11 January 2018
EMA/PRAC/64990/2018
Inspections, Human Medicines Pharmacovigilance and Committees Division

Pharmacovigilance Risk Assessment Committee (PRAC)

Minutes of the meeting on 27 – 30 November 2017

Chair: June Raine – Vice-Chair: Almath Spooner

Health and safety information

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

Disclaimers

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

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

Note on access to documents

Some documents mentioned in the minutes cannot be released at present following a request for access to documents within the framework of Regulation (EC) No 1049/2001 as they are subject to 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 27-30 November 2017 meeting by welcoming all participants.

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

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

The PRAC chairperson announced that Katarzyna Ziolkowska had been appointed as the new alternate for Poland, replacing Magdalena Budny.

1.2. Agenda of the meeting on 27-30 November 2017

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

1.3. Minutes of the previous meeting on 23-26 October 2017

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

Post-meeting note: the PRAC minutes of the meeting held on 23-26 October 2017 were published on the EMA website on 05 January 2018 (EMA/PRAC/782491/2017).

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

2.1. Newly triggered procedures

None

2.2. Ongoing procedures

2.2.1. Hydroxyethyl starch (HES)[1] (NAP) - EMEA/H/A-107i/1457

Applicants: Fresenius Kabi Deutschland GmbH (Volulyte, Voluven), B. Braun Melsungen AG (Tetraspan, Venofundin), Serumwerk Bernburg AG (Hesra); various

PRAC Rapporteur: Patrick Batty; PRAC Co-rapporteur: Ulla Wändel Liminga

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

Background

Hydroxyethyl starch (HES) is a colloid indicated for the treatment of hypovolaemia due to acute blood loss when crystalloids alone are not considered sufficient.

A referral procedure under Article 107i of Directive 2001/83/EC is ongoing for the review of HES-containing solutions further to the results of drug utilisation studies (DUS) requested by PRAC as a condition to their marketing authorisations in line with the conclusions of two previous referrals under Article 31 of Directive 2001/83/EC (EMEA/H/A-31/1348) and Article 107i of Directive 2001/83/EC (EMEA/H/A-107i/1376) respectively conducted by the PRAC in 2013 for those medicinal products. For further background, see PRAC minutes October 2013, PRAC minutes July 2014, PRAC minutes October 2014, PRAC minutes February 2015, PRAC minutes July 2015, PRAC minutes October 2017.and PRAC minutes November 2017.

Summary of recommendation(s)/conclusions

- The Committee adopted a revised timetable for the procedure (EMA/PRAC/691227/2017 rev.1). In addition, the PRAC discussed a draft list of experts (LoE) for an ad-hoc expert group meeting organised on 18 December 2017.

Post-meeting note: On 14 December 2017, the PRAC adopted by written procedure the LoE for the ad-hoc expert group meeting.

2.3. Procedures for finalisation

None

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

3.1. Newly triggered procedures

3.1.1. Radium (^{223}Ra) dichloride - XOFIGO (CAP) – EMEA/H/A-20/1459

Applicant: Bayer AG

PRAC Rapporteur: Patrick Batty; PRAC Co-rapporteur: Valerie Strassmann

[1] Solution for infusion

Scope: Review of the benefit-risk balance following notification by the European Commission of a referral under Article 20 of Regulation (EC) No 726/2004 based on pharmacovigilance data

Background

The European Commission (EC) sent a letter of notification dated 30 November 2017 triggering a procedure under Article 20 of Regulation (EC) No 726/2004 for the review of Xofigo (radium-223 dichloride), a centrally authorised medicine, indicated for the treatment of adults with castration-resistant prostate cancer (CRPC), symptomatic bone metastases and no known visceral metastases.

The review was initiated following the notification of the MAH's intention to unblind an ongoing randomised, double-blind, placebo-controlled, multicentre phase 3 trial[2] evaluating the safety and efficacy of radium-223 dichloride in combination with abiraterone acetate and prednisone/prednisolone in the treatment of asymptomatic or mildly symptomatic chemotherapy-naïve subjects with bone predominant metastatic CRPC. The MAH was following the recommendation of the independent data monitoring committee (IDMC) that found that, based on uncleaned data and prior to survival sweep, the incidences of treatment emergent fractures and deaths in this clinical trial were increased in the treatment arm (radium-223 dichloride plus abiraterone acetate and prednisone/prednisolone) compared to the control arm (placebo plus abiraterone acetate and prednisone/prednisolone). See also under 4.2.1.

Taking into account the seriousness of the emerging safety data, concerns were raised on their potential impact on the benefit-risk balance of Xofigo (radium-223 dichloride) in its approved therapeutic indication. As a consequence, the EC initiated a procedure under Article 20 of Regulation (EC) No 726/2004 and requested the EMA to assess the impact of the available evidence on the benefit-risk balance for Xofigo (radium-223 dichloride).

The EC requested the EMA to give its opinion at the latest by 31 May 2018 on whether the marketing authorisation(s) for this medicinal product should be maintained, varied, suspended or revoked.

Discussion

The PRAC noted the notification letter from the EC.

The PRAC appointed Patrick Batty as Rapporteur and Valerie Strassmann as Co-Rapporteur for the procedure.

The PRAC discussed a list of questions (LoQ) to be addressed during the procedure together with a timetable for conducting the review.

The PRAC also discussed the option to conduct a public hearing in the context of the current procedure according to the pre-defined criteria set out in the rules of procedure[3] (EMA/363479/2015). It was agreed by the Committee that at this stage of the procedure, in light of the currently available data and the need to determine the appropriate approach to stakeholder engagement, a public hearing would not be appropriate. The PRAC can come back to reconsider this at a later stage of the procedure as needed.

[2] Study 15396 (ERA-223): a phase 3 randomized, double-blind, placebo-controlled trial of radium-223 dichloride in combination with abiraterone acetate and prednisone/prednisolone in the treatment of asymptomatic or mildly chemotherapy-naïve subjects with bone predominant metastasic CRPC (NCT02043678)
[3] Rules of procedure on the organisation and conduct of public hearings at the PRAC

Summary of recommendation(s)/conclusions

- The Committee adopted a LoQ to the MAH (EMA/PRAC/790594/2017) and a timetable for the procedure (EMA/PRAC/791811/2017).

3.1.2. Ulipristal acetate - ESMYA (CAP) – EMEA/H/A-20/1460

Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Ulla Wändel Liminga; PRAC Co-rapporteur: Menno van der Elst

Scope: Review of the benefit-risk balance following notification by the European Commission of a referral under Article 20 of Regulation (EC) No 726/2004 based on pharmacovigilance data

Background

The European Commission (EC) sent a letter of notification dated 29 November 2017 triggering a procedure under Article 20 of Regulation (EC) No 726/2004 for the review of Esmya (ulipristal acetate), a centrally authorised medicine, indicated for pre-operative treatment as well as intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age.

The review was initiated following the reporting of a case of fulminant hepatitis leading to liver transplantation in a patient treated with Esmya (ulipristal acetate) for uterine fibroids as well as further cases including two retrieved of hepatitis resulting in liver transplantation as well as other cases of hepatic disorders reported as per the most recent periodic safety update report (PSUR). See also under 6.4.2. .

Moreover, further to a review of the EudraVigilance database performed in November 2017 using 'hepatic disorders' as MedDRA SMQ[4] and 'liver transplantation' as MedDRA PT[5], there were four cases of serious hepatic injury reported among 150,000 patient-years of exposure, for which a causal relationship for Esmya (ulipristal acetate) in the development of acute hepatitis is considered as at least a reasonable possibility.

Acknowledging the uncertainty regarding the background incidence of hepatotoxicity in this population and the information on reported cases, the Committee considered that the reported cases with at least a possible causal relationship with Esmya (ulipristal acetate) raised concerns. As a consequence, taking into consideration the seriousness of the reported reactions and the possible causal relationship between Esmya (ulipristal acetate) treatment and acute liver failure, the EC initiated a procedure under Article 20 of Regulation (EC) No 726/2004 and requested the EMA to assess the above concerns and their impact on the benefit-risk balance for Esmya.

The EC also requested the EMA to give its opinion at the latest by 31 May 2018 on whether the marketing authorisation(s) for this medicinal product should be maintained, varied, suspended or revoked.

Discussion

The PRAC noted the notification letter from the EC.

[4] Medical dictionary for regulatory activities – Standardised MedDRA Query
[5] Medical dictionary for regulatory activities – Preferred term

The PRAC appointed Ulla Wändel Liminga as Rapporteur and Menno van der Elst as Co-Rapporteur for the procedure.

The PRAC discussed a list of questions (LoQ) to be addressed during the procedure together with a timetable for conducting the review.

The PRAC also discussed the option to conduct a public hearing in the context of the current procedure according to the pre-defined criteria set out in the rules of procedure[6] (EMA/363479/2015). It was agreed by the Committee that at this stage of the procedure, in light of the currently available data and the need to determine the appropriate approach to stakeholder engagement, a public hearing would not be appropriate. The PRAC can come back to reconsider this at a later stage of the procedure as needed.

Summary of recommendation(s)/conclusions

- The Committee adopted a LoQ to the MAH (EMA/PRAC/791195/2017) and a timetable for the ongoing procedure (EMA/PRAC/791197/2017).

3.2. Ongoing procedures

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

Applicant(s): Eisai Ltd (Panretin, Targretin), various

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

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

Background

A referral procedure under Article 31 of Directive 2001/83/EC is ongoing for retinoid-containing medicines (acitretin; adapalene; alitretinoin; bexarotene; isotretinoin; tazarotene; tretinoin) indicated for the treatment of several conditions mainly affecting the skin such as acne, severe chronic hand eczema unresponsive to corticosteroids, severe forms of psoriasis and keratinisation disorders[7] to evaluate measures currently in place for pregnancy prevention and the possible risk of neuropsychiatric disorders for oral and topical retinoids. For further background, see PRAC minutes July 2016, PRAC minutes September 2016, PRAC minutes October 2016, PRAC minutes December 2016, PRAC minutes January 2017, PRAC minutes March 2017 and PRAC minutes May 2017.

Summary of recommendation(s)/conclusions

The PRAC discussed the joint assessment report prepared by the Rapporteurs.

- The PRAC adopted a third list of outstanding issues (LoOI) to be addressed by the MAHs together with a revised timetable for conducting the review (EMA/PRAC/461927/2016 Rev 3).

[6] Rules of procedure on the organisation and conduct of public hearings at the PRAC
[7] Tretinoin may also be used to treat promyelocytic leukaemia

- The PRAC also adopted list of questions (LoQ) to healthcare professionals (HCPs) and patients to be consulted by written consultation.

3.2.2. Valproate and related substances: sodium valproate, valproic acid, valproate semisodium, valpromide (NAP) - EMEA/H/A-31/1454

Applicant(s): Sanofi-Aventis, various

PRAC Rapporteur: Sabine Straus; PRAC Co-rapporteur: Jean-Michel Dogné

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

Background

A referral procedure under Article 31 of Directive 2001/83/EC is ongoing for medicinal products containing valproate and related substances indicated for the treatment of bipolar disorder, epilepsy and in some Member States for the treatment of migraine, in order to assess the evidence in support of a contraindication in the treatment of bipolar disorder during pregnancy and in women of childbearing potential who are not on effective contraception, and to review the effectiveness of the current risk minimisation measures (RMMs) across all indications. For further background, see PRAC minutes March 2017, PRAC minutes June 2017, PRAC minutes July 2017, PRAC minutes September 2017 and PRAC minutes October 2017.

Summary of recommendation(s)/conclusions

The PRAC discussed the joint assessment report prepared by the Rapporteurs including the outcome of the public hearing held on 26 September 2017. The PRAC discussed as well the conclusions reached by the SAG neurology (SAG-N), the SAG psychiatry (SAG-P), both held on 12 October 2017, as well as the Stakeholders meeting held on 13 October 2017 and the Working Group on Quality Review of Documents (QRD) meeting held on 19 October 2017.

- The PRAC adopted a second list of outstanding issues (LoOI) to be addressed by the MAHs in accordance with a revised timetable for the procedure (EMA/PRAC/154221/2017 rev. 3).

3.3. Procedures for finalisation

None

3.4. Re-examination procedures[8]

3.4.1. Paracetamol[9] (NAP); paracetamol, tramadol[10] (NAP) - EMEA/H/A-31/1445

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

PRAC Rapporteur: Željana Margan Koletić; PRAC Co-rapporteur: Adam Przybylkowski

[8] Re-examination of PRAC recommendation under Article 32 of Directive 2001/83/EC
[9] Modified release formulations
[10] Modified release formulations

Scope: Review of the benefit-risk balance of modified release paracetamol-containing products following notification by Sweden of a referral under Article 31 of Directive 2001/83/EC, based on pharmacovigilance data

Background

Following the PRAC recommendation adopted at the September 2017 PRAC meeting[11], to suspend the marketing authorisations of modified release (MR) paracetamol-containing products, two MAHs concerned by this referral procedure conducted under Article 31 of Directive 2001/83/EC, requested a re-examination of the PRAC recommendation in line with Article 32 of Directive 2001/83/EC. For further background, see PRAC minutes July 2016, PRAC minutes November 2016, PRAC minutes February 2017, PRAC minutes March 2017, PRAC minutes July 2017, PRAC minutes September 2017, PRAC minutes October 2017 and PRAC minutes November 2017.

Discussion

The PRAC considered the re-examination of the procedure under Article 31 of Directive 2001/83/EC for MR paracetamol-containing medicinal products.

The PRAC confirmed that the efficacy of MR paracetamol, as a single ingredient or in combination with tramadol, has been documented in representative acute and chronic pain models, and that the benefits of paracetamol as well as tramadol in general, are well established. The PRAC noted the claimed specific benefits of the MR paracetamol-containing formulations related to a reduction of daily tablet intake from 4 to 3 times daily dosing for the single ingredient products, and the simplified regimen of 2 from 4 tablets for the combination products.

The PRAC reviewed all the available data submitted with regard to overdose with the MR paracetamol-containing products, including intentional and accidental overdose. This included the responses submitted by the MAHs in writing and during oral explanations, the grounds for the re-examination as submitted by the two concerned MAHs, as well as the advice from the two ad-hoc expert group meetings on the management of poisoning, pain management and pharmacokinetics, published studies and spontaneous reports of overdose. The PRAC also considered risk management of overdoses with paracetamol in general, both in the EU and worldwide.

In addition, the PRAC considered the highly variable pharmacokinetic (PK) profile of overdoses with MR paracetamol formulations, and the uncertainties related to the quantity and the formulation of the product that the patient has ingested, increase the challenges in effectively minimising the risk for paracetamol toxicity.

The PRAC also noted that in addition to the uncertainties on how to minimise the risk for paracetamol toxicity, the safety profile of tramadol was considered to present additional challenges for minimising the risks for toxicity (e.g. central nervous system (CNS) effects, high-risk of seizures and renal failure) following an overdose with a prolonged release combination product of paracetamol and tramadol.

Moreover, the PRAC considered the proposed risk minimisation measures to reduce the risk of overdose through education, communication and restricting availability and concluded that these measures would not be sufficient to minimise the risk of intentional and accidental overdoses to an acceptable level. Furthermore, the risk minimisation measures intended to

[11] Held on 29 August-1 September 2017

reduce the risk for hepatic injury following an overdose with an MR formulation of paracetamol or the combination of paracetamol and tramadol were not considered to be sufficiently effective and reliable.

The Committee concluded, in view of the available data including the detailed grounds submitted by MAHs during the re-examination phase, that the risk for serious hepatic injury following an overdose with MR paracetamol-containing products, could not be adequately minimised such as this risk could be outweighed by the benefits of these products in the treatment of pain and fever.

Therefore, the PRAC concluded that the benefit-risk balance of MR paracetamol-containing products is no longer favourable and recommended that the marketing authorisations of these products should be suspended.

Summary of recommendation(s)/conclusions

Further to the initial assessment and the re-examination procedure, the PRAC maintained its conclusion that the benefit-risk balance of MR paracetamol-containing products is no longer favourable and recommended that the marketing authorisations of these products should be suspended.

The PRAC agreed some key elements for a direct healthcare professional communication (DHPC) together with a communication plan as the Committee considered that a DHPC is required to communicate the conclusion of this procedure to healthcare professionals (HCPs) of relevant specialties.

To lift the suspension, the PRAC recommended that the MAHs should provide evidence of proportionate, feasible and effective measures to minimise the risk for hepatic injury following intentional or accidental overdoses with modified release paracetamol containing products.

See EMA press release (EMA/786784/2017 rev. 1) entitled 'PRAC confirms that modified-release paracetamol should be suspended from market - Overdose complex and difficult to manage with modified-release products'.

Nineteen members voted in favour of the recommendation whilst fourteen members had divergent views[12]. The Norwegian PRAC member diverged from the recommendation.

Post-meeting note: the press release entitled 'Modified-release paracetamol-containing products to be suspended from EU market' (EMA/811872/2017) representing the position adopted by the CMDh was published on the EMA website on 15 December 2017.

3.5. Others

None

[12]The relevant AR containing the divergent views will be published on the EMA website once the procedure is fully concluded

4. Signals assessment and prioritisation[13]

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. Radium (^{223}Ra) dichloride - XOFIGO (CAP)

Applicant: Bayer AG

PRAC Rapporteur: Patrick Batty

Scope: Signal of fractures and fatal cases in chemotherapy-naïve patients

EPITT 19132 – New signal

Lead Member State: UK

Background

Xofigo, a centrally authorised medicine containing radium-223 dichloride, is indicated for the treatment of adults with castration-resistant prostate cancer (CRPC), symptomatic bone metastases and no known visceral metastases. It is estimated to have been used by approximately 32,848 patients cumulatively worldwide, in the period from 2013 to 2017.

Since 2013, the MAH has been conducting a randomised, double-blind, placebo-controlled, multicentre phase 3 trial, study 15396[14], to evaluate radium-223 dichloride in combination with abiraterone acetate and prednisone/prednisolone compared with abiraterone acetate and prednisone/prednisolone in metastatic CRPC patients. The enrolment was completed in September 2016 and the last scheduled administration of Xofigo (radium-223 dichloride) occurred in February 2017. Following the independent data monitoring committee (IDMC) recommendation to the study sponsor on 15 November 2017 to unblind the study based on a post hoc analysis revealing significant imbalances concerning treatment emergent fractures, symptomatic skeletal event-free survival (SSE-FS), and total deaths between two blinded treatment arms, a signal of fractures and fatal cases in chemotherapy-naïve patients was identified by EMA. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information on the fractures and fatal cases in chemotherapy-naïve patients and having considered the available evidence from the ongoing clinical trial 15396, the PRAC agreed that a thorough evaluation of the issue should be undertaken.

[13] 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

[14] Study 15396 (ERA-223); NCT02043678

The PRAC appointed Patrick Batty as Rapporteur for the signal.

Summary of recommendation(s)

- Having considered the seriousness of the increased risk of death and fractures potentially arising from the use of this combination, the PRAC agreed that the MAH should distribute a direct healthcare professional communication (DHPC) for Xofigo (radium-223 dichloride) regarding its concomitant use with abiraterone and prednisolone/prednisone, strongly advising against the use of this combination. The PRAC agreed the content of the DHPC together with a communication plan.
- The PRAC supported that a thorough evaluation is performed within the procedure initiated under Article 20 of Regulation (EC) 726/2004. See under 3.1.1.

For the full PRAC recommendation, see EMA/PRAC/610978/2017 published on 04/01/2018 on the EMA website.

4.3. Signals follow-up and prioritisation

4.3.1. Insulin[15]: insulin aspart – NOVOMIX (CAP) - EMEA/H/C/000308/SDA/054, NOVORAPID (CAP)- EMEA/H/C/000258/SDA/047; insulin bovine (NAP); insulin degludec – TRESIBA (CAP) - EMEA/H/C/002498/SDA/011; insulin degludec, insulin aspart – RYZODEG (CAP) - EMEA/H/C/002499/SDA/006, insulin degludec, liraglutide – XULTOPHY (CAP) - EMEA/H/C/002647/SDA/003; insulin detemir – LEVEMIR (CAP) - EMEA/H/C/000528/SDA/052; insulin glargine – ABASAGLAR (CAP) - EMEA/H/C/002835/SDA/004, LANTUS (CAP) - EMEA/H/C/000284/SDA/053, LUSDUNA (CAP) - EMEA/H/C/004101/SDA/002, TOUJEO (CAP) - EMEA/H/C/000309/SDA/052; insulin glulisine – APIDRA (CAP) - EMEA/H/C/000557/SDA/041; insulin human (rDNA) – ACTRAPHANE (CAP) - EMEA/H/C/000427/SDA/024, ACTRAPID (CAP) - EMEA/H/C/000424/SDA/025, INSULATARD (CAP), INSULIN HUMAN WINTHROP (CAP) - EMEA/H/C/000761/SDA/008, INSUMAN (CAP) - EMEA/H/C/000201/SDA/048, MIXTARD (CAP) - EMEA/H/C/000428/SDA/026, PROTAPHANE (CAP) - EMEA/H/C/000442/SDA/028; insulin human, insulin isophane (NAP); insulin lispro – HUMALOG (CAP) - EMEA/H/C/000088/SDA/031, LIPROLOG (CAP) - EMEA/H/C/000393/SDA/024; insulin porcine (NAP)

Applicant(s): Eli Lilly Regional Operations GmbH (Abasaglar); Eli Lilly Nederland B.V. (Humalog, Liprolog); Novo Nordisk A/S (Actraphane, Actrapid, Insulatard, Levemir, Mixtard, NovoMix, NovoRapid, Protaphane, Ryzodeg, Tresiba, Xultophy); Merck Sharp & Dohme Limited (Lusduna); Sanofi-aventis Deutschland GmbH (Apidra, Lantus, Toujeo, Insulin Human Winthrop, Insuman); various

PRAC Rapporteur: Julie Williams

Scope: Signal of potential increased risk of medication error associated with withdrawing insulin from pre-filled pens and cartridges, leading to dysglycaemia

EPITT 18893 – Follow-up to October 2017

Background

[15] Pre-filled pens and cartridges

For background information, see PRAC minutes October 2017.

The Rapporteur assessed the healthcare professional (HCP) experts' and patients' input further to their consultation on the signal of potential increased risk of medication error associated with withdrawing insulin from pre-filled pens and cartridges, leading to dysglycaemia.

Discussion

Having considered the available evidence, including the views of the HCP experts on medication errors and diabetes and the views of patients, and the data submitted by the MAHs, the PRAC agreed that it would be appropriate to update the product information of standard or low strength insulin-containing medicinal products in cartridges (for use with reusable pens) and prefilled pens accordingly. For high-strength and fixed-combination insulin-containing products, the PRAC already adopted a recommendation published on 29 May 2017. For further background, see PRAC minutes May 2017.

Summary of recommendation(s)

- The MAHs for standard or low strength insulin-containing medicinal products in cartridges (for use with reusable pens) and prefilled pens should submit to EMA, within 60 days, a variation for amending the product information[16] to clarify that the product is only suitable for subcutaneous injection and that in case an administration by syringe (intravenous (IV) injection or infusion pump) is necessary, a vial should be used if available. It was also recommended that where 'umbrella' product information (for different presentations of the same product) exists it should make it clear that administration by syringe and/or other devices (and different routes of administration) does not apply to use with pre-filled pens/cartridges for reusable pens. Thus, the layout/order of text as well as the actual language used should be reviewed and amended as necessary. In addition, references to different routes of administration (e.g. IV use, infusion pumps) that are inappropriate for use with pre-filled pens/cartridges for reusable pens, should be deleted from individual product information (PI).
- Finally, key messages for communication to HCPs and patients at national level were agreed.

For the full PRAC recommendation, see EMA/PRAC/610978/2017 published on 04/01/2018 on the EMA website. For the previous PRAC recommendation on high-strength and fixed-combination insulin, see EMA/PRAC/252869/2017 published on 29/05/2017.

4.3.2. mTOR[17] inhibitors: everolimus – AFINITOR (CAP) - EMEA/H/C/001038/SDA/030, VOTUBIA (CAP) - EMEA/H/C/002311/SDA/030, NAP; sirolimus – RAPAMUNE (CAP) - EMEA/H/C/000273/SDA/053; temsirolimus – TORISEL (CAP) - EMEA/H/C/000799/SDA/037

Applicant(s): Novartis Europharm Ltd (Afinitor, Votubia), Pfizer Limited (Rapamune, Torisel), various

PRAC Rapporteur: Martin Huber

Scope: Signal of optic neuropathy and papilloedema

[16] Update of SmPC sections 4.2 and/or 4.4 as applicable as well as section 6.6. The package leaflet is to be updated accordingly

[17] Mechanistic target of rapamycin

EPITT 18901 – Follow-up to June 2017

Background

For background information, see PRAC minutes June 2017.

The MAH(s) replied to the request for information on the signal of optic neuropathy and papilloedema and the responses were assessed by the Rapporteur.

Discussion

Having considered the cumulative reviews submitted by the concerned MAHs, the PRAC agreed that the cases of optic neuropathy and papilloedema with a temporal relationship to mTOR-inhibitors exhibit confounding factors or are otherwise inconclusive. Therefore, the PRAC considered that the likelihood of a causal relationship between treatment with mTOR-inhibitors and either optic neuropathy or papilloedema is insufficiently strong at this stage to warrant regulatory action.

Summary of recommendation(s)

- The MAHs of mTOR-inhibitor-containing products should continue to monitor the events of optic neuropathy and papilloedema as part of routine safety surveillance.

4.3.3. Phenprocoumon (NAP)

Applicant: various

PRAC Rapporteur: Martin Huber

Scope: Signal related to risk of birth defects and foetal loss following first trimester exposure as a function of the time of withdrawal

EPITT 18902 – Follow-up to June 2017

Background

For background information, see PRAC minutes June 2017.

The MAH(s) replied to the request for information on the signal related to the risk of birth defects and foetal loss following first trimester exposure as a function of the time of withdrawal and the responses were assessed by the Rapporteur.

Discussion

Having considered the known embryotoxic risk of phenprocoumon, and the available evidence in the literature including the study by *Hüttel et al.*[18], the PRAC agreed that it would be useful to update the product information to appropriately reflect the new data available.

Summary of recommendation(s)

- The MAH(s) for phenprocoumon-containing products should submit to the EMA, within 60 days, a proposal for amending the product information[19].
- A 60-day timetable was recommended for the assessment of this proposal leading to a further PRAC recommendation.

[18] Hüttel E, Padberg S, Meister R, Beck E, Schaefer C. Pregnancy outcome of first trimester exposure to the vitamin K antagonist phenprocoumon depends on duration of treatment. Thromb Haemost. 2017 May 3;117(5):870-879
[19] Update of SmPC section 4.6. The package leaflet is to be updated accordingly

4.3.4. Ritonavir - NORVIR (CAP) - EMEA/H/C/000127/SDA/050; lopinavir, ritonavir – KALETRA (CAP) – EMEA/H/C/000368/SDA/120; levothyroxine (NAP)

Applicant(s): AbbVie Ltd. (Kaletra, Norvir), various

PRAC Rapporteur: Menno van der Elst

Scope: Signal of interaction possibly leading to decreased levothyroxine efficacy and hypothyroidism

EPITT 18896 – Follow-up to July 2017

Background

For background information, see PRAC minutes July 2017.

The MAH replied to the request for information on the signal of interaction possibly leading to decreased levothyroxine efficacy and hypothyroidism and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence, including the responses from the MAH for Norvir (ritonavir) and Kaletra (lopinavir, ritonavir), the PRAC agreed that it would be useful to seek the views of the Pharmacokinetics Working Party (PKWP).

Summary of recommendation(s)

- The PRAC agreed to seek the views of the PKWP on the level of evidence to establish a drug-drug interaction (DDI) between levothyroxine and ritonavir. The PKWP advice will be discussed at the February 2018 PRAC meeting.

4.3.5. Tofacitinib – XELJANZ (CAP) – EMEA/H/C/004214/SDA/005

Applicant(s): Pfizer Limited

PRAC Rapporteur: Sabine Straus

Scope: Signal of angioedema

EPITT 18904 – Follow-up to July 2017

Background

For background information, see PRAC minutes July 2017.

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

Discussion

Having considered the available evidence in EudraVigilance and the data submitted by the MAH on the association of tofacitinib and angioedema, the PRAC agreed that it would be useful to update the product information with respect to this.

Summary of recommendation(s)

- The MAH for Xeljanz (tofacitinib) should submit to EMA, within 60 days, a variation for amending the product information[20] to add a special warning and precaution for use on hypersensitivity as well as to include hypersensitivity, angioedema and urticaria in the undesirable effects of unknown frequency.

For the full PRAC recommendation, see EMA/PRAC/610978/2017 published on 04/01/2018 on the EMA website.

5. Risk management plans (RMPs)

5.1. Medicines in the pre-authorisation phase

See also Annex I 15.1.

5.1.1. Axicabtagene ciloleucel - EMEA/H/C/004480, Orphan

Applicant: Kite Pharma EU B.V.; ATMP[21]

Scope (accelerated assessment): Treatment of diffuse large B-cell lymphoma (DLBCL), primary mediastinal B-cell lymphoma (PMBCL) and transformed follicular lymphoma (TFL)

5.1.2. Eteplirsen – EMEA/H/C/004355, Orphan

Applicant: Avi Biopharma International Ltd

Scope: Treatment of Duchenne muscular dystrophy

5.1.3. Gemtuzumab ozogamicin - EMEA/H/C/004204, Orphan

Applicant: Pfizer Limited

Scope: Treatment of adult patients with previously untreated, de novo acute myeloid leukaemia (AML), combination therapy with daunorubicin (DNR) and cytarabine (AraC)

5.1.4. Metreleptin - EMEA/H/C/004218, Orphan

Applicant: Aegerion Pharmaceuticals Limited

Scope: Treatment of leptin deficiency (lipodystrophy)

5.1.5. Pegfilgrastim - EMEA/H/C/004413

Scope: Treatment of neutropenia

[20] Update of SmPC sections 4.4 and 4.8. The package leaflet should be updated accordingly.
[21] Advanced therapy medicinal product

5.1.6. Voretigene neparvovec - EMEA/H/C/004451, Orphan

Applicant: Spark Therapeutics Ireland Ltd; ATMP[22]

Scope: Treatment of patients with vision loss due to Leber congenital amaurosis or retinitis pigmentosa inherited retinal dystrophy

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

See Annex I 15.2.

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

See also Annex I 15.3.

5.3.1. Blinatumomab - BLINCYTO (CAP) - EMEA/H/C/003731/II/0011, Orphan

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Eva Jirsová

Scope: Extension of indication to include the treatment of adults with minimal residual disease (MRD) positive B-cell precursor acute lymphoblastic leukaemia (ALL). As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated in order to add the new indication and its relevant posology, and amend the safety information. The Labelling and the RMP (version 4.0) are updated accordingly

Background

Blinatumomab is an antineoplastic agent indicated for the treatment of adults with Philadelphia chromosome negative relapsed or refractory B-precursor acute lymphoblastic leukaemia (ALL).

The CHMP is evaluating an extension of the therapeutic indication for Blincyto, a centrally authorised product containing blinatumomab, to include the treatment of adults with minimal residual disease (MRD) positive B-cell precursor acute lymphoblastic leukaemia (ALL). 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 Blincyto (blinatumomab) in the context of the extension of indication under evaluation by the CHMP could be considered acceptable provided that an update to RMP version 4.1 and satisfactory responses to the request for supplementary information (RSI) are submitted. In particular, the PRAC considered that proposed key element 'infusion reactions into educational materials for physicians, nurses and patients' should not be included in the RMP at the time of the finalisation of the variation procedure by the CHMP.

[22] Advanced therapy medicinal product

5.3.2. Emtricitabine, tenofovir disoproxil - TRUVADA (CAP) - EMEA/H/C/000594/II/0135

Applicant: Gilead Sciences International Limited

PRAC Rapporteur: Julie Williams

Scope: Extension of indication to include pre-exposure prophylaxis of human immunodeficiency virus (HIV) infection in adolescents aged 12 to < 18 years at high risk. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated based on extrapolation of data for emtricitabine, tenofovir disoproxil fumarate, and Truvada in HIV-infected and uninfected subjects. The Package Leaflet and the RMP (version 15) are updated accordingly. In addition, the MAH took the opportunity to introduce minor linguistic amendments to the Product Information

Background

Emtricitabine and tenofovir disoproxil are antivirals for systemic use for the treatment of human immunodeficiency virus (HIV) infections. Truvada (emtricitabine, tenofovir disoproxil) is indicated in antiretroviral combination therapy for the treatment of HIV-1 infected adults. Truvada is also indicated for the treatment of HIV-1 infected adolescents, with nucleoside reverse transcriptase inhibitor (NRTI) resistance or toxicities precluding the use of first line agents, aged 12 to <18 years, and, in combination with safer sex practices for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 infection in adults at high risk.

The CHMP is evaluating an extension of the therapeutic indication for Truvada (emtricitabine, tenofovir disoproxil) to include the pre-exposure prophylaxis of human immunodeficiency virus (HIV) infection in adolescents aged 12 to <18 years at high risk. 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 Truvada (emtricitabine, tenofovir disoproxil) in the context of the extension of indication under evaluation by the CHMP could be considered acceptable provided that an update to RMP version 15 and satisfactory responses to the request for supplementary information (RSI) are submitted. In particular, the PRAC requested that further changes to the pharmacovigilance plan and the risk minimisation measures are included before finalisation of the variation procedure by the CHMP. This includes encouraging the MAH to have greater Member States' participation in the PrEP registry as appropriate.

5.3.3. Idelalisib - ZYDELIG (CAP) - EMEA/H/C/003843/II/0038

Applicant: Gilead Sciences International Limited

PRAC Rapporteur: Patrick Batty

Scope: Update of sections 4.2, 4.4 and 4.8 of the SmPC in order to reflect information from a recent cumulative safety review of cases of organising pneumonia. The Package Leaflet and Labelling are updated accordingly. The RMP (version 2.6) is also updated to extend the deadlines for submission of final clinical study report (CSR) for three studies linked to Annex II conditions

See also under 10.1.1.

Background

Zydelig (idelalisib) is a phosphatidylinositol 3-kinase p110δ (PI3Kδ) inhibitor, indicated in combination with an anti-CD20 monoclonal antibody (rituximab or ofatumumab) for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy, or as first line treatment in the presence of 17p deletion or TP53 mutation in patients who are not eligible for any other therapies. Zydelig (idelalisib) is also indicated as monotherapy for the treatment of adult patients with follicular lymphoma (FL) that is refractory to two prior lines of treatment.

Summary of advice

- The RMP for Zydelig (idelalisib) in the context of the variation under evaluation by the CHMP could be considered acceptable provided that an update to RMP version 2.6 and satisfactory responses to the request for supplementary information (RSI) are submitted. In particular, the MAH should provide supplementary information and comprehensive justification regarding the proposed postponement of the date to submit the final study reports for three category 1 studies (study GS-US-312-0117[23], study 101-09[24] and study 101-99[25]).

  See also under 10.1.1.

5.3.4. Olaparib - LYNPARZA (CAP) - EMEA/H/C/003726/X/0016/G, Orphan

Applicant: AstraZeneca AB

PRAC Rapporteur: Carmela Macchiarulo

Scope: Grouped application consisting of: 1) extension application (line extension) to add a new pharmaceutical form (film-coated tablets) associated with a new strength (100 mg and 150 mg); 2) alignment of the product information (PI) for the approved capsule presentation with the PI proposed for the tablet presentation. The RMP (version 15) is updated accordingly

Background

Lynparza (olaparib) is an antineoplasic agent indicated as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed BRCA-mutated (germline and/or somatic) high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy.

The CHMP is evaluating a grouped application for Lynparza, a centrally authorised product containing olaparib, with an extension application (line-extension) to include a new pharmaceutical form (film-coated tablets) associated with a new strength (100 mg and 150 mg) and an alignment of the product information (PI) for the approved capsule presentation with the PI proposed for the new applied tablet presentation. The PRAC is responsible for

[23] A multicentre, 2-arm, double-blind extension study evaluating the efficacy and safety of two different dose levels of single-agent idelalisib for previously treated chronic lymphocytic leukaemia
[24] A phase 2 study to assess the efficacy and safety of idelalisib in subjects with indolent B-cell non-Hodgkin lymphoma refractory to rituximab and alkylating agents
[25] An extension study to investigate the safety and durability of clinical activity of idelalisib in subjects with hematologic malignancies

providing advice to the CHMP on the necessary updates to the RMP to support this procedure.

Summary of advice

- The RMP for Lynparza (olaparib) in the context of the procedure under evaluation by the CHMP could be considered acceptable provided that an update to RMP version 15 and satisfactory responses to the request for supplementary information (RSI) are submitted, taking into account PRAC concerns over the risk of medication errors due to the introduction of a new pharmaceutical form. In particular, further information should be provided on the ongoing availability of both the tablet and capsule formulations after approval of the tablets.

6. Periodic safety update reports (PSURs)

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

See also Annex I 16.1.

6.1.1. Apixaban - ELIQUIS (CAP) - PSUSA/00000226/201705

Applicant: Bristol-Myers Squibb / Pfizer EEIG

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

Background

Apixaban is a factor Xa inhibitor indicated for the prevention of venous thromboembolic events (VTE) and the prevention of stroke and systemic embolism (SE) in adult patients under certain conditions. It is also indicated for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent of recurrent DVT and PE in adult patients.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Eliquis (apixaban) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAH should provide a cumulative safety review of cases of vasculitis and keep alopecia under monitoring. The need to update the product information should be discussed accordingly. Moreover, the MAH should perform a qualitative research study designed to understand the prescribers' rationale behind dosing strategies in those situations where a lower dose of apixaban is prescribed without meeting SmPC dose reduction advice. A report on the progress of this study

should be provided in the next PSUR, or earlier if the results warrant an update of the the product information.

- The MAH should submit to EMA, within 60 days, a cumulative review of cases of headache, dizziness, and abdominal, as well as a cumulative review of cases of liver injury, and discuss the need for an update of the product information as applicable. In addition, the MAH should review the concomitant use of apixaban and moderate inhibitors of CYP3A4[26] and P-glycoprotein, update the product information if considered appropriate, and submit the findings to EMA within 90 days.

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. Decitabine - DACOGEN (CAP) - PSUSA/00009118/201705

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

Background

Decitabine is a cytidine deoxynucleoside analogue indicated for the treatment of adult patients with newly diagnosed de novo or secondary acute myeloid leukaemia (AML), according to the World Health Organisation (WHO) classification, who are not candidates for standard induction chemotherapy.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Dacogen (decitabine) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- The MAH should submit to EMA, within 60 days, a cumulative review of cases of hepatic failure, fibrosis, cirrhosis and other liver damage-related conditions, and discuss the need for an update of the product information to reflect the risk of hepatic failure.

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. Febuxostat - ADENURIC (CAP) - PSUSA/00001353/201704

Applicant: Menarini International Operations Luxembourg S.A.

PRAC Rapporteur: Jan Neuhauser

[26] Cytochrome P450 3A4

Scope: Evaluation of a PSUSA procedure

Background

Febuxostat is a selective inhibitor of xanthine oxidase, indicated for the treatment of chronic hyperuricaemia in conditions where urate deposition has already occurred, as well as for the prevention and treatment of hyperuricaemia in adult patients undergoing chemotherapy for haematologic malignancies at intermediate to high risk of tumour lysis syndrome (TLS).

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Adenuric, a centrally authorised medicine containing febuxostat, 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 Adenuric (febuxostat) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include agranulocytosis as an undesirable effect with a rare frequency. Therefore the current terms of the marketing authorisation(s) should be varied[27].
- In the next PSUR, the MAH should submit cumulative reviews of thromboembolic events, hepatic failure, fatal cases and cases of blood creatine phosphokinase (CPK) increase.

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. Ibrutinib - IMBRUVICA (CAP) - PSUSA/00010301/201705

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

Background

Ibrutinib is an inhibitor of Bruton's tyrosine kinase indicated for the treatment of mantle cell lymphoma, chronic lymphocytic leukaemia/small lymphocytic lymphoma (CLL/SLL), CLL/SLL with deletion 17p under certain conditions. In addition, ibrutinib is indicated for the treatment of Waldenstrom's macroglobulinaemia, marginal zone lymphoma, and for the treatment of patients with chronic graft versus host disease, under certain conditions.

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

[27] Update of SmPC section 4.8. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

- Nevertheless, the product information should be updated to include t panniculitis as an undesirable effect with an uncommon frequency. Therefore the current terms of the marketing authorisation(s) should be varied[28].
- In the next PSUR, the MAH should provide an estimated figure for hepatic failure based on clinical data and amend the product information with the updated frequency. In addition the MAH should report if there is any new safety signal for the authorised use, after the investigation of the use of ibrutinib and bortezomib with or without dexamethasone. Finally, the MAH should provide a cumulative review of cases of cardiac failure, decreased left ventricular ejection fraction (LVEF) and atrio-ventricular block with ibrutinib, as well as a cumulative review of cases of peripheral neuropathy, and discuss the need to update the product information as applicable.

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

6.1.5. Lumacaftor, ivacaftor - ORKAMBI (CAP) - PSUSA/00010455/201705

Applicant: Vertex Pharmaceuticals (Europe) Ltd.

PRAC Rapporteur: Almath Spooner

Scope: Evaluation of a PSUSA procedure

Background

Lumacaftor is a cystic fibrosis transmembrane conductance regulator (CFTR) corrector and ivacaftor is a CFTR potentiator. Their combination is indicated for the treatment of cystic fibrosis (CF) in patients aged 12 years and older who are homozygous for the *F508del* mutation in the CFTR gene.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Orkambi, a centrally authorised medicine containing lumacaftor/ivacaftor, 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 Orkambi (lumacaftor/ivacaftor) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include the undesirable effect 'blood creatine phosphokinase increased' with a common frequency. Therefore the current terms of the marketing authorisation(s) should be varied[29].
- In the next PSUR, the MAH should discuss the impact of lumacaftor/ivacaftor during acute infection or pulmonary exacerbation and the need for an update of the product information with respect to use during acute infectious pulmonary exacerbations.

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

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

6.1.6. Methylthioninium chloride - METHYLTHIONINIUM CHLORIDE PROVEBLUE (CAP) - PSUSA/00002029/201705

Applicant: Provepharm SAS

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

Background

Methylthioninium chloride is an antidote indicated for the acute symptomatic treatment of medicinal and chemical product-induced methaemoglobinaemia in adults, children and adolescents (aged 0 to 17 years old).

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Methylthioninium chloride Proveblue, a centrally authorised medicine containing methylthioninium chloride, 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 Methylthioninium chloride Proveblue (methylthioninium chloride) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning on the use of methylthioninium chloride in combination with serotonergic drugs, as it may cause serotonergic syndrome, and a warning on photosensitivity, in order to advise patients to take protective measures against exposure to light. In addition 'serotonin syndrome with concomitant use of serotonergic drugs' and 'photosensitivity' should be added to the product information as undesirable effects with an unknown frequency. Therefore the current terms of the marketing authorisation(s) should be varied[30].

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

6.1.7. Pixantrone - PIXUVRI (CAP) - PSUSA/00009261/201705

Applicant: CTI Life Sciences Limited

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

Background

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

Pixantrone is an aza-anthracenedione indicated for the treatment of multiply relapsed or refractory aggressive non-Hodgkin B-cell lymphoma (NHL).

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Pixuvri (pixantrone) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include 'sepsis' as an undesirable effect with a common frequency. Therefore the current terms of the marketing authorisation(s) should be varied[31].
- In the next PSUR, the MAH should submit a cumulative review on cases of hepatotoxicity, as well as a discussion on the risk of under-dosing due to incorrectly prepared doses.

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

6.1.8. Simeprevir - OLYSIO (CAP) - PSUSA/00010255/201705

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

Background

Simeprevir is a serine protease inhibitor indicated in combination with other medicinal products for the treatment of chronic hepatitis C (CHC) in adult patients under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Olysio, a centrally authorised medicine containing simeprevir, 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 Olysio (simeprevir) in the approved indication(s) remains unchanged.
- Nevertheless, the existing warning on photosensitivity should be updated in order to better reflect the severity of the reported post-marketing cases and also to strengthen the information on sun protective measures to be considered during treatment. Therefore the current terms of the marketing authorisation(s) should be varied[32].

[31] 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
[32] Update of SmPC sections 4.4 and 4.8. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

- In the next PSUR, the MAH should discuss the reporting rate and reporting rate trend of spontaneous cases reporting simeprevir use in patients with moderate or severe hepatic impairment and decompensated liver 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.

6.1.9. Tilmanocept - LYMPHOSEEK (CAP) - PSUSA/00010313/201705

Applicant: Norgine B.V.

PRAC Rapporteur: Jolanta Gulbinovic

Scope: Evaluation of a PSUSA procedure

Background

Tilmanocept is a diagnostic agent indicated for imaging and intraoperative detection of sentinel lymph nodes draining a primary tumour in adult patients with breast cancer, melanoma, or localised squamous cell carcinoma of the oral cavity.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Lymphoseek, a centrally authorised medicine containing tilmanocept, 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 Lymphoseek (tilmanocept) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.

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.

6.1.10. Vedolizumab - ENTYVIO (CAP) - PSUSA/00010186/201705

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

Background

Vedolizumab is a monoclonal antibody indicated for the treatment of moderately to severely active ulcerative colitis and for the treatment of Crohn's disease, in adult patients under certain conditions.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Entyvio (vedolizumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include 'pneumonia' and 'blurred vision' as undesirable effects with a very rare frequency. Therefore the current terms of the marketing authorisation(s) should be varied[33].
- In the next PSUR, the MAH should submit a cumulative safety review of cases of tuberculosis, meningitis and anaphylactic reaction, and discuss the need to update the product information as applicable.

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

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

See also Annex I 16.2.

6.2.1. Bortezomib - BORTEZOMIB ACCORD (CAP); BORTEZOMIB HOSPIRA (CAP); BORTEZOMIB SUN (CAP); VELCADE (CAP); NAP - PSUSA/00000424/201704

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

PRAC Rapporteur: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure

Background

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

Based on the assessment of the PSURs, the PRAC reviewed the benefit-risk balance of Bortezomib Accord, Velcade, Bortezomib Hospira and Bortezomib Sun, centrally authorised medicine(s) containing bortezomib, and nationally authorised medicines containing bortezomib, and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

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

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

- The current terms of the marketing authorisations should be maintained.
- In the next PSUR, MAHs should closely monitor cases of of 'chalazion and blepharitis', 'thrombotic microangiopathy' and 'demyelinating polyneuropathy'.

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. Mycophenolate mofetil - CELLCEPT (CAP); MYCLAUSEN (CAP); MYCOPHENOLATE MOFETIL TEVA (CAP); MYFENAX (CAP), NAP mycophenolic acid (NAP) - PSUSA/00010550/201705

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

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

Background

Mycophenolate mofetil (MMF) and mycophenolate acid (MPA), which is a prodrug of MMF, are immunosuppressive agents indicated for the prevention of acute transplant rejection in patients who have received allogeneic renal, cardiac or hepatic transplants, in combination with ciclosporin and corticosteroids.

Based on the assessment of the PSURs, the PRAC reviewed the benefit-risk balance of CellCept, Myclausen, Mycophenolate mofetil Teva and Myfenax, centrally authorised medicines containing mycophenolate mofetil, and nationally authorised medicines containing mycophenolate acid, 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 mycophenolate mofetil- and mycophenolate acid-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to revise the warnings on teratogenic effects, pregnancy and the contraception recommendations including those for male patients. Therefore the current terms of the marketing authorisations should be varied[34].
- The educational materials should also be updated accordingly. The changes introduced in this procedure should be communicated to healthcare professionals via a direct healthcare professional communication (DHPC). The PRAC agreed the content of the DHPC together with a communication plan.
- In the next PSUR, the MAHs should submit a review of pregnancy cases, a review of bronchiectasis as well as a cumulative review of rejection rates in patients of black ethnicity. the MAH should also discuss the need to update the product information as applicable.

[34] Update of SmPC sections 4.4 and 4.6. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

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

6.2.3. Somatropin - NUTROPINAQ (CAP); OMNITROPE (CAP); SOMATROPIN BIOPARTNERS[35]; NAP - PSUSA/00002772/201703

Applicants: Ipsen Pharma (NutropinAq), Sandoz GmbH (Omnitrope), BioPartners GmbH (Somatropin Biopartners), various

PRAC Rapporteur: Doris Stenver

Scope: Evaluation of a PSUSA procedure

Background

Somatropin is a polypeptide hormone indicated for the treatment of growth hormone deficiency (GHD), growth and body composition disturbances associated with Prader-Willi syndrome, growth disturbance in short children/adolescents born small for gestational age, and growth disturbance associated with Turner syndrome, chronic renal insufficiency, idiopathic short stature, and with short stature homeobox-containing gene deficiency.

Based on the assessment of the PSURs, the PRAC reviewed the benefit-risk balance of NutropinAq, Omnitrope, and Somatropin Biopartners, centrally authorised medicines containing somatropin, and nationally authorised medicines containing somatropin, 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 somatropin-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include new information on a possible need for dose optimisation of somatropin in women and a warning about the concomitant use of oral oestrogen therapy and somatropin. Moreover, a warning on the possible need for dose adjustment of glucocorticoid replacement therapy should be included, as well as information on interactions between somatropin and glucocorticoids Therefore the current terms of the marketing authorisations should be varied[36].
- In the next PSUR, the MAHs should submit a cumulative review on cases of gynecomastia and acute pancreatitis, and discuss the need for an update of the product information.

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

[35] Marketing authorisation for Somatropin Partners expired on 9 November 2017
[36] Update of SmPC sections 4.2, 4.4 and 4.5. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

6.2.4. Telmisartan - KINZALMONO (CAP), MICARDIS (CAP), PRITOR (CAP); telmisartan, hydrochlorothiazide - KINZALKOMB (CAP), MICARDISPLUS (CAP), PRITORPLUS (CAP); NAP - PSUSA/00002882/201704

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

PRAC Rapporteur: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure

Background

Telmisartan is an angiotensin II receptor antagonist and hydrochlorothiazide is a thiazide diuretic. Telmisartan is indicated as monotherapy for the treatment of essential hypertension and prevention of cardiovascular morbidity and mortality in patients 55 years or older at high risk of cardiovascular disease. Telmisartan in combination with hydrochlorothiazide is indicated for the treatment of essential hypertension in patients whose blood pressure is not adequately controlled with telmisartan or hydrochlorothiazide alone.

Based on the assessment of the PSURs, the PRAC reviewed the benefit-risk balance of Micardis, MicardisPlus, Kinzalkomb, Kinzalmono, Pritor, and PritorPlus, centrally authorised medicines containing telmisartan or telmisartan/hydrochlorothiazide- and nationally authorised medicines containing telmisartan or telmisartan/hydrochlorothiazide 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 telmisartan-, telmisartan/hydrochlorothiazide-containing medicinal products in the approved indications remains unchanged.
- The current terms of the marketing authorisations should be maintained.
- In the next PSUR, the MAHs should closely monitor cases of 'erythema multiforme' and cases of 'rhabdomyolysis'.

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. Cefuroxime sodium[37] (NAP) - PSUSA/00000615/201704

Applicant(s): various

PRAC Lead: Maia Uusküla

Scope: Evaluation of a PSUSA procedure

[37] All routes of administration except intracameral use

Background

Cefuroxime sodium is a cephalosporin antibiotic indicated for the treatment of community acquired pneumonia, acute exacerbations of chronic bronchitis, complicated urinary tract infections, soft-tissue infections, intra-abdominal infections and as prophylaxis against infection in gastrointestinal, orthopaedic, cardiovascular and gynaecological surgery.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing cefuroxime sodium (for all routes of administration except intracameral use), and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of cefuroxime sodium-containing medicinal products under review in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include a warning regarding off-label intracameral use and associated eye disorders. Therefore the current terms of the marketing authorisation(s) should be varied[38].

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. Chloroprocaine hydrochloride (NAP) - PSUSA/00010078/201703

Applicant(s): various

PRAC Lead: Željana Margan Koletić

Scope: Evaluation of a PSUSA procedure

Background

Chloroprocaine hydrochloride is a local anaesthetic indicated for spinal anaesthesia in adults where planned surgical procedure should not exceed 40 minutes.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing chloroprocaine hydrochloride, 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 chloroprocaine hydrochloride-containing medicinal products in the approved indications remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAHs should submit a cumulative review of cases of lack of anaesthetic efficacy. In addition, the MAHs should provide a summary in a tabular form

[38] Update of SmPC section 4.4. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

reflecting the impact of the actions made to ensure proper education of healthcare professionals.

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

6.3.3. Clarithromycin (NAP) - PSUSA/00000788/201704

Applicant(s): various

PRAC Lead: Almath Spooner

Scope: Evaluation of a PSUSA procedure

Background

Clarithromycin is a macrolide antibiotic indicated for the treatment of infections due to susceptible organisms in adults and children over 6 months including lower and upper respiratory tract infections, skin and soft tissue infections and mycobacterial infections including treatment of *Mycobacterium avium* complex in human immunodeficiency virus (HIV) infected patients. Clarithromycin is also indicated for treatment of odontogenic infections and for the eradication of *H. pylori* infection.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing clarithromycin, 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 clarithromycin-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to reflect the latest available evidence from epidemiological studies, some of which report a rare risk of adverse cardiovascular outcomes. Therefore the current terms of the marketing authorisation(s) should be varied[39].
- In the next PSUR, the MAHs should discuss the cardiovascular risk of clarithromycin, the implications of exposure during pregnancy, and the potential interaction of clarithromycin via organic anion-transporting polypeptides (OATP) mediated mechanisms. In addition, the MAHs should provide a detailed review on the risk of infantile pyloric stenosis with clarithromycin.

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

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

6.3.4. Epoprostenol (NAP) - PSUSA/00001242/201703

Applicant(s): various

PRAC Lead: Almath Spooner

Scope: Evaluation of a PSUSA procedure

Background

Epoprostenol is a prostaglandin indicated for the treatment of pulmonary arterial hypertension (PAH) in patients under certain conditions, as well as for use in haemodialysis in emergency situations when use of heparin carries a high risk of causing or exacerbating bleeding or when heparin is otherwise contraindicated.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing epoprostenol, 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 epoprostenol-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include 'high output cardiac failure' as an undesirable effect with an unknown frequency. Therefore, the current terms of the marketing authorisation(s) should be varied[40].
- In the next PSUR, the MAHs should submit a review of fatal cases associated with medication error reported with epoprostenol, and a review of any serious undesirable effects which occur within the context of very high doses of epoprostenol.

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. Fenspiride (NAP) - PSUSA/00001368/201704

Applicant(s): various

PRAC Lead: Caroline Laborde

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 medicines containing fenspiride, and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

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

- Based on the review of the data on safety and efficacy, the benefit-risk balance of fenspiride-containing medicinal products in the approved indications remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAHs should submit to EMA a cumulative analysis of severe cutaneous adverse reactions (SCARs) as well as a cumulative analysis of torsade de pointes and prolonged electrocardiogram QT. In addition, the MAHs should provide a cumulative review of cases of headache, dyspnoea and increased blood pressure as well as a discussion on the need to update the product information.

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.

6.3.6. Gentamicin[41] (NAP) - PSUSA/00009159/201703

Applicant(s): various

PRAC Lead: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure

Background

Gentamicin is an antibiotic indicated for the treatment of renal and urinary tract infections, respiratory tract infections, intra-abdominal infections, central nervous system infections, bacteraemia, septicaemia, severe neonatal infections, as well as skin, bones, subcutaneous tissue and burn infections.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicines for systemic use containing gentamicin, 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 gentamicin-containing medicinal products for systemic use in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include the undesirable effects 'acute renal failure' and 'Fanconi-like syndrome in patients treated with a prolonged course of high-dose' with a very rare frequency as well as 'irreversible hearing loss' and 'deafness' with an unknown frequency where these are not already reflected. Therefore, the current terms of the marketing authorisation(s) should be varied[42].
- In the next PSUR, the MAHs should submit cumulative reviews of cases related to Stevens-Johnson syndrome (SJS) and toxic epidermal necrosis.

[41] For systemic use only
[42] 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

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

6.3.7. Glucosamine (NAP) - PSUSA/00001539/201703

Applicant(s): various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

Background

Glucosamine is a normal constituent of the polysaccharide chains of cartilage matrix and synovial fluid glucosaminoglycans, indicated for the relief of symptoms in mild to moderate osteoarthritis of the knee.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing glucosamine, 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 glucosamine-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include the interaction between oral vitamin K antagonists and glucosamine. Therefore, the current terms of the marketing authorisation(s) should be varied[43].
- In the next PSUR, the MAHs should submit cumulative reviews of glucosamine and tubulo-interstitial nephropathy (TIN), gastro-intestinal bleeding without non-steroidal anti-inflammatory drug (NSAID) treatment, increased intraocular pressure, and severe cutaneous reactions.

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

6.3.8. Ivermectin[44] (NAP) - PSUSA/00010376/201704

Applicant(s): various

PRAC Lead: Caroline Laborde

Scope: Evaluation of a PSUSA procedure

Background

Ivermectin is a macrocyclic lactone indicated (for topical use) for the treatment of inflammatory lesions of rosacea (papulopustular) in adult patients.

[43] Update of SmPC section 4.5. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position
[44] For topical use only

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of Soolantra and Efacti, nationally authorised medicines containing ivermectin, 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 ivermectin-containing medicinal products under review in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include 'facial swelling' as an undesirable effect with an unknown frequency. Therefore, the current terms of the marketing authorisation(s) should be varied[45].
- In the next PSUR, the MAHs should propose an update of the product information related to aggravation of rosacea.

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

6.3.9. Lanthanum (NAP) - PSUSA/00003175/201703

Applicant(s): various

PRAC Lead: Roxana Stefania Stroe

Scope: Evaluation of a PSUSA procedure

Background

Lanthanum is a phosphate binding agent indicated for the treatment of hyperphosphatemia in chronic renal failure patients on haemodialysis or continuous ambulatory peritoneal dialysis (CAPD) and in adult patients with chronic kidney disease under certain conditions.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing lanthanum, and issued a recommendation on their marketing authorisations. For further background, see PRAC minutes November 2017.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of lanthanum-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to revise the warning on the risk of lanthanum deposition and to strengthen the warning on the risk of gastrointestinal obstruction, ileus, subileus and perforation. Additionally, a warning should be included on the risk of serious gastrointestinal complications associated with unchewed or incompletely chewed tablets. Therefore, the current terms of the marketing authorisation(s) should be varied[46].

[45] 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
[46] Update of SmPC section 4.4. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

- In the next PSUR, the MAH should submit cumulative reviews for tablets and oral powder of fatal cases. In addition, the MAH should undertake a comparison between cases reported for the two formulations.

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

6.3.10. Paracetamol[47] (NAP) - PSUSA/00002311/201705

Applicant(s): various

PRAC Lead: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

Background

Paracetamol is a para-aminophenol derivative indicated as intravenous formulation for the short-term treatment of moderate pain, especially following surgery and for the short-term treatment of fever, when administration by the intravenous route is clinically justified by an urgent need to treat pain or pyrexia and/or when other routes of administration are not possible.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing paracetamol intravenous formulation, 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 paracetamol-containing medicinal products under review in the approved indications remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.

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.

6.3.11. Racecadotril (NAP) - PSUSA/00002602/201703

Applicant(s): various

PRAC Lead: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

Background

Racecadotril is an enkephalinase inhibitor indicated for the symptomatic treatment of acute diarrhoea.

[47] Intravenous (IV) formulation(s) only

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine containing racecadotril, 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 racecadotril-containing medicinal products in the approved indications remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAH should submit a cumulative review of cases relating to the risks of nervous system disorders.

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.

6.3.12. Simvastatin (NAP) - PSUSA/00002709/201704

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

Background

Simvastatin is a 3 hydroxy-3 methylglutaryl (HMG)-CoA reductase inhibitor indicated for the treatment of patients at high risk of coronary heart disease (CHD) or with existing CHD, patients with hyperlipidaemia, and paediatric patients with heterozygous familial hypercholesterolemia. It is also indicated for hypercholesterolaemia, homozygous familial hypercholesterolaemia and cardiovascular prevention.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine containing simvastatin, 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 simvastatin-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include the undesirable effect anaphylaxis with a very rare frequency. Therefore, the current terms of the marketing authorisation(s) should be varied[48].

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.

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

6.3.13. Vinorelbine (NAP) - PSUSA/00003124/201704

Applicant(s): various

PRAC Lead: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

Background

Vinorelbine is an antineoplastic compound and immuno-modulating agent, indicated in intravenous use for the treatment of non-small cell lung cancer, advanced breast cancer and for treatment of hormone-resistant prostate cancer in association with low doses of oral corticosteroids. Vinorelbine in soft capsules is indicated for the treatment of non-small cell lung cancer and advanced breast cancer.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing vinorelbine, 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 vinorelbine-containing medicinal products in the approved indications remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAHs should provide an analysis of reports where any strong CYP3A4[49] inducer/inhibitor was concomitantly administered with vinorelbine together with a discussion on any potential interactions.

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.

6.3.14. Zidovudine (NAP) - PSUSA/00003143/201703

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

Background

Zidovudine is a nucleoside analogue reverse transcriptase inhibitor indicated for the treatment of human immunodeficiency virus (HIV) infection, in combination with other antiretroviral agents.

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

Summary of recommendation(s) and conclusions

[49] Cytochrome P450 3A4

- Based on the review of the data on safety and efficacy, the benefit-risk balance of zidovudine-containing medicinal products in the approved indications remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAH should provide a review of cases of necrotizing enterocolitis in neonates, and discuss the need for an update of the product information.

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

6.4. Follow-up to PSUR/PSUSA procedures

See also Annex I 16.4.

6.4.1. Rituximab - MABTHERA (CAP) - EMEA/H/C/000165/LEG 096

Applicant: Roche Registration Limited

PRAC Rapporteur: Doris Stenver

Scope: Cumulative review of T lymphocyte decrease overall in particular CD4+ and CD8+ lymphocyte decrease, using all relevant data sources (spontaneous reports, clinical trials, literature) split by indication, focussing on data in which rituximab was used as monotherapy. In addition, cumulative review on the incidence of progressive multifocal leukoencephalopathy (PML) in rituximab-treated patients stratified by indication and clinical setting using all available information, including an in-depth review of all risk factors for PML in rituximab treated patients, a discussion on the need for PML risk stratification strategies and proposals for a risk stratification algorithm and risk minimisation measures depending on the risk level, as requested in the conclusions of PSUSA/00002652/201611 adopted in June 2017

Background

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

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 2017). The PRAC discussed the MAH's responses together with the report from the inter-committee Scientific Advisory Group on oncology (IC-SAG-O). For further background, see PRAC minutes November 2017.

Summary of advice/conclusion(s)

- Based on the PRAC review of available data on CD4 depletion and risk of progressive multifocal leukoencephalopathy (PML) in relation to rituximab treatment, and following

advice from the IC-SAG-O, the PRAC agreed that the benefit-risk balance of rituximab remains unchanged and that no variation of the marketing authorisation is warranted. The PRAC agreed that no changes to the current risk management of PML in patients treated with rituximab can be recommended based on the available evidence.

- In future PSURs, the MAH is requested to report any new significant findings which may emerge from ongoing clinical trials and basic research regarding an association between rituximab treatment, as monotherapy or in combination with other anti-cancer agents, and depletion within T-cell (sub-) populations and about the pathophysiology and risk factors for PML in the context of anti-CD-20 treatment.

6.4.2. Ulipristal acetate - ESMYA (CAP) - EMEA/H/C/001241/LEG 019

Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of a cumulative review on the important potential risk 'drug induced liver injury', as requested in the conclusions of PSUSA/00009325/201702 adopted at the October 2017 PRAC meeting

Background

Ulipristal acetate is a selective progesterone receptor modulator indicated, as Esmya, for the treatment of moderate to severe symptoms of uterine fibroids.

Following the evaluation of the most recently submitted PSURs for the above mentioned medicine(s) and the report of a case of fulminant hepatitis leading to liver transplantation in a patient treated with Esmya (ulipristal acetate) for uterine fibroids and further cases including two cases of hepatitis resulting in liver transplantation as well as other cases of hepatic disorders according to the most recent periodic safety update report (PSUR), the MAH was requested to provide a cumulative review of the important potential risk of 'drug induced liver injury' and to discuss the need to update the product information and/or the RMP accordingly. For further background, see PRAC minutes October 2017. The responses were assessed by the Rapporteur for further PRAC advice.

Summary of advice/conclusion(s)

- In view of the seriousness of the reactions reported and the possible causal relationship between Esmya (ulipristal acetate) and acute liver failure, the PRAC supported the conduct of a more in-depth investigation of this risk and a review on its impact on the benefit-risk balance of the medicinal product.
- In view of the above, the seriousness of the reported reactions and the possible causal relationship between Esmya (ulipristal acetate) treatment and acute liver failure, the EC initiated a procedure under Article 20 of Regulation (EC) No 726/2004 and requested the EMA to assess the above concerns and their impact on the benefit-risk balance for Esmya (ulipristal acetate). See under 3.1.2.
- With regard to the comment on potential effects on the bile salt export pump (BSEP), it is noted that ulipristal acetate did not cause inhibition of [3H]-taurocholic acid (TCA) uptake into human bile BSEP vesicles.

7. Post-authorisation safety studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)[50]

See Annex I 17.1.

7.2. Protocols of PASS non-imposed in the marketing authorisation(s)[51]

See Annex I 17.2.

7.3. Results of PASS imposed in the marketing authorisation(s)[52]

7.3.1. Pirfenidone – ESBRIET (CAP) - EMEA/H/C/PSR/S/0011

Applicant: Roche Registration Limited

PRAC Rapporteur: Julie Williams

Scope: Final study report for an imposed PASS: a prospective observational registry to evaluate the long-term safety of Esbriet (pirfenidone) in a real-world setting (passport)

Background

Esbriet (pirfenidone) is an immunosuppressant indicated in adults for the treatment of mild to moderate idiopathic pulmonary fibrosis (IPF). The MAH was required as a condition to the marketing authorisation (Annex IID) to set up a post-authorisation safety study[53] (PASS) in the form of an observational registry in order to collect information on demographics of patients prescribed Esbriet and also on suspected adverse drug reactions (ADRs) and to further characterise the long term safety profile of pirfenidone based on the important identified, potential risks and missing information as detailed in the RMP.

The final study report was submitted to EMA by MAH Roche Registration Limited on 15 September 2017. The PRAC discussed the final study results.

Summary of recommendation(s) and conclusions

- Based on the review of the final report of the non-interventional PASS entitled 'post-authorisation safety study of Esbriet (pirfenidone): a prospective observational registry to evaluate long-term safety in a real-world setting (passport)', the PRAC considered that the risk-benefit balance of medicinal products containing the active substance pirfenidone concerned by the PASS final report version 1 remains unchanged but recommended that the terms of the marketing authorisation(s) for Esbriet (pirfenidone) should be varied to remove the condition from Annex II.

[50] In accordance with Article 107n of Directive 2001/83/EC
[51] 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
[52] In accordance with Article 107p-q of Directive 2001/83/EC
[53] EUPAS2165. Post-Authorisation Safety Study of Esbriet (pirfenidone): A prospective observational registry to evaluate long-term safety in a real-world setting

- In addition, as this imposed PASS is the only requirement which meets the criteria for additional monitoring, the deletion of the black symbol and the related statement in the product information is warranted.
- The PRAC considered that the current RMP version 8.2 is acceptable. In addition, minor revisions were recommended to be taken into account at the next RMP update.

7.4. Results of PASS non-imposed in the marketing authorisation(s)[54]

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 also Annex I 17.5.

7.5.1. Belatacept - NULOJIX (CAP) - EMEA/H/C/002098/MEA 026

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Interim report for study BMS IM103077: a retrospective analysis of data from collaborative transplant study (CTS) to describe the pattern of Nulojix (belatacept) use at the time of transplant

Background

Nulojix (belatacept) is an immunosuppressant indicated in combination with corticosteroids and mycophenolic acid (MPA), for prophylaxis of graft rejection in adults receiving a renal transplant. It is recommended to add an interleukin (IL)-2 receptor antagonist for induction therapy to this belatacept-based regimen.

The MAH had committed to perform five post-marketing epidemiology studies according to the RMP (category 3 studies) at the time of the marketing authorisation (2011). Two were observational studies using data from EU-based registries (IM103077[55] and IM103089) and the other 3 were observational studies using data from US-based registries (IM103061, IM103074[56], and IM103075[57]). In 2012, the MAH also committed to add an additional study using data from a US registry (IM103076[58]). Interim results from these studies have been scheduled for reporting annually initially via the annual PSUR. Further to the change of the PSUR cycle, the interim results from the remaining ongoing 4 epidemiology studies (IM103074, IM103075, IM103076 and IM103077) are now to be submitted as separate stand-alone post-approval measure (PAM) procedures.

The interim results of study IM103077 entitled 'Belatacept in renal transplantation: patterns of use analysis using the collaborative transplant study' describing the pattern of belatacept use at the time of transplantation and up to 3 years post-transplantation among solid organ

[54] 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
[55] Belatacept in renal transplantation: patterns of use analysis using the collaborative transplant study
[56] Pattern of use of belatacept in us transplant recipients
[57] Belatacept and risk of post-transplant lymphoproliferative disease (PTLD) in US renal transplant recipients
[58] Evaluating Nulojix long-term safety in transplant (ENLiST)

transplant recipients overall and by Epstein-Barr virus (EBV) serostatus and cytomegalovirus (CMV) serostatus with or without CMV prophylaxis among belatacept users, as well as assessing the temporal trend in the pattern of use post-regulatory approval of belatacept, were evaluated by the Rapporteur for PRAC review in the concerned procedure.

Summary of advice

- The majority of the belatacept-treated patients had characteristics consistent with the approved label recommendations. However, the proportion of subjects treated with belatacept despite negative or unknown EBV serostatus was overall high (almost 20%). The PRAC endorsed the MAH's proposal to close study IM103077 at the end of 2017 further to the observation that the number of belatacept-treated patients in study IM103077 over the course of 6 years had been much smaller than expected, and that consequently it was not likely that an adequate number of belatacept-treated subjects can be accrued within a reasonable time frame.
- The final study report for study IM103077 is expected during 2018. The PRAC accepted following up the safety concerns addressed in study IM103077 in study IM103074 despite the fact that the data may not be fully representative for the EU market given that only US transplant patients are recorded in the UNOS[59] database, as the possibility of accessing this knowledge via the CTS database[60] at this time is not considered practicable.

7.6. Others

See Annex I 17.6.

7.7. New Scientific Advice

None

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.

[59] UNOS: United network for organ sharing, a non-profit organisation
[60] CTSdatabase: Clinical trial subject registry

8.2. Conditional renewals of the marketing authorisation

See Annex I 18.2.

8.3. Renewals of the marketing authorisation

See Annex I 18.3.

9. Product related pharmacovigilance inspections

9.1. List of planned pharmacovigilance inspections

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

Scope: Pharmacovigilance inspection programme 2017-2020 (second revision for 2017)

The PRAC agreed the list of planned pharmacovigilance inspections for 2017-2020, the second revision having been agreed by the Pharmacovigilance Inspector Working Group (PhV IWG) and reviewed according to a risk-based approach. This list is subsequently due for adoption at CHMP. For further background, see PRAC minutes June 2017.

Post-meeting note: On 14 December 2017, the CHMP adopted the pharmacovigilance inspection programme 2017-2020, second revision.

9.2. Ongoing or concluded pharmacovigilance inspections

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

9.3. Others

None

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

10.1. Safety related variations of the marketing authorisation

10.1.1. Idelalisib - ZYDELIG (CAP) - EMEA/H/C/003843/II/0038

Applicant: Gilead Sciences International Limited

PRAC Rapporteur: Patrick Batty; PRAC Co-rapporteur: Ulla Wändel Liminga

Scope: CHMP request for PRAC advice on a variation to update sections 4.2, 4.4 and 4.8 of the SmPC in order to reflect information from a recent cumulative safety review of cases of organising pneumonia. The Package Leaflet and Labelling are updated accordingly. The RMP (version 2.6) is also updated to extend the deadlines for submission of final clinical study report (CSR) for three studies linked to Annex II conditions

See also under 5.3.3.

Background

Zydelig (idelalisib) is a phosphatidylinositol 3-kinase p110δ (PI3Kδ) inhibitor, indicated in combination with an anti-CD20 monoclonal antibody (rituximab or ofatumumab) for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy, or as first line treatment in the presence of 17p deletion or TP53 mutation in patients who are not eligible for any other therapies. Zydelig (idelalisib) is also indicated as monotherapy for the treatment of adult patients with follicular lymphoma (FL) that is refractory to two prior lines of treatment.

A type II variation proposing to update the product information of Zydelig (idelalisib) in order to reflect information from a recent cumulative safety review of cases of organising pneumonia is under evaluation at the CHMP. The PRAC was requested to provide advice on this variation. For further background, see 5.3.3.

Summary of advice

- Based on the review of the available information, the PRAC supported the proposed changes to the product information[61] for Zydelig (idelalisib) with some minor linguistic comments.

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.

[61] Update of SmPC sections 4.2, 4.4 and 4.8

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. Lenalidomide - DK/H/2772-2773, 2775, NL/H/4067-68/001-007/DC, DE/H/5336/01-07/DC, NL/H/4082/001-7/DC

PRAC Lead: Martin Huber

Scope: PRAC consultation on the evaluation of initial marketing authorisation applications under the decentralised procedure for generic lenalidomide-containing medicinal on request of Germany

Background

Lenalidomide is an immunomodulatory drug indicated for the treatment of multiple myeloma (MM), myelodysplatic syndromes (MDS) and mantle cell lymphoma (MCL) under certain conditions.

Revlimid (lenalidomide), reference medicinal product, is authorised with orphan indications in MDS and MCL. Therefore marketing authorisation applications (MAA) for generic medicinal products only pertain to the MM indication. For the MM indication, the RMP for the reference medicinal product undertakes a number of PASS as additional pharmacovigilance activities and additional risk minimisation measures. Some of these apply to MCL or MDS indications and are not considered in the scope of the ongoing MAA procedures.

In the context of the evaluation by BfArM of a MAA for a generic medicinal product containing lenalidomide, Germany requested PRAC advice on its assessment.

Summary of advice

- The PRAC supported that in general the same additional pharmacovigilance activities should be performed for the generic medicinal products as for the reference medicinal product Revlimid (lenalidomide) if considered justified. Furthermore, the same additional risk minimisation measures should also be implemented.

12. Organisational, regulatory and methodological matters

12.1. Mandate and organisation of the PRAC

None

12.2. Coordination with EMA Scientific Committees or CMDh

12.2.1. Advanced therapy medicinal products (ATMP) - Revision of procedural advice on the evaluation of ATMP in accordance with Article 8 of Regulation (EC) No 1394/2007

Following the previous PRAC discussion on the draft revised procedural advice on the evaluation of ATMP in accordance with Article 8 of Regulation (EC) No 1394/2007 (see PRAC minutes September 2017), PRAC adopted the document due for further endorsement at CAT and CHMP.

Post-meeting note: the revised procedural advice was adopted by CAT and CHMP at their respective December 2017 meeting.

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

12.3.1. Scientific advice working party (SAWP) – re-nomination of PRAC representative(s)

The topic was deferred to the January 2018 PRAC meeting.

12.4. Cooperation within the EU regulatory network

12.4.1. Brexit: preparedness of the regulatory network and capacity increase

The topic was deferred to the January 2018 PRAC meeting.

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 2018 – preparation

PRAC lead: June Raine, Almath Spooner

The topic was deferred to the January 2018 PRAC meeting.

12.8. Planning and reporting

None

12.9. Pharmacovigilance audits and inspections

12.9.1. Pharmacovigilance systems and their quality systems

None

12.9.2. Pharmacovigilance inspections

None

12.9.3. Pharmacovigilance audits

None

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

12.10.1. Periodic safety update reports

None

12.10.2. Granularity and Periodicity Advisory Group (GPAG)

PRAC lead: Menno van der Elst, Maia Uusküla

At the organisational matters teleconference held on 14 December 2017, the PRAC was updated on the activities of the GPAG, focussing on harmonising and streamlining the EURD list, and noted the progress made.

12.10.3. PSURs repository

None

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

At the organisational matters teleconference held on 14 December 2017, the PRAC endorsed the draft revised EURD list version December 2017 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 of December 2017, the updated EURD list was adopted by the CHMP and CMDh at their December 2017 meetings and published on the EMA website on 19/12/2017, see:

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

(PSURs)

12.11. Signal management

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

PRAC lead: Sabine Straus

At the organisational matters teleconference held on 14 December 2017, the PRAC was updated on the outcome of the SMART Working Group (SMART WG) work stream WS1 meeting held on 27 November 2017. Following the requirements outlined in GVP module IX on 'signal management' revision 1, the SMART WG on Processes (previously WS1) discussed a draft standalone 'signal notification form' to be used by MAHs starting from 22 February 2018. The form was circulated to the PRAC for comments. The WG also discussed a possible revision of the criteria regarding the requirement for plenary discussion for signals in the context of a future revision of the 'Best Practice guidance on using PRAC plenary time efficiently and effectively'.

12.12. Adverse drug reactions reporting and additional reporting

12.12.1. Management and reporting of adverse reactions to medicinal products

None

12.12.2. Additional monitoring

None

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

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

Post-meeting note: The updated additional monitoring list was published on 15/12/2017 on the EMA website (see: Home>Human Regulatory>Human medicines>Pharmacovigilance>Signal management>List of medicines under additional monitoring).

12.13. EudraVigilance database

12.13.1. Activities related to the confirmation of full functionality - EudraVigilance auditable requirement project – update and next steps

Following previous discussions (see PRAC minutes June 2017, PRAC minutes July 2017, PRAC minutes September 2017 and PRAC minutes November 2017), the EMA Secretariat further updated the PRAC on the EudraVigilance auditable requirement project following the

go-live of the new EudraVigilance system on 22 November 2017. The PRAC congratulated the EudraVigilance team on this major step forward for further strengthening public health protection in EU in relation to timely signal detection.

12.13.2. Activities related to the confirmation of full functionality - EudraVigilance auditable requirement project – new functionalities

Following the go-live of the new EudraVigilance system on 22 November 2017, the EMA Secretariat presented to the PRAC in detail the new functionalities available. The PRAC welcomed demonstration of the new EudraVigilance functionalities and strongly endorsed supporting their optimal use.

12.14. Risk management plans and effectiveness of risk minimisations

12.14.1. Risk management systems

None

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

None

12.15. Post-authorisation safety studies (PASS)

12.15.1. Post-authorisation Safety Studies – imposed PASS

None

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

None

12.16. Community procedures

12.16.1. Referral procedures for safety reasons

None

12.17. Renewals, conditional renewals, annual reassessments

None

12.18. Risk communication and transparency

12.18.1. Public participation in pharmacovigilance

None

12.18.2. Safety communication

None

12.19. Continuous pharmacovigilance

12.19.1. Incident management

None

12.20. Others

12.20.1. Committees/EMA external representation - user manual

At the organisational matters teleconference held on 14 December 2017, the PRAC welcomed the update by the EMA Secretariat on the new user manual describing the process for allowing a scientific committee (CxMP), working party (WP) or scientific advisory group (SAG) chair, member, alternate or expert to participate in an external meeting or conference representing the CxMP or the EMA in an official capacity, where the participation is fully or partially reimbursed by the EMA or by the organiser of the meeting or conference. The user manual elaborates the principles on participation in conferences and other forums from the 'Policy on scientific publication and representation' (EMA/231477/2005 rev.1) and has been effective since 30 June 2017.

12.20.2. Strategy on measuring the impact of pharmacovigilance – revised strategy and work plan 2018

PRAC lead: Marieke de Bruin

The PRAC adopted revision 1 of the 'PRAC strategy on measuring the impact of pharmacovigilance activities' (EMA/165407/2017) including the PRAC impact work plan for 2018. In addition, a call for expression of interest to join the PRAC interest group (IG) impact, including a new chair, was launched. At the organisational matters teleconference held on 14 December 2017, the PRAC endorsed the new memberships of the PRAC IG impact to start as of January 2018.

13. Any other business

None

14. Annex I – Signals assessment and prioritisation[62]

14.1. New signals detected from EU spontaneous reporting systems

As per agreed criteria for new signal(s), the PRAC adopted without further plenary discussion the recommendation of the Rapporteur to request MAH(s) to submit a cumulative review following standard timetables[63].

14.1.1. Daratumumab – DARZALEX (CAP)

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Signal of cytomegalovirus (CMV) reactivation

EPITT 19087 – New signal

Lead Member State: PT

14.1.2. Nivolumab – OPDIVO (CAP)

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Signal of tumour lysis syndrome

EPITT 19086 – New signal

Lead Member State: DE

14.1.3. Human normal immunoglobulin – FLEBOGAMMA DIF (CAP), HIZENTRA (CAP), HYQVIA (CAP), KIOVIG (CAP), PRIVIGEN (CAP); NAPs

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

PRAC Rapporteur: Brigitte Keller Stanislawski

Scope: Signal of lupus-like syndrome and related terms

EPITT 19098 – New signal

Lead Member State: DE

[62] 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

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

14.1.4. Vortioxetine – BRINTELLIX (CAP)

Applicant: H. Lundbeck A/S

PRAC Rapporteur: Laurence de Fays

Scope: Signal of angioedema

EPITT 19099 – New signal

Lead Member State: BE

14.2. New signals detected from other sources

14.2.1. Dasatinib – SPRYCEL (CAP)

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Doris Stenver

Scope: Signal of cytomegalovirus (CMV) reactivation

EPITT 19111 – New signal

Lead Member State: DK

14.2.2. Lapatinib – TYVERB (CAP)

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of pulmonary hypertension

EPITT 19089 – New signal

Lead Member State: SE

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. Efavirenz, emtricitabine, tenofovir disoproxil – EMEA/H/C/004274

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

15.1.2. Prasugrel - EMEA/H/C/004644

Scope: Treatment and prevention of atherothrombotic events

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

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

15.2.1. Empagliflozin - JARDIANCE (CAP) - EMEA/H/C/002677/WS1164/0033; Empagliflozin, linagliptin - GLYXAMBI (CAP) - EMEA/H/C/003833/WS1164/0008; Empagliflozin, metformin - SYNJARDY (CAP) - EMEA/H/C/003770/WS1164/0030

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Dolores Montero Corominas

Scope: Updated RMPs (Jardiance (version 12.1), Glyxambi (version 3.0), Synjardy (version 9.2)) to reflect changes requested in the PRAC recommendation for the referral procedure under Article 20 of Regulation (EC) No 726/2004 on lower limb amputation in relation to the use of sodium-glucose co-transporter-2 (SGLT-2) inhibitors completed in February 2017 (EMEA/H/A-20/1442). In addition, the RMPs are updated to include pancreatitis as an important potential risk for empagliflozin-containing medicines following the PRAC recommendation for the PSUSA procedure for canagliflozin-containing products (PSUSA/00010077/201603) adopted in October 2016

15.2.2. Ofatumumab - ARZERRA (CAP) - EMEA/H/C/001131/II/0054, Orphan

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Doris Stenver

Scope: Updated RMP (version 14.0) to reflect changes in the pharmacovigilance activities pertaining to the timelines of study OMB112517 (PROLONG study): a phase 3, open label, randomised, multicentre trial of ofatumumab maintenance treatment versus no further treatment in subjects with relapsed chronic lymphocytic leukaemia (CLL) who have responded to induction therapy; as well as to study OMB110913 (Complement 2): a phase 3, open label, randomised trial of ofatumumab added to fludarabine-cyclophosphamide *vs* fludarabine-cyclophosphamide combination in subjects with relapsed CLL. In addition, changes have been implemented in the safety specifications as previously agreed with CHMP

15.2.3. Pioglitazone - ACTOS (CAP) - EMEA/H/C/000285/WS1294/0078; GLUSTIN (CAP) - EMEA/H/C/000286/WS1294/0077; pioglitazone, glimepiride - TANDEMACT (CAP) - EMEA/H/C/000680/WS1294/0056 pioglitazone, metformin - COMPETACT (CAP) - EMEA/H/C/000655/WS1294/0068; GLUBRAVA (CAP) - EMEA/H/C/000893/WS1294/0055

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Almath Spooner

Scope: Updated RMPs for Actos, Glustin (version 24.0), Tandemact (version 22.0), Competact and Glubrava (version 25.0) to reflect a bone mechanistic addendum report for study AD4833-402: a randomised, double-blind, placebo-controlled, multicentre study to evaluate the effect of pioglitazone on bone mass and metabolism in postmenopausal women with impaired fasting plasma glucose. In addition, the RMPs for Competact and Glubrava, are updated to include the lactic acidosis questionnaire as requested in the conclusions of variations EMEA/H/C/000655/WS0991/0062 and EMEA/H/C/000893/WS0991/0047 adopted in January 2017

15.2.4. Telbivudine - SEBIVO (CAP) - EMEA/H/C/000713/II/0048

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Caroline Laborde

Scope: Updated RMP (version 11.0) in order to reclassify the risk of lactic acidosis from an important potential risk to an important identified risk and to include a targeted questionnaire for fatal cases as additional risk minimisation measure as requested by the PRAC as part of the assessment of PSUSA/00002880/201608 adopted in April 2017

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

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

15.3.1. Adalimumab - IMRALDI (CAP) - EMEA/H/C/004279/II/0002/G

Applicant: Samsung Bioepis UK Limited (SBUK)

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Quality grouped variations. The RMP (version 2.0) is updated accordingly. The MAH also took the opportunity to introduce some editorial changes to the product information

15.3.2. Ataluren - TRANSLARNA (CAP) - EMEA/H/C/002720/II/0037, Orphan

Applicant: PTC Therapeutics International Limited

PRAC Rapporteur: Sabine Straus

Scope: Extension of indication to include a new population: children from 2 to less than 5 years of age. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet and RMP (version 7.1) are updated accordingly

15.3.3. Atazanavir, cobicistat - EVOTAZ (CAP) - EMEA/H/C/003904/WS1292/0019; atazanavir - REYATAZ (CAP) - EMEA/H/C/000494/WS1292/0114

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Caroline Laborde

Scope: Update of section 4.3 and 4.5 of the SmPC in order to add a contraindication with

lurasidone to reflect this interaction based on literature data. The Package Leaflet and the RMP (version 14 for Reyataz; version 6 for Evotaz) are updated accordingly

15.3.4. Atezolizumab - TECENTRIQ (CAP) - EMEA/H/C/004143/II/0002/G

Applicant: Roche Registration Limited

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Grouped variations consisting of: 1) update of sections 4.2, 4.4 and 4.8 of the SmPC in order to add myocarditis as a new adverse reaction based on the results of a cumulative review of cases of suspected myocarditis. As a consequence, the information regarding the posology and special warnings have been updated. Annex II, the Package Leaflet and the RMP (version 2.0) have been updated accordingly; 2) update of the RMP to add haemolytic anaemia as a new important potential risk

15.3.5. Baricitinib - OLUMIANT (CAP) - EMEA/H/C/004085/II/0003

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Patrick Batty

Scope: Update of section 4.4 of the SmPC in order to include results of a vaccination sub-study of the long term extension study I4V-MC-JADY: a phase 3, multicentre study to evaluate the long-term safety and efficacy of baricitinib in patients with rheumatoid arthritis. The RMP (version 4.0) is updated accordingly

15.3.6. Cabozantinib - CABOMETYX (CAP) - EMEA/H/C/004163/II/0003

Applicant: Ipsen Pharma

PRAC Rapporteur: Sabine Straus

Scope: Extension of indication to include for the treatment of advanced renal cell carcinoma the 'treatment-naïve adults with intermediate or poor risk per IMDC criteria'. As a consequence, sections 4.1, 4.4, 4.8 and 5.1 of the SmPC are updated in order to add a warning on dose reductions and dose interruptions and to update the safety information. The final report of study A031203: a randomized phase 2 study comparing cabozantinib with commercially supplied sunitinib in patients with previously untreated locally advanced or metastatic renal cell carcinoma is submitted in support of this application. The package leaflet and the RMP (version 3.0) are updated accordingly. In addition, the MAH took the opportunity to introduce some editorial changes in the product information

15.3.7. Carfilzomib - KYPROLIS (CAP) - EMEA/H/C/003790/II/0017/G, Orphan

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Grouped variations consisting of: 1) update of sections 4.8 and 5.1 of the SmPC in order to update the efficacy and safety information based on the second interim analysis of the overall survival data from study ENDEAVOR (study 20130398): a randomised, multicentre, open-label, phase 3 study of carfilzomib and dexamethasone compared to

bortezomib with dexamethasone in patients with relapse multiple myeloma. The Package Leaflet and the RMP (version 9.0) are updated accordingly; 2) update of section 4.8 of the SmPC in order to revise the frequencies of certain adverse drug reactions based on the pooled data set including ENDEAVOR and seven recently completed studies. In addition, the MAH took the opportunity to add editorial changes in sections 4.2, 4.4, 6.3 and 6.6 of the SmPC. Several editorial changes are also included in the package leaflet and labelling

15.3.8. Crizotinib - XALKORI (CAP) - EMEA/H/C/002489/II/0050

Applicant: Pfizer Limited

PRAC Rapporteur: Ghania Chamouni

Scope: Update of sections 4.2, 4.3, 4.4, 4.8 and 5.2 of the SmPC in order to update the information about hepatic impairment based on the results of study A8081012: a phase 1 study evaluating the effect of hepatic impairment on the pharmacokinetics and safety of crizotinib in advanced cancer patients. The package leaflet and the RMP (version 7.4) are updated accordingly. The final study report of study A8081012 is included

15.3.9. Defibrotide - DEFITELIO (CAP) - EMEA/H/C/002393/II/0026, Orphan

Applicant: Gentium S.r.l.

PRAC Rapporteur: Julie Williams

Scope: Update of sections 4.8 and 5.1 of the SmPC in order to update the frequencies of adverse reactions included in the tabulated list of adverse reactions and to update the clinical efficacy and safety information based on the results from study 2006-05 (listed as category 3 in the RMP): a phase 3, open-label expanded access study designed to provide access to defibrotide as an investigational new drug to patients with severe hepatic veno-occlusive disease. The package leaflet and the RMP (version 3.0) are updated accordingly. In addition, the MAH took the opportunity to bring the SmPC in line with the latest QRD template (version 10), to update the list of local representatives in the package leaflet and to correct a translation error in the Polish, Finnish, Danish and Latvian versions

15.3.10. Dulaglutide - TRULICITY (CAP) - EMEA/H/C/002825/II/0022

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Carmela Macchiarulo

Scope: Update of sections 4.2, 5.1 and 5.2 of the SmPC following completion of a phase 3 study H9X-MCGBDX (GBDX) comparing the effect of once-weekly Trulicity with insulin glargine on glycaemic control over 52 weeks in patients with type 2 diabetes mellitus (T2DM) and moderate or severe chronic kidney disease. In addition, an update to the anatomical therapeutic chemical (ATC) code and a correction to section 6.6 of the SmPC are introduced. The RMP (version 1.11) is updated accordingly

15.3.11. Eculizumab - SOLIRIS (CAP) - EMEA/H/C/000791/II/0098, Orphan

Applicant: Alexion Europe SAS

PRAC Rapporteur: Eva Segovia

Scope: Update of sections 4.6 and 5.3 of the SmPC in order to update the safety information related to pregnancy, lactation and fertility following the review of data in PSUR#13 and PSUR#14. Annex II, the Package Leaflet and the RMP (version 17) are updated accordingly

15.3.12. Eliglustat - CERDELGA (CAP) - EMEA/H/C/003724/II/0015/G, Orphan

Applicant: Genzyme Europe BV

PRAC Rapporteur: Dolores Montero Corominas

Scope: Grouped variations consisting of an update of sections 4.2, 4.3, 4.4, 4.5 and 5.2 of the SmPC based on the final data from: 1) study POP13777: an open-label pharmacokinetic and tolerability study of eliglustat tartrate given as a single dose in subjects with mild and moderate hepatic impairment, and in matched subjects with normal hepatic function (MEA003.3) and; 2) study POP13778: an open-label two-stage pharmacokinetic and tolerability study of eliglustat tartrate given as a single dose in subjects with mild, moderate and severe renal impairment, and in matched subjects with normal renal function (MEA004.3). Annex II D, the package leaflet and the RMP (version 5.0) are updated accordingly

15.3.13. Enoxaparin sodium - INHIXA (CAP) - EMEA/H/C/004264/X/0018

Applicant: Techdow Europe AB

PRAC Rapporteur: Menno van der Elst

Scope: Extension application to add two new strengths of 12,000 IU (120 mg)/0.8 mL and 15,000 IU (150 mg)/1 mL for enoxaparin sodium solution for injection in pre-filled syringe, for subcutaneous, extracorporeal and intravenous administration. The RMP (version 2) is updated accordingly

15.3.14. Evolocumab - REPATHA (CAP) - EMEA/H/C/003766/II/0017/G

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Kimmo Jaakkola

Scope: Grouped variations consisting of an extension of indication to include the reduction of atherosclerotic cardiovascular disease risk in adults with high cardiovascular risk based on the results from study 20110118: a double-blind, randomized, placebo-controlled, multicentre study assessing the impact of additional low-density lipoprotein (LDL)-cholesterol reduction on major cardiovascular events when evolocumab (AMG 145) is used in combination with statin therapy in patients with clinically evident cardiovascular disease (category 3 pharmacovigilance activity in the RMP, MEA 004). As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to update section 5.1 of the SmPC to include important mechanistic information for healthcare professionals based on study 20120153 (a double-blind, randomized, multicentre, placebo-controlled, parallel group study to determine the effects of evolocumab (AMG 145) treatment on atherosclerotic disease burden as measured by intravascular ultrasound in subjects undergoing coronary

catheterisation, a category 3 pharmacovigilance activity, MEA 006). The RMP (version 2.0) is also updated in order to add two category 3 studies in the RMP (study 20160250: a multicentre, open-label, single-arm, extension study to assess long-term safety of evolocumab therapy in subjects with clinically evident cardiovascular disease in selected European countries and study 20150338: a multicentre, controlled, open-label extension (OLE) study to assess the long-term safety and efficacy of evolocumab (AMG 145)) as well as to update the milestones of five category 3 studies (study 20110110: multicentre, controlled, OLE study to assess the long-term safety and efficacy of evolocumab; study 20110271: multicentre, open-label study to assess the long-term safety, tolerability, and efficacy of evolocumab on low-density lipoprotein cholesterol (LDL-C) in subjects with severe familial hypercholesterolaemia (including homozygous familial hypercholesterolemia (HoFH)); study 20120138: a multicentre, controlled, OLE study to assess the long-term safety and efficacy of evolocumab; study 20130286: a double blind, randomized, placebo controlled, multicentre study to evaluate safety, tolerability, and efficacy on LDL-C of evolocumab in human immunodeficiency virus (HIV) positive patients with hyperlipidemia and mixed dyslipidemia; and study 20130295: a multicentre, OLE study to assess long-term safety and efficacy of evolocumab therapy in patients with clinically evident cardiovascular disease (FOURIER-OLE)

15.3.15. Ferric maltol - FERACCRU (CAP) - EMEA/H/C/002733/II/0010

Applicant: Shield TX (UK) Ltd

PRAC Rapporteur: Adam Przybylkowski

Scope: Extension of indication to widen the indication from 'the treatment in adults with iron deficiency anaemia' in patients with inflammatory bowel disease (IBD) to 'the treatment of adults with iron deficiency'. As a consequence, sections 4.1, 4.4, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet and the RMP (version 8.0) are updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet

15.3.16. Fidaxomicin - DIFICLIR (CAP) - EMEA/H/C/002087/II/0032/G

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Qun-Ying Yue

Scope: Grouped variations consisting of: 1) update of sections 4.2, 4.4 and 5.1 of the SmPC in order to update the safety information following final results from study ANEMONE listed as an additional pharmacovigilance activity in the RMP: a drug utilisation study (DUS) of the use of oral fidaxomicin in routine clinical settings. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet; 2) Update of sections 4.4 and 5.2 of the SmPC in order to update the safety information based on results from the PROFILE study: an open label study designed to evaluate the pharmacokinetics of fidaxomicin in inflammatory bowel disease (IBD) subjects with *Clostridium difficile* infection (CDI). The Package Leaflet and the RMP (version 9.0) are updated accordingly

15.3.17. Human normal immunoglobulin - HIZENTRA (CAP) - EMEA/H/C/002127/II/0087

Applicant: CSL Behring GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include immunomodulatory therapy for the treatment of patients with chronic inflammatory demyelinating polyneuropathy (CIDP) as maintenance therapy to prevent relapse of neuromuscular disability and impairment. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet and the RMP (version 4.0) are updated accordingly

15.3.18. Ipilimumab - YERVOY (CAP) - EMEA/H/C/002213/II/0044

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Sabine Straus

Scope: Extension of indication to include the treatment of advanced (unresectable or metastatic) melanoma in children and adolescents 12 years of age and older. As a consequence sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet and the RMP (version 15) are updated accordingly

15.3.19. Ivacaftor - KALYDECO (CAP) - EMEA/H/C/002494/II/0063/G, Orphan

Applicant: Vertex Pharmaceuticals (Europe) Ltd.

PRAC Rapporteur: Dolores Montero Corominas

Scope: Grouped variations consisting of; 1) extension of indication to include the combination regimen of the ivacaftor 150 mg evening dose and Symkevi (tezacaftor/ivacaftor); to add a blister card pack presentation containing 28-tablets for the 150 mg film-coated tablets (EU/1/12/782/005); 2) addition of a blister pack presentation containing 28-tablets for the 150 mg film-coated tablets (EU/1/12/782/006). As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 6.5 and 8 of the SmPC are updated. Annex A, the Package Leaflet, Labelling and RMP (version 6.0) are updated accordingly

15.3.20. Ixekizumab - TALTZ (CAP) - EMEA/H/C/003943/II/0009

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include alone or in combination with conventional disease-modifying anti-rheumatic drug (cDMARD) the treatment of active psoriatic arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more DMARD therapies. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated to reflect the new safety and efficacy information. The Package Leaflet and the RMP (version 5) are updated accordingly

15.3.21. Nitric oxide - INOMAX (CAP) - EMEA/H/C/000337/II/0051

Applicant: Linde Healthcare AB

PRAC Rapporteur: Julie Williams

Scope: Quality variation to introduce an additional container closure system. The RMP (version 6.0) is updated to reflect post-authorisation experience with the new cylinder closure system

15.3.22. Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/II/0039

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include treatment of adult patients with advanced or recurrent gastric or gastroesophageal junction (GEJ) cancer after two or more prior systemic therapies, based on data from study ONO-4538-12: a Phase 3 study, multicentre, double-blind, randomized study in patients with unresectable advanced or recurrent gastric cancer. As a consequence, sections 4.1, 4.4, 4.8, and 5.1 of the SmPC are updated. Annex II, package leaflet and the RMP (version 11.0) are updated accordingly

15.3.23. Palbociclib - IBRANCE (CAP) - EMEA/H/C/003853/II/0007

Applicant: Pfizer Limited

PRAC Rapporteur: Doris Stenver

Scope: Update of sections 4.2, 4.4 and 5.2 of the SmPC to reflect the results of study A5481013: a phase 1, open-label, single dose 75 mg palbociclib), parallel-cohort study to evaluate the pharmacokinetics of palbociclib in subjects with impaired hepatic function, and study A5481014: a phase 1, open-label, single dose (125 mg palbociclib), parallel-group study to evaluate the pharmacokinetics of palbociclib in subjects with impaired renal function. The RMP (version 1.4) is updated accordingly

15.3.24. Pegfilgrastim - NEULASTA (CAP) - EMEA/H/C/000420/II/0093/G

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Patrick Batty

Scope: Grouped variations consisting of: 1) addition of a new device: the on-body injector (Onpro kit) to be used with Neulasta, 6mg solution for injection, pre-filled syringe; 2) change the fill volume for Neulasta, 6 mg, solution for injection pre-filled syringe co-packed with the on-body injector (Onpro kit). In addition, the MAH took the opportunity to introduce editorial changes to module 3.2.P.2.4 on container closure system. As a consequence, sections 3, 4.2, 5.1, 6.4, 6.5, 6.6 and 8 of the SmPC are updated. The Labelling, Package Leaflet and the RMP (version 4.2) are updated accordingly. In addition the MAH took the opportunity to update the list of local representatives in the Package Leaflet, to include some editorial changes and correct some typos throughout the product information. Finally, the MAH brought the product information in line with the latest QRD template (version 10)

15.3.25. Pembrolizumab - KEYTRUDA (CAP) - EMEA/H/C/003820/II/0037/G

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Sabine Straus

Scope: Update of sections 4.4 and 4.8 of the SmPC to add information regarding the risks of encephalitis, sarcoidosis and graft versus host disease (GVHD) that have been reported in patients treated with pembrolizumab. The package leaflet, the 'additional risk minimization measures' section (educational material) in Annex II and the RMP (version 13.0) are updated accordingly. In addition, the MAH has implemented minor changes in the SmPC section 5.1 and editorial changes in the package leaflet

15.3.26. Pertuzumab - PERJETA (CAP) - EMEA/H/C/002547/II/0034

Applicant: Roche Registration Limited

PRAC Rapporteur: Doris Stenver

Scope: Extension of indication for Perjeta in combination with trastuzumab and chemotherapy for the adjuvant treatment of adult patients with human epidermal growth factor receptor 2 (HER2)-positive early breast cancer. The submission is based on the primary analysis of efficacy and safety data from the pivotal Phase 3 study BIG-4-11/BO25126/TOC4939g (APHINITY): a randomized multicentre, double-blind, placebo-controlled comparison of chemotherapy plus trastuzumab plus placebo versus chemotherapy plus trastuzumab plus pertuzumab as adjuvant therapy in patients with operable HER2-positive primary breast cancer. The MAH also aims to fulfil Annex IID obligation from the approval of the neoadjuvant indication of Perjeta granted in 2015. As a consequence, sections 4.2, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. Annex II, the Package Leaflet and the RMP (version 10.0) are updated accordingly

15.3.27. Rituximab - BLITZIMA (CAP) - EMEA/H/C/004723/WS1248/0002/G, RITEMVIA (CAP) - EMEA/H/C/004725/WS1248/0002/G, RITUZENA (CAP) - EMEA/H/C/004724/WS1248/0003/G

Applicant: Celltrion Healthcare Hungary Kft.

PRAC Rapporteur: Doris Stenver

Scope: Grouped variations consisting of addition of a new pack size of 2 vials with a fill weight/fill volume of rituximab concentrate solution for infusion of 100 mg/10 mL to the existing pack size of 1 vial of 500 mg rituximab concentrate for infusion without changing the concentration. A 24 month shelf life of the new vial (rituximab 100 mg concentrate solution for infusion) is proposed, and the new presentation is intended to be single-dose, partial use. The RMP (version 8.0) is updated accordingly

15.3.28. Roflumilast - DALIRESP (CAP) - EMEA/H/C/002398/X/0031

Applicant: AstraZeneca AB

PRAC Rapporteur: Dolores Montero Corominas

Scope: Line extension application to add a new strength of 250 µg in a polyvinyl chloride (PVC)/ polyvinylidine chloride (PVDC)/aluminium (Alu) blister of 28 tablets. The RMP

(version 18) is updated accordingly

15.3.29. Roflumilast - DAXAS (CAP) - EMEA/H/C/001179/X/0035

Applicant: AstraZeneca AB

PRAC Rapporteur: Dolores Montero Corominas

Scope: Line extension application to add a new strength of 250 µg in a polyvinyl chloride (PVC)/ polyvinylidine chloride (PVDC)/aluminium (Alu) blister of 28 tablets. The RMP (version 18) is updated accordingly

15.3.30. Roflumilast - LIBERTEK (CAP) - EMEA/H/C/002399/X/0032

Applicant: AstraZeneca AB

PRAC Rapporteur: Dolores Montero Corominas

Scope: Line extension application to add a new strength of 250 µg in a polyvinyl chloride (PVC)/ polyvinylidine chloride (PVDC)/aluminium (Alu) blister of 28 tablets. The RMP (version 18) is updated accordingly

15.3.31. Rufinamide - INOVELON (CAP) - EMEA/H/C/000660/II/0045, Orphan

Applicant: Eisai Ltd

PRAC Rapporteur: Ghania Chamouni

Scope: Extension of indication to include the treatment of seizures associated with Lennox Gastaut syndrome in patients of 1 year of age and older as adjunctive therapy. As a consequence, sections 4.1, 4.2, 4.5, 5.1 and 5.2 are updated. The package leaflet and the RMP (version 10.0) are updated accordingly. In addition the MAH took the opportunity to include minor corrections in the product information and to update the name and contact details of the local representative in Belgium and Luxembourg. Furthermore, the product information is brought in line with the latest QRD template version 10

15.3.32. Sapropterin - KUVAN (CAP) - EMEA/H/C/000943/II/0052, Orphan

Applicant: BioMarin International Limited

PRAC Rapporteur: Almath Spooner

Scope: Update of section 4.4 of the SmPC to add a warning regarding gastritis and update of section 4.8 to add the following adverse events regarding gastrointestinal tract and respiratory irritation: oropharyngeal pain, oesophageal pain, dyspepsia, nausea, gastritis and pharyngitis. The package leaflet and the RMP (version 13.0) are updated accordingly

15.3.33. Siltuximab - SYLVANT (CAP) - EMEA/H/C/003708/II/0026/G, Orphan

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Grouped variations consisting of an update of sections 4.4, 4.8, 5.1 and 5.2 of the

SmPC in order to update the product information following final results from: 1) study CNTO328MCD2001: a randomized, double blind, placebo controlled study to assess the efficacy and safety of siltuximab plus best supportive care compared with best supportive care in subjects with multicentric Castleman's disease;2) study CNTO328MCD2002: an open-label, multicenter study to evaluate the safety of long-term treatment with siltuximab in subjects with multicentric Castleman's disease, both listed as imposed obligations in Annex II. The package leaflet and the RMP (version 4.0) are updated accordingly

15.3.34. Simoctocog alfa - NUWIQ (CAP) - EMEA/H/C/002813/X/0020

Applicant: Octapharma AB

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension application (line extension) to add new strengths of 2500 IU, 3000 IU, 4000 IU for Nuwiq, powder and solvent for solution for injection. The RMP (version 5.4) is updated accordingly

15.3.35. Tedizolid phosphate - SIVEXTRO (CAP) - EMEA/H/C/002846/II/0019

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Dolores Montero Corominas

Scope: Update of section 4.8 of the SmPC of Sivextro concentrate for solution for infusion formulation in order to add information from study BAY119-2631/16121: a phase 3 randomized, double-blind, multicentre study comparing the efficacy and safety of intravenous to oral 6-day tedizolid phosphate and intravenous to oral 10 day linezolid for the treatment of acute bacterial skin and skin structure infections (ABSSSI) and change the reported expected frequency of the adverse reaction 'infusion site phlebitis' from 'uncommon' to 'common'. The Package Leaflet is updated accordingly. The RMP (version 3.0) is also updated and includes a proposal to collect safety information regarding tedizolid phosphate by conducting three investigator initiated studies and deleting the original proposed long term safety study. The MAH also took the opportunity to make minor editorial corrections throughout the product information

15.3.36. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/II/0006

Applicant: Pfizer Limited

PRAC Rapporteur: Sabine Straus

Scope: Extension of indication to include treatment of adult patients with active psoriatic arthritis who have had an inadequate response or who have been intolerant to a prior disease-modifying anti-rheumatic drug (DMARD) therapy, based on data from study A3921091: a phase 3, randomized, double-blind, placebo-controlled study of the efficacy and safety of 2 doses of tofacitinib or adalimumab in subjects with active psoriatic arthritis; study A3921092: a long term, open label extension study of tofacitinib for the treatment of psoriatic arthritis); study A3921125: a phase 3, randomized, double-blind, placebo-controlled study of the efficacy and safety of 2 doses of tofacitinib in subjects with active psoriatic arthritis and an inadequate response to at least one tumour necrosis factor (TNF) inhibitor. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are

updated. The package leaflet and the RMP (version 3.0) are updated accordingly. In addition, the MAH took the opportunity to update Annex II with minor editorial changes

15.3.37. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/X/0005/G

Applicant: Pfizer Limited

PRAC Rapporteur: Sabine Straus

Scope: Grouped variations consisting of: 1) extension application (line extension) to introduce a new strength (10 mg film coated tablets); 2) extension of indication to include 'the induction and maintenance of treatment of adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic agent'. The RMP (version 2.0) is updated accordingly

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

Applicant: Genzyme Europe BV

PRAC Rapporteur: Ghania Chamouni

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

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

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

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

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

16.1.1. Abiraterone acetate - ZYTIGA (CAP) - PSUSA/00000015/201704

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

16.1.2. Aclidinium, formoterol - BRIMICA GENUAIR (CAP); DUAKLIR GENUAIR (CAP) - PSUSA/00010307/201705

Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.3. Alipogene tiparvovec - GLYBERA[64] - PSUSA/00010056/201704

Applicant: uniQure biopharma B.V.

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.4. Bezlotoxumab - ZINPLAVA (CAP) - PSUSA/00010576/201704

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.5. Catumaxomab - REMOVAB (CAP) - PSUSA/00000581/201704 (with RMP)

Applicant: Neovii Biotech GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.6. Ceritinib - ZYKADIA (CAP) - PSUSA/00010372/201704

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.7. Cholera vaccine (inactivated, oral) - DUKORAL (CAP) - PSUSA/00000730/201704

Applicant: Valneva Sweden AB

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

[64] Marketing authorisation for Glybera expired on 28 October 2017

16.1.8. Cobicistat, elvitegravir, emtricitabine, tenofovir alafenamide - GENVOYA (CAP) - PSUSA/00010449/201705

Applicant: Gilead Sciences International Limited

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.1.9. Dalbavancin - XYDALBA (CAP) - PSUSA/00010350/201705

Applicant: Allergan Pharmaceuticals International Ltd

PRAC Rapporteur: Jolanta Gulbinovic

Scope: Evaluation of a PSUSA procedure

16.1.10. Daratumumab - DARZALEX (CAP) - PSUSA/00010498/201705

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Evaluation of a PSUSA procedure

16.1.11. Darunavir, cobicistat - REZOLSTA (CAP) - PSUSA/00010315/201705

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.1.12. Delamanid - DELTYBA (CAP) - PSUSA/00010213/201704

Applicant: Otsuka Novel Products GmbH

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.13. Dihydroartemisinin, piperaquine tetraphosphate - EURARTESIM (CAP) - PSUSA/00001069/201704

Applicant: Alfasigma S.p.A.

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.14. Edoxaban - LIXIANA (CAP); ROTEAS (CAP) - PSUSA/00010387/201704

Applicant: Daiichi Sankyo Europe GmbH

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.15. Empagliflozin, linagliptin - GLYXAMBI (CAP) - PSUSA/00010539/201705

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.16. Etelcalcetide - PARSABIV (CAP) - PSUSA/00010533/201705

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.1.17. Fentanyl[65] - IONSYS (CAP) - PSUSA/00010453/201705

Applicant: Incline Therapeutics Europe Ltd

PRAC Rapporteur: Almath Spooner

Scope: Evaluation of a PSUSA procedure

16.1.18. Fesoterodine - TOVIAZ (CAP) - PSUSA/00001387/201704

Applicant: Pfizer Limited

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

16.1.19. Fluticasone furoate, vilanterol - RELVAR ELLIPTA (CAP); REVINTY ELLIPTA (CAP) - PSUSA/00010099/201705

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

16.1.20. Follitropin beta - FERTAVID (CAP); PUREGON (CAP) - PSUSA/00001465/201705

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

[65] Transdermal system - centrally authorised product only

16.1.21. Fulvestrant - FASLODEX (CAP) - PSUSA/00001489/201704

Applicant: AstraZeneca UK Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.22. Golimumab - SIMPONI (CAP) - PSUSA/00001560/201704

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.23. Insulin glargine - ABASAGLAR (CAP); LANTUS (CAP); LUSDUNA (CAP); TOUJEO (CAP) - PSUSA/00001751/201704

Applicants: Eli Lilly Regional Operations GmbH (Abasaglar), Sanofi-Aventis Deutschland GmbH (Lantus, Toujeo), Merck Sharp & Dohme Limited (Lusduna)

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.24. Insulin lispro - HUMALOG (CAP); LIPROLOG (CAP) - PSUSA/00001755/201704

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.25. Ixazomib - NINLARO (CAP) - PSUSA/00010535/201705

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.26. Ketoconazole[66] - KETOCONAZOLE HRA (CAP) - PSUSA/00010316/201705

Applicant: Laboratoire HRA Pharma

PRAC Rapporteur: Željana Margan Koletić

Scope: Evaluation of a PSUSA procedure

[66] Centrally authorised product only

16.1.27. Lidocaine, prilocaine[67] - FORTACIN (CAP) - PSUSA/00010110/201705

Applicant: Plethora Solutions Limited

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

16.1.28. Mitotane - LYSODREN (CAP) - PSUSA/00002075/201704

Applicant: Laboratoire HRA Pharma

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

16.1.29. Necitumumab - PORTRAZZA (CAP) - PSUSA/00010471/201705

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

16.1.30. Obinutuzumab - GAZYVARO (CAP) - PSUSA/00010279/201704

Applicant: Roche Registration Limited

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

16.1.31. Osimertinib - TAGRISSO (CAP) - PSUSA/00010472/201705

Applicant: AstraZeneca AB

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUSA procedure

16.1.32. Palbociclib - IBRANCE (CAP) - PSUSA/00010544/201705

Applicant: Pfizer Limited

PRAC Rapporteur: Doris Stenver

Scope: Evaluation of a PSUSA procedure

16.1.33. Pandemic influenza vaccine (H5N1) (live attenuated, nasal) - PANDEMIC INFLUENZA VACCINE H5N1 ASTRAZENECA (CAP) - PSUSA/00010501/201705

Applicant: AstraZeneca AB

[67] Centrally authorised product only

PRAC Rapporteur: Daniela Philadelphy

Scope: Evaluation of a PSUSA procedure

16.1.34. Pandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) - ADJUPANRIX (CAP); Prepandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) - PREPANDRIX (CAP) - PSUSA/00002281/201705

Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.35. Parecoxib - DYNASTAT (CAP) - PSUSA/00002314/201703

Applicant: Pfizer Limited

PRAC Rapporteur: Almath Spooner

Scope: Evaluation of a PSUSA procedure

16.1.36. Propranolol[68] - HEMANGIOL (CAP) - PSUSA/00010250/201704

Applicant: Pierre Fabre Dermatologie

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

16.1.37. Radium (^{223}Ra) dichloride - XOFIGO (CAP) - PSUSA/00010132/201705

Applicant: Bayer AG

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

16.1.38. Ramucirumab - CYRAMZA (CAP) - PSUSA/00010323/201704

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.39. Shingles (herpes zoster) vaccine (live) - ZOSTAVAX (CAP) - PSUSA/00009289/201705

Applicant: MSD Vaccins

PRAC Rapporteur: Brigitte Keller-Stanislawski

[68] Centrally authorised product only

Scope: Evaluation of a PSUSA procedure

16.1.40. Siltuximab - SYLVANT (CAP) - PSUSA/00010254/201704

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.41. Sunitinib - SUTENT (CAP) - PSUSA/00002833/201704

Applicant: Pfizer Limited

PRAC Rapporteur: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure

16.1.42. Susoctocog alfa - OBIZUR (CAP) - PSUSA/00010458/201705

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.43. Tafamidis - VYNDAQEL (CAP) - PSUSA/00002842/201705

Applicant: Pfizer Limited

PRAC Rapporteur: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

16.1.44. Talimogene laherparepvec - IMLYGIC (CAP) - PSUSA/00010459/201704

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.45. Tenofovir alafenamide - VEMLIDY (CAP) - PSUSA/00010575/201705

Applicant: Gilead Sciences International Limited

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.1.46. Tofacitinib - XELJANZ (CAP) - PSUSA/00010588/201705

Applicant: Pfizer Limited

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUSA procedure

16.1.47. Tolvaptan[69] - JINARC (CAP) - PSUSA/00010395/201705

Applicant: Otsuka Pharmaceutical Europe Ltd

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.48. Tolvaptan[70] - SAMSCA (CAP) - PSUSA/00002994/201705

Applicant: Otsuka Pharmaceutical Europe Ltd

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.49. Trifluridine, tipiracil - LONSURF (CAP) - PSUSA/00010517/201704

Applicant: Les Laboratoires Servier

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.50. Ulipristal acetate[71] - ELLAONE (CAP) - PSUSA/00003074/201705

Applicant: Laboratoire HRA Pharma

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

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

16.2.1. Amlodipine, telmisartan - TWYNSTA (CAP); NAP - PSUSA/00000180/201704

Applicants: Boehringer Ingelheim International GmbH (Twynsta), various

PRAC Rapporteur: Valerie Strassmann

Scope: Evaluation of a PSUSA procedure

16.2.2. Cytarabine - DEPOCYTE (CAP); NAP - PSUSA/00000911/201703

Applicants: Pacira Ltd (DepoCyte), various

PRAC Rapporteur: Patrick Batty

[69] Indicated for adults with autosomal dominant polycystic kidney disease (ADPKD)
[70] Indicated for adults with hyponatraemia secondary to syndrome of inappropriate antidiuretic hormone secretion (SIADH)
[71] Female emergency contraceptive

Scope: Evaluation of a PSUSA procedure

16.2.3. Efavirenz - STOCRIN (CAP); SUSTIVA (CAP); NAP - PSUSA/00001200/201704

Applicants: Merck Sharp & Dohme Limited (Stocrin), Bristol-Myers Squibb Pharma EEIG (Sustiva), various

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.2.4. Ivabradine - CORLENTOR (CAP); IVABRADINE ANPHARM (CAP); PROCORALAN (CAP); NAP - PSUSA/00001799/201704

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

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

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

16.3.1. Aceclofenac (NAP) - PSUSA/00000022/201703

Applicant(s): various

PRAC Lead: Julia Pallos

Scope: Evaluation of a PSUSA procedure

16.3.2. Carvedilol (NAP) - PSUSA/00000575/201704

Applicant(s): various

PRAC Lead: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

16.3.3. Cefodizime (NAP) - PSUSA/00000595/201703

Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.3.4. Cefuroxime axetil (NAP) - PSUSA/00009099/201704

Applicant(s): various

PRAC Lead: Maia Uusküla

Scope: Evaluation of a PSUSA procedure

16.3.5. Deoxycholic acid (NAP) - PSUSA/00010525/201704

Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.3.6. Diphtheria, tetanus, pertussis (acellular, component) vaccine (adsorbed) (NAP); diphtheria, tetanus, pertussis (acellular, component) vaccine (adsorbed) reduced antigens contents (NAP) - PSUSA/00001125/201703

Applicant(s): various

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.3.7. Doxylamine (NAP) - PSUSA/00001174/201704

Applicant(s): various

PRAC Lead: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.3.8. Estradiol (17-beta), trimegestone (NAP) - PSUSA/00001275/201703

Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.3.9. Estradiol, norethisterone (NAP) - PSUSA/00001278/201703

Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.3.10. Etoricoxib (NAP) - PSUSA/00001334/201703

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.3.11. Isotretinoin[72] (NAP) - PSUSA/00010488/201705

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.3.12. Itraconazole (NAP) - PSUSA/00001798/201703

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.3.13. Ivabradine, metoprolol (NAP) - PSUSA/00010381/201704

Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.3.14. Latanoprost[73] (NAP) - PSUSA/00001834/201704

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.3.15. Lidocaine, prilocaine[74] (NAP) - PSUSA/00001867/201703

Applicant(s): various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

16.3.16. Linezolid (NAP) - PSUSA/00001888/201704

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.3.17. Moclobemide (NAP) - PSUSA/00002079/201704

Applicant(s): various

[72] Oral formulations only
[73] Medicinal products with paediatric indication(s)
[74] Centrally authorised product(s) excluded

PRAC Lead: Sabine Straus

Scope: Evaluation of a PSUSA procedure

16.3.18. Mupirocin (NAP) - PSUSA/00002096/201703

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.3.19. Omeprazole (NAP) - PSUSA/00002215/201704

Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.3.20. Piribedil (NAP) - PSUSA/00002436/201703

Applicant(s): various

PRAC Lead: Zane Neikena

Scope: Evaluation of a PSUSA procedure

16.3.21. Piroxicam (NAP) - PSUSA/00002438/201704

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.3.22. Porfimer (NAP) - PSUSA/00010332/201704

Applicant(s): various

PRAC Lead: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

16.3.23. Pravastatin (NAP) - PSUSA/00002500/201703

Applicant(s): various

PRAC Lead: Caroline Laborde

Scope: Evaluation of a PSUSA procedure

16.3.24. Sertraline (NAP) - PSUSA/00002696/201703

Applicant(s): various

PRAC Lead: Sabine Straus

Scope: Evaluation of a PSUSA procedure

16.3.25. Tioconazole (NAP); tioconazole, hydrocortisone (NAP) - PSUSA/00010382/201704

Applicant(s): various

PRAC Lead: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.3.26. Tretinoin[75] (NAP) - PSUSA/00003015/201703

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.3.27. Triptorelin (NAP) - PSUSA/00003048/201703

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.3.28. Urofollitropin (NAP) - PSUSA/00003082/201703

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.4. Follow-up to PSUR procedures

16.4.1. Anakinra - KINERET (CAP) - EMEA/H/C/000363/LEG 028.1

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Doris Stenver

Scope: MAH's response to LEG 028 [review on the feasibility of conducting a PASS in order to evaluate the risk of adverse cardiovascular events associated with long-term use of anakinra in patients with rheumatoid arthritis (RA) as requested in the conclusions of EMEA/H/C/PSUSA/00000209/201605 adopted by PRAC in December 2016] as per the request for supplementary information (RSI) adopted in June 2017

[75] Oral formulation(s) only

16.4.2. Ticagrelor - BRILIQUE (CAP) - EMEA/H/C/001241/LEG 022

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Submission of a detailed review on the potential interaction of ticagrelor with morphine as requested in the conclusions of PSUSA/00002948/201612 adopted in July 2017

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)[76]

17.1.1. Direct acting antivirals (DAAV) indicated for the treatment of hepatitis C: Daclatasvir – DAKLINZA (CAP); dasabuvir - EXVIERA (CAP); elbasvir, grazoprevir – ZEPATIER (CAP); glecaprevir, pibrentasvir – MAVIRET (CAP); ledipasvir, sofosbuvir - HARVONI (CAP); ombitasvir, peritepreviri, ritonavir – VIEKIRAX (CAP); simeprevir - OLYSIO (CAP); sofosbuvir – SOVALDI (CAP); sofosbuvir, velpatasvir – EPCLUSA (CAP); sofosbuvir, velpatasvir, voxilaprevir – VOSEVI (CAP) - EMEA/H/N/PSP/J/0056.1

Applicant(s): AbbVie Limited (Exviera, Maviret, Viekirax), Bristol-Myers Squibb Pharma EEIG (Daklinza), Gilead Sciences International Ltd (Epclusa, Harvoni, Sovaldi, Vosevi), Janssen-Cilag International NV (Olysio), Merck Sharp & Dohme Limited (Zepatier)

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: MAH's response to PSP/J/0056 [Joint PASS protocol for a prospective, non-interventional study evaluating the risk of early recurrence of hepatocellular carcinoma (HCC) in hepatitis C virus (HCV)-infected patients after direct-acting antiviral (DAAV) therapy compared to HCV-infected patients without previous DAA therapy during routine clinical care with previous successfully treated HCC, as per the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on DAAV indicated for treatment of hepatitis C (interferon-free) completed in December 2016 (EMEA/H/A-20/1438)] as per the request for supplementary information (RSI) adopted at the September 2017 PRAC meeting

17.1.2. Lenalidomide – REVLIMID (CAP) - EMEA/H/C/PSA/S/0016.2

Applicant: Celgene Europe Limited

PRAC Rapporteur: Ghania Chamouni

Scope: MAH's response to PSA/S/0016.1 [amended protocol for study for study CC-5013-

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

MDS-012: a post-authorisation, non-interventional, retrospective, drug-utilisation study to describe the pattern of use of lenalidomide in patients with myelodysplastic syndromes (MDS) as agreed in the conclusions of EMEA/H/C/PSA/S/0016 in April 2017] as per the request for supplementary information (RSI) adopted at the October 2017 PRAC meeting

17.1.3. Parathyroid hormone – NATPAR (CAP) - EMEA/H/C/PSP/S/0058.1

Applicant: Shire Pharmaceuticals Ireland

PRAC Rapporteur: Almath Spooner

Scope: MAH's response to PSP/S/0058 [PASS protocol for a registry for subjects with chronic hypoparathyroidism (PARADIGHM: physicians advancing disease knowledge in hypoparathyroidism)] as per the request for supplementary information adopted at the September 2017 PRAC meeting

17.1.4. Rivaroxaban – XARELTO (CAP) - EMEA/H/C/PSA/S/0018.1

Applicant: Bayer AG

PRAC Rapporteur: Qun-Ying Yue

Scope: MAH's response to PSA/S/0018 [substantial amendment to the previously agreed protocol for an observational post-authorisation safety specialist cohort event monitoring study (SCEM) to monitor the safety and utilisation of Xarelto (rivaroxaban) initiated in secondary care for the prevention of atherothrombotic events in patients who have had acute coronary syndrome in England and Wales (previous conclusions of procedure EMEA/H/C/PSP/0026 adopted by PRAC in June 2015)] as per the request for supplementary information adopted in July 2017

17.2. Protocols of PASS non-imposed in the marketing authorisation(s)[77]

17.2.1. Arsenic trioxide - TRISENOX (CAP) - EMEA/H/C/000388/MEA 050.1

Applicant: Teva B.V.

PRAC Rapporteur: Ghania Chamouni

Scope: MAH's response to MEA 050 including a revised protocol [submission of a protocol for a post-authorisation long term safety cohort study in acute promyelocytic leukaemia (APL) patients treated with Trisenox (arsenic trioxide) to assess the long-term safety of all-trans retinoic acid (ATRA) + arsenic trioxide (ATO) in newly diagnosed low to intermediate risk APL patients in a real-world clinical practice setting as requested in the conclusions of variation II/0058 finalised in October 2016] as per the request for supplementary information (RSI) adopted in June 2017

[77] 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

17.2.2. Baricitinib - OLUMIANT (CAP) - EMEA/H/C/004085/MEA 003

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Patrick Batty

Scope: Protocol for an observational safety study using an existing database, study I4V-MC-B004: a retrospective cohort study to assess the long-term safety of baricitinib compared with other therapies used in the treatment of adults with moderate-to-severe rheumatoid arthritis in the course of routine clinical care [final report due date: 31/03/2031] (from initial opinion/MA)

17.2.3. Baricitinib - OLUMIANT (CAP) - EMEA/H/C/004085/MEA 004

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Patrick Batty

Scope: Protocol for assessing the effectiveness of the patient alert card and healthcare professional educational material, study I4V-MC-B010: a rheumatologist survey to assess the effectiveness of the risk minimisation measures (RMM) for Olumiant (baricitinib); and objective 3 of study I4V-MC-B011: a retrospective cohort study to assess the safety of baricitinib compared with other therapies used in the treatment of rheumatoid arthritis in Nordic countries [final report anticipated within 4 months following the end of data] (from initial opinion/MA)

17.2.4. Baricitinib - OLUMIANT (CAP) - EMEA/H/C/004085/MEA 005

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Patrick Batty

Scope: Protocol for an observational post marketing disease registry in EU patients, study I4V-MC-B011: a retrospective cohort study to assess the safety of baricitinib compared with other therapies used in the treatment of rheumatoid arthritis in Nordic countries (from initial opinion/MA)

17.2.5. Baricitinib - OLUMIANT (CAP) - EMEA/H/C/004085/MEA 008

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Patrick Batty

Scope: Protocol for an observational post marketing disease registry in EU patients, study I4V-MC-B012: a post-marketing safety surveillance of baricitinib in three European registers (from initial opinion/MA)

17.2.6. Golimumab - SIMPONI (CAP) - EMEA/H/C/000992/MEA 033.1

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: MAH's response to MEA 033 [protocol for study MK-8259-050: an observational

PASS for golimumab in treatment of poly-articular juvenile idiopathic arthritis (pJIA) using the German Biologics JIA registry (BiKeR) as requested in the conclusions of variation procedure II/63] as per the request for supplementary information (RSI) adopted in May 2017

17.2.7. Insulin detemir - LEVEMIR (CAP) - EMEA/H/C/000528/MEA 045.7

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Doris Stenver

Scope: Submission of a substantial protocol amendment to the ongoing diabetes pregnancy registry (NN304-4016): an international non-interventional prospective cohort study to evaluate the safety of treatment with Levemir (insulin detemir) in pregnancy women with diabetes mellitus in order to reduce the total sample size [protocol previously adopted within procedure EMEA/H/C/000528/MEA 045.3 in May 2015]

17.2.8. Levetiracetam - KEPPRA (CAP) - EMEA/H/C/000277/MEA 086.2

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Laurence de Fays

Scope: MAH's response to MEA 086 [Protocol for PASS study EPD172 comparing the incidence of renal failure in patients with epilepsy exposed to levetiracetam or other antiepileptic drugs (final study report: 31 December 2017)] as adopted in July 2017

17.2.9. Loxapine - ADASUVE (CAP) - EMEA/H/C/002400/MEA 001.3

Applicant: Ferrer Internacional s.a.

PRAC Rapporteur: Sabine Straus

Scope: MAH's response to MEA 001.2 [revised protocols for: 1) study AMDC-204-401 (PASS): a post-authorisation observational study to evaluate the safety of Adasuve (loxapine for inhalation) in agitated persons in routine clinical care and study; 2) study 204-403 (drug utilisation study (DUS)): a multinational retrospective medical record to evaluate utilisation patterns of Adasuve (loxapine for inhalation) in agitated persons in routine clinical care] as per the request for supplementary information (RSI) adopted in June 2017

17.2.10. Olaratumab - LARTRUVO (CAP) - EMEA/H/C/004216/MEA 001.1

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Sabine Straus

Scope: MAH's response to MEA 001 [protocol for study I5B-MC-B001: an observational PASS to evaluate the safety and effectiveness of olaratumab in combination with doxorubicin in patients with advanced soft tissue sarcoma (STS) including rare subtypes (as requested in the conclusions of the initial opinion/MA)] as per the request for supplementary information (RSI) adopted in May 2017

17.2.11. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/MEA 002

Applicant: Pfizer Limited

PRAC Rapporteur: Sabine Straus

Scope: Protocol for study A3921133 (RMP category 3): a phase 3B/4 randomised safety endpoint study of 2 doses of tofacitinib in comparison to a tumour necrosis factor (TNF) inhibitor in subjects with rheumatoid arthritis (RA) [final report due date: by 31 December 2020] (from initial opinion/MA)

17.3. Results of PASS imposed in the marketing authorisation(s)[78]

None

17.4. Results of PASS non-imposed in the marketing authorisation(s)[79]

17.4.1. Aclidinium bromide - BRETARIS GENUAIR (CAP) - EMEA/H/C/002706/WS1207/0034; EKLIRA GENUAIR (CAP) - EMEA/H/C/002211/WS1207/0034

Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

Scope: Submission of the final report for study D6560R00005: a drug utilisation post-authorisation safety studies (DUS 1) in the United Kingdom, Denmark, and Germany listed as a category 3 study in the RMP (MEA002) aiming at describing the characteristics of new users of aclidinium bromide and of other chronic obstructive pulmonary disease (COPD) medications, evaluating the potential off-label use of aclidinium bromide in adults, pregnant women, and children, identifying and describing users of aclidinium bromide in patient subgroups for which there is missing information in the EU-RMP, and establishing a cohort of new users of aclidinium bromide for the future evaluation of safety concerns described in the RMP. The RMP (version 6.0) is updated accordingly

17.4.2. Aflibercept - EYLEA (CAP) - EMEA/H/C/002392/II/0039

Applicant: Bayer AG

PRAC Rapporteur: Ghania Chamouni

Scope: Submission of the final report for PASS study 16526 (RMP category 3 study): an observational study to evaluate the physician and patient knowledge of safety and safe use information for aflibercept in Europe as stated in the EU educational material of Eylea

17.4.3. Apixaban - ELIQUIS (CAP) - EMEA/H/C/002148/II/0048

Applicant: Bristol-Myers Squibb, Pfizer EEIG

[78] In accordance with Article 107p-q of Directive 2001/83/EC
[79] 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

PRAC Rapporteur: Menno van der Elst

Scope: Submission of the final report for study B0661073 (RMP category 4 study): a non-interventional PASS on the utilisation patterns of apixaban in Denmark. The RMP (version 18.0) is updated accordingly

17.4.4. Belatacept - NULOJIX (CAP) - EMEA/H/C/002098/II/0047/G

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Grouped variations consisting of: 1) submission of the final report for study IM103061 (RMP category 3 study): an epidemiological study on pregnancy outcome among belatacept users in the US; 2) submission of the final report for study IM103089 (RMP category 3 study): evaluation of retrospective data to assess the association between belatacept and the risk of post-transplant lymphoproliferative disorder (PTDL) in renal transplant recipients in Europe. The RMP (version 15) is updated accordingly

17.4.5. Dapagliflozin - EDISTRIDE (CAP) - EMEA/H/C/004161/WS1229/0019, FORXIGA (CAP) - EMEA/H/C/002322/WS1229/0039 dapagliflozin, metformin - EBYMECT (CAP) - EMEA/H/C/004162/WS1229/0025, XIGDUO (CAP) - EMEA/H/C/002672/WS1229/0036

Applicant: AstraZeneca AB

PRAC Rapporteur: Qun-Ying Yue

Scope: Submission of the final report from study D1690R00013. listed as a category 3 study in the RMP: incidence of diabetic ketoacidosis (DKA) among patients with type 2 diabetes (T2DM) in the United States. The RMPs (Forxiga, Edistride (version 15); Xigduo, Ebymect (version 10)) are updated accordingly

17.4.6. Dapagliflozin - EDISTRIDE (CAP) - EMEA/H/C/004161/WS1259/0018, FORXIGA (CAP) - EMEA/H/C/002322/WS1259/0038 dapagliflozin, metformin - EBYMECT (CAP) - EMEA/H/C/004162/WS1259/0024, XIGDUO (CAP) - EMEA/H/C/002672/WS1259/0035

Applicant: AstraZeneca AB

PRAC Rapporteur: Qun-Ying Yue

Scope: Submission of the final report for a drug utilisation study (DUS) MB102-134, listed as a category 3 study in the RMP: an observational single-cohort data base study of dapagliflozin use in Europe. The RMPs (Forxiga, Edistride (version 15); Xigduo, Ebymect (version 10)) are updated accordingly

17.4.7. Duloxetine - ARICLAIM (CAP) - EMEA/H/C/000552/WS1264/0068, CYMBALTA (CAP) - EMEA/H/C/000572/WS1264/0072, DULOXETINE LILLY (CAP) - EMEA/H/C/004000/WS1264/0008, XERISTAR (CAP) - EMEA/H/C/000573/WS1264/0075, YENTREVE (CAP) - EMEA/H/C/000545/WS1264/0058

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Dolores Montero Corominas

Scope: Submission of the final report from study F1J-MC-B056, listed as a category 3 study in the RMP: a non-interventional non-imposed study aimed to investigate the association between duloxetine exposure and suicide-related behaviours and ideation in women with stress urinary inconsistence (SUI). The RMP (version 12.3) is updated accordingly

17.4.8. Idelalisib - ZYDELIG (CAP) - EMEA/H/C/003843/II/0035/G

Applicant: Gilead Sciences International Limited

PRAC Rapporteur: Patrick Batty

Scope: Grouped variations consisting of an update of section 5.3 of the SmPC in order to revise the carcinogenicity information for idelalisib based on final results from two long term carcinogenicity studies: 1) study TX-312-2017: a 2-year oral (gavage) carcinogenicity study of idelalisib in sprague dawley rats; 2) study TX-312-2019: a 26-week oral gavage carcinogenicity and toxicokinetic study with idelalisib in RasH2 [001178-T (hemizygous), CByB6F1-Tg(HRAS)2Jic] mice. The RMP (version 2.3) is updated accordingly. In addition, the MAH took the opportunity to bring the product information in line with the latest QRD template (version 10.0)

17.4.9. Interferon beta-1b - BETAFERON (CAP) - EMEA/H/C/000081/II/0118

Applicant: Bayer AG

PRAC Rapporteur: Julie Williams

Scope: Submission of the final report from study BETAPAEDIC, listed as a category 3 study in the RMP: a non-interventional study evaluating safety and tolerability of Betaferon (interferon beta-1b) in paediatric patients with multiple sclerosis. The RMP (version 3.2) is updated accordingly

17.4.10. Rivaroxaban - XARELTO (CAP) - EMEA/H/C/000944/II/0055

Applicant: Bayer AG

PRAC Rapporteur: Qun-Ying Yue

Scope: Submission of the final study report for study 16171, a non-interventional PASS listed as a category 3 study in the RMP (MEA 019): an observational post-authorisation safety specialist cohort event monitoring study (SCEM) to monitor the safety and utilisation of rivaroxaban (Xarelto) for the prevention of stroke in patients with atrial fibrillation (AF), treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and the prevention of recurrent DVT and PE in the secondary care setting in England and Wales (ROSE study)

17.4.11. Ledipasvir, sofosbuvir - HARVONI (CAP) - EMEA/H/C/003850/WS1256/0059; Sofosbuvir - SOVALDI (CAP) - EMEA/H/C/002798/WS1256/0044

Applicant: Gilead Sciences International Limited

PRAC Rapporteur: Julie Williams

Scope: Submission of the final report for study GS-EU-337-2030, listed as a category 3 study in the RMP: an observational, cross-sectional post-authorisation safety study to assess healthcare provider awareness of risks related to sofosbuvir and ledipasvir/sofosbuvir

17.5. Interim results of imposed and non-imposed PASS submitted before the entry into force of the revised variation regulation[80]

17.5.1. Adalimumab - HUMIRA (CAP) - EMEA/H/C/000481/MEA 046.7

Applicant: AbbVie Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Eight annual interim report for study P10-262, a registry study in juvenile idiopathic arthritis (JIA) patients: a long term, multicentre, longitudinal post-marketing, observational study to assess long term safety and effectiveness of Humira (adalimumab) in children with moderately to severely active polyarticular or polyarticular-course JIA – STRIVE [final study report due date: 31 December 2024] (from variation II/39)

17.5.2. Adalimumab - HUMIRA (CAP) - EMEA/H/C/000481/MEA 075.6

Applicant: AbbVie Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Fifth annual interim study report for Humira ulcerative colitis registry P11-282: a long-term non-interventional post-marketing study to assess safety and effectiveness of Humira (adalimumab) in patients with moderately to severely active ulcerative colitis (UC)

17.5.3. Adalimumab - HUMIRA (CAP) - EMEA/H/C/000481/MEA 080.5

Applicant: AbbVie Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Third annual interim report for P11-292 registry: a long-term non-interventional registry to assess safety and effectiveness of Humira (adalimumab) in paediatric patients with moderately to severely active Crohn's disease (CD) CAPE

17.5.4. Belatacept - NULOJIX (CAP) - EMEA/H/C/002098/MEA 023

Applicant: Bristol-Myers Squibb Pharma EEIG

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

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Interim report for study BMS IM103-074: a retrospective analysis of data from the United Network for Organ Sharing (UNOS) to describe the pattern of Nulojix (belatacept) use at the time of transplant pregnancy outcome among belatacept users in the US

17.5.5. Belatacept - NULOJIX (CAP) - EMEA/H/C/002098/MEA 024

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

17.5.6. Belatacept - NULOJIX (CAP) - EMEA/H/C/002098/MEA 025

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Ulla Wändel Liminga

Scope: 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

17.5.7. Colistimethate sodium - COLOBREATHE (CAP) - EMEA/H/C/001225/MEA 013

Applicant: Teva B.V.

PRAC Rapporteur: Julie Williams

Scope: Second to sixth interim reports 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

17.5.8. Golimumab – SIMPONI (CAP) - EMEA/H/C/000992/MEA 007.2

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Third annual report from a pregnancy research initiative to study the exposure to golimumab during pregnancy in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis: a review and analysis of birth outcomes from the Swedish, Danish, and Finnish medical birth registers (CNTO148ART4001)

17.5.9. Insulin lispro - HUMALOG (CAP) - EMEA/H/C/000088/MEA 028.5

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Julie Williams

Scope: Fifth interim report of a PASS study, listed as a category 3 study in the RMP: a post-approval safety surveillance for monthly lot-specific adverse event review and analysis to evaluate any potential change in the frequency of hypersensitivity and immunogenicity events with the altered manufacturing process (sKPB) of Humalog and Liprolog. This fourth interim report covers the batches released to the market between 15 October 2013 and 31 January 2017

17.5.10. Insulin lispro - LIPROLOG (CAP) - EMEA/H/C/000393/MEA 021.5

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Julie Williams

Scope: Fifth interim report of a PASS study, listed as a category 3 study in the RMP: a post-approval safety surveillance for monthly lot-specific adverse event review and analysis to evaluate any potential change in the frequency of hypersensitivity and immunogenicity events with the altered manufacturing process (sKPB) of Humalog and Liprolog. This fourth interim report covers the batches released to the market between 15 October 2013 and 31 January 2017

17.5.11. Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/MEA 008.3

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

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

17.5.12. Sapropterin - KUVAN (CAP) - EMEA/H/C/000943/MEA 003.7

Applicant: BioMarin International Limited

PRAC Rapporteur: Almath Spooner

Scope: Seventh annual interim report for the Kamper registry, study EMR700773-001: a non-imposed, non-interventional exploring the long-term safety of Kuvan (sapropterin) use in patients with hyperphenylalaninaemia (HPA) as well as information regarding Kuvan use during pregnancy in women with HPA and data regarding childhood growth and neurocognitive outcomes

17.5.13. Simoctocog alfa - NUWIQ (CAP) - EMEA/H/C/002813/MEA 004.1

Applicant: Octapharma AB

PRAC Rapporteur: Ulla Wändel Liminga

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

17.5.14. Simoctocog alfa - VIHUMA (CAP) - EMEA/H/C/004459/MEA 004

Applicant: Octapharma AB

PRAC Rapporteur: Ulla Wändel Liminga

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

17.6. Others

17.6.1. Rituximab - RIXATHON (CAP) - EMEA/H/C/003903/MEA 004

Applicant: Sandoz GmbH

PRAC Rapporteur: Doris Stenver

Scope: Interim report for study GP13-302, listed as a category 3 study in the RMP: a randomized, double-blind, controlled, parallel-group, multicentre study to assess the safety and immunogenicity of transitioning to GP2013 (Rixathon/Riximyo (biosimilar rituximab)) or retreatment with Rituxan/MabThera (rituximab) in patients with active rheumatoid arthritis, previously treated with Rituxan/MabThera. (12 week interim report: after EC decision) (from initial opinion/MA)

17.6.2. Rituximab - RIXIMYO (CAP) - EMEA/H/C/004729/MEA 004

Applicant: Sandoz GmbH

PRAC Rapporteur: Doris Stenver

Scope: Interim report for study GP13-302, listed as a category 3 study in the RMP: a randomized, double-blind, controlled, parallel-group, multicentre study to assess the safety and immunogenicity of transitioning to GP2013 (Rixathon/Riximyo (biosimilar rituximab)) or retreatment with Rituxan/MabThera (rituximab) in patients with active rheumatoid arthritis, previously treated with Rituxan/MabThera. (12 week interim report: after EC decision) (from initial opinion/MA)

17.7. New Scientific Advice

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

17.8. Ongoing Scientific Advice

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

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

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

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

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

18.1. Annual reassessments of the marketing authorisation

18.1.1. Antithrombin alfa - ATRYN (CAP) - EMEA/H/C/000587/S/0030 (without RMP)

Applicant: GTC Biotherapeutics UK Limited

PRAC Rapporteur: Caroline Laborde

Scope: Annual reassessment of the marketing authorisation

18.1.2. Asfotase alfa - STRENSIQ (CAP) - EMEA/H/C/003794/S/0024 (without RMP)

Applicant: Alexion Europe SAS

PRAC Rapporteur: Almath Spooner

Scope: Annual reassessment of the marketing authorisation

18.2. Conditional renewals of the marketing authorisation

18.2.1. Blinatumomab - BLINCYTO (CAP) - EMEA/H/C/003731/R/0013 (without RMP)

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Eva Jirsová

Scope: Conditional renewal of the marketing authorisation

18.2.2. Bosutinib - BOSULIF (CAP) - EMEA/H/C/002373/R/0027 (without RMP)

Applicant: Pfizer Limited

PRAC Rapporteur: Martin Huber

Scope: Conditional renewal of the marketing authorisation

18.2.3. Vandetanib - CAPRELSA (CAP) - EMEA/H/C/002315/R/0027 (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. Avanafil - SPEDRA (CAP) - EMEA/H/C/002581/R/0029 (without RMP)

Applicant: Menarini International Operations Luxembourg S.A.

PRAC Rapporteur: Dolores Montero Corominas

Scope: 5-year renewal of the marketing authorisation

18.3.2. Elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil - STRIBILD (CAP) - EMEA/H/C/002574/R/0086 (with RMP)

Applicant: Gilead Sciences International Limited

PRAC Rapporteur: Julie Williams

Scope: 5-year renewal of the marketing authorisation

18.3.3. Enzalutamide - XTANDI (CAP) - EMEA/H/C/002639/R/0037 (without RMP)

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Eva Segovia

Scope: 5-year renewal of the marketing authorisation

18.3.4. Memantine - MEMANTINE RATIOPHARM (CAP) - EMEA/H/C/002671/R/0011 (without RMP)

Applicant: ratiopharm GmbH

PRAC Rapporteur: Dolores Montero Corominas

Scope: 5-year renewal of the marketing authorisation

18.3.5. Micafungin - MYCAMINE (CAP) - EMEA/H/C/000734/R/0034 (without RMP)

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Martin Huber

Scope: 5-year renewal of the marketing authorisation

18.3.6. Ponatinib - ICLUSIG (CAP) - EMEA/H/C/002695/R/0042 (without RMP)

Applicant: Incyte Biosciences UK Ltd

PRAC Rapporteur: Patrick Batty

Scope: 5-year renewal of the marketing authorisation

18.3.7. Thalidomide - THALIDOMIDE CELGENE (CAP) - EMEA/H/C/000823/R/0054 (without RMP)

Applicant: Celgene Europe Limited

PRAC Rapporteur: Ghania Chamouni

Scope: 5-year renewal of the marketing authorisation

18.3.8. Voriconazole - VORICONAZOLE ACCORD (CAP) - EMEA/H/C/002669/R/0017 (without RMP)

Applicant: Accord Healthcare Limited

PRAC Rapporteur: Menno van der Elst

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 27-30 November 2017 meeting.

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
June Munro Raine	Chair	United Kingdom	No interests declared	Full involvement
Jan Neuhauser	Member	Austria	No interests declared	Full involvement
Daniela Philadelphy	Alternate	Austria	No interests declared	Full involvement
Jean-Michel Dogné	Member	Belgium	No restrictions applicable to this meeting	Full involvement
Laurence De Fays	Alternate	Belgium	No interests declared	Full involvement
Maria Popova-Kiradjieva	Member	Bulgaria	No interests declared	Full involvement
Nikica Mirošević Skvrce	Member	Croatia	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
Zeljana Margan Koletić	Alternate	Croatia	No interests declared	Full involvement
Andri Andreou	Member	Cyprus	No restrictions applicable to this meeting	Full involvement
Eva Jirsová	Member	Czech Republic	No interests declared	Full involvement
Doris Stenver	Member	Denmark	No interests declared	Full involvement
Maia Uusküla	Member	Estonia	No interests declared	Full involvement
Kirsti Villikka	Member	Finland	No interests declared	Full involvement
Ghania Chamouni	Member	France	No restrictions applicable to this meeting	Full involvement
Caroline Laborde	Alternate	France	No interests declared	Full involvement
Martin Huber	Member	Germany	No interests declared	Full involvement
Valerie Strassmann	Alternate	Germany	No interests declared	Full involvement
Sophia Trantza	Alternate	Greece	No interests declared	Full involvement
Julia Pallos	Member	Hungary	No interests declared	Full involvement
Almath Spooner	Member (Vice-Chair)	Ireland	No interests declared	Full involvement
Rhea Fitzgerald	Alternate	Ireland	No restrictions applicable to this meeting	Full involvement
Carmela Macchiarulo	Member	Italy	No interests declared	Full involvement
Amelia Cupelli	Alternate	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
Sabine Straus	Member	Netherlands	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
Menno van der Elst	Alternate	Netherlands	No interests declared	Full involvement
David Olsen	Member	Norway	No participation in discussion, final deliberations and voting on:	4.2.3 - Radium (223Ra) dichloride - XOFIGO 6.2.8. Telmisartan - KINZALMONO (CAP), MICARDIS (CAP), PRITOR (CAP); telmisartan, hydrochlorothiazide - KINZALKOMB (CAP), MICARDISPLUS (CAP), PRITORPLUS (CAP); NAP
Adam Przybylkowski	Member	Poland	No interests declared	Full involvement
Katarzyna Ziolkowska	Alternate	Poland	No interests declared	Full involvement
Ana Diniz Martins	Member	Portugal	No interests declared	Full involvement
Marcia Silva	Alternate	Portugal	No interests declared	Full involvement
Roxana Stefania Stroe	Member	Romania	No interests declared	Full involvement
Tatiana Magálová	Member	Slovakia	No interests declared	Full involvement
Gabriela Jazbec	Alternate	Slovenia	No interests declared	Full involvement
Dolores Montero Corominas	Member	Spain	No interests declared	Full involvement
Eva Segovia	Alternate	Spain	No interests declared	Full involvement
Ulla Wändel Liminga	Member	Sweden	No interests declared	Full involvement
Qun-Ying Yue	Alternate	Sweden	No interests declared	Full involvement
Julie Williams	Member	United Kingdom	No interests declared	Full involvement
Patrick Batty	Alternate	United Kingdom	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Marie Louise (Marieke) De Bruin	Member	Independent scientific expert	No restrictions applicable to this meeting	Full involvement
Stephen J. W. Evans	Member	Independent scientific expert	No interests declared	Full involvement
Brigitte Keller-Stanislawski	Member	Independent scientific expert	No interests declared	Full involvement
Herve Le Louet	Member	Independent scientific expert	No restrictions applicable to this meeting	Full involvement
Thierry Trenque	Member	Independent scientific expert	No interests declared	Full involvement
Lennart Waldenlind	Member	Independent scientific expert	No interests declared	Full involvement
Raymond Anderson	Member	Healthcare Professionals' Representative	No restrictions applicable to this meeting	Full involvement
Kirsten Myhr	Alternate	Healthcare Professionals' Representative	No interests declared	Full involvement
Marco Greco	Member	Patients' Organisation Representative	No interests declared	Full involvement
Albert van der Zeijden	Alternate	Patients' Organisation Representative	No restrictions applicable to this meeting	Full involvement
Andrea Laslop	Expert - in person*	Austria	No interests declared	Full involvement
Marianne Depreter	Expert - via telephone*	Belgium	No interests declared	Full involvement
Sophie Goethals	Expert - via telephone*	Belgium	No restrictions applicable to this meeting	Full involvement
Jamila Hamdani	Expert - via telephone*	Belgium	No interests declared	Full involvement
Fabrice Moore	Expert - via telephone*	Belgium	No interests declared	Full involvement
Anne-Catherine Thomas	Expert - via telephone*	Belgium	No interests declared	Full involvement
Veerle Verlinden	Expert - via telephone*	Belgium	No interests declared	Full involvement
Sanja Prpić	Expert - via telephone*	Croatia	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
Torbjorn Callreus	Expert - in person*	Denmark	No restrictions applicable to this meeting	Full involvement
Kaarlo Magnus Hoppu	Expert - via telephone*	Finland	No restrictions applicable to this meeting	Full involvement
Serge Bakchine	Expert - via telephone*	France	No interests declared	Full involvement
Céline Druet	Expert - via telephone*	France	No interests declared	Full involvement
Annabelle Page	Expert - via telephone*	France	No interests declared	Full involvement
Cyndie Picot	Expert - via telephone*	France	No interests declared	Full involvement
Nils Lilienthal	Expert - via telephone*	Germany	No interests declared	Full involvement
Ruchika Sharma	Expert - via telephone*	Ireland	No restrictions applicable to this meeting	Full involvement
Liana Gross-Martirosyan	Expert - in person*	Netherlands	No interests declared	Full involvement
Peter Mol	Expert - in person*	Netherlands	No interests declared	Full involvement
Estíbaliz Espinosa Crespo	Expert - in person*	Spain	No interests declared	Full involvement
Charlotte Backman	Expert - in person*	Sweden	No interests declared	Full involvement
Jonas Bergh	Expert - via telephone*	Sweden	No restrictions applicable to this meeting	Full involvement
Annika Folin	Expert - in person*	Sweden	No interests declared	Full involvement
Jan Sjöberg	Expert - in person*	Sweden	No restrictions applicable to this meeting	Full involvement
Miriam Taekema	Expert - via telephone*	Sweden	No interests declared	Full involvement
Mårten Wendt	Expert - via telephone*	Sweden	No interests declared	Full involvement
Jo Lyn Chooi	Expert - in person*	United Kingdom	No interests declared	Full involvement
Emma Cornforth	Expert - via telephone*	United Kingdom	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Max Lagnado	Expert - in person*	United Kingdom	No interests declared	Full involvement
Sarah Mee	Expert - in person*	United Kingdom	No restrictions applicable to this meeting	Full involvement
Janet Nooney	Expert - via telephone*	United Kingdom	No interests declared	Full involvement
David Owens	Expert - via telephone*	United Kingdom	No restrictions applicable to this meeting	Full involvement
Beatrice Panico	Expert - via telephone*	United Kingdom	No interests declared	Full involvement
A representative from the European Commission attended the meeting				
Representatives from the Medicines Evaluation Board (the Netherlands) visited the Committee				
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/