab - TECENTRIQ (CAP) - EMEA/H/C/004143/MEA 010.1

Applicant: Roche Registration GmbH

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: MAH's response to MEA 010 [submission of a protocol for study WO40486: an observational study to evaluate the effectiveness of healthcare professional (HCP) educational materials, in particular the HCP brochure aiming at facilitating early recognition and intervention of the following important immune-related risks: pneumonitis, hepatitis, colitis, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, type 1 diabetes mellitus (T1DM), neuropathies, meningoencephalitis, pancreatitis, and infusion-related reactions [submission of the final clinical study report (CSR): December 2022]] as per the request for supplementary information (RSI) adopted in May 2018

17.2.3. Emtricitabine, tenofovir disoproxil - TRUVADA (CAP) - EMEA/H/C/000594/MEA 047.1

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Julie Williams

Scope: MAH's response to MEA 047 [protocol for study No GS EU 276 4487: a prospective, longitudinal, observational registry of emtricitabine/tenofovir disoproxil fumarate for human immunodeficiency virus 1 (HIV-1) pre-exposure prophylaxis (PrEP) in the European Union] as per the request for supplementary information (RSI) adopted in June 2018

⁶⁹ 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. Guselkumab - TREMFYA (CAP) - EMEA/H/C/004271/MEA 004

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Protocol for study CSIMM000265: a retrospective cohort study using health administrative claims databases to assess adverse pregnancy and infant outcomes in women with psoriasis who were exposed to guselkumab versus other biologic therapies during pregnancy

17.2.5. Infliximab - FLIXABI (CAP) - EMEA/H/C/004020/MEA 007.2

Applicant: Samsung Bioepis UK Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: MAH's response to MEA 007.1 [protocol for study SB2-G42-CD: a prospective observational cohort study in Crohn's disease (CD) for two years to observe safety, efficacy and immunogenicity of Flixabi (infliximab) with active comparator in CD] as per the request for supplementary information (RSI) adopted in May 2018

17.2.6. Ipilimumab - YERVOY (CAP) - EMEA/H/C/002213/MEA 036.1

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to MEA 036 [protocol for the extension of the Dutch melanoma treatment registry (DMTR) to include paediatric subjects and collect safety data to obtain additional safety information in paediatric patients [final clinical study report (CSR) expected in December 2028]] as per the request for supplementary information (RSI) adopted in June 2018

17.2.7. Lipegfilgrastim - LONQUEX (CAP) - EMEA/H/C/002556/MEA 004.6

Applicant: Sicom Biotech UAB

PRAC Rapporteur: Patrick Batty

Scope: Updated protocol for study XM22-ONC-50002: a multi-country, multicentre, retrospective observational drug utilisation study (DUS) to describe the pattern of lipegfilgrastim use and specifically to quantify the extent of lipegfilgrastim off-label use in routine clinical practice in several countries in the European Union (EU) as requested in the outcome of MEA 004.5 adopted in June 2018

17.2.8. Tocilizumab - ROACTEMRA (CAP) - EMEA/H/C/000955/MEA 041.5

Applicant: Roche Registration GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Amended protocol for study WA29358 (paediatric registry) previously agreed in September 2015: an observational safety and effectiveness study of patients with polyarticular juvenile idiopathic arthritis treated with tocilizumab

17.3. Results of PASS imposed in the marketing authorisation(s)⁷⁰

17.3.1. Valproate (NAP) - EMEA/H/N/PSI/J/0003

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

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Third interim result report for a joint drug utilisation study (DUS) of valproate and related substances conducted in Europe aiming at describing the prescribing practices before and after the dissemination of risk minimisation measures (RMM) (i.e. educational materials and direct healthcare professional communication (DHPC)) and assessing the effectiveness of these measures using databases, as requested in the outcome of the referral procedure on valproate and related substances (EMEA/H/A-31/1387) concluded in 2014

17.4. Results of PASS non-imposed in the marketing authorisation(s)⁷¹

17.4.1. Adalimumab - HUMIRA (CAP) - EMEA/H/C/000481/II/0173

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of the final report from study BSRBR-RA (British Society for Rheumatology Biologics Registers Rheumatoid Arthritis): a registry in the UK, evaluating the influence of tumour necrosis factor (TNF) inhibitor treatment on cancer incidence in rheumatoid arthritis (RA) patients with a history of malignancy. No changes to the product information are proposed

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

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Ulla Wändel Liminga

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

⁷⁰ In accordance with Article 107p-q of Directive 2001/83/EC

⁷¹ 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

PTLD and central nervous system (CNS) PTLN in adult renal transplant recipients treated with belatacept in the US

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

Applicant: Teva B.V.

PRAC Rapporteur: Julie Williams

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

17.4.4. Trastuzumab - HERCEPTIN (CAP) - EMEA/H/C/000278/II/0147

Applicant: Roche Registration GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Submission of the final report from the pregnancy registry H4621g study (MoTHER) (listed as a category 3 study in the RMP): an observational study of pregnancy and pregnancy outcome in women with breast cancer treated with trastuzumab, pertuzumab in combination with trastuzumab, or ado-trastuzumab emtansine during pregnancy or within 7 months prior to conception. The RMP is updated accordingly (version 20.0) and in line with the outcome of variation EMEA/H/C/000278/II/140 finalised in March 2018

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

17.5.1. Belatacept - NULOJIX (CAP) - EMEA/H/C/002098/MEA 024.1

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Interim report for study BMS IM103-075: a retrospective analysis of data from the United Network for Organ Sharing (UNOS) to assess the association between Nulojix (belatacept) use and risk of post-transplant lymphoproliferative disorder (PTLD) in renal transplant recipients in the US

17.5.2. Belatacept - NULOJIX (CAP) - EMEA/H/C/002098/MEA 025.1

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Interim study reports / IM103-076 Prospective ENLIST Registry Study

Interim report for study BMS IM103076: a prospective registry study evaluating Nulojix (belatacept) long-term safety in transplant (ENLIST) to describe the pattern of Nulojix (belatacept) use at the time of transplant

17.5.3. Colistimethate sodium - COLOBREATHE (CAP) - EMEA/H/C/001225/MEA 013.1

Applicant: Teva B.V.

PRAC Rapporteur: Julie Williams

Scope: Seventh interim report for study CLB-MD-05: an open-label observational safety study of Colobreathe (colistimethate sodium dry powder for inhalation) compared with other inhaled antipseudomonal antibiotics in cystic fibrosis patients using cystic fibrosis registries

17.5.4. Ibrutinib - IMBRUVICA (CAP) - EMEA/H/C/003791/MEA 025

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Patrick Batty

Scope: Year 4 interim report for study 3038-1: FDA annual post-marketing long-term safety update (from variation II/40/G finalised in March 2018) to characterize the safety of long-term exposure to ibrutinib based on data and pooled analyses from trials of patients with mantle cell lymphoma and chronic lymphocytic leukaemia

17.5.5. Imiglucerase - CERZYME (CAP) - EMEA/H/C/000157/MEA 040.10

Applicant: Genzyme Europe BV

PRAC Rapporteur: Menno van der Elst

Scope: Eighth report from the Gaucher pregnancy and lactation sub-registry to assess the pregnancy outcomes including adverse events in women with Gaucher disease, untreated and treated with Cerezyme during pregnancy. This report covers the period from 02 May 2015 to 04 May 2018

17.5.6. Mixture of polynuclear iron(III)-oxyhydroxide, sucrose and starches - VELPHORO (CAP) - EMEA/H/C/002705/MEA 002.8

Applicant: Vifor Fresenius Medical Care Renal Pharma France

PRAC Rapporteur: Julie Williams

Scope: Second interim report (24 months) for study VFMCRP-MEAF-PA21-01-EU (VERIFIE: Velphoro Evaluation of Real-Life saFety, effectIveness and adherencE): a non-interventional study to investigate the short- and long-term real-life safety, effectiveness, and adherence of Velphoro (mixture of polynuclear iron(III)-oxyhydroxide, sucrose and starches) in patients with hyperphosphataemia undergoing haemodialysis or peritoneal dialysis (PD)

17.5.7. Roflumilast - DAXAS (CAP) - EMEA/H/C/001179/ANX 002.7

Applicant: AstraZeneca AB

PRAC Rapporteur: Maria del Pilar Rayon

Scope: MAH's response to ANX 002.5 and ANX 002.6 [first and second interim results for PASS D7120R00003 (previously RO-2455-403-RD): a long-term post-marketing observational study exploring the safety of roflumilast in the treatment of chronic obstructive pulmonary disease (COPD), combined data results from Sweden, Germany and

the US (Annex II-D condition) [final clinical study report (CSR) expected in March 2021]] as per the request for supplementary information (RSI) adopted at the September 2018 PRAC meeting

17.6. Others

17.6.1. Canagliflozin - INVOKANA (CAP) - EMEA/H/C/002649/MEA 006.10

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Martin Huber

Scope: Bi-annual status report for study DNE3001 (CREDENCE): a randomised, double-blind, event-driven, placebo-controlled, multicentre study of the effects of canagliflozin on renal and cardiovascular outcomes in subjects with type 2 diabetes mellitus and diabetic nephropathy) from the Independent Data Monitoring Committee (IDMC) (eighth IDMC report dated July 2018)

17.6.2. Canagliflozin, metformin - VOKANAMET (CAP) - EMEA/H/C/002656/MEA 005.10

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Menno van der Elst

Scope: Bi-annual status report for study DNE3001 (CREDENCE): a randomised, double-blind, event-driven, placebo-controlled, multicentre study of the effects of canagliflozin on renal and cardiovascular outcomes in subjects with type 2 diabetes mellitus and diabetic nephropathy) from the Independent Data Monitoring Committee (IDMC) (eighth IDMC report dated July 2018)

17.7. New Scientific Advice

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

17.8. Ongoing Scientific Advice

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

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

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

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

Based on the review of the available pharmacovigilance data for the medicines listed below and the CHMP Rapporteur's assessment report, the PRAC considered that either the renewal of the marketing authorisation procedure could be concluded - and supported the renewal of their marketing authorisations for an unlimited or additional period, as applicable - or no

amendments to the specific obligations of the marketing authorisation under exceptional circumstances for the medicines listed below were recommended. As per agreed criteria, the procedures were finalised at the PRAC level without further plenary discussion.

18.1. Annual reassessments of the marketing authorisation

18.1.1. Cerliponase alfa - BRINEURA (CAP) - EMEA/H/C/004065/S/0009 (without RMP)

Applicant: BioMarin International Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Annual reassessment of the marketing authorisation

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

Applicant: BioMarin International Limited

PRAC Rapporteur: Patrick Batty

Scope: Annual reassessment of the marketing authorisation

18.1.3. Lomitapide - LOJUXTA (CAP) - EMEA/H/C/002578/S/0032 (without RMP)

Applicant: Amryt Pharmaceuticals DAC

PRAC Rapporteur: Menno van der Elst

Scope: Annual reassessment of the marketing authorisation

18.1.4. Modified vaccinia Ankara virus - IMVANEX (CAP) - EMEA/H/C/002596/S/0037 (without RMP)

Applicant: Bavarian Nordic A/S

PRAC Rapporteur: Julie Williams

Scope: Annual reassessment of the marketing authorisation

18.1.5. Nelarabine - ATRIANCE (CAP) - EMEA/H/C/000752/S/0044 (without RMP)

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Anette Kirstine Stark

Scope: Annual reassessment of the marketing authorisation

18.2. Conditional renewals of the marketing authorisation

18.2.1. Bedaquiline - SIRTURO (CAP) - EMEA/H/C/002614/R/0031 (without RMP)

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Conditional renewal of the marketing authorisation

18.2.2. Burosumab - CRYSVITA (CAP) - EMEA/H/C/004275/R/0002 (without RMP)

Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Conditional renewal of the marketing authorisation

18.2.3. Cabozantinib - COMETRIQ (CAP) - EMEA/H/C/002640/R/0029 (without RMP)

Applicant: Ipsen Pharma

PRAC Rapporteur: Menno van der Elst

Scope: Conditional renewal of the marketing authorisation

18.2.4. Ex vivo expanded autologous human corneal epithelial cells containing stem cells - HOLOCLAR (CAP) - EMEA/H/C/002450/R/0021 (with RMP)

Applicant: Chiesi Farmaceutici S.p.A., ATMP⁷²

PRAC Rapporteur: Julie Williams

Scope: Conditional renewal of the marketing authorisation

18.2.5. Vandetanib - CAPRELSA (CAP) - EMEA/H/C/002315/R/0032 (without RMP)

Applicant: Genzyme Europe BV

PRAC Rapporteur: Ghania Chamouni

Scope: Conditional renewal of the marketing authorisation

18.3. Renewals of the marketing authorisation

18.3.1. Capsaicin - QUTENZA (CAP) - EMEA/H/C/000909/R/0047 (with RMP)

Applicant: Grunenthal GmbH

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: 5-year renewal of the marketing authorisation

18.3.2. Indacaterol, glycopyrronium - ULUNAR BREEZHALER (CAP) - EMEA/H/C/003875/R/0028 (without RMP)

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Anette Kirstine Stark

Scope: 5-year renewal of the marketing authorisation

18.3.3. Propranolol - HEMANGIOL (CAP) - EMEA/H/C/002621/R/0018 (without RMP)

Applicant: Pierre Fabre Dermatologie

⁷² Advanced therapy medicinal product

PRAC Rapporteur: Eva Segovia

Scope: 5-year renewal of the marketing authorisation

18.3.4. Riociguat - ADEMPAS (CAP) - EMEA/H/C/002737/R/0026 (without RMP)

Applicant: Bayer AG

PRAC Rapporteur: Julie Williams

Scope: 5-year renewal of the marketing authorisation

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

Applicant: Genzyme Europe BV

PRAC Rapporteur: Laurence de Fays

Scope: 5-year renewal of the marketing authorisation

18.3.6. Umeclidinium, vilanterol - ANORO ELLIPTA (CAP) - EMEA/H/C/002751/R/0022 (without RMP)

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Amelia Cupelli

Scope: 5-year renewal of the marketing authorisation

18.3.7. Umeclidinium, vilanterol - LAVENTAIR ELLIPTA (CAP) - EMEA/H/C/003754/R/0025 (without RMP)

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Amelia Cupelli

Scope: 5-year renewal of the marketing authorisation

18.3.8. Umeclidinium bromide - INCRUSE ELLIPTA (CAP) - EMEA/H/C/002809/R/0021 (with RMP)

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Amelia Cupelli

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 29-31 October 2018 meeting.

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Sabine Straus	Chair	The Netherlands	No interests declared	Full involvement
Jan Neuhauser	Member	Austria	No interests declared	Full involvement
Jean-Michel Dogné	Member	Belgium	No interests declared	Full involvement
Laurence de Fays	Alternate	Belgium	No interests declared	Full involvement
Yuliyán Eftimov	Alternate	Bulgaria	No interests declared	Full involvement
Željana Margan Koletić	Alternate	Croatia	No interests declared	Full involvement
Jana Lukacisinova	Alternate	Czech Republic	No interests declared	Full involvement
Doris Stenver	Member	Denmark	No interests declared	Full involvement
Anette Stark	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
Ghania Chamouni	Member	France	No restrictions applicable to this meeting	Full involvement
Adrien Inoubli	Alternate	France	No interests declared	Full involvement
Martin Huber	Member (Vice-Chair)	Germany	No interests declared	Full involvement
Brigitte Keller-Stanislawski	Alternate	Germany	No interests declared	Full involvement
Julia Pallos	Member	Hungary	No interests declared	Full involvement
Guðrún Stefánsdóttir	Member	Iceland	No participation in final deliberations and voting	4.3.3. Tacrolimus – ADVAGRAF (CAP), ENVARSUS

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			on:	(CAP), MODIGRAF (CAP), TACFORIUS (CAP), NAP
Rhea Fitzgerald	Member	Ireland	No restrictions applicable to this meeting	Full involvement
Amelia Cupelli	Member	Italy	No interests declared	Full involvement
Zane Neikena	Member	Latvia	No interests declared	Full involvement
Jolanta Gulbinovic	Member	Lithuania	No interests declared	Full involvement
Marcel Bruch	Member	Luxembourg	No interests declared	Full involvement
Anne-Cécile Vuillemin	Alternate - via telephone*	Luxembourg	No restrictions applicable to this meeting	Full involvement
John Joseph Borg	Member (CHMP member)	Malta	No interests declared	Full involvement
Menno van der Elst	Member	Netherlands	No interests declared	Full involvement
Liana Gross-Martirosyan	Alternate	Netherlands	No interests declared	Full involvement
David Olsen	Member	Norway	No participation in final deliberations and voting on:	4.2.1. Rivaroxaban – XARELTO (CAP) 6.3.1. Bacillus Calmette-Guerin (BCG) (NAP) - PSUSA/00000303/201803 4.3.2. Paracetamol (NAP)
Karen Pernille Harg	Alternate	Norway	No interests declared	Full involvement
Katarzyna Ziolkowska	Alternate	Poland	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
Ana Diniz Martins	Member	Portugal	No interests declared	Full involvement
Roxana Stefania Stroe	Member	Romania	No interests declared	Full involvement
Michal Radik	Member	Slovakia	No restrictions applicable to this meeting	Full involvement
Gabriela Jazbec	Member	Slovenia	No interests declared	Full involvement
Eva Segovia	Member	Spain	No interests declared	Full involvement
Maria del Pilar Rayon	Alternate	Spain	No interests declared	Full involvement
Ulla Wändel Liminga	Member	Sweden	No interests declared	Full involvement
Annika Folin	Alternate	Sweden	No interests declared	Full involvement
Julie Williams	Member	United Kingdom	No interests declared	Full involvement
Patrick Batty	Alternate	United Kingdom	No interests declared	Full involvement
Birgitta Grundmark	Member	Independent scientific expert	No interests declared	Full involvement
Daniel Morales	Member	Independent scientific expert	No interests declared	Full involvement
Hedvig Nordeng	Member	Independent scientific expert	No interests declared	Full involvement
Antoine Pariente	Member	Independent scientific expert	No participation in final deliberations and voting on:	4.3.2. Paracetamol (NAP) 6.3.6. Nitrofurantoin, nifurtoinol (NAP) - PSUSA/00002174/201802
Livia Puljak	Member	Independent scientific expert	No interests declared	Full involvement
Stefan Weiler	Member	Independent scientific expert	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
Raymond Anderson	Member	Healthcare Professionals' Representative	No interests declared	Full involvement
Albert van der Zeijden	Alternate	Patients' Organisation Representative	No restrictions applicable to this meeting	Full involvement
Pieter Van De Vijver	Expert - via telephone*	Belgium	No interests declared	Full involvement
Karen Van Malderen	Expert - via telephone*	Belgium	No interests declared	Full involvement
Kirsten Egebjerg Juul	Expert - in person*	Denmark	No interests declared	Full involvement
Päivi Susanna Worsøe	Expert - in person*	Denmark	No restrictions applicable to this meeting	Full involvement
Valerie Strassman	Expert - in person*	Germany	No interests declared	Full involvement
Grainne Kirwan	Expert - in person*	Netherlands	No interests declared	Full involvement
Justyna Pilecka	Expert - via telephone*	Poland	No interests declared	Full involvement
Charlotte Backman	Expert - in person*	Sweden	No interests declared	Full involvement
Sofia Bosdotter Enroth	Expert - via telephone*	Sweden	No interests declared	Full involvement

A representative from the European Commission attended the meeting

Meeting run with support from relevant EMA staff

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

20. Annex III - List of acronyms and abbreviations

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

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

21. Explanatory notes

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

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

(Items 2 and 3 of the PRAC minutes)

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

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

Signals assessment and prioritisation

(Item 4 of the PRAC minutes)

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

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

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

Risk Management Plans (RMPs)

(Item 5 of the PRAC minutes)

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

Assessment of Periodic Safety Update Reports (PSURs)

(Item 6 of the PRAC minutes)

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

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

Post-authorisation Safety Studies (PASS)

(Item 7 of the PRAC minutes)

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

Product related pharmacovigilance inspections

(Item 9 of the PRAC minutes)

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

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

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