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Pharmacovigilance Risk Assessment Committee (PRAC) Minutes of the meeting on 05-08 February 2018

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 05-08 February 2018 meeting by welcoming all participants.

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

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

The PRAC Chairperson announced that Roxana Dondera was the new alternate for Romania replacing Nicolae Fotin and noted that Nadine Petitpain stepped down from her position of alternate for Luxembourg.

1.2. Agenda of the meeting on 05-08 February 2018

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

1.3. Minutes of the previous meeting on 08-11 January 2018

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

Post-meeting note: the PRAC minutes of the meeting held on 08-11 January 2018 were published on the EMA website on 02 March 2018 ([EMA/PRAC/71458/2018](#)).

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

2.1. Newly triggered procedures

None

2.2. Ongoing procedures

None

2.3. Procedures for finalisation

None

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

3.1. Newly triggered procedures

None

3.2. Ongoing procedures

3.2.1. Fluoroquinolones for systemic and inhalation use: ciprofloxacin (NAP); enoxacin (NAP); flumequin (NAP); levofloxacin – QUINSAIR (CAP), NAP; lomefloxacin (NAP); moxifloxacin (NAP); norfloxacin (NAP); ofloxacin (NAP); pefloxacin (NAP); prulifloxacin (NAP); rufloxacin (NAP) Quinolones for systemic and inhalation use: cinoxacin (NAP); nalidixic acid (NAP); pipemidic acid (NAP) - EMEA/H/A-31/1452

Applicant(s): Raptor Pharmaceuticals Europe BV (Quinsair), various

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

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

Background

A referral procedure under Article 31 of Directive 2001/83/EC is ongoing for quinolone- and fluoroquinolone-containing medicines for systemic and inhalational use, indicated for the treatment of bacterial infections, in particular those which are serious and life-threatening, in order to assess the persistence of side effects known to occur with quinolone and fluoroquinolone antibiotics, following reports of long-lasting side effects mainly affecting musculoskeletal and nervous systems. The ongoing review also assesses the need for adequate and consistent risk minimisation measures (RMMs) and the impact of this safety concern if confirmed on the overall benefit-risk balance of quinolones and fluoroquinolones for systemic and inhalational use, especially in authorised indications which are related to treatment of non-serious/non-severe infections. For further background, see [PRAC minutes February 2017](#), [PRAC minutes June 2017](#), [PRAC minutes October 2017](#) and [PRAC minutes November 2017](#).

Summary of recommendation(s)/conclusions

- The PRAC discussed the joint assessment report prepared by the Rapporteurs.
- The PRAC adopted a second list of questions (LoQ) to the CHMP Infectious Disease Working Party ([IDWP](#)) to be consulted in writing. In addition, the PRAC adopted a second list of outstanding issues (LoOI) to be addressed by the MAHs for quinolone- and fluoroquinolone- containing medicinal products together with a revised timetable for conducting the review ([EMA/PRAC/638618/2017 Rev. 4](#)).

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

A referral procedure under Article 20 of Regulation (EC) No 726/2004 is ongoing for Esmya (ulipristal acetate), a centrally authorised product indicated for pre-operative treatment as well as intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age, in order to investigate the risk of liver injury and assess its impact on the benefit-risk balance of the medicinal product. For further background, see [PRAC minutes December 2017](#).

Discussion

The PRAC discussed the assessment report prepared by the Rapporteurs, heard the MAH in an oral explanation and discussed the need for provisional measures to protect public health, while the review of liver safety is ongoing.

During the ongoing review of safety and efficacy data in relation to the overall risk of liver injury with Esmya, the PRAC reviewed all data currently available from post-marketing settings and from clinical trials, as well as the responses provided by the MAH on cases of serious liver injury reported with Esmya.

The PRAC noted that four cases of acute liver failure leading to liver transplantation had been reported with Esmya, including one with fatal outcome. The PRAC considered that the use of Esmya could potentially be associated with a risk of serious liver injury. In view of the seriousness of the cases, the PRAC concurred that provisional measures were needed at this stage to minimise this risk and protect patients, while the review is ongoing and a thorough assessment of all available data related to the benefit-risk of Esmya is performed.

The PRAC recommended that no new patients should be treated with the medicinal product while the review is ongoing. The provisional measures also include limitation of use of the medicinal product to patients that are currently under therapeutic treatment. With regards to patients under intermittent treatment, the use of the medicinal product should be discontinued in patients who have finalised a previous treatment course.

In addition, the PRAC recommended monitoring of liver function at least monthly in patients under treatment as well as up to four weeks after the discontinuation of treatment. These investigations should be undertaken immediately if a patient shows signs or symptoms compatible with liver injury. Patients who develop transaminase levels > 2 times the upper level of normal during Esmya treatment should stop treatment and be closely monitored.

Furthermore, the PRAC recommended that a healthcare professional communication should be disseminated to inform healthcare professionals (HCPs) about the precautionary measures, awaiting the outcome of the full review of the benefit-risk of Esmya.

Summary of recommendation(s)/conclusions

- The Committee adopted a recommendation to vary¹ the terms of the marketing authorisation(s) for Esmya (ulipristal acetate) as a provisional measure, without prejudice to the final conclusions of the ongoing procedure under Article 20 of Regulation (EC) 726/2004. See EMA press release ([EMA/76828/2018](#)) entitled 'Women taking Esmya for uterine fibroids to have regular liver tests while EMA review is ongoing - No new patients should start treatment for the time being'.
- The PRAC agreed the distribution of a direct healthcare professional communication (DHPC) together with a communication plan.

Post-meeting note: On 16 February 2018, the European Commission issued a Commission Decision on the provisional measures. The PRAC assessment report on provisional measures ([EMA/97889/2018](#)) was published on the EMA website on 21 February 2018.

3.3. Procedures for finalisation

3.3.1. Flupirtine (NAP) - EMEA/H/A-31/1458

Applicant(s): various

PRAC Rapporteur: Ana Sofia Diniz Martins; PRAC Co-rapporteur: Martin Huber

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

Background

A referral procedure under Article 31 of Directive 2001/83/EC conducted to investigate the risk of hepatotoxicity and assess its impact on the benefit-risk balance of flupirtine-containing medicines is to be concluded. The review was initiated further to the results of observational studies indicating a low degree of compliance to restrictions and risk minimisation measures implemented in 2013 as a conclusion of a previous referral procedure under Article 107i of Directive 2001/83/EC ([EMEA/H/A-107i/1363](#)), in view of the risk of liver injury. In addition, cases of drug induced liver injury (DILI), including serious cases, continued to be received in EudraVigilance (EV) with flupirtine-containing medicinal products reported as suspected or interacting products. A final assessment of the data submitted was produced by the Rapporteurs according to the agreed timetable. For further background, see [PRAC minutes March 2013](#), [PRAC minutes May 2013](#), [PRAC minutes June 2013](#), [PRAC minutes May 2014](#), [PRAC minutes June 2014](#), [PRAC Minutes December 2014](#), [PRAC minutes March 2015](#), [PRAC minutes July 2015](#), [PRAC minutes March 2017](#) and [PRAC minutes November 2017](#).

Discussion

The PRAC discussed the conclusion reached by the Rapporteurs and reviewed all newly available safety and efficacy data, including information provided by the MAHs on cases of liver injury, results of observational studies, data available in EudraVigilance and the scientific literature, in the context of the data reviewed in the previous referral procedure in 2013 under Article 107i of Directive 2001/83/EC and in relation to the risk of hepatotoxicity associated to flupirtine-containing medicinal products.

The PRAC considered that there is no new significant information on the demonstrated efficacy of flupirtine in the management of acute (nociceptive) pain (mild, moderate and

¹ Update of SmPC sections 4.2 and 4.4. The package leaflet is updated accordingly

severe). In addition, the PRAC concluded that the safety data confirm that the use of flupirtine-containing medicinal products is associated with a risk of unpredictable and potentially fatal liver injury.

Considering the new reports of liver injury, together with the results of observational studies, indicating a very low compliance to the measures recommended in 2013 to minimise the risk of hepatotoxicity, the PRAC concluded that these measures have not been effective in adequately minimising the risk of hepatotoxicity.

Moreover, the PRAC discussed further risk minimisation proposals and concluded that no feasible measures would ensure effective minimisation of the risk of hepatotoxicity to an acceptable level and therefore this risk outweighs the benefits of flupirtine in the treatment of acute pain, when treatment with other analgesics is contraindicated.

Furthermore, the PRAC could not identify any condition, the fulfilment of which would demonstrate a positive benefit-risk balance for flupirtine-containing medicinal products in their current indication.

The Committee, as a consequence, considered that the benefit-risk balance of flupirtine-containing medicinal products is no longer favourable. Therefore, pursuant to Article 116 of Directive 2001/83/EC, the Committee recommended the revocation of the marketing authorisations for flupirtine-containing medicinal products.

Summary of recommendation(s)/conclusions

- The PRAC adopted a recommendation to revoke the marketing authorisations for flupirtine-containing medicines to be considered by CMDh for a position – see EMA Press Release ([EMA/66114/2018](#)) entitled 'PRAC recommends that the marketing authorisation of the painkiller flupirtine be withdrawn - Serious liver problems continued to be reported despite previous restrictions in use'.
- The PRAC agreed the distribution of a direct healthcare professional communication (DHPC) together with a communication plan.

Post-meeting note: the press release entitled 'Withdrawal of pain medicine flupirtine endorsed – Serious liver problems continued to be reported despite previous restrictions in use' (EMA/153044/2018) representing the position of the CMDh was published on the EMA website on 23/03/2018.

3.3.2. 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 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 to be concluded 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 disorders² to evaluate measures currently in place for oral and topical retinoids for pregnancy prevention and the possible risk of neuropsychiatric disorders. A final assessment of the data submitted was produced by the Rapporteurs according to the agreed timetable. 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](#).

Discussion

The PRAC discussed the conclusion reached by the Rapporteurs. The PRAC considered the totality of the data submitted, including responses from the marketing authorisation holders with regard to the consistency and effectiveness of existing routine and additional risk minimisation measures for oral and topical retinoid-containing medicinal products in relation to teratogenic effects and neuropsychiatric disorders. In addition, the PRAC considered the views of patients and healthcare professionals in relation to their understanding and awareness of the teratogenic risk associated with the use of retinoid-containing medicines.

With regards to the teratogenic risk, the PRAC confirmed that all oral retinoids (acitretin, alitretinoin, bexarotene, isotretinoin and tretinoin) are highly teratogenic and therefore must continue to be contraindicated during pregnancy or in women of child bearing potential unless they are using effective contraception. Given the indications and patient populations that use acitretin, alitretinoin and isotretinoin it was considered that any use of these oral retinoids in female patients at risk of pregnancy must be in accordance with the conditions of a pregnancy prevention programme (PPP). For tretinoin and bexarotene, it was considered that, in light of the oncological indications, specialist management in a hospital setting and population at risk, existing risk minimisation was appropriate and proportionate.

The PRAC also concluded that there was a need to further harmonise and streamline the measures in the PPP including associated educational materials for the oral retinoids acitretin, alitretinoin and isotretinoin, to ensure these are optimal to support discussions between patients and healthcare professionals on the risks and the associated risk minimisation measures.

The PRAC further considered that for the oral retinoids acitretin, alitretinoin and isotretinoin a drug utilisation study (DUS) with a complementary survey should be conducted to assess the effectiveness of the proposed updated risk minimisation measures.

A direct healthcare professional communication (DHPC) was also considered appropriate for all oral and topical retinoids.

With regards to the teratogenic risk of topical retinoids (adapalene, alitretinoin, isotretinoin, tretinoin and tazarotene), the PRAC concluded that the available data show that after topical application, systemic exposure is expected to be negligible and unlikely to result in adverse foetal outcomes. Nevertheless, given that humans are the most sensitive species to retinoid embryopathy and that several other factors may contribute to an increased systemic exposure, such as excessive use and a damaged skin barrier, the PRAC agreed that the teratogenic risk cannot be completely excluded. Therefore, the PRAC recommended that the use of topical retinoids should be contraindicated during pregnancy and in women planning a pregnancy given the non-life-threatening nature of the indications.

² Tretinoin may also be used to treat promyelocytic leukaemia

With regards to neuropsychiatric disorders, the PRAC noted the limitations of the available data and considered that a clear causal relationship could not be established with the oral retinoids. Nevertheless, taking into account the target patient population, the PRAC recognised the possible underlying risk of psychiatric disorders, and therefore recommended some changes to the product information such as warnings and precautions, so that the current level of available evidence is appropriately reflected. Furthermore, the PRAC noted the extremely limited data relating to neuropsychiatric reactions after topical administration of retinoids. Given this and the negligible systemic exposure following topical use, the PRAC considered that no further risk minimisation activities were deemed necessary.

Overall, the PRAC considers that the benefit-risk balance of retinoid-containing medicinal products remains favourable subject to the agreed amendments to the product information and risk management plan, the conditions to the marketing authorisations and the related communication.

The PRAC, as a consequence, recommends the variation to the terms of the marketing authorisations for retinoid-containing medicinal products.

Summary of recommendation(s)/conclusions

- The PRAC adopted, by majority³, a recommendation to vary⁴ the terms of the marketing authorisations for retinoid-containing medicines to be considered by CHMP for an opinion – see EMA Press Release ([EMA/69925/2018](#)) entitled 'PRAC recommends updating measures for pregnancy prevention during retinoid use - Warning on possible risk of neuropsychiatric disorders also to be included for all oral retinoids'.
- The PRAC agreed the distribution of a direct healthcare professional communication (DHPC) together with a communication plan.

Post-meeting note: the press release entitled 'Updated measures for pregnancy prevention during retinoid use - Warning on possible risk of neuropsychiatric disorders also to be included for oral retinoids' (EMA/165360/2018) representing the opinion adopted by the CHMP was published on the EMA website on 23/03/2018.

3.3.3. 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 to be concluded 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

³ The relevant AR containing the divergent views will be published on the EMA website once the procedure is fully concluded

⁴ For all oral retinoids containing acitretin, alitretinoin and isotretinoin: update of SmPC section 4.4. The package leaflet and the labelling are updated accordingly. For all oral retinoids containing acitretin, tretinoin and bexarotene: update of SmPC section 4.4. The package leaflet is updated accordingly. For all oral retinoids products containing alitretinoin and isotretinoin: update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. For all topical retinoids containing adapalene, alitretinoin, isotretinoin, tretinoin and tazarotene: update of SmPC sections 4.3 and 4.6. The package leaflet is updated accordingly

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. A final assessment of the data submitted was produced by the Rapporteurs according to the agreed timetable. For further background, see [PRAC minutes March 2017](#), [PRAC minutes June 2017](#), [PRAC minutes July 2017](#), [PRAC minutes September 2017](#), [PRAC minutes October 2017](#) and [PRAC minutes December 2017](#).

Discussion

The PRAC discussed the conclusion reached by the Rapporteurs. The PRAC considered the totality of the data submitted for valproate and related substances with regard to the teratogenic and neurodevelopmental risks, the use in clinical practice and the effectiveness of the risk minimisation measures in place. This included the responses submitted by the MAHs in writing as well as the outcomes of the scientific advisory groups in neurology and psychiatry. In addition, the PRAC considered the views of patient organisations, patients, families and carers, and the views of healthcare professionals in a public hearing and a dedicated meeting.

The PRAC confirmed the known risk of intra-uterine exposure to valproate and related substances, associated with an increased risk of developmental disorders and congenital anomalies in the offspring. No new significant information was identified regarding this risk.

The PRAC concluded that the risk minimisation measures in place have not been sufficiently effective to prevent unintended *in utero* exposure to valproate and related substances in all indications.

The PRAC also concluded that the risk minimisation measures for medicinal products containing valproate or related substances should be strengthened through contraindication in all indications (epilepsy, bipolar disorders and prophylaxis of migraine) in women/girls of childbearing potential unless the conditions of the pregnancy prevention programme are complied with.

In addition, the PRAC considered that the pregnancy prevention programme (PPP) should reflect that in the indication in epilepsy, if a woman is planning to become pregnant, a specialist experienced in the management of epilepsy must reassess valproate therapy and consider alternative treatment options. Every effort should be made to switch to appropriate alternative treatment prior to conception, and before contraception is discontinued. If switching is not possible, the woman should receive further counselling regarding the valproate risks for the unborn child to support her informed decision making regarding family planning. For their use in pregnancy for the treatment of epilepsy, the PRAC concluded that these medicinal products are contraindicated unless there is no suitable alternative treatment option. For their use in the treatment of bipolar disorders and prophylaxis of migraine these products are contraindicated in pregnancy.

Moreover, the PRAC recommended other changes to the product information such as warnings and precautions for use and updated information on the risks related to exposure during pregnancy to better inform the healthcare professionals and patients.

The PRAC also concluded that there was a need to update the educational materials aimed to fully inform patients and healthcare professionals on the risks to the unborn child when exposed *in utero* to valproate, and to implement some further risk minimisation measures such as a visual reminder on the outer packaging, a patient card and an acknowledgment form to raise awareness about the risks and the need for contraception. The PRAC also recommended post-authorisation studies to assess the effectiveness of the risk minimisation

measures. Core elements of a direct healthcare professional communication (DHPC) were agreed, together with the timelines for its distribution.

Furthermore, the PRAC reviewed the available scientific evidence on the risk of malformations and neurodevelopmental disorders in offspring after paternal exposure, the risk of malformations and neurodevelopmental disorders in the third generation offspring and considered that further research is needed before conclusions can be drawn. The PRAC requested the conduct of post-authorisation studies.

Overall, the Committee considered that the benefit-risk balance of medicinal products containing substances related to valproate remains favourable subject to the agreed conditions to the marketing authorisations, and taking into account the agreed amendments to the product information and other risk minimisation measures.

As a consequence, the Committee recommended the variation to the terms of the marketing authorisations for medicinal products containing substances related to valproate.

Summary of recommendation(s)/conclusions

- The PRAC adopted, by majority⁵, a recommendation to vary⁶ the terms of the marketing authorisations for valproate-containing medicines to be considered by CMDh for a position – see EMA Press Release ([EMA/67672/2018](#)) entitled 'PRAC recommends new measures to avoid valproate exposure in pregnancy - New restrictions on use; pregnancy prevention programme to be put in place'.
- A direct healthcare professional communication (DHPC) and communication plan were also endorsed.

Post-meeting note: the press release entitled 'New measures to avoid valproate exposure in pregnancy endorsed Member State representatives agree new restrictions and pregnancy prevention programme' (EMA/145600/2018) representing the position of the CMDh was published on the EMA website on 23/03/2018.

3.4. Re-examination procedures⁷

None

3.5. Others

None

4. Signals assessment and prioritisation⁸

4.1. New signals detected from EU spontaneous reporting systems

None

⁵ The relevant AR containing the divergent views will be published on the EMA website once the procedure is fully concluded

⁶ Update of SmPC sections 4.2, 4.3, 4.4 and 4.6. The package leaflet is updated accordingly

⁷ Re-examination of PRAC recommendation under Article 32 of Directive 2001/83/EC

⁸ Each signal refers to a substance or therapeutic class. The route of marketing authorisation is indicated in brackets (CAP for Centrally Authorised Products; NAP for Nationally Authorised Products including products authorised via Mutual Recognition Procedures and Decentralised Procedure). Product names are listed for reference Centrally Authorised Products (CAP) only. PRAC recommendations will specify the products concerned in case of any regulatory action required

4.2. New signals detected from other sources

See also Annex I 14.2.

4.2.1. Biotin (NAP)

Applicant(s): various

PRAC Rapporteur: To be appointed

Scope: Signal of interference with clinical laboratory tests

EPITT 19156 – New signal

Background

Biotin is a water-soluble B-vitamin used for the prophylaxis and therapy of biotin deficiency, for the therapy of biotin dependent multiple carboxylase deficiency, and as a traditional use to support the function of the skin or used as vitamin replacement as part of parenteral nutrition.

Following the publication by the FDA of a 'safety communication' alerting to a finding that biotin can significantly interfere with certain laboratory tests and cause incorrect results which may go undetected, a signal of interference with clinical laboratory tests was identified by Germany based on 11 cases of interference retrieved from EudraVigilance as well as from additional literature sources (*Picketty et al.*⁹, *Sharma et al.*¹⁰, *Biscolla et al.*¹¹, *Li et al.*¹²) indicating that even in lower doses (10mg daily) biotin in adults may cause clinically significant interference with clinical laboratory tests. Germany confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

Having considered the available evidence arising from EudraVigilance and other sources, the PRAC agreed that the MAH of Cernevit (biotin) should provide a comprehensive analysis on the risk of biotin interference with laboratory tests including the risk in patients receiving very low doses of biotin (e.g. as part of nutritional therapy) as well as a discussion on the need for risk minimisation activities regarding biotin interference, a discussion of relevant biotin dosage and on the need to update the product information.

The PRAC appointed Valerie Strassman as Rapporteur for the signal.

Summary of recommendation(s)

- The MAH for Cernevit (biotin), Baxter, should submit to EMA, within 60 days, a comprehensive analysis on the risk of biotin interference with laboratory tests including the risk in patients receiving very low doses of biotin, as well as a discussion on the need for risk minimisation activities regarding biotin interference including a discussion on the relevant biotin dosage and a proposal for amending the product information.

⁹ Picketty ML, Polak M, Flechtner I, Gonzales-Briceño L, Souberbielle JC. False biochemical diagnosis of hyperthyroidism in streptavidin-biotin-based immunoassays: the problem of biotin intake and related interferences. *Clin Chem Lab Med.* 2017; 55(6): 780-788

¹⁰ Sharma A, Baumann NA, Shah P. Biotin-induced biochemical grave disease. *JAMA.* 2017; 177(4). doi: 10.1001/jamainternmed.2016.9295

¹¹ Biscolla RPM, Chiamolera MI, Kanashiro I, Maciel RMB, Vieira JGH. A single 10 mg oral dose of biotin interferes with thyroid function tests. *Thyroid.* 2017; 27(8): 1099-1100.

¹² Li D, Radulescu A, Shrestha RT, et al. Association of biotin ingestion with performance of hormone and nonhormone assays in healthy adults. *JAMA.* 2017; 318(12): 1150-1160. doi: 10.1001/jama.2017.13705

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

4.2.2. Human coagulation(plasma-derived) factor VIII:
 human coagulation factor VIII (antihemophilic factor A) (NAP); human coagulation factor VIII (inhibitor bypassing fraction) (NAP); human coagulation factor VIII, human von Willebrand factor - VONCENTO (CAP)
 Recombinant factor VIII:
 antihemophilic factor (recombinant) (NAP); efmoctocog alfa – ELOCTA (CAP); lonoctocog alfa – AFSTYLA (CAP); moroctocog alfa – REFACTO AF (CAP); octocog alfa – ADVATE (CAP), HELIXATE NEXGEN (CAP), IBLIAS (CAP), KOGENATE BAYER (CAP), KOVALTRY (CAP); simoctocog alfa – NUWIQ (CAP), VIHUMA (CAP); susoctocog alfa – OBIZUR (CAP); turoctocog alfa – NOVOEIGHT (CAP); NAP

Applicant(s): Baxalta Innovations GmbH (Obizur), Baxter AG (Advate), Bayer AG (Helixate Nexgen, Iblis, Kogenate Bayer, Kovaltry), CSL Behring GmbH (Afstyla, Voncento), Novo Nordisk A/S (NovoEight), Octapharma AB (Nuwiq, Vihuma), Pfizer Limited (ReFacto AF), Swedish Orphan Biovitrum AB (publ) (Elocta), various

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Signal of inhibitor development in previously untreated patients (PUPs) with haemophilia A treated with plasma-derived vs recombinant coagulation factor VIII concentrates

EPITT 18701 – Related to signal recommendation dated July 2016

Background

Factor VIII-containing medicines are anti-haemorrhagic agents indicated for the treatment of congenital haemophilia A.

Following the publication in the journal *Haematologica* by Calvez T. *et al.*¹³ of complementary data to the dataset assessed by PRAC in 2014 (for further background, see [PRAC minutes November 2014](#) and [PRAC minutes December 2014](#) (EPITT 18134)) for the FranceCoag¹⁴ cohort with an extended follow-up, a higher number of enrolled patients and inclusion of patients treated with a plasma derived factor VIII product, a signal of inhibitor development in previously untreated patients (PUPs) with haemophilia A treated with plasma-derived vs. recombinant coagulation factor VIII concentrates was identified by France. France confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the results from the FranceCoag study and agreed that they are in line with the conclusions of the recently concluded referral procedure under Article 31 of Directive 2001/83/EC on this topic (for further background, see [PRAC minutes May 2017](#) and [PRAC minutes September 2017 \(EMA/H/A-31/1448\)](#)) and that no regulatory action was warranted at this stage. The PRAC noted the importance of data from well-conducted registry studies such as FranceCoag for the pharmacovigilance of haemophilia treatments.

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

¹³ Calvez T, Chambost H, d'Oiron R, Dalibard V, Demiguel V, Doncarli A, Gruel Y, Huguenin Y, Lutz P, Rothschild C, Vinciguerra C, Goudemand J; for FranceCoag Collaborators. Analyses of the FranceCoag cohort support differences in immunogenicity among one plasma-derived and two recombinant factor VIII brands in boys with severe hemophilia A. *Haematologica*. 2018 Jan; 103(1): 179-189. doi: 10.3324/haematol.2017.174706. Epub 2017 Oct 12.

¹⁴ FranceCoag network is a cohort of French patients suffering from inherited deficiencies of coagulation proteins, such as haemophilia A and B, Von Willebrand's disease or other rare inherited bleeding disorders

Summary of recommendation(s)

- The MAHs of human coagulation factor VIII-containing products as well as recombinant factor VIII-containing products should continue to monitor newly emerging data on the incidence of inhibitors in PUPs and review the data in future PSURs.

4.2.3. Paracetamol (NAP)

Applicant(s): various

PRAC Rapporteur: Laurence de Fays

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

EPITT 17796 – Related to signal recommendation dated January 2017

Background

Since the PRAC recommendation dated May 2014 on paracetamol and the signal on ‘drug exposure in pregnancy’ (see [PRAC minutes May 2014](#)), results of several epidemiological studies investigating the effect of exposure to paracetamol during pregnancy and neurodevelopmental outcomes in childhood have become available. The Rapporteur further assessed the newly available data, taking into account the findings and limitations of the studies. For background information, see [PRAC Minutes October 2016](#) and [PRAC minutes January 2017](#).

Discussion

The PRAC discussed the summary of data prepared by Belgium from newly published studies on neurodevelopmental outcomes and urogenital disorders. The PRAC recommended further assessment of the data as regards the validity of available non-clinical studies and existing gaps via a list of questions (LoQ) to the CHMP Safety Working Party ([SWP](#)).

The PRAC appointed Laurence de Fays as Rapporteur for the signal.

The PRAC also recommended that the EMA support the Rapporteur in further assessment of the strengths and limitations of available observational studies.

Summary of recommendation(s)

- The PRAC adopted a LoQ to the SWP.
- The PRAC agreed that the Rapporteur, supported by EMA, will further assess the strengths and limitations of available observational studies.
- The assessment of this review leading to a further PRAC recommendation expected at the PRAC meeting September 2018.

4.3. Signals follow-up and prioritisation

4.3.1. Apixaban - ELIQUIS (CAP) - EMEA/H/C/002148/SDA/026; dabigatran etexilate – PRADAXA (CAP) - EMEA/H/C/000829/SDA/048; edoxaban - LIXIANA (CAP) - EMEA/H/C/002629/SDA/009; rivaroxaban - XARELTO (CAP) - EMEA/H/C/000944/SDA/041

Applicant(s): Bayer AG (Xarelto), Boehringer Ingelheim International GmbH (Pradaxa), Bristol-Myers Squibb- Pfizer EEIG (Eliquis), Daiichi Sankyo Europe GmbH (Lixiana)

PRAC Rapporteur: Menno van der Elst

Scope: Signal of cholesterol embolisms

EPITT 19078 – Follow-up to October 2017

Background

For background information, see [PRAC minutes October 2017](#).

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

Discussion

Having considered the available evidence, the PRAC agreed that the number of possible cases of cholesterol embolism with direct oral anticoagulants (DOAC) is very low in the context of overall usage and that the likelihood of a causal relationship between DOAC treatment and cholesterol embolism is insufficiently robust at this stage. Therefore, the PRAC considered that no regulatory action is necessary at this stage. Nevertheless, the MAHs of DOAC-containing products should continue to monitor these events as part of routine safety surveillance, and present new relevant data in future PSURs. In this respect, due attention should be paid to any relevant new findings from pre-clinical or well-designed observational studies as these may have a greater potential to re-open the signal than additional post-marketing cases.

Summary of recommendation(s)

- No regulatory action is deemed warranted at this stage. Nevertheless, MAHs of DOAC-containing products should continue to monitor these events as part of routine safety surveillance, and present new relevant data in future PSURs.

4.3.2. Baricitinib - OLUMIANT (CAP) - EMEA/H/C/004085/SDA/007

Applicant(s): Eli Lilly Nederland B.V.

PRAC Rapporteur: Patrick Batty

Scope: Signal of pneumonia

EPITT 18950 – Follow-up to October 2017

Background

For background information, see [PRAC minutes October 2017](#).

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

Discussion

Having considered the data from the cumulative review including clinical trial data submitted by the MAH of Olumiant (baricitinib) and in light of the biological plausibility of baricitinib treatment predisposing patients to infections, the PRAC agreed that the available evidence is considered sufficient to warrant an update of the product information accordingly.

Summary of recommendation(s)

- The MAH for Olumiant (baricitinib) should submit to EMA, within 60 days, a variation in view of amending the product information¹⁵.
- In future PSURs, the MAH should closely monitor cases of *Pneumocystis jirovecii* pneumonia.

For the full PRAC recommendation, see [EMA/PRAC/59224/2018](#) published on 05/03/2018 on the EMA website.

4.3.3. [Filgrastim - ACCOFIL \(CAP\) - EMEA/H/C/003956/SDA/002, FILGRASTIM HEXAL \(CAP\) - EMEA/H/C/000918/SDA/020, GRASTOFIL \(CAP\) - EMEA/H/C/002150/SDA/003, NIVESTIM \(CAP\) - EMEA/H/C/001142/SDA/016, RATIOGRASTIM \(CAP\) - EMEA/H/C/000825/SDA/021, TEVAGRASTIM \(CAP\) - EMEA/H/C/000827/SDA/021, ZARZIO \(CAP\) - EMEA/H/C/000917/SDA/020, NAP; lenograstim \(NAP\); lipegfilgrastim – LONQUEX \(CAP\) - EMEA/H/C/002556/SDA/013; pegfilgrastim – NEULASTA \(CAP\) - EMEA/H/C/000420/SDA/058](#)

Applicant(s): Accord Healthcare Limited (Accofil), Amgen Europe B.V. (Neulasta), Apotex Europe BV (Grastofil), Hexal AG (Filgrastim Hexal), Hospira UK Limited (Nivestim), Ratiopharm GmbH (Ratiograstim), Sandoz GmbH (Tevagrastim), Sicor Biotech UAB (Lonquex), Teva GmbH; various

PRAC Rapporteur: Patrick Batty

Scope: Signal of aortitis

EPITT 18940 – Follow-up to September 2017

Background

For background information, see [PRAC minutes September 2017](#).

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

Discussion

Having considered the evidence from MAHs of filgrastim-, lenograstim-, lipegfilgrastim- and pegfilgrastim-containing products, the PRAC agreed that there is at least a reasonable possibility of a causal association between aortitis and granulocyte colony stimulating factor (G-CSF)-containing treatment. The PRAC recommended that MAHs of filgrastim-, lenograstim-, lipegfilgrastim- and pegfilgrastim-containing products should submit a variation in view of amending the product information accordingly.

Summary of recommendation(s)

- The MAHs for filgrastim-, lenograstim-, lipegfilgrastim- and pegfilgrastim-containing products should submit to EMA or to the relevant national competent authorities of the MSs, within 60 days, a variation for amending the product information¹⁶.

For the full PRAC recommendation, see [EMA/PRAC/59224/2018](#) published on 05/03/2018 on the EMA website.

¹⁵ Update of SmPC section 4.8. The package leaflet is to be updated accordingly

¹⁶ Update of SmPC sections 4.4 and 4.8. The package leaflet is to be updated accordingly

4.3.4. Hydroxycarbamide - SIKLOS (CAP) - EMEA/H/C/000689/SDA/033, NAP

Applicant(s): Addmedica, various

PRAC Rapporteur: Laurence de Fays

Scope: Signal of cutaneous lupus erythematosus

EPITT 18939 – Follow-up to September 2017

Background

For background information, see [PRAC minutes September 2017](#).

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

Discussion

Having considered the evidence from MAHs of hydroxycarbamide, the PRAC recommended that MAHs of hydroxycarbamide-containing products should submit a variation in view of amending the product information.

Summary of recommendation(s)

- The MAH(s) for hydroxycarbamide-containing products should submit to EMA or to the relevant national competent authorities of the Member States (MSs), within 60 days, a variation for amending the product information¹⁷.

For the full PRAC recommendation, see [EMA/PRAC/59224/2018](#) published on 05/03/2018 on the EMA website.

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

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 December 2017

Background

For background information, see [PRAC minutes December 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 data from EudraVigilance and the literature, the response from the MAH for Norvir (lopinavir) and Kaletra (lopinavir/ritonavir) and the advice from the CHMP Pharmacokinetics Working Party ([PKWP](#)), the PRAC concluded that an interaction between levothyroxine and ritonavir cannot be ruled out based on

¹⁷ Update of SmPC section 4.8. The package leaflet is to be updated accordingly

spontaneous reports and should therefore be reflected in the product information of all ritonavir- and levothyroxine-containing medicinal products.

Summary of recommendation(s)

- The MAHs for ritonavir-medicinal products (including fixed dose combinations used in hepatitis C treatment) and levothyroxine-containing products with product information that does not mention a possible interaction with protease inhibitors should submit to EMA or to the relevant national competent authorities of the MSs, within 90 days, a variation for amending the product information¹⁸.
- The PRAC also recommended that MSs should consider communicating the outcome of the signal assessment to appropriate patient organisations at national level.

For the full PRAC recommendation, see [EMA/PRAC/59224/2018](#) published on 05/03/2018 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. [Adalimumab - EMEA/H/C/004866](#)

Scope: Treatment of rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis, paediatric plaque psoriasis, hidradenitis suppurativa, uveitis, paediatric uveitis

5.1.2. [Adalimumab - EMEA/H/C/004865](#)

Scope: Treatment of juvenile idiopathic arthritis, axial spondyloarthritis, psoriatic arthritis, psoriasis, paediatric plaque psoriasis, hidradenitis suppurativa, uveitis, paediatric uveitis

5.1.3. [Adalimumab - EMEA/H/C/004320](#)

Scope: Treatment of rheumatoid arthritis, juvenile idiopathic arthritis, axial spondyloarthritis, psoriatic arthritis, psoriasis, paediatric plaque psoriasis, hidradenitis suppurativa, Crohn's disease, paediatric Crohn's disease, ulcerative colitis, uveitis, paediatric uveitis

5.1.4. [Bictegravir, emtricitabine, tenofovir alafenamide - EMEA/H/C/004449](#)

Scope: treatment of adults infected with human immunodeficiency virus-1 (HIV-1)

5.1.5. [Daunorubicin, cytarabine - EMEA/H/C/004282, Orphan](#)

Applicant: Jazz Pharmaceuticals Ireland Limited

Scope (accelerated assessment): Treatment of adults with high-risk acute myeloid leukaemia (AML)

¹⁸ Update of SmPC section 4.5. The package leaflet is to be updated accordingly

5.1.6. Erenumab - EMEA/H/C/004447

Scope: Prophylaxis of migraine in adults

5.1.7. Infliximab - EMEA/H/C/004647

Scope: Treatment of rheumatoid arthritis, Crohn's disease, ankylosing spondylitis, psoriatic arthritis, psoriasis and ulcerative colitis

5.1.8. Inotersen - EMEA/H/C/004782, Orphan

Applicant: Ionis USA Ltd

Scope (accelerated assessment): Treatment of adult patients with hereditary transthyretin amyloidosis (hATTR)

5.1.9. Naldemedine - EMEA/H/C/004256

Scope: Treatment of opioid-induced constipation (OIC) in adult patients

5.1.10. Sodium benzoate - EMEA/H/C/004150, Orphan

Applicant: Lucane Pharma

Scope: Treatment of non-ketotic hyperglycinemia, urea cycle disorders including carbamoyl-phosphate synthase-1 deficiency, ornithine transcarbamylase deficiency, citrullinaemia type 1, argininosuccinic aciduria, hyperargininaemia, N-acetylglutamate synthase deficiency, ornithine translocase deficiency and lysinuric protein intolerance

5.1.11. Sufentanil - EMEA/H/C/004335

Scope: Management of acute moderate to severe pain

5.1.12. Vestronidase alfa - EMEA/H/C/004438, Orphan

Applicant: Ultragenyx Germany GmbH

Scope: Treatment of mucopolysaccharidosis VII (MPS VII; Sly syndrome) for patients of all ages

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. 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

Olaparib is a human poly (ADP¹⁹-ribose) polymerase enzyme inhibitor indicated in 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, including an extension application (line-extension) to introduce 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 providing advice to the CHMP on the necessary updates to the RMP to support this procedure. For further background, see [PRAC minutes September 2017](#) and [PRAC minutes December 2017](#).

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 15.3 and satisfactory responses to the request for supplementary information (RSI) are submitted.
- With regard to the risk of medication error, the PRAC considered that the proposed wording regarding the non-interchangeability of the capsule and tablet formulations was sufficiently reflected in the product information. Therefore, the PRAC supported removing the proposed pictorial representation from the package leaflet. Nevertheless, the PRAC considered that a communication should be sent to healthcare professionals (HCPs) at the time of the launch of the tablet formulation in each Member State in order to raise awareness and minimise the risks associated with medication errors. It was agreed that no additional educational material would be required. Furthermore, the PRAC emphasized the importance of minimising as much as possible the concomitant availability of both formulations on the market and advised careful management of the withdrawal of the capsule formulation from the market.

5.3.2. Oseltamivir - TAMIFLU (CAP) - EMEA/H/C/000402/II/0128

Applicant: Roche Registration Limited

PRAC Rapporteur: Kirsti Villikka

Scope: Update of section 4.6 of the SmPC in order to reflect the final study results from a non-interventional safety study BV29684, which assessed the safety of oseltamivir exposure in pregnant women (listed as a category 3 study in the RMP (MEA099)). The RMP (version 15.0) is updated accordingly

¹⁹ Adenosine diphosphate

Background

Oseltamivir is a selective inhibitor of influenza virus neuraminidase enzymes indicated for the treatment of influenza in adults and children including full term neonates who present symptoms typical of influenza, when influenza virus is circulating in the community. In addition, oseltamivir is indicated for the prevention of influenza in post-exposure prevention in individuals of one year of age or older following contact with a clinically diagnosed influenza case when influenza virus is circulating in the community, for seasonal prevention in individuals one year of age or older in exceptional situations as well as for post-exposure prevention of influenza in infants less than 1 year of age during a pandemic influenza outbreak.

The CHMP is evaluating a type II variation procedure for Tamiflu, a centrally authorised product containing oseltamivir, to reflect the final study results from a non-interventional safety study BV29684, which assessed the safety of oseltamivir in pregnant women (RMP category 3 study) in the product information. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this type II variation. For further background, see [PRAC minutes July 2017](#) and [PRAC minutes November 2017](#). See also under 10.1.1.

Summary of advice

- The RMP for Tamiflu (oseltamivir) in the context of the procedure under evaluation by the CHMP could be considered acceptable provided that an update to RMP version 15.1 and satisfactory responses to the request for supplementary information (RSI) are submitted. The PRAC supported to maintain 'pregnancy' as an important potential risk and to continue to assess annual reviews of pregnancy cases until further notice.
- The PRAC supported maintaining 'exposure during pregnancy' as an important potential risk in the RMP.

See also under 10.1.1.

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. Botulinum B toxin - NEUROBLOC (CAP) - PSUSA/00000428/201706 (with RMP)

Applicant: Eisai Ltd

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

Background

Botulinum B toxin is a neuromuscular blocking agent indicated for the treatment of cervical dystonia (torticollis) in adults.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of NeuroBloc, a centrally authorised medicine containing botulinum B toxin, 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 NeuroBloc (botulinum B toxin) in the approved indication(s) remains unchanged.
- Regarding the effectiveness of the existing educational material for the important identified risks of off-label use and toxin spread, the PRAC noted the poor response rate to the established questionnaires. Taking into account that the product has been on the market for many years, that there has been a decrease in sales and patient exposure, as well as the low number of adverse drug reactions (ADR) reported, the PRAC considered that, at this stage, routine risk minimisation measures and routine pharmacovigilance activities are sufficient. As a consequence, the educational materials should be discontinued and removed as a condition to the marketing authorisation. Therefore the current terms of the marketing authorisation(s) should be varied²⁰.

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. Carfilzomib - KYPROLIS (CAP) - PSUSA/00010448/201707

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

Background

Carfilzomib is a tetrapeptide epoxyketone proteasome inhibitor indicated in combination with either lenalidomide and dexamethasone or dexamethasone alone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Kyprolis (carfilzomib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include 'herpes zoster infection' and 'confusional state' as undesirable effects with a common frequency. The posology and method of administration section is aligned accordingly regarding 'herpes zoster infection'. Therefore the current terms of the marketing authorisation(s) should be varied²¹.
- In the next PSUR, the MAH should refine its review of cases of medication error to define if those were reported with or without lenalidomide in combination. In addition, the MAH

²⁰ Update of Annex IID. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

²¹ Update of SmPC sections 4.2 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

should monitor cases reporting re-activation of viral infection and efforts should be made to gather information on whether antiviral prophylaxis was used. Moreover, the MAH should provide a cumulative analysis of cases of progressive multifocal leukoencephalopathy (PML) and disorders other than PML that are caused by JC²² virus. The discussion should include a discussion on the impact of duration of treatment.

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. Icatibant - FIRAZYR (CAP) - PSUSA/00001714/201707

Applicant: Shire Orphan Therapies GmbH

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

Background

Icatibant is a selective competitive antagonist at the bradykinin type 2 (B2) receptor indicated for symptomatic treatment of acute attacks of hereditary angioedema (HAE) in adults, adolescents and children aged 2 years and older, with C1-esterase-inhibitor deficiency.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Firazyr, a centrally authorised medicine containing icatibant, 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 Firazyr (icatibant) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include 'urticaria' as an undesirable effect of unknown frequency. Therefore the current terms of the marketing authorisation(s) should be varied²³.

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. Idelalisib - ZYDELIG (CAP) - PSUSA/00010303/201707

Applicant: Gilead Sciences International Limited

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

Background

Idelalisib is a phosphatidylinositol 3-kinase p110 δ (PI3K δ) inhibitor indicated in combination with an anti-CD20 monoclonal antibody (rituximab or ofatumumab) for the treatment of adult

²² John Cunningham virus

²³ 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

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. 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.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Zydelig, a centrally authorised medicine containing idelalisib, 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 Zydelig (idelalisib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning on reported cases of progressive multifocal leukoencephalopathy (PML). Therefore the current terms of the marketing authorisation(s) should be varied²⁴.
- In the next PSUR, the MAH should follow-up and provide further details to confirm the indications reported in some of the off label use cases.

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

6.1.5. Perampanel - FYCOMPA (CAP) - PSUSA/00009255/201707

Applicant: Eisai Europe Ltd.

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

Background

Perampanel is a selective, non-competitive antagonist of the ionotropic α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptor on post-synaptic neurons and is indicated for the adjunctive treatment of partial-onset seizures with or without secondarily generalised seizures in adult and adolescent patients from 12 years of age with epilepsy. Perampanel is also indicated for the adjunctive treatment of primary generalised tonic-clonic seizures in adult and adolescent patients from 12 years of age with idiopathic generalised epilepsy.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Fycompa, a centrally authorised medicine containing perampanel, 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 Fycompa (perampanel) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add a warning on severe cutaneous adverse reactions (SCARs) including drug reaction with eosinophilia and

²⁴ Update of SmPC section 4.4. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

systemic symptoms (DRESS) in association with perampanel treatment. In addition, SCARs should be added as an undesirable effect with an unknown frequency. Therefore the current terms of the marketing authorisation(s) should be varied²⁵.

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. Temozolomide - TEMODAL (CAP) - PSUSA/00002886/201707

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Temozolomide is a triazene indicated for the treatment of adult patients with newly-diagnosed glioblastoma multiforme concomitantly with radiotherapy (RT) and subsequently as monotherapy treatment as well as for the treatment of children from the age of three years, adolescents and adult patients with malignant glioma, such as glioblastoma multiforme or anaplastic astrocytoma, showing recurrence or progression after standard therapy.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Temodal, a centrally authorised medicine containing temozolomide, and issued a recommendation on its marketing authorisations.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Temodal (temozolomide) in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include 'sepsis' as an undesirable effect with an uncommon frequency. Therefore the current terms of the marketing authorisations should be varied²⁶.

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

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

See also Annex I 16.2.

²⁵ Update of SmPC sections 4.2 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

²⁶ Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

6.2.1. Fentanyl²⁷ - EFFENTORA (CAP), INSTANYL (CAP), PECFENT (CAP); NAP - PSUSA/00001369/201704

Applicants: Teva B.V. (Effentora), Takeda Pharma A/S (Instanyl), Archimedes Development Limited (PecFent), various

PRAC Rapporteur: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

Background

Fentanyl is an opioid analgesic indicated²⁸ for the treatment of breakthrough pain (BTP) in adults with cancer who are already receiving maintenance opioid therapy for chronic cancer pain.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Effentora, Instanyl and Pecfent, centrally authorised medicines containing fentanyl, as well as nationally authorised medicines containing fentanyl under review, and issued a recommendation on their marketing authorisations²⁹.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of fentanyl-containing medicinal products (transmucosal route of administration) in the approved indications remains unchanged.
- Nevertheless, the product information³⁰ should be updated to include a warning on hyperalgesia and absence of adequate pain control; to introduce information on the possible mechanistic effects of fentanyl on the hypothalamic-pituitary-adrenal or – gonadal axes; and to modify the warning on iatrogenic addiction following opioid abuse from rare to unknown as well as to include ‘drug dependence (addiction)’ and ‘drug abuse’ as undesirable effects of unknown frequency, together with ‘neonatal withdrawal syndrome’. Therefore the current terms of the marketing authorisations should be varied^{31,32}.
- In the next PSUR³³, the MAHs should provide further information on the safety concerns of overdose, respiratory depression, misuse, drug dependence, drug abuse, and off-label use. In addition, the MAHs should provide detailed cases of medication error and discuss the definition of long-term use which appeared different among the MAHs. Moreover, the MAH for Actiq (oral transmucosal fentanyl citrate) and Effentora (fentanyl citrate buccal tablet) should, in relation to the brain lesion safety concern, discuss the mechanism of mineralisation and necrosis observed in rats together with its relevance to humans.

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.

²⁷ Transmucosal route of administration only

²⁸ Transmucosal route of administration only

²⁹ Transmucosal route of administration only

³⁰ Transmucosal route of administration only

³¹ Transmucosal route of administration only

³² Update of SmPC sections 4.2, 4.4, 4.8 and 5.1. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

³³ Transmucosal route of administration only

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

See also Annex I 16.3.

6.3.1. Interferon alfa-2a (NAP) - PSUSA/00009197/201706

Applicant(s): various

PRAC Lead: Sabine Straus

Scope: Evaluation of a PSUSA procedure

Background

Interferon alfa-2a is a recombinant interferon, an antiviral and antineoplastic agent, indicated for the treatment of neoplasms of the lymphatic or hematopoietic system (Hairy cell leukaemia, multiple myeloma, cutaneous T-cell lymphoma, Philadelphia chromosome-positive chronic myelogenous leukemia, thrombocytosis associated with myeloproliferative diseases) as well as an adjunctive treatment to chemotherapy (with or without radiotherapy) in patients with low-grade non-Hodgkin's lymphoma. Interferon alfa-2a is also indicated for the treatment of solid neoplasms (acquired immune deficiency syndrome (AIDS)-related Kaposi's sarcoma in patients without a history of opportunistic infection, advanced renal cell carcinoma, metastatic malignant melanoma, and surgically-resected malignant melanoma without nodal or distant metastases) as well as for the treatment of viral diseases (chronic hepatitis B in patients with elevated serum alanine transaminase (ALT) and markers for viral replication, chronic hepatitis C (CHC) in patients who are positive for hepatitis C virus antibodies and have elevated serum ALT without liver decompensation (Child's class A), and condylomata acuminata).

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine containing interferon alfa-2a, 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 interferon alfa-2a-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include 'skin depigmentation' and 'hearing impairment' as undesirable effects with an unknown frequency. Therefore the current terms of the marketing authorisation(s) should be varied³⁴.
- In the next PSUR, the MAHs should provide a review of the risk of 'thrombotic microangiopathy' from all sources together with a detailed discussion. Based on the review, the MAH should propose an update of 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.

³⁴ 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

6.3.2. Ibuprofen, pseudoephedrine (NAP) - PSUSA/00001711/201707

Applicant(s): various

PRAC Lead: Caroline Laborde

Scope: Evaluation of a PSUSA procedure

Background

Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID) and pseudoephedrine hydrochloride is a sympathomimetic agent. In combination, ibuprofen/pseudoephedrine is indicated for the symptomatic relief of nasal/sinus congestion with headache, fever and pain associated with the common cold and flu in adults and adolescents over 12 or 15 years of age.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of ibuprofen/pseudoephedrine-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include severe skin reactions including acute generalised exanthematous pustulosis (AGEP) as a warning and as an undesirable effect with an unknown frequency to underline that AGEP may occur with pseudoephedrine-containing products. Therefore the current terms of the marketing authorisation(s) should be varied³⁵.
- In the next PSUR, the MAHs should provide cumulative reviews of serious cases of liver injury and cases of ischemic colitis, including data from clinical trials, reports from post-marketing experience for the ibuprofen/pseudoephedrine combination as well as literature data relating to ibuprofen, pseudoephedrine and the ibuprofen/pseudoephedrine combination. MAHs should provide detailed analyses on a possible causal relationship and propose risk minimisation measures as applicable. The MAH Sanofi should also provide a cumulative review of cases of vasculitis associated with the use of the ibuprofen/pseudoephedrine combination and discuss the need for product information updates accordingly.

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. Misoprostol³⁶ (NAP) - PSUSA/00010291/201706

Applicant(s): various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

³⁵ Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

³⁶ Gastrointestinal indication only

Background

Misoprostol is a synthetic prostaglandin E1 analogue with ulcer healing, gastric acid anti-secretory and mucosal protective properties. Misoprostol is indicated (in the gastrointestinal therapeutic area) in co-administration with nonsteroidal anti-inflammatory drugs (NSAIDs) for the treatment and prevention of gastric and duodenal ulcers, haemorrhagic lesions, and erosions induced by NSAIDs.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing misoprostol under review, 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 misoprostol-containing medicinal products in the approved indications³⁷ in the gastrointestinal therapeutic area remains unchanged.
- Nevertheless, the product information³⁸ should be updated to revise the warning on teratogenicity, including adapting the contraindication in woman of childbearing potential accordingly, and changing the MedDRA PT³⁹ of the undesirable effect 'birth defect' for 'foetal malformation'. In addition, the frequency of the undesirable effects 'foetal malformation' and 'uterine rupture' should be changed respectively to common and to rare. Therefore the current terms of the marketing authorisation(s) should be varied⁴⁰.
- In the next PSUR, the MAHs should provide a cumulative review of cardiovascular events in relation to misoprostol use, together with a discussion on the risk of cardiovascular adverse events per indication of use (i.e. gastrointestinal indication as well as gynaecological and obstetric indications), dosage and route of administration as well as a discussion on the need to update the product information as applicable. In addition, the MAHs should provide a cumulative review and interval analysis of off-label use as well as a discussion on the need of additional risk minimisation measures to minimise the risks associated with off-label use.

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

6.3.4. Nitrous oxide (NAP); nitrous oxide, oxygen (NAP) - PSUSA/00010572/201706

Applicant(s): various

PRAC Lead: Amy Tanti

Scope: Evaluation of a PSUSA procedure

Background

Nitrous oxide (N₂O) is a colourless, sweet smelling gas. It is mainly administered with varying concentrations of oxygen, in anaesthesia, in combination with other inhalation

³⁷ Gastrointestinal indication only

³⁸ Gastrointestinal indication only

³⁹ Medical dictionary for regulatory activities – Preferred Terms

⁴⁰ Update of SmPC section 4.3, 4.6 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

anaesthetics or intravenous anaesthetics, and in analgesia where it is used in situations where pain relief/sedation of rapid onset and rapid offset are desirable.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine containing nitrous oxide, 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 nitrous oxide-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to add a warning on the risks of addiction and abuse of nitrous oxide and the inactivation of vitamin B12, as well as to include 'addiction, myeloneuropathy, neuropathy, subacute degeneration of the spinal cord' as undesirable effects of unknown frequency. Therefore the current terms of the marketing authorisation(s) should be varied⁴¹.
- In the next PSUR, the MAH should discuss the important emerging safety and efficacy findings for nitrous oxide through scientific publications, investigate the signal of cardiovascular disorders through a literature and case review of the related MedDRA PTs⁴² and also investigate the signal of sensory disorders through a literature and case review of the related MedDRA PTs.

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

6.4. Follow-up to PSUR/PSUSA procedures

See also Annex I 16.4.

6.4.1. Abatacept - ORENCIA (CAP) - EMEA/H/C/000701/LEG 057

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Kirsti Villikka

Scope: Submission of a cumulative review of cases on *Pneumocystis jirovecii* infections as requested in the conclusions of PSUSA/00000013/201612 adopted in September 2017

Background

Abatacept is a selective co-stimulation modulator indicated in combination with methotrexate for the treatment of moderate to severe rheumatoid arthritis (RA) in adult patients who responded inadequately to previous therapy with one or more disease-modifying anti-rheumatic drugs (DMARDs), for the treatment of highly active and progressive disease in adult patients with rheumatoid arthritis not previously treated with methotrexate as well as for the treatment of moderate to severe active polyarticular juvenile idiopathic arthritis (JIA) in paediatric patients 6 years of age and older under certain conditions. In addition, alone or

⁴¹ Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

⁴² Medical dictionary for regulatory activities – Preferred Terms

in combination with methotrexate, abatacept is indicated for the treatment of active psoriatic arthritis (PsA) in adult patients under certain conditions.

Following the evaluation of the most recently submitted PSUR for the above mentioned medicine(s), the PRAC requested the MAH to submit further data (for background, see [PRAC minutes September 2017](#)). The responses were assessed by the Rapporteur for further PRAC advice.

Summary of advice/conclusion(s)

- Based on the evidence from a dedicated pre-clinical study, clinical trials of abatacept vs placebo and post-marketing data, the PRAC agreed that a causal association between abatacept use and *Pneumocystis jirovecii* infections cannot be established at this stage. Overall, the PRAC agreed that data do not indicate a specific risk of *Pneumocystis jirovecii* infection. Therefore, the PRAC concluded that any new data can be reviewed in future PSURs. The MAH should closely monitor cases of *Pneumocystis jirovecii* infections.

6.4.2. Sorafenib - NEXAVAR (CAP) - EMEA/H/C/000690/LEG 038

Applicant: Bayer AG

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of an updated cumulative review on hypoglycaemia as requested in the conclusions of PSUSA/00002773/201612 adopted in September 2017

Background

Sorafenib is a multikinase inhibitor indicated for the treatment of hepatocellular carcinoma, for the treatment of patients with advanced renal cell carcinoma who have failed prior interferon-alpha or interleukin-2 based therapy or are considered unsuitable for such therapy, as well as for the treatment of patients with progressive, locally advanced or metastatic, differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma, refractory to radioactive iodine.

Following the evaluation of the most recently submitted PSUR for the above mentioned medicine(s), the PRAC requested the MAH to submit further data (for background, see [PRAC minutes September 2017](#)). The responses were assessed by the Rapporteur for further PRAC advice.

Summary of advice/conclusion(s)

- Based on the evidence from the pre-clinical study, pooled data from randomized clinical studies of sorafenib vs placebo, cases with positive dechallenge and dechallenge-rechallenge from the post marketing safety database as well as from the supportive literature, the PRAC considered that a causal association between sorafenib and hypoglycaemia could not be excluded. Therefore, the PRAC agreed that this should be reflected in the product information.
- The MAH should submit a variation to EMA, within 60 days, to update the product information to add hypoglycaemia as a warning and as an undesirable effect.

7. Post-authorisation safety studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)⁴³

See also Annex I 17.1.

7.1.1. Chenodeoxycholic acid – CHENODEOXYCHOLIC ACID LEADIANT (CAP) - EMEA/H/C/PSP/S/0057

Applicant: Leadiant GmbH

PRAC Rapporteur: Adam Przybylkowski

Scope: Protocol for a cerebrotendinous xanthomatosis registry: a long term non-interventional follow-up of safety and effectiveness of Chenodeoxycholic acid Leadiant (chenodeoxycholic acid)

Background

Chenodeoxycholic acid Leadiant is a centrally authorised medicine containing chenodeoxycholic acid, a primary bile acid preparation. It is indicated for the treatment of inborn errors of primary bile acid synthesis due to sterol-27-hydroxylase deficiency (presenting as cerebrotendinous xanthomatosis (CTX)) in infants, children and adolescents aged 1 month to 18 years and adults.

Since Chenodeoxycholic acid Leadiant has been approved under exceptional circumstances, pursuant to Article 14(8) of Regulation (EC) No 726/2004, the MAH should submit as a post authorisation measure the results of a study deriving from a registry of patients with inborn errors of primary bile acid synthesis due to sterol-27-hydroxylase deficiency in infants, children and adolescents aged 1 month to 18 years and adults in order to collect long-term safety and efficacy data in patients treated with chenodeoxycholic acid. As part of this specific obligation, the MAH had to submit the corresponding protocol by 30 November 2011. The procedure started on 11 December 2017.

Endorsement/Refusal of the protocol

- The PRAC, having considered the amended protocol version 1.0 in accordance with Article 107n of Directive 2001/83/EC, objected to the protocol for the above listed medicinal product, as the Committee considered that that the design of the study did not fulfil the study objectives.
- The PRAC therefore recommended that the MAH amend the protocol accordingly and provide the composition of the scientific committee, the precise definition of the endpoints of effectiveness, clarification on variables, a definition of the sample size, as well as discuss the feasibility of inclusion of a natural historical cohort.
- The MAH should submit a revised PASS protocol within 60 days to EMA. A 60 days-assessment timetable will be applied.

7.2. Protocols of PASS non-imposed in the marketing authorisation(s)⁴⁴

See also Annex I 17.2.

⁴³ In accordance with Article 107n of Directive 2001/83/EC

⁴⁴ 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

7.2.1. Canagliflozin - INVOKANA (CAP) - EMEA/H/C/002649/MEA 013.1

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Valerie Strassmann

Scope: MAH's response to MEA 013 [PASS protocol for a US epidemiology database study to further characterise the incidence of below-knee lower limb amputation in patients taking canagliflozin (listed as a category 3 study in RMP) as per the outcome of 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)] as requested in the request for supplementary information (RSI) adopted in September 2017

Background

Invokana is a centrally authorised medicine containing canagliflozin, a sodium-glucose cotransporter-2 (SGLT2) inhibitor indicated in adults aged 18 years and older with type 2 diabetes mellitus (T2DM) to improve glycaemic control as monotherapy or as add-on therapy.

As part of the RMP for Invokana (canagliflozin), as modified as per the outcome of the referral under 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](#)), the MAH for canagliflozin was required to provide for review by PRAC a PASS protocol for a planned US epidemiology database study to further characterise the incidence of below-knee lower limb amputation in patients taking canagliflozin. The MAH was requested to provide supplementary information by PRAC in September 2017 (for further background, see [PRAC minutes February 2017](#) and [PRAC minutes September 2017](#)). The MAH submitted in November 2017 their responses for the requested supplementary information and a new protocol version 1.0, for a PASS study entitled 'Comparison of canagliflozin vs. alternative antihyperglycemic treatments on risk of heart failure hospitalisation and amputation for patients with Type 2 Diabetes Mellitus and the subpopulation with established cardiovascular disease' (as part of the RMP but outside the scope of Article 107n of Directive 2001/83/EC). These were assessed by the Rapporteur. The PRAC was requested to provide advice to CHMP on this new protocol version 1 submitted by the MAH

Summary of advice

- The PRAC considered the proposed study design does not fulfil the study objectives, and the study protocol for Invokana (canagliflozin) could only be acceptable provided that an updated protocol including the primary objective of the study limited to the evaluation of lower limb amputation only, and satisfactory responses to a list of questions agreed by the PRAC, is submitted to EMA within 60 days.

7.2.2. Canagliflozin, metformin - VOKANAMET (CAP) - EMEA/H/C/002656/MEA 012.1

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to MEA 012 [PASS protocol for a US epidemiology database study to further characterise the incidence of below-knee lower limb amputation in patients taking canagliflozin (listed as a category 3 study in RMP) as per the outcome of 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 (EMA/H/A-20/1442)] as requested in the request for supplementary information (RSI) adopted in September 2017

Background

Vokanamet is a centrally authorised combination medicine containing canagliflozin, a sodium-glucose cotransporter-2 (SGLT2) inhibitor, and metformin, a biguanide. Canagliflozin, in combination with metformin, is indicated in adults aged 18 years and older with T2DM as an adjunct to diet and exercise to improve glycaemic control under certain conditions.

As part of the RMP for Vokanamet (canagliflozin/metformin), as modified as per the outcome of the referral under 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 ([EMA/H/A-20/1442](#)), the MAH for canagliflozin was required to provide for review by PRAC a PASS protocol for a planned US epidemiology database study to further characterise the incidence of below-knee lower limb amputation in patients taking canagliflozin. The MAH was requested to provide supplementary information by PRAC in September 2017 (for further background, see [PRAC minutes February 2017](#) and [PRAC minutes September 2017](#)). The MAH submitted in November 2017 their responses for the requested supplementary information and a new protocol version 1.0, for a PASS study entitled 'Comparison of canagliflozin vs. alternative antihyperglycemic treatments on risk of heart failure hospitalisation and amputation for patients with Type 2 Diabetes Mellitus and the subpopulation with established cardiovascular disease' (as part of the RMP but outside the scope of Article 107n of Directive 2001/83/EC). These were assessed by the Rapporteur. The PRAC was requested to provide advice to CHMP on this new protocol version 1 submitted by the MAH.

Summary of advice

- The study protocol for Vokanamet (canagliflozin/metformin) could only be acceptable provided that an updated protocol including the primary objective of the study limited to evaluation of lower limb amputation, and satisfactory responses to a list of questions agreed by the PRAC, is submitted to EMA within 60 days.

7.3. Results of PASS imposed in the marketing authorisation(s)⁴⁵

7.3.1. Rivaroxaban – XARELTO (CAP) - EMA/H/C/PSR/S/0012

Applicant: Bayer AG

PRAC Rapporteur: Qun-Ying Yue

Scope: Results of an observational post-authorisation modified prescription-event monitoring (M-PEM) safety study to monitor the safety and utilisation of Xarelto (rivaroxaban) for the prevention of stroke in patients with atrial fibrillation (AF), treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE following an acute DVT in the primary care setting in England, extended to include acute coronary syndrome patients

Background

⁴⁵ In accordance with Article 107p-q of Directive 2001/83/EC

Xarelto is a centrally authorised medicine containing rivaroxaban, a direct factor Xa inhibitor, that, co-administered with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine, is indicated for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers.

The MAH was required as a condition to the marketing authorisation ([Annex II](#)) to conduct a post-authorisation study program that addresses the safety of rivaroxaban in the secondary prevention of acute coronary syndrome (ACS) outside the clinical trial setting, especially with regard to incidence, severity, management and outcome of bleeding events in all populations and particularly in patients at increased risk of bleeding. The timeframe stated the submission of annual interim analyses reports provided beginning Q4 2015 until completion of the study program, the submission of a cumulative interim report by Q4 2017 and the submission of final study reports by Q4 2020. For background information, see [PRAC minutes March 2016](#). The MAH submitted the final study report which was assessed by the Rapporteur.

Summary of advice

- Based on the review of the final report of the non-interventional PASS version 1, the PRAC considered that further supplementary information should be requested before a recommendation can be made.
- The PRAC considered that the MAH should provide a discussion on potential consequences of the response rate based on any available comparisons that can be made between responders and non-responders, considering patient, facility and practitioner characteristics. In addition, the MAH should further discuss if early onset of DVT and PE within the DVT/PE indication group suggests any new safety concern and provide further information to enable better understanding of the discrepancy in mortality between different studies.
- The MAH should submit responses to the request for supplementary information within 60 days to EMA. A 60 days-assessment timetable will be applied.

7.3.2. Thiocolchicoside (NAP) - EMEA/H/N/PSR/J/0008

Applicant: Sanofi

PRAC Rapporteur: Amelia Cupelli

Scope: Results for a joint PASS survey evaluating the effectiveness of risk minimisation measures among healthcare professionals to assess their knowledge and attitudes on prescribing conditions of thiocolchicoside-containing medicinal products for systemic use in France, Greece, Italy and Portugal

Background

Thiocolchicoside is a semi-synthetic sulfurated colchicoside derivative with a muscle relaxant pharmacological activity indicated as an adjuvant for the treatment of painful muscle contractures in acute spinal pathology in adults and adolescents from 16-years onwards.

In line with the conclusions of a referral procedure under Article 31 of Directive 2001/83/EC conducted in 2014 for thiocolchicoside-containing medicines ([EMEA/H/A-1361](#)), MAHs were required ([Annex IV](#)) as a condition to the marketing authorisations to provide within the risk management plan submission, a protocol for a drug utilisation study to characterise prescribing practices for the medicinal products during typical clinical use in representative

groups of prescribers and to assess the main reasons for prescription. The final study report had to be submitted by November 2017. For background information, see [PRAC minutes September 2015](#), [PRAC minutes October 2015](#), [PRAC minutes March 2016](#) and [PRAC minutes September 2016](#). The MAH submitted the final study report which was assessed by the Rapporteur.

Summary of advice

- Based on the review of the final report of the non-interventional PASS version 3.0, PRAC considered that the benefit-risk balance of medicinal products containing thiocolchicoside concerned by the PASS final report remains unchanged. Nevertheless, the PRAC recommended that the terms of the marketing authorisation(s) should be varied to update the condition set in the Annex IV in order to require the submission of the results of the drug utilisation study to characterise prescribing practices for the medicinal products during typical clinical use in representative groups of prescribers and to assess the main reasons for prescription by November 2019.

7.4. Results of PASS non-imposed in the marketing authorisation(s)⁴⁶

See also Annex I 17.4.

7.4.1. 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 (listed as a category 3 study in the RMP): 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

Background

Eylea is a centrally authorised medicine containing aflibercept, an ophthalmological antineovascularisation agent. Eylea (aflibercept) is indicated in adults for the treatment of neovascular (wet) age-related macular degeneration (AMD), for the treatment of visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO), for the treatment of visual impairment due to diabetic macular oedema (DME) and for the treatment of visual impairment due to myopic choroidal neovascularisation (myopic CNV).

As stated in the RMP of Eylea (aflibercept), the MAH for Eylea (aflibercept) conducted a non-imposed non-interventional PASS (study 16526) to evaluate the physician and patient knowledge of safety and safe use information for aflibercept in Europe as stated in the EU Educational Material for Eylea (aflibercept). The Rapporteur assessed the MAH's final study report.

Summary of advice

- Based on the available data and the Rapporteur's review, the PRAC considered that supplementary information should be submitted by the MAH before conclusions can be drawn.

⁴⁶ In accordance with Article 61a (6) of Regulation (EC) No 726/2004, in line with the revised variations regulation for any submission as of 4 August 2013

- The MAH should submit an updated RMP, in order to include the commitment for updating and re-distributing the educational materials, and especially to conduct a follow-up survey. In addition, the MAH is requested to capture in the RMP, with regards to the follow-up survey (a category 3 study), the provision of submission of a corresponding study protocol for review and endorsement by PRAC within 3 months from the EC decision, as well as the provision for submission of the corresponding final study report within 6 months after completion of the follow-up survey.

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. Pegvisomant - SOMAVERT (CAP) - EMEA/H/C/000409/MEA 061.1

Applicant: Pfizer Limited

PRAC Rapporteur: Caroline Laborde

Scope: MAH's response to MEA 061 [Interim report from study A6291010 (ACROSTUDY): a multicentre, post marketing surveillance study of pegvisomant therapy in patients with acromegaly [due date: final report due date: 2019]] as per the request for supplementary information (RSI) adopted in September 2017

Background

Somavert is a centrally authorised medicine containing pegvisomant, a growth hormone receptor antagonist, indicated for the treatment of adult patients with acromegaly who have had an inadequate response to surgery and/or radiation therapy and in whom an appropriate medical treatment with somatostatin analogues did not normalize insulin-like growth factor 1 (IGF-1) concentrations or was not tolerated.

As a condition to the marketing authorisation, the MAH had the obligation to provide safety information from 1,000 patients with acromegaly treated with Somavert (pegvisomant) and monitored for at least 5 years and consequently set up the Acromegaly study (ACROSTUDY), initiated in 2004, as a non-randomized, open-label, multinational, multicentre, non-interventional PASS. Once the condition was fulfilled in 2013, the MAH decided to extend the study and modify the study protocol. Further to the submission of the interim results (interim study report versions 1.0 and 2.0), the MAH was requested to submit supplementary information (for further background, see [PRAC minutes September 2017](#)). The requested supplementary information was assessed by the Rapporteur for PRAC review.

Summary of advice

- The safety data from Acrostudy patients was considered in line with the outcome of the data assessed within the last PSUSA (PSUSA/00002328/201611 concluded in July 2017). Overall, there was no new safety concern arising from the analysis of PASS interim results. The final study report is expected by 2019.
- The post-authorisation measure is considered fulfilled and the MAH should submit a variation to EMA within 60 days in view of amending the product information regarding the hepatic risk.

7.6. Others

See also Annex I 17.6.

7.6.1. Cariprazine - REAGILA (CAP) - EMEA/H/C/002770/MEA 005

Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Protocol for a PASS RGH-188-303: a randomized, open-label, ophthalmologist-masked study in approximately 1,000 patients with schizophrenia to compare lens opacity changes during long-term treatment with cariprazine versus risperidone (from initial opinion/MA)

Background

Reagila is a centrally authorised medicine containing cariprazine, an anti-psychotic indicated for the treatment of schizophrenia in adult patients.

As part of the RMP, the MAH was required to perform a long-term safety study to detect cataractogenic changes to further characterize the safety concern of 'ocular adverse events (lenticular changes and cataract)' in clinical practice. The MAH submitted in October 2017 an initial study protocol for the PASS study entitled 'a multicentre, open label, flexible-dose, parallel-group evaluation of the cataractogenic potential of cariprazine and risperidone in the long-term treatment of patients with schizophrenia (CLARITY)' which was assessed by the Rapporteur. For further background, see [PRAC minutes January 2018](#).

Summary of advice

- The PRAC considered that a clinical trial would be very difficult to achieve, given the weak effect of cariprazine on cataract formation and its similarity with placebo and other anti-psychotic drugs.
- The issue of potential cataract formation was considered as currently sufficiently covered in the product information and could be further monitored via routine pharmacovigilance. Therefore, the PRAC considered that the proposed study is not considered warranted, at this stage, from a safety perspective.
- An updated RMP should be submitted at the next regulatory opportunity, to remove the study from the pharmacovigilance plan.

7.7. 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.

7.8. Ongoing Scientific Advice

None

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

None

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

8.1. Annual reassessments of the marketing authorisation

See Annex I 18.1.

8.2. Conditional renewals of the marketing authorisation

See Annex I 18.2.

8.3. Renewals of the marketing authorisation

See also Annex I 18.3.

8.3.1. Lipegfilgrastim - LONQUEx (CAP) - EMEA/H/C/002556/R/0039 (with RMP)

Applicant: Sicor Biotech UAB

PRAC Rapporteur: Patrick Batty

Scope: 5-year renewal of the marketing authorisation

Background

Lonquex is a centrally authorised medicine authorised in 2013, containing lipegfilgrastim, a recombinant pegylated granulocyte colony stimulating factor (G-CSF). Lonquex (lipegfilgrastim) is indicated for the reduction in the duration of neutropenia and the incidence of febrile neutropenia in adult patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes).

The MAH submitted an application for renewal of the marketing authorisation for opinion by the CHMP. The PRAC is responsible for providing advice to the CHMP on this renewal with regard to safety and risk management aspects.

Summary of advice

- Based on the review of the available pharmacovigilance data for Lonquex (lipegfilgrastim) and the CHMP Rapporteur's assessment report, the PRAC considered that a second five-year renewal of the marketing authorisation is warranted on the basis of pharmacovigilance grounds relating to the ongoing imposed PASS (XM22-ONC-40041⁴⁷). The final study report is expected by December 2018.
- In addition, the PRAC supported updating the product information⁴⁸ to include a warning on glomerulonephritis as well as to add 'renal and urinary disorders' and 'glomerulonephritis' as undesirable effects given that glomerulonephritis can be severe and is considered to be a class effect for G-CSFs with cases reported in healthy donors and in cancer patients.

⁴⁷ PASS to further investigate the risks of disease progression and mortality associated with Lonquex in patients with malignancy treated with cytotoxic chemotherapy

⁴⁸ Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly

8.3.2. Lomitapide - LOJUXTA (CAP) - EMEA/H/C/002578/R/0029 (with RMP)

Applicant: Aegerion Pharmaceuticals Limited

PRAC Rapporteur: Menno van der Elst

Scope: 5-year renewal of the marketing authorisation

Background

Lojuxta is a centrally authorised medicine authorised in 2013, containing lomitapide, a selective inhibitor of microsomal transfer protein (MTP). Lojuxta (lomitapide) is indicated as an adjunct to a low-fat diet and other lipid-lowering medicinal products with or without low density lipoprotein (LDL) apheresis in adult patients with homozygous familial hypercholesterolaemia (HoFH).

The MAH submitted an application for renewal of the marketing authorisation for opinion by the CHMP. The PRAC is responsible for providing advice to the CHMP on this renewal with regard to safety and risk management aspects.

Summary of advice

- Based on the review of the available pharmacovigilance data for Lojuxta (lomitapide) and the CHMP Rapporteur's assessment report, the PRAC considered that a second five-year renewal of the marketing authorisation(s) is warranted on the basis of pharmacovigilance grounds relating to one specific obligation that is still pending, due to the fact that two registry studies (LOWER⁴⁹ and PER⁵⁰) are still ongoing, which will generate further clinical (safety and effectiveness) data.
- Considering the safety profile of Lojuxta (lomitapide), the PRAC concluded that the MAH should continue to submit PSURs on a yearly frequency.

8.3.3. Pomalidomide - IMNOVID (CAP) - EMEA/H/C/002682/R/0028 (without RMP)

Applicant: Celgene Europe Limited

PRAC Rapporteur: Patrick Batty

Scope: 5-year renewal of the marketing authorisation

Background

Imnovid is a centrally authorised medicine authorised in 2013 containing pomalidomide, an immunomodulating agent. Imnovid (pomalidomide) is indicated in combination with dexamethasone in the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least two prior treatment regimens, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy.

The MAH submitted an application for renewal of the marketing authorisation for opinion by the CHMP. The PRAC is responsible for providing advice to the CHMP on this renewal with regard to safety and risk management aspects.

Summary of advice

⁴⁹ Lomitapide (Juxtapid and Lojuxta) Observational Worldwide Evaluation Registry. EUPASS5326. NCT02135705

⁵⁰ Global Lomitapide (Juxtapid and Lojuxta) Pregnancy Exposure Registry. EUPASS5329

- Based on the review of the available pharmacovigilance data for Imnovid (pomalidomide) and the CHMP Rapporteur's assessment report, the PRAC considered that a second five-year renewal of the marketing authorisation(s) is warranted on the basis of pharmacovigilance grounds relating to the ongoing category 1 PASS⁵¹ to better characterise the risks of treatment with Imnovid (pomalidomide) in clinical practice which could have an impact on the benefit-risk balance. Due to a slower recruitment than expected, the final study report is planned by Q4 2023.

9. Product related pharmacovigilance inspections

9.1. List of planned pharmacovigilance inspections

None

9.2. Ongoing or concluded pharmacovigilance inspections

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

9.3. Others

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. Oseltamivir – TAMIFLU (CAP) - EMEA/H/C/000402/II/128

Applicant: Roche Registration Limited

PRAC Rapporteur: Kirsti Villikka

Scope: PRAC consultation on a variation to update of section 4.6 of the SmPC in order to reflect the final study results from a non-interventional safety study BV29684, which assessed the safety of oseltamivir exposure in pregnant women (listed as a category 3 study in the RMP (MEA099)). The RMP (version 15.0) is updated accordingly

Background

Oseltamivir is a selective inhibitor of influenza virus neuraminidase enzymes indicated for the treatment of influenza in adults and children including full term neonates who present with symptoms typical of influenza, when influenza virus is circulating in the community. In addition, oseltamivir is indicated for the prevention of influenza in post-exposure prevention in individual of one year of age or older following contact with a clinically diagnosed influenza case when influenza virus is circulating in the community, for seasonal prevention in

⁵¹ A non-interventional post-authorisation registry of patients treated with pomalidomide for relapsed and refractory multiple myeloma to monitor incidence of adverse reactions and to monitor the implementation and compliance of Celgene pregnancy prevention programme and off-label use and controlled distribution system on a country basis in agreement with relevant National Competent Authorities

individuals one year of age or older in exceptional situations as well as for post-exposure prevention of influenza in infants less than 1 year of age during a pandemic influenza outbreak. The CHMP requested advice from the PRAC, based on the conclusion that a small risk of congenital heart defects in neonates exposed to oseltamivir during pregnancy could not be completely excluded, and the consequent MAH's proposal for update of the product information. The PRAC was presented the conclusion from the assessment of the final study report of study BV29684 assessing the safety of prenatal exposure to oseltamivir. For further background, see [PRAC minutes July 2017](#) and [PRAC minutes November 2017](#). See also under under 5.3.2.

Summary of advice

- Based on the review of the available information and assessment, the PRAC agreed that the excess risk observed for late pregnancy exposure of oseltamivir and congenital heart defects can be explained by uncontrolled detection bias. The PRAC expressed reservations about the ability of signal detection activities based on spontaneous reporting to detect small risks of congenital malformations. Therefore, the PRAC supported continuing activities such as annual review of pregnancy cases, monitoring within future PSURs, and making use of alternative data sources such as EUROCAT⁵² or ENTIS⁵³ to monitor the safety concern. In addition, the PRAC supported the proposed product information amendments as they adequately reflect the data from the completed study and this conveys an appropriate message to prescribers regarding use in pregnancy.

See also under under 5.3.2.

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

None

10.3. Other requests

None

10.4. Scientific Advice

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

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

11.1. Safety related variations of the marketing authorisation

None

⁵² European surveillance of congenital anomalies

⁵³ European network of teratology information services

11.2. Other requests

11.2.1. Dienogest, estradiol valerate (NAP) - NL/H/1230/001/II/034

Applicant: Bayer BV (Qlaira)

PRAC Lead: Menno van der Elst

Scope: PRAC consultation on a national variation to assess the final results of an imposed cohort study INAS-SCORE, an 'international active surveillance study, safety of contraceptives: role of estrogens' conducted in the US and Europe and the proposed amendments to the product information on the risk of venous thromboembolism (VTE), on request of the Netherlands (Reference Member State).

Background

Qlaira, a combined oral contraceptive (COC) containing estradiol valerate (EV) as an oestrogen and dienogest (DNG) as a progesterone component is used for contraception and the treatment of heavy menstrual bleeding in women without organ pathology who desire oral contraception.

The MAH submitted the final study report II of INAS-SCORE, performed to assess the risk of VTE associated with Qlaira (DNG/EV). Based on the final study analyses, the MAH proposed to update the product information⁵⁴.

The Netherlands requested PRAC advice on its assessment of the final results of the INAS-SCORE study and proposals for updating the product information to include the findings of this study.

Summary of advice

- Based on the review of the available information, the PRAC noted the assessment, conclusions and recommendations made by the Netherlands, as detailed in the assessment report on the final results of the INAS-SCORE study, but highlighted some uncertainties with regard to the robustness and validity of the study results. It was considered that further clarifications are needed before any conclusions can be drawn regarding the risk of VTE associated with Qlaira (DNG/EV). As a result, the PRAC supported addressing a list of questions (LoQ) to the MAH in relation to the study results, in order to obtain in particular more insight into the risk of VTE in other COCs containing drospirenone, desogestrel or gestodene, clarification on the methods of adjustment for risk factors and the adjudication process for VTE cases, detailed information on the univariate associations with each of the adjusting variables, the cumulative hazard curves for the unadjusted data for each of the groups, clarification on how the adjustment for age has been made and the sensitivity analyses to evaluate further the potential for bias and confounding. The PRAC highlighted that clarification on these above aspects is necessary before any recommendations for product information amendments of Qlaira (DNG/EV) to update the warning section on the risk of VTE by including the findings of the INAS-SCORE study can be approved.

⁵⁴ Proposal to update section 4.4 of the SmPC. The package leaflet is updated accordingly

12. Organisational, regulatory and methodological matters

12.1. Mandate and organisation of the PRAC

None

12.2. Coordination with EMA Scientific Committees or CMDh-v

None

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

None

12.4. Cooperation within the EU regulatory network

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

The topic was deferred to the March 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

None

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

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

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

Post-meeting note: following the PRAC meeting of February 2018, the updated EURD list was adopted by the CHMP and CMDh at their February 2018 meetings and published on the EMA website on 28/02/2018, see:

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

12.11. Signal management

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

None

12.11.2. Signal management – Guidance for signal detection of terms related to listed terms

At the organisational matters teleconference held on 22 February 2018, the EMA Secretariat presented to PRAC the revised 'guidance for signal detection of terms related to listed terms' used internally by EMA. The purpose of the document is to compile and further develop the guidance for signal detection of related terms with the aim of increasing the signal detection efficiency and consistency in signal detection performed by EMA. It was considered that it could be useful to use this guidance within the network. PRAC delegates were invited to send comments by 9 March 2018. A follow-up discussion will be scheduled in due course.

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 – experience analysis

Further to the [implementation of the Pharmacovigilance legislation](#) in 2012, [additional monitoring](#) has been introduced for medicines that are being monitored particularly closely by regulatory authorities and that have an inverted black triangle printed on the product information. In February 2017, the EMA Secretariat updated the PRAC on an ongoing project to analyse the experience with additional monitoring in preparation for a European Commission (EC) report mandated by the legislation. In May 2017, the PRAC adopted the outline of the study aiming at describing the experience with the use of the additional monitoring list from its creation in 2013 until December 2016, as well as to investigate whether the inclusion of a product on the additional monitoring list has an effect on reporting of adverse drug reactions (ADRs). For further background, see [PRAC minutes February 2017](#), [PRAC minutes April 2017](#) and [PRAC minutes May 2017](#).

The collection of data and analysis of the above-mentioned study started in May 2017. The PRAC was updated on the preliminary data analysis in preparation for the PRAC consultation on the study preliminary report.

Post-meeting note: On 19 February 2018, the EMA Secretariat circulated to PRAC the draft report of the 'EMA and Member States report to the European Commission on the experience with the list of products subject to additional monitoring' for comments by 2 March 2018 in view of a further discussion provisionally scheduled at the March 2018 PRAC meeting.

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

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

Post-meeting note: The updated additional monitoring list was published on 28/02/2018 on the EMA website (see: [Home>Human Regulatory>Human medicines>Pharmacovigilance>Signal management>List of medicines under additional monitoring](#)).

12.13. EudraVigilance database

12.13.1. Activities related to the confirmation of full functionality

None

12.14. 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. Public hearing – Outcome report

The topic was deferred to the March 2018 PRAC meeting.

12.20.2. Guideline on Good Pharmacovigilance Practices (GVP) – Product- or population-specific considerations V on ‘Medicines used by the older population’

At the organisational matters teleconference held on 22 February 2018, and in line with the PRAC work plan 2018 ([EMA/PRAC/139104/2018](https://www.ema.europa.eu/en/documents/work-plan/prac-work-plan-2018_en.pdf)), the PRAC was presented with a draft

version of the 'Guideline on Good Pharmacovigilance Practices (GVP) – Product- or population- specific considerations V on 'Medicines used by the older population'. PRAC members were invited to send written comments by 9 March 2018. A follow-up discussion will be scheduled in March/April 2018.

13. Any other business

Next meeting on: 05-08 March 2018

14. Annex I – Signals assessment and prioritisation⁵⁵

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 timetables⁵⁶.

14.2. New signals detected from other sources

14.2.1. Varenicline – CHAMPIX (CAP)

Applicant(s): Pfizer Limited

PRAC Rapporteur: Doris Stenver

Scope: Signal of loss of consciousness

EPITT 19146 – New signal

Lead Member State: DK

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. Beclometasone dipropionate anhydrous, formoterol fumarate –EMA/H/C/004836

Scope: Symptomatic treatment and reduction of exacerbations in adult patients with chronic obstructive pulmonary disease (COPD) with airflow limitation and who are at risk of exacerbations

⁵⁵ 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

⁵⁶ 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

15.1.2. Beclometasone dipropionate anhydrous, formoterol fumarate – EMEA/H/C/004702

Scope: Symptomatic treatment and reduction of exacerbations in adult patients with chronic obstructive pulmonary disease (COPD) with airflow limitation and who are at risk of exacerbations

15.1.3. Nitisinone - EMEA/H/C/004582

Scope: Treatment of hereditary tyrosinemia type 1

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

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

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

Applicant: GlaxoSmithKline Trading Services Limited

PRAC Rapporteur: Julie Williams

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

15.2.2. Defibrotide - DEFITELIO (CAP) - EMEA/H/C/002393/II/0027, Orphan

Applicant: Gentium S.r.l.

PRAC Rapporteur: Julie Williams

Scope: Updated RMP (version 4.0) in order to re-classify an imposed non-interventional PASS listed as a category 2 study in the RMP (specific obligation) to a study listed as a category 3 in the RMP (required additional pharmacovigilance activities). This study is an observational registry (DF-VOD2013-03-REG) aiming at recording safety and outcome data in patients diagnosed with severe veno-occlusive disease (VOD) following haematopoietic stem cell transplantation (HSCT) treated or not with Defitelio. Annex II of the product information is updated accordingly

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. [Alectinib - ALECENSA \(CAP\) - EMEA/H/C/004164/II/0010](#)

Applicant: Roche Registration Limited

PRAC Rapporteur: Patrick Batty

Scope: Update of sections 4.2 and 5.2 of the SmPC in order to update information on effect of hepatic impairment on pharmacokinetic (PK) of alectinib based on final results from study NP29783: a multicentre, open label study following single oral dosing of alectinib to subjects with hepatic impairment and matched healthy subjects with normal hepatic function. The Package Leaflet and the RMP (version 3.0) are updated accordingly. In addition, the MAH took the opportunity to bring the product information in line with the latest EC guidance regarding warning statements on sodium

15.3.2. [Anakinra - KINERET \(CAP\) - EMEA/H/C/000363/II/0056](#)

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Doris Stenver

Scope: Extension of indication to include a new indication for Kineret 100 mg/0.67 mL solution for injection in pre-filled syringe for the treatment of active Still's disease, including systemic juvenile idiopathic arthritis and adult-onset Still's disease. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 4.9, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet and the RMP (version 4.0) are updated accordingly. In addition, the MAH took the opportunity to make some editorial changes in the SmPC and package leaflet

15.3.3. [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 the RMP (version 7.1) are updated accordingly

15.3.4. [Atazanavir, cobicistat - EVOTAZ \(CAP\) - EMEA/H/C/003904/WS1292/0019;](#) [Atazanavir, atazanavir sulfate - 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

15.3.5. [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 identified potential risk

15.3.6. [Bosutinib - BOSULIF \(CAP\) - EMEA/H/C/002373/II/0025/G, Orphan](#)

Applicant: Pfizer Limited

PRAC Rapporteur: Martin Huber

Scope: Grouped variations consisting of an extension of indication to include treatment of adult patients with newly diagnosed Philadelphia chromosome positive (Ph+) chronic phase (CP) chronic myelogenous leukaemia (CML) for Bosulif based on study AV001: a multicentre phase 3 randomized, open-label study of bosutinib versus imatinib in adult patients with newly diagnosed CP CML. In addition, the MAH updated the SmPC with safety and efficacy data from study B1871006: a phase 1/2 study of bosutinib in Ph+ leukaemias, and study B1871008: a phase 3 randomized, open-label study of bosutinib versus imatinib in subjects with newly diagnosed CP Ph+ CML. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The Package Leaflet and the RMP (version 4.0) are updated accordingly. Furthermore, Annex IIIA is brought in line with the latest QRD template (version 10)

15.3.7. [Trametinib - MEKINIST \(CAP\) - EMEA/H/C/002643/WS1274/0023;](#) [Dabrafenib - TAFINLAR \(CAP\) - EMEA/H/C/002604/WS1274/0031](#)

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension of indication to include the combination adjuvant treatment with trametinib and dabrafenib of adult patients with stage III melanoma with a BRAF V600 mutation, following complete resection. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 of the Mekinist and Tafinlar SmPCs are updated. The Package Leaflet and the RMP (version 14.0 for Mekinist and version 9.0 for Tafinlar) are updated accordingly. In addition, the MAH took the opportunity to correct some typos throughout the Mekinist and Tafinlar product information, to include a cross reference to the Mekinist SmPC in section 4.6 of the Tafinlar SmPC regarding fertility as well as to update the list of local representatives for Bulgaria, Hungary, Estonia, Latvia and Lithuania in the Package Leaflet of both products

15.3.8. [Darunavir, cobicistat, emtricitabine, tenofovir alafenamide - SYMTUZA \(CAP\) - EMEA/H/C/004391/II/0003/G](#)

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Julie Williams

Scope: Grouped variations consisting of: update of sections 4.4, 4.8, 5.1 and 5.2 of the SmPC in order to reflect the week-48 results from two studies listed as category 3 studies in the RMP, namely study TMC114FD2HTX3001: evaluation of the efficacy and safety of darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) once daily fixed-dose combination regimen versus a regimen consisting of darunavir/cobicistat (DRV/COBI) fixed dose combination (FDC) co-administered with emtricitabine/tenofovir alafenamide (FTC/TDF) FDC in antiretroviral (ARV) treatment-naïve human immunodeficiency virus 1

(HIV-1) infected subjects; and TMC114IFD3013: evaluation of switching to a D/C/F/TAF once-daily single-tablet regimen versus continuing the current regimen consisting of a boosted protease inhibitor combined with FTC/TDF in virologically-suppressed, HIV-1 infected subjects. The RMP (version 2.0) is updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet and to make minor editorial revision in the product information

[15.3.9. Dasatinib - SPRYCEL \(CAP\) - EMEA/H/C/000709/X/0056/G](#)

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Doris Stenver

Scope: Grouped application consisting of: 1) extension application (line extension) to introduce a new pharmaceutical form (powder for oral suspension) associated with a new strength (10 mg/mL); 2) extension of indication to include the treatment of children and adolescents aged 1 year to 18 years with Ph+ chronic phase in chronic myeloid leukaemia (CML). As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated in order to add the new indication and its relevant posology, to add a warning on effects on growth and development in the paediatric population and to update the safety information. The Package Leaflet and the RMP (version 15.0) are updated accordingly

[15.3.10. 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

[15.3.11. Denosumab - XGEVA \(CAP\) - EMEA/H/C/002173/II/0055](#)

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension of indication to include the prevention of skeletal related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with multiple myeloma and in adults with bone metastases from solid tumours for Xgeva. 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 24.0) are updated accordingly

[15.3.12. Dimethyl fumarate - TECFIDERA \(CAP\) - EMEA/H/C/002601/II/0037](#)

Applicant: Biogen Idec Ltd

PRAC Rapporteur: Martin Huber

Scope: Submission of a clinical study report (CSR) for study 109MS307: an open-label study to assess the immune response to vaccination in Tecfidera-treated versus interferon-treated subjects with relapsing forms of multiple sclerosis (category 3). As a consequence, section 4.5 of the SmPC is updated. The Package Leaflet and the RMP (version 9.0) are updated accordingly

15.3.13. [Efavirenz, emtricitabine, tenofovir disoproxil - ATRIPLA \(CAP\) - EMEA/H/C/000797/II/0127/G](#)

Applicant: Bristol-Myers Squibb and Gilead Sciences Ltd.

PRAC Rapporteur: Martin Huber

Scope: Grouped variations consisting of: 1) update of sections 4.3, 4.4, 4.5 and 5.1 of the SmPC to include the results of the final study report for study AI266959: an interventional study to determine the concentration-electrocardiographic effects of efavirenz in healthy subjects enriched for CYP2B6⁵⁷ polymorphism, as requested by PRAC in the recommendation for PSUSA procedure (PSUSA/00001200/201604) on Stocrin/Sustiva (efavirenz) finalised in November 2016; 2) update of sections 4.4 and 4.8 of the SmPC to add catatonia as a psychiatric symptom following an assessment of catatonia cases reported in the literature and the US FDA adverse event reporting system (FAERS); 3) the RMP (version 17) is updated to remove malignant neoplasms as a potential risk. The MAH took the opportunity to implement minor editorial changes in the product information and minor linguistic amendments to the following languages: Danish, German, Finnish, French Hungarian, Icelandic, Maltese, Norwegian, Portuguese, Spanish and Swedish

15.3.14. [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

15.3.15. [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, randomised, placebo-controlled,

⁵⁷ Cytochrome P450, family 2, subfamily B, polypeptide 6

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, randomised, multicentre, placebo-controlled, parallel group study to determine the effects of evolocumab (AMG 145) treatment on stherosclerotic 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, randomised, 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))

15.3.16. 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

15.3.17. Florbetapir (¹⁸F) - AMYVID (CAP) - EMEA/H/C/002422/II/0029

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Valerie Strassmann

Scope: Update of section 4.4 of the SmPC following the final report from study I6E-MC-AVBF (listed as a category 3 study in the RMP): a non-interventional category 3 study, a European drug usage survey to assess the usage pattern of Amyvid in the EU. The RMP (version 3.1) is updated accordingly

15.3.18. Ibrutinib - IMBRUVICA (CAP) - EMEA/H/C/003791/X/0037, Orphan

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Patrick Batty

Scope: Extension application to introduce a new pharmaceutical form (film-coated tablets) associated with new strengths (140 mg, 280 mg, 420 mg and 560 mg). The RMP (version 8.0) is updated accordingly

15.3.19. Insulin degludec, liraglutide - XULTOPHY (CAP) - EMEA/H/C/002647/II/0023

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Menno van der Elst

Scope: Update of sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC in order to update the safety information based on cardiovascular outcomes studies conducted for each of the monocomponents of Xultophy, namely: study LEADER (liraglutide cardiovascular outcomes trial): a long term, multicentre, randomised double-blind placebo-controlled trial to determine liraglutide effects on cardiovascular events, and study DEVOTE (Insulin degludec cardiovascular outcomes trial): a trial comparing cardiovascular safety of insulin degludec versus insulin glargine in subjects with type 2 diabetes at high risk of cardiovascular events. The MAH also proposed to reorganise parts of section 5.1 to improve the reader friendliness and to remove Xultophy from the list of medicines under additional monitoring. The Package Leaflet and the RMP (version 7.0) are updated accordingly

15.3.20. Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/WS1278/0042; ipilimumab - YERVOY (CAP) - EMEA/H/C/002213/WS1278/0053

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

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

15.3.21. Ledipasvir, sofosbuvir - HARVONI (CAP) - EMEA/H/C/003850/II/0064

Applicant: Gilead Sciences International Limited

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Update of section 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC in order to update the safety and efficacy information based on interim results from study GS-US-334-0154 (listed as a category 3 study in the RMP): a study to evaluate the safety, efficacy and pharmacokinetics in patients treated with ledipasvir/sofosbuvir fixed-dose combination for 12 weeks in genotype 1 or 4 HCV-infected subjects with renal insufficiency. The Package Leaflet and the RMP (version 3.2) are updated accordingly

15.3.22. Lenvatinib - LENVIMA (CAP) - EMEA/H/C/003727/II/0011/G, Orphan

Applicant: Eisai Europe Ltd.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Grouped variations consisting of: 1) extension of indication to include treatment of hepatocellular carcinoma (HCC) based on pivotal study 304: a multicentre, randomized, open-label, phase 3 trial to compare the efficacy and safety of lenvatinib versus sorafenib in first-line treatment of subjects with unresectable HCC. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 10) are updated accordingly; 2) section 4.2 of the SmPC is updated to add that the medicinal product can be administered as a suspension in water or apple juice. In addition, the labelling is updated to include a unique identifier

15.3.23. Nusinersen - SPINRAZA (CAP) - EMEA/H/C/004312/II/0004, Orphan

Applicant: Biogen Idec Ltd

PRAC Rapporteur: Qun-Ying Yue

Scope: Update of section 4.8 of the SmPC to include new safety information related to hydrocephalus. The Package Leaflet and the RMP (version 7.0) are updated accordingly. In addition, the MAH took the opportunity to correct some typographical errors in section 5.1 of the SmPC

15.3.24. Osimertinib - TAGRISSO (CAP) - EMEA/H/C/004124/II/0019

Applicant: AstraZeneca AB

PRAC Rapporteur: Sabine Straus

Scope: Extension of indication to include first-line treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) whose tumours have epidermal growth factor receptor exon 19 deletions or exon 21 (L858R) substitution mutations, based on data from the FLAURA study (D5160C00007): a phase 3, double-blind, randomised study to assess the efficacy and safety of osimertinib versus a standard of care epidermal growth factor receptor-tyrosine kinase inhibitor as first-line treatment in patients with epidermal growth factor receptor mutation-positive, locally-advanced or metastatic NSCLC. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 of the SmPC are updated. The Package Leaflet and the RMP (version 8) are updated accordingly. In addition, the MAH took the opportunity to implement editorial changes in the SmPC and Package Leaflet. As part of this application, the MAH requested an additional year of market protection

15.3.25. 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 regarding the 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)

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

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Sabine Straus

Scope: Grouped variations consisting of an 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 minimisation measures' section (educational material) in Annex II and the RMP (version 13.0) are updated accordingly. In addition, the MAH implemented minor changes in the SmPC section 5.1 and editorial changes in the package leaflet

15.3.27. Raltegravir - ISENTRESS (CAP) - EMEA/H/C/000860/II/0064/G

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Julie Williams

Scope: Grouped variations consisting of: 1) extension of indication for Isentress 100 mg granules for oral suspension to include the treatment of human immunodeficiency virus type 1 (HIV-1) in exposed full-term neonates under the age of 4 weeks based on safety and pharmacokinetic (PK) data from a pivotal phase 1 study IMPAACT P1110 (protocol 080) conducted in a total of 42 HIV-1 exposed full-term infants (defined as ≥ 37 weeks gestational age and $\geq 2,000$ g), who received either 2 single doses of oral suspension within 48 hours of birth and day 7-10 of age (cohort I), or a multiple-dose regimen of raltegravir over the first 6 weeks of age (cohort II). As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated accordingly. The provision of the results of IMPAACT P1110 study addresses the final paediatric investigation plan (PIP) measure, i.e. study 4, conducted to generate PK, safety, and tolerability data in HIV exposed neonates and infants <6 weeks of age born to HIV infected mothers; 2) update of the suspension volume from 5 mL to 10 mL for a final suspension concentration of 10 mg/mL to facilitate accurate measurements of the smaller doses required for neonates. As a consequence, the 5 mL syringe supplied in the current commercial kit is replaced with 3 new oral dosing syringes, and sizes (1 mL, 3 mL, and 10 mL) from a different (new) supplier. As a consequence, sections 6.5 and 6.6 of the SmPC are updated. The labelling, the instructions for use in the Package Leaflet and the RMP (version 12.0) are updated accordingly

15.3.28. Rivaroxaban - XARELTO (CAP) - EMEA/H/C/000944/II/0058

Applicant: Bayer AG

PRAC Rapporteur: Qun-Ying Yue

Scope: Extension of indication to include the prevention of stroke, myocardial infarction and

cardiovascular death, and for the prevention of acute limb ischaemia and mortality in adult patients with coronary artery disease (CAD) or peripheral artery disease (PAD) for Xarelto 2.5 mg co-administered with acetylsalicylic acid. As a consequence, sections 4.1, 4.2, 4.4, 4.8, and 5.1 of the SmPC are updated. The Package Leaflet, Labelling and the RMP (version 11.1) are updated accordingly. In addition, section 4.8 of the SmPC is updated for all other dose strengths (10/15/20 mg) of Xarelto with relevant exposure information based on the provided clinical data

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

Applicant: AstraZeneca AB

PRAC Rapporteur: Dolores Montero Corominas

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

15.3.30. Sevelamer carbonate - SEVELAMER CARBONATE ZENTIVA (CAP) - EMEA/H/C/003971/X/0011

Applicant: Genzyme Europe BV

PRAC Rapporteur: Laurence de Fays

Scope: Extension application to add a new strength of 0.8 g powder for oral suspension. The RMP (version 9.0) is updated accordingly

15.3.31. Sevelamer carbonate - RENVELA (CAP) - EMEA/H/C/000993/X/0039

Applicant: Genzyme Europe BV

PRAC Rapporteur: Laurence de Fays

Scope: Extension application to add a new strength of 0.8 g powder for oral suspension. The RMP (version 9.0) is updated accordingly

15.3.32. Sunitinib - SUTENT (CAP) - EMEA/H/C/000687/II/0065

Applicant: Pfizer Limited

PRAC Rapporteur: Carmela Macchiarulo

Scope: Extension of indication to include the adjuvant treatment of patients at high risk of recurrent renal cell carcinoma (RCC) following nephrectomy. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated based on study A6181109: 'a randomized double-blind phase 3 study of adjuvant sunitinib vs. placebo in subjects at high risk of recurrent RCC'. The Package Leaflet and the RMP (version 16) are updated accordingly. In addition, the MAH took the opportunity to make minor editorial changes to the SmPC and Package Leaflet. This procedure fulfils PAM (FU2 22.5). Furthermore, the product information (PI) is brought in line with the latest QRD template (version 10)

15.3.33. Telotristat ethyl - XERMELO (CAP) - EMEA/H/C/003937/II/0002/G, Orphan

Applicant: Ipsen Pharma

PRAC Rapporteur: Adam Przybylkowski

Scope: Grouped variations consisting of: 1) Submission of the final report for study LX301 (pivotal phase 3 study, listed as category 3 studies in the RMP): a randomised, multicentre, double-blind, placebo-controlled study evaluating the efficacy and safety of telotristat etiprate in patients with carcinoid syndrome not adequately controlled by somatostatin analogue (SSA) therapy; 2) Submission of the final report for study LX303 (pivotal phase 3 study, listed as category 3 studies in the RMP): a randomised, multicentre, double-blind, placebo-controlled study evaluating the safety and efficacy of telotristat etiprate in patients with carcinoid syndrome. The MAH also took the opportunity to provide updated safety data from the long-term extension study LX302: a phase 3, multicentre, open-label study to further evaluate the safety and tolerability of telotristat. As a consequence, the RMP (version 3.0) is updated

15.3.34. Tivozanib - FOTIVDA (CAP) - EMEA/H/C/004131/II/0002

Applicant: EUSA Pharma (UK) Limited

PRAC Rapporteur: Jolanta Gulbinovic

Scope: Update of the section 5.2 of the SmPC with additional information on transporter proteins based on the results of an in vitro interaction transporter study. The updated RMP (version 2.0) is updated accordingly

15.3.35. Tocilizumab - ROACTEMRA (CAP) - EMEA/H/C/000955/II/0072

Applicant: Roche Registration Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include the treatment of juvenile idiopathic polyarthritis (pJIA) rheumatoid factor positive or negative and extended oligoarthritis in patients of 2 years of age and older, who have responded inadequately to previous therapy with methotrexate. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet and the RMP (version 23.1) are updated accordingly

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

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

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

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

16.1.1. Aclidinium bromide - BRETARIS GENUAIR (CAP), EKLIRA GENUAIR (CAP) - PSUSA/00009005/201707

Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.2. Albutrepenonacog alfa - IDELVION (CAP) - PSUSA/00010497/201707

Applicant: CSL Behring GmbH

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUSA procedure

16.1.3. Antithrombin alfa - ATRYN (CAP) - PSUSA/00000224/201707

Applicant: Laboratoire Francais du Fractionnement et des Biotechnologies

PRAC Rapporteur: Caroline Laborde

Scope: Evaluation of a PSUSA procedure

16.1.4. Asparaginase⁵⁸ - SPECTRILA (CAP) - PSUSA/00010445/201707

Applicant: Medac Gesellschaft für klinische Spezialpräparate mbH

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

16.1.5. Ataluren - TRANSLARNA (CAP) - PSUSA/00010274/201707

Applicant: PTC Therapeutics International Limited

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUSA procedure

16.1.6. Atazanavir, cobicistat - EVOTAZ (CAP) - PSUSA/00010404/201707

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Caroline Laborde

Scope: Evaluation of a PSUSA procedure

16.1.7. Birch bark extract⁵⁹ - EPISALVAN (CAP) - PSUSA/00010446/201707

Applicant: Amryt AG

⁵⁸ Centrally authorised product(s) only

⁵⁹ Centrally authorised product(s) only

PRAC Rapporteur: Zane Neikena

Scope: Evaluation of a PSUSA procedure

16.1.8. [Brivaracetam - BRIVIACT \(CAP\) - PSUSA/00010447/201707](#)

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.9. [Dapagliflozin, metformin - EBYMECT \(CAP\), XIGDUO \(CAP\) - PSUSA/00010294/201707](#)

Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.10. [Elbasvir, grazoprevir - ZEPATIER \(CAP\) - PSUSA/00010519/201707](#)

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.1.11. [Etanercept⁶⁰ - BENEPALI \(CAP\) - PSUSA/00010452/201707](#)

Applicant: Samsung Bioepis UK Limited

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

16.1.12. [Evolocumab - REPATHA \(CAP\) - PSUSA/00010405/201707](#)

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

16.1.13. [Idursulfase - ELAPRASE \(CAP\) - PSUSA/00001722/201707](#)

Applicant: Shire Human Genetic Therapies AB

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

16.1.14. [Ingenol mebutate - PICATO \(CAP\) - PSUSA/00010035/201707](#)

Applicant: LEO Laboratories Ltd

⁶⁰ For biosimilar Benepali only

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

[16.1.15. Insulin glargine, lixisenatide - SULIQUA \(CAP\) - PSUSA/00010577/201707](#)

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

[16.1.16. Lipegfilgrastim - LONQUEx \(CAP\) - PSUSA/00010111/201707](#)

Applicant: Sicor Biotech UAB

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

[16.1.17. Lomitapide - LOJUXTA \(CAP\) - PSUSA/00010112/201707](#)

Applicant: Aegerion Pharmaceuticals Limited

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

[16.1.18. Mercaptamine⁶¹ - CYSTADROPS \(CAP\) - PSUSA/00010574/201707](#)

Applicant: Orphan Europe SARL

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

[16.1.19. Modified vaccinia Ankara virus - IMVANEX \(CAP\) - PSUSA/00010119/201707 \(with RMP\)](#)

Applicant: Bavarian Nordic A/S

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

[16.1.20. Nateglinide - STARLIX \(CAP\) - PSUSA/00002128/201706](#)

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

[16.1.21. Palbociclib - IBRANCE \(CAP\) - PSUSA/00010544/201708](#)

Applicant: Pfizer Limited

⁶¹ Indicated in the treatment of corneal cystine crystal deposits

PRAC Rapporteur: Doris Stenver

Scope: Evaluation of a PSUSA procedure

16.1.22. Palivizumab - SYNAGIS (CAP) - PSUSA/00002267/201706

Applicant: AbbVie Limited

PRAC Rapporteur: Doris Stenver

Scope: Evaluation of a PSUSA procedure

16.1.23. Pegaspargase⁶² - ONCASPAR (CAP) - PSUSA/00010457/201707

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

16.1.24. Peginterferon alfa-2a - PEGASYS (CAP) - PSUSA/00009254/201707

Applicant: Roche Registration Limited

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

16.1.25. Peginterferon beta-1a - PLEGRIDY (CAP) - PSUSA/00010275/201707

Applicant: Biogen Idec Ltd

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.26. Phenylephrine, ketorolac - OMIDRIA (CAP) - PSUSA/00010419/201707

Applicant: Omeros London Limited

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.27. Rotavirus vaccine monovalent (live, oral) - ROTARIX (CAP) - PSUSA/00002665/201707

Applicant: GlaxoSmithKline Biologicals S.A.

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

16.1.28. Sacubitril, valsartan - ENTRESTO (CAP), NEPARVIS (CAP) - PSUSA/00010438/201707

Applicant: Novartis Europharm Limited

⁶² Centrally authorised product(s) only

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.29. [Saxagliptin, dapagliflozin - QTERN \(CAP\) - PSUSA/00010520/201707](#)

Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.30. [Tocofersolan - VEDROP \(CAP\) - PSUSA/00002981/201707](#)

Applicant: Orphan Europe SARL

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

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

16.2.1. [Aripiprazole - ABILIFY \(CAP\), ABILIFY MAINTENA \(CAP\), ARIPIPRAZOLE SANDOZ \(CAP\); NAP - PSUSA/00000234/201707](#)

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

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.2.2. [Nitric oxide - INOMAX \(CAP\); NAP - PSUSA/00002172/201706](#)

Applicants: Linde Healthcare AB (INOMax), various

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.3. [PSUR single assessment \(PSUSA\) procedures including nationally authorised products \(NAPs\) only](#)

16.3.1. [Amikacin \(NAP\) - PSUSA/00000143/201706](#)

Applicant(s): various

PRAC Lead: Maia Uusküla

Scope: Evaluation of a PSUSA procedure

16.3.2. [Benserazide, levodopa \(NAP\) - PSUSA/00000330/201706](#)

Applicant(s): various

PRAC Lead: Julia Pallos

Scope: Evaluation of a PSUSA procedure

16.3.3. [Cilastatin, imipenem \(NAP\) - PSUSA/00000748/201706](#)

Applicant(s): various

PRAC Lead: Kristin Thorseng Kvande

Scope: Evaluation of a PSUSA procedure

16.3.4. [Hepatitis A \(inactivated\), typhoid polysaccharide vaccine \(adsorbed\) \(NAP\) - PSUSA/00001594/201706](#)

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.3.5. [Latanoprost, timolol \(NAP\) - PSUSA/00001833/201706](#)

Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.3.6. [Pentamidine \(NAP\) - PSUSA/00002338/201706](#)

Applicant(s): various

PRAC Lead: Laurence de Fays

Scope: Evaluation of a PSUSA procedure

16.3.7. [Solifenacin \(NAP\) - PSUSA/00002769/201706](#)

Applicant(s): various

PRAC Lead: Sabine Straus

Scope: Evaluation of a PSUSA procedure

16.3.8. [Pitavastatin \(NAP\) - PSUSA/00010502/201707](#)

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.3.9. [Sulfamethizole \(NAP\) - PSUSA/00010561/201706](#)

Applicant(s): various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

16.3.10. Levonorgestrel/ethinylestradiol, ethinylestradiol⁶³ (NAP) - PSUSA/00010442/201707

Applicant(s): various

PRAC Lead: Caroline Laborde

Scope: Evaluation of a PSUSA procedure

16.3.11. Technetium (^{99m}Tc) sestamibi (NAP) - PSUSA/00002868/201706

Applicant(s): various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

16.4. Follow-up to PSUR procedures

16.4.1. Alendronic acid, colecalciferol - ADROVANCE (CAP) - EMEA/H/C/000759/LEG 015

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Julie Williams

Scope: Submission of a detailed review on cases of osteonecrosis other than the jaw and external auditory canal, including information on diagnostic criteria applied and results of diagnostic tests, discussion on potential influence of local anatomy and discussion on underlying pathophysiological mechanism and possible risk factors as requested for bisphosphonate-containing products following the conclusions of PSUSA/00003149/201608 for zoledronic acid (indicated in the treatment of cancer and fractures) adopted in April 2017

16.4.2. Alendronic acid, colecalciferol - FOSAVANCE (CAP) - EMEA/H/C/000619/LEG 016

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Julie Williams

Scope: Submission of a detailed review on cases of osteonecrosis other than the jaw and external auditory canal, including information on diagnostic criteria applied and results of diagnostic tests, discussion on potential influence of local anatomy and discussion on underlying pathophysiological mechanism and possible risk factors as requested for bisphosphonate-containing products following the conclusions of PSUSA/00003149/201608 for zoledronic acid (indicated in the treatment of cancer and fractures) adopted in April 2017

16.4.3. Alendronic acid, colecalciferol - VANTAVO (CAP) - EMEA/H/C/001180/LEG 008

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Julie Williams

Scope: Submission of a detailed review on cases of osteonecrosis other than the jaw and external auditory canal, including information on diagnostic criteria applied and results of

⁶³ Combination pack

diagnostic tests, discussion on potential influence of local anatomy and discussion on underlying pathophysiological mechanism and possible risk factors as requested for bisphosphonate-containing products following the conclusions of PSUSA/00003149/201608 for zoledronic acid (indicated in the treatment of cancer and fractures) adopted in April 2017

16.4.4. Bosentan - STAYVEER (CAP) - EMEA/H/C/002644/LEG 010

Applicant: Marklas Nederlands BV

PRAC Rapporteur: Caroline Laborde

Scope: Submission of an overview of the educational materials with the controlled distribution systems implemented at national levels, together with a discussion on the effectiveness of each measure in place to minimise any risk (including educational material and controlled distribution system), as requested in the conclusions of PSUSA/00000425/201611 adopted in July 2017

16.4.5. Bosentan - TRACLEER (CAP) - EMEA/H/C/000401/LEG 086

Applicant: Actelion Registration Limited

PRAC Rapporteur: Caroline Laborde

Scope: Submission of an overview of the educational materials with the controlled distribution systems implemented at national levels, together with a discussion on the effectiveness of each measure in place to minimise any risk (including educational material and controlled distribution system), as requested in the conclusions of PSUSA/00000425/201611 adopted in July 2017

16.4.6. Vemurafenib - ZELBORAF (CAP) - EMEA/H/C/002409/LEG 035.1

Applicant: Roche Registration Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: MAH's response to LEG 035 [Review of cases of posterior reversible encephalopathy syndrome (PRES) as requested in the conclusions of PSUSA/00009329/201608 adopted in March 2017] as per the request for supplementary information (RSI) adopted at the October 2017 PRAC meeting

16.4.7. Vemurafenib - ZELBORAF (CAP) - EMEA/H/C/002409/LEG 036.1

Applicant: Roche Registration Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: MAH's response to LEG 036 [Review of cases of sarcoidosis as requested in the conclusions of PSUSA/00009329/201608 adopted in March 2017] as per the request for supplementary information (RSI) adopted at the October 2017 PRAC meeting

16.4.8. Vemurafenib - ZELBORAF (CAP) - EMEA/H/C/002409/LEG 037.1

Applicant: Roche Registration Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: MAH's response to LEG 037 [Review of cases of lymphopenia as requested in the conclusions of PSUSA/00009329/201608 adopted in March 2017] as per the request for supplementary information (RSI) adopted at the October 2017 PRAC meeting

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)⁶⁴

17.1.1. Glycerol phenylbutyrate – RAVICTI (CAP) - EMEA/H/C/PSA/S/0025

Applicant: Horizon Pharma Ireland Limited

PRAC Rapporteur: Carmela Macchiarulo

Scope: Protocol for a European post-authorisation registry for Ravicti (glycerol phenylbutyrate) oral liquid in partnership with the European Registry and network for intoxication type

17.1.2. Levonorgestrel (NAP) - EMEA/H/N/PSA/S/0020.2

Applicant: Bayer Pharma AG

PRAC Rapporteur: Ulla Wändel Liminga

Scope: MAH's response to PSA/S/0020.1 [Amended protocol for EURAS-LCS12 study: a European active surveillance study of LCS-12 (levonorgestrel intrauterine contraceptive system releasing 12 µg levonorgestrel/24h in vitro), an intra-uterine device (IUD) for Jaydess and Luadei (levonorgestrel) to investigate whether LCS-12 is associated with an increased risk of unintended pregnancy compared to Mirena and to copper IUDs] as per the request for supplementary information (RSI) adopted at the October 2017 PRAC meeting

17.1.3. Valproate (NAP) - EMEA/H/N/PSA/J/0015.2

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

PRAC Rapporteur: Sabine Straus

Scope: MAH's response to PSA/J/0015.1 [Protocol for a joint drug utilisation study (DUS) using EU databases to study the effectiveness of the imposed risk minimisation measures following the conclusion of the referral procedure under Article 31 of Directive 2001/83/EC completed in 2014 (EMEA/H/A-31/1387) and to further characterise the prescribing patterns for valproate] as per the request for supplementary information (RSI) adopted at the September 2017 PRAC meeting

⁶⁴ In accordance with Article 107n of Directive 2001/83/EC

17.2. Protocols of PASS non-imposed in the marketing authorisation(s)⁶⁵

17.2.1. Canagliflozin - INVOKANA (CAP) - EMEA/H/C/002649/MEA 012.2

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Valerie Strassmann

Scope: MAH's response to MEA 012.1 [PASS protocol for an epidemiological study to evaluate the risk of acute pancreatitis in patients with type 2 diabetes mellitus (T2DM) newly exposed to canagliflozin-containing products compared to patients with T2DM exposed to non-sodium-glucose co-transporter-2 (SGLT2) inhibitor anti-hyperglycaemic agents: a retrospective cohort study using large claims databases in the United States] as requested in the request for supplementary information (RSI) adopted in September 2017

17.2.2. Canagliflozin, metformin - VOKANAMET (CAP) - EMEA/H/C/002656/MEA 011.2

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to MEA 011.1 [PASS protocol for an epidemiological study to evaluate the risk of acute pancreatitis in patients with type 2 diabetes mellitus (T2DM) newly exposed to canagliflozin-containing products compared to patients with T2DM exposed to non-sodium-glucose co-transporter-2 (SGLT2) inhibitor anti-hyperglycaemic agents: a retrospective cohort study using large claims databases in the United States] as requested in the request for supplementary information (RSI) adopted in September 2017

17.2.3. Cladribine - MAVENCLAD (CAP) - EMEA/H/C/004230/MEA 003

Applicant: Merck Serono Europe Limited

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Protocol for a PASS focusing on pregnancy aimed at assessing the occurrence of major congenital abnormalities (MCA), estimating proportions of pregnancy outcomes, proportions of alterations in foetal growth and pre-term births in pregnant women exposed to oral cladribine and in pregnancies fathered by male partner exposed to oral cladribine, and comparison of study outcomes with pregnant women with multiple sclerosis (MS) not exposed to any disease modifying drugs (DMDs) (from initial opinion/MA) [final study report due date: Q1/2028]

17.2.4. Cobimetinib - COTELLIC (CAP) - EMEA/H/C/003960/MEA 003.1

Applicant: Roche Registration Limited

PRAC Rapporteur: Sabine Straus

Scope: MAH's response to MEA 003 [Protocol for study ML939302 (COVENIS): a non-interventional study to investigate the effectiveness, safety and utilisation of cobimetinib and vemurafenib in patients with and without brain metastasis with BRAF V600 mutant melanoma under real world conditions (final clinical study report (CSR) due date: December 2022)]

⁶⁵ In accordance with Article 107m of Directive 2001/83/EC, supervised by PRAC in accordance with Article 61a (6) of Regulation (EC) No 726/2004

17.2.5. Lidocaine, prilocaine - FORTACIN (CAP) - EMEA/H/C/002693/MEA 004.1

Applicant: Recordati Ireland Ltd

PRAC Rapporteur: Dolores Montero Corominas

Scope: MAH's response to MEA 004 [Protocol for a drug utilisation study (DUS) in Europe for Fortacin (lidocaine, prilocaine) (listed as a category 3 study in RMP): a retrospective cohort study using electronic medical records database aiming at characterising the population of patients who are prescribed the medicinal product and at describing the real-life prescribing patterns] as per the request for supplementary information (RSI) adopted in September 2017

17.2.6. Mercaptamine - CYSTADROPS (CAP) - EMEA/H/C/003769/MEA 001

Applicant: Orphan Europe SARL

PRAC Rapporteur: Dolores Montero Corominas

Scope: PASS protocol for study CYT-DS-001 (listed as a category 3 study in the RMP): an open-label longitudinal PASS to assess the safety of Cystadrops (mercaptamine) in paediatric and adult cystinosis patients in long term use [final clinical study report (CSR) due date: by 2021] (from initial opinion/MA)

17.2.7. Sodium oxybate - XYREM (CAP) - EMEA/H/C/000593/MEA 019.2

Applicant: UCB Pharma Limited

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: MAH's response to MEA 019.1 [Protocol for study NA0001 (EU PAS register EUPAS15024): a non-interventional PASS on the effectiveness of the educational materials] as per the request for supplementary information (RSI) adopted in September 2017

17.3. Results of PASS imposed in the marketing authorisation(s)⁶⁶

None

17.4. Results of PASS non-imposed in the marketing authorisation(s)⁶⁷

17.4.1. Dimethyl fumarate - TECFIDERA (CAP) - EMEA/H/C/002601/II/0045

Applicant: Biogen Idec Ltd

PRAC Rapporteur: Martin Huber

Scope: Submission of the final report for study 109MS419 (listed as a category 3 study in the RMP): a retrospective, multicentre, observational study aimed to assess the effect of Tecfidera delayed-release capsules on lymphocyte subsets in patients with relapsing forms of multiple sclerosis

⁶⁶ In accordance with Article 107p-q of Directive 2001/83/EC

⁶⁷ In accordance with Article 61a (6) of Regulation (EC) No 726/2004, in line with the revised variations regulation for any submission as of 4 August 2013

17.4.2. Dimethyl fumarate - TECFIDERA (CAP) - EMEA/H/C/002601/II/0049

Applicant: Biogen Idec Ltd

PRAC Rapporteur: Martin Huber

Scope: Submission of the final report from study 109MS409 (listed as a category 3 study in the RMP): an observation study aimed to estimate the proportion of dimethyl fumarate use that is prescribed 'on-label' versus 'off-label' in Germany

17.4.3. 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 incontinence (SUI). The RMP (version 12.3) is updated accordingly

17.4.4. Glycopyrronium bromide - ENUREV BREEZHALER (CAP) - EMEA/H/C/002691/WS1299/0025; SEEBRI BREEZHALER (CAP) - EMEA/H/C/002430/WS1299/0025; TOVANOR BREEZHALER (CAP) - EMEA/H/C/002690/WS1299/0028

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Doris Stenver

Scope: Submission of the final study report for study CNVA237A2402T (a category 1 study in the RMP and marketing authorisations): a multinational, multi-database cohort study to assess adverse cardiovascular and cerebrovascular outcomes and mortality in association with inhaled glycopyrronium bromide (NVA237) in Europe. As a consequence, Annex II is updated. In addition, the additional monitoring list is to be updated by removing Enurev Breezhaler, Seebri Breezhaler, Tovanor Breezhaler. As a consequence, Annex I and IIIB are updated. The MAH also took this opportunity to update the local representatives. The RMP (version 8) is also updated accordingly

17.4.5. Indacaterol, glycopyrronium - ULTIBRO BREEZHALER (CAP) - EMEA/H/C/002679/WS1340/0022; ULUNAR BREEZHALER (CAP) - EMEA/H/C/003875/WS1340/0022; XOTERNA BREEZHALER (CAP) - EMEA/H/C/003755/WS1340/0025

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Doris Stenver

Scope: Submission of the final report for study CQVA149A2401: a multinational, multi-database drug utilisation study of indacaterol/glycopyrronium bromide (QVA149) in Europe with the objective to estimate the use of QVA149 off-label and in the subpopulations with missing information mentioned in the RMP

17.4.6. [Infliximab - INFLECTRA \(CAP\) - EMEA/H/C/002778/II/0054](#)

Applicant: Hospira UK Limited

PRAC Rapporteur: Patrick Batty

Scope: Submission of the final study report for a post-marketing surveillance study for Inflectra 100 mg (infliximab) to evaluate its safety and efficacy in Korea: study intended to identify any unexpected adverse events, serious adverse events and frequencies, pattern of occurrence of adverse events under the condition of general clinical practice as well as to determine any factor that may affect the safety and efficacy

17.4.7. [Infliximab - REMSIMA \(CAP\) - EMEA/H/C/002576/II/0045](#)

Applicant: Celltrion Healthcare Hungary Kft.

PRAC Rapporteur: Patrick Batty

Scope: Submission of the final study report for a post-marketing surveillance study for Remsima 100 mg (infliximab) to evaluate its safety and efficacy in Korea: study intended to identify any unexpected adverse event, serious adverse event and frequencies, pattern of occurrence of adverse events under the condition of general clinical practice as well as to determine any factor that may affect the safety and efficacy

17.5. [Interim results of imposed and non-imposed PASS submitted before the entry into force of the revised variation regulation⁶⁸](#)

17.5.1. [Aclidinium bromide - BRETARIS GENUAIR \(CAP\) - EMEA/H/C/002706/ANX 001.4](#)

Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

Scope: First interim report for imposed study D6560R00004: a PASS evaluating the risk of cardiovascular endpoints of aclidinium bromide-containing products. The report addresses the all-cause mortality component of the PASS programme

17.5.2. [Aclidinium bromide - EKLIRA GENUAIR \(CAP\) - EMEA/H/C/002211/ANX 001.4](#)

Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

Scope: First interim report for imposed study D6560R00004: a PASS evaluating the risk of cardiovascular endpoints of aclidinium bromide-containing products. The report addresses the all-cause mortality component of the PASS programme

17.5.3. [Aclidinium bromide, formoterol fumarate dihydrate - BRIMICA GENUAIR \(CAP\) - EMEA/H/C/003969/ANX 003.1](#)

Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

Scope: First interim report for imposed study D6560R00004: a PASS evaluating the risk of

⁶⁸ In line with the revised variations regulation for any submission before 4 August 2013

cardiovascular endpoints of acclidinium bromide-containing products. The report addresses the all-cause mortality component of the PASS programme

17.5.4. [Aclidinium bromide, formoterol fumarate dihydrate - DUAKLIR GENUAIR \(CAP\) - EMEA/H/C/003745/ANX 003.1](#)

Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

Scope: First interim report for imposed study D6560R00004: a PASS evaluating the risk of cardiovascular endpoints of acclidinium bromide-containing products in new users. The report addresses the all-cause mortality component of the PASS programme

17.5.5. [Catridecacog - NOVOTHIRTEEN \(CAP\) - EMEA/H/C/002284/MEA 015.1](#)

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Ghania Chamouni

Scope: Second interim study report for study NN1841-3868: a multicentre observational study on the use of recombinant factor XIII (FXIII) in the treatment of congenital FXIII deficiency aiming at investigating the incidence of specific adverse drug reactions [final report due date: December 2019]

17.5.6. [Certolizumab pegol - CIMZIA \(CAP\) - EMEA/H/C/001037/MEA 005.5](#)

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: MAH's response to MEA 005.4 [annual reports from rheumatoid arthritis registries from the US National Databank of Rheumatic Diseases (RA0005), German Register for Rheumatoid Arthritis Observation of Biologic Therapy (RABBIT) (RA0020), Register for Antirheumatic Therapies in Sweden (ARTIS) (RA0021), British Society for Rheumatology Biologicals Register (BSRBR) (RA0022)] as per the request for supplementary information (RSI) adopted at the October 2017 PRAC meeting

17.5.7. [Filgrastim - FILGRASTIM HEXAL \(CAP\) - EMEA/H/C/000918/MEA 006.3](#)

Applicant: Hexal AG

PRAC Rapporteur: Patrick Batty

Scope: MAH's response to MEA 006.2 [Sixth annual interim safety report for study EP006-401: safety follow-up of severe chronic neutropenia (SCN) patients included in phase IV study; safety data are collected via cooperation with the Severe Chronic Neutropenia International Registry and reported annually. Patients are followed-up for a total of five years (one year in the SCN study and four years within the registry) [final clinical study report (CSR) due date: 31/12/2019]] as per the request for supplementary information (RSI) adopted at the October 2017 PRAC meeting

17.5.8. [Filgrastim - NIVESTIM \(CAP\) - EMEA/H/C/001142/MEA 015.2](#)

Applicant: Hospira UK Limited

PRAC Rapporteur: Kirsti Villikka

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

17.5.9. [Filgrastim - ZARZIO \(CAP\) - EMEA/H/C/000917/MEA 006.3](#)

Applicant: Sandoz GmbH

PRAC Rapporteur: Patrick Batty

Scope: MAH's response to MEA-006.2 [Sixth annual interim safety report for study EP006-401: safety follow-up of severe chronic neutropenia (SCN) patients included in phase IV study; safety data are collected via cooperation with the Severe Chronic Neutropenia International Registry and reported annually. Patients are followed-up for a total of five years (one year in the SCN study and four years within the registry) [final clinical study report (CSR) due date: 31/12/2019]] as per the request for supplementary information (RSI) adopted at the October 2017 PRAC meeting

17.5.10. [Lumacaftor, ivacaftor - ORKAMBI \(CAP\) - EMEA/H/C/003954/ANX 003.1](#)

Applicant: Vertex Pharmaceuticals (Europe) Ltd.

PRAC Rapporteur: Almath Spooner

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

17.5.11. [Meningococcal group B vaccine \(rDNA, component, adsorbed\) - BEXSERO \(CAP\) - EMEA/H/C/002333/MEA 017.4](#)

Applicant: GSK Vaccines S.r.l

PRAC Rapporteur: Qun-Ying Yue

Scope: Fourth interim report for study V72_36OB: a post-licensure observational safety study after Bexsero (meningococcal B vaccine 4CMenB) vaccination in routine UK care [final report due date: 31/12/2019]

17.5.12. [Mixture of polynuclear iron\(III\)-oxyhydroxide, sucrose and starches - VELPHORO \(CAP\) - EMEA/H/C/002705/MEA 002.6](#)

Applicant: Vifor Fresenius Medical Care Renal Pharma France

PRAC Rapporteur: Julie Williams

Scope: Third interim report for study VFMCRRP-MEAF-PA21-01-EU (Velporo Evaluation of Real-life saFety, effectIveness and adherence 'VERIFY' study): a non-interventional study to investigate the short and long-term real-life safety, effectiveness, and adherence of Velporo in patients with hyperphosphataemia undergoing haemodialysis or peritoneal dialysis (PD)

17.6. Others

17.6.1. Bazedoxifene - CONBRIZA (CAP) - EMEA/H/C/000913/MEA 012.11

Applicant: Pfizer Limited

PRAC Rapporteur: Martin Huber

Scope: MAH's response to MEA 012.10 [Statistical analysis plan (SAP) for PASS B1781044: a cohort study of venous thromboembolism and other clinical endpoints among osteoporotic women prescribed bazedoxifene, bisphosphonates or raloxifene in Europe], as per the request for supplementary information (RSI) adopted in September 2017

17.6.2. Etanercept - ENBREL (CAP) - EMEA/H/C/000262/MEA 166.1

Applicant: Pfizer Limited

PRAC Rapporteur: Patrick Batty

Scope: Interim analysis report for study B1801023: an open-label extension study to assess the long-term safety and clinical benefit of etanercept in children and adolescents with extended oligoarticular juvenile idiopathic arthritis, enthesitis-related arthritis, or psoriatic arthritis who were previously enrolled in protocol 0881A1-3338-WW (B1801014)

17.6.3. Etanercept - LIFMIOR (CAP) - EMEA/H/C/004167/MEA 002

Applicant: Pfizer Limited

PRAC Rapporteur: Patrick Batty

Scope: Interim analysis report for study B1801023: an open-label extension study to assess the long-term safety and clinical benefit of etanercept in children and adolescents with extended oligoarticular juvenile idiopathic arthritis, enthesitis-related arthritis, or psoriatic arthritis who were previously enrolled in protocol 0881A1-3338-WW (B1801014)

17.6.4. Liraglutide - SAXENDA (CAP) - EMEA/H/C/003780/MEA 014.3

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Menno van der Elst

Scope: Pilot study report for study NN8022-4241 (MEA014): a drug utilisation study (DUS) in Europe including retrospective chart review. The study consists of two parts: the pilot study and the full study. The objective of the pilot study is to evaluate the feasibility of conducting the full study in order to evaluate whether Saxenda is used according to approved indication and posology and whether Victoza (liraglutide) is used for weight management

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. Cholic acid - ORPHACOL (CAP) - EMEA/H/C/001250/S/0022 (without RMP)

Applicant: Laboratoires CTRS

PRAC Rapporteur: Patrick Batty

Scope: Annual reassessment of the marketing authorisation

Action: For adoption of advice to CHMP

18.1.2. Idebenone - RAXONE (CAP) - EMEA/H/C/003834/S/0009 (without RMP)

Applicant: Santhera Pharmaceuticals (Deutschland) GmbH

PRAC Rapporteur: Carmela Macchiarulo

Scope: Annual reassessment of the marketing authorisation

18.1.3. Mecasermin - INCRELEX (CAP) - EMEA/H/C/000704/S/0050 (without RMP)

Applicant: Ipsen Pharma

PRAC Rapporteur: Kirsti Villikka

Scope: Annual reassessment of the marketing authorisation

18.1.4. Susoctocog alfa - OBIZUR (CAP) - EMEA/H/C/002792/S/0016 (without RMP)

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Annual reassessment of the marketing authorisation

18.1.5. Tocofersolan - VEDROP (CAP) - EMEA/H/C/000920/S/0027 (without RMP)

Applicant: Orphan Europe SARL

PRAC Rapporteur: Patrick Batty

Scope: Annual reassessment of the marketing authorisation

18.2. Conditional renewals of the marketing authorisation

18.2.1. Delamanid - DELTYBA (CAP) - EMEA/H/C/002552/R/0027 (with RMP)

Applicant: Otsuka Novel Products GmbH

PRAC Rapporteur: Julie Williams

Scope: Conditional renewal of the marketing authorisation

18.3. Renewals of the marketing authorisation

18.3.1. Atosiban - ATOSIBAN SUN (CAP) - EMEA/H/C/002329/R/0012 (with RMP)

Applicant: Sun Pharmaceutical Industries Europe B.V.

PRAC Rapporteur: Amelia Cupelli

Scope: 5-year renewal of the marketing authorisation

18.3.2. 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

18.3.3. Dabrafenib - TAFINLAR (CAP) - EMEA/H/C/002604/R/0030 (without RMP)

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: 5-year renewal of the marketing authorisation

18.3.4. 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

18.3.5. [Esomeprazole - NEXIUM CONTROL \(CAP\) - EMEA/H/C/002618/R/0021 \(without RMP\)](#)

Applicant: Pfizer Consumer Healthcare Limited

PRAC Rapporteur: Simona Kudeliene

Scope: 5-year renewal of the marketing authorisation

18.3.6. [Follitropin alfa - OVALEAP \(CAP\) - EMEA/H/C/002608/R/0023 \(without RMP\)](#)

Applicant: Teva B.V.

PRAC Rapporteur: Menno van der Elst

Scope: 5-year renewal of the marketing authorisation

18.3.7. [Human coagulation factor VIII, human von willebrand factor - VONCENTO \(CAP\) - EMEA/H/C/002493/R/0032 \(without RMP\)](#)

Applicant: CSL Behring GmbH

PRAC Rapporteur: Sabine Straus

Scope: 5-year renewal of the marketing authorisation

18.3.8. [Imatinib - IMATINIB MEDAC \(CAP\) - EMEA/H/C/002692/R/0008 \(with RMP\)](#)

Applicant: Medac Gesellschaft für klinische Spezialpräparate mbH

PRAC Rapporteur: Eva Segovia

Scope: 5-year renewal of the marketing authorisation

18.3.9. [Infliximab - INFLECTRA \(CAP\) - EMEA/H/C/002778/R/0056 \(without RMP\)](#)

Applicant: Hospira UK Limited

PRAC Rapporteur: Patrick Batty

Scope: 5-year renewal of the marketing authorisation

18.3.10. [Infliximab - REMSIMA \(CAP\) - EMEA/H/C/002576/R/0047 \(without RMP\)](#)

Applicant: Celltrion Healthcare Hungary Kft.

PRAC Rapporteur: Patrick Batty

Scope: 5-year renewal of the marketing authorisation

18.3.11. [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

18.3.12. Modified vaccinia Ankara virus - IMVANEX (CAP) - EMEA/H/C/002596/R/0032 (without RMP)

Applicant: Bavarian Nordic A/S

PRAC Rapporteur: Julie Williams

Scope: 5-year renewal of the marketing authorisation

18.3.13. Pandemic influenza vaccine (H5N1) (live attenuated, nasal) - PANDEMIC INFLUENZA VACCINE H5N1 ASTRAZENECA (CAP) - EMEA/H/C/003963/R/0011 (without RMP)

Applicant: AstraZeneca AB

PRAC Rapporteur: Daniela Philadelphia

Scope: 5-year renewal of the marketing authorisation

18.3.14. Regorafenib - STIVARGA (CAP) - EMEA/H/C/002573/R/0025 (without RMP)

Applicant: Bayer AG

PRAC Rapporteur: Sabine Straus

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 05-08 February 2018 meeting.

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
June Munro Raine	Chair	United Kingdom	No interests declared	Full involvement
Jan Neuhauser	Member	Austria	No interests declared	Full involvement
Jean-Michel Dogné	Member	Belgium	No interests declared	Full involvement
Laurence Defays	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
Željana Margan Koletić	Alternate	Croatia	No interests declared	Full involvement
Andri Andreou	Member	Cyprus	No restrictions	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			applicable to this meeting	
Eva Jirsovà	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
Kimmo Jaakkola	Alternate - via telephone*	Finland	No interests declared	Full involvement
Ghania Chamouni	Member	France	No participation in discussion, final deliberations and voting on:	3.2.1 Fluoroquinolones for systemic and inhalation use – Art 31
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
Melinda Palfi	Alternate - via telephone*	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

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Zane Neikena	Member	Latvia	No interests declared	Full involvement
Jolanta Gulbinovic	Member	Lithuania	No interests declared	Full involvement
Sabine Straus	Member	Netherlands	No interests declared	Full involvement
David Olsen	Member	Norway	No participation in discussion, final deliberations and voting on:	3.2.1 Fluoroquinolones for systemic and inhalation use – Art 31 4.1.1 Biotin 4.2.1 Human coagulation(plasma-derived) factor VIII 4.2.3 Paracetamol 4.3.1 Apixaban – ELIQUIS 6.4.7 Sorafenib - NEXAVAR 7.3.1 Rivaroxaban– XARELTO 7.3.2 Thiocolchicoside 7.4.1 Aflibercept - EYLEA 11.2.1 Dienogest, estradiol valerate
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

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
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 - via telephone*	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
Marie Louise (Marieke) De Bruin	Member	Independent scientific expert	No restrictions applicable to this meeting	Full involvement
Stephen J. W. Evans	Member - via telephone*	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 interests declared	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 interests declared	Full involvement
Kirsten Myhr	Alternate	Healthcare Professionals' Representative	No interests declared	Full involvement
Marco Greco	Member	Patients' Organisation Representative	No restrictions applicable to this meeting	Full involvement
Marianne Depreter	Expert - via telephone*	Belgium	No interests declared	Full involvement
Sophie Goethals	Expert - via telephone*	Belgium	No interests declared	Full involvement
Jamila Hamdani	Expert - via	Belgium	No interests	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
	telephone*		declared	
Fabrice Moore	Expert - via telephone*	Belgium	No interests declared	Full involvement
Karen Van Malderen	Expert - via telephone*	Belgium	No interests declared	Full involvement
Veerle Verlinden	Expert - via telephone*	Belgium	No interests declared	Full involvement
Jana Koprušáková	Expert - via telephone*	Czech Republic	No interests declared	Full involvement
Jana Lukačšínová	Expert - via telephone*	Czech Republic	No interests declared	Full involvement
Květoslava Mičochová	Expert - via telephone*	Czech Republic	No interests declared	Full involvement
Jana Pavelková	Expert - via telephone*	Czech Republic	No interests declared	Full involvement
Radim Tobolka	Expert - via telephone*	Czech Republic	No interests declared	Full involvement
Terhi Lehtinen	Expert - via telephone*	Finland	No interests declared	Full involvement
Outi Mäki-Ikola	Expert - via telephone*	Finland	No restrictions applicable to this meeting	Full involvement
Päivi Ruokoniemi	Expert - via telephone*	Finland	No interests declared	Full involvement
Myriam Bouslama	Expert - in person*	France	No interests declared	Full involvement
Pierre Demolis	Expert - in person*	France	No interests declared	Full involvement
Guillem Fite	Expert - in person*	France	No interests declared	Full involvement
Ines Flügge	Expert - via telephone*	Germany	No interests declared	Full involvement
Thomas Grüger	Expert - via telephone*	Germany	No interests declared	Full involvement
Frankziska Heinrich	Expert - via telephone*	Germany	No interests declared	Full involvement
Jelena Katic	Expert - via telephone*	Germany	No interests declared	Full involvement
Dario Ortiz de Orué Lucana	Expert - via telephone*	Germany	No interests declared	Full involvement
Ellen Pantke	Expert - via	Germany	No interests	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
	telephone*		declared	
Jens Rotthauwe	Expert - via telephone*	Germany	No interests declared	Full involvement
Janet Schriever	Expert - via telephone*	Germany	No interests declared	Full involvement
Ruchika Sharma	Expert - via telephone*	Ireland	No interests declared	Full involvement
Desiree Bergamin-Egenberger	Expert - via telephone*	Netherlands	No interests declared	Full involvement
Irene Bosselaers	Expert - via telephone*	Netherlands	No interests declared	Full involvement
Liana Gross-Martirosyan	Expert - in person*	Netherlands	No interests declared	Full involvement
Marcel Kwa	Expert - via telephone*	Netherlands	No interests declared	Full involvement
Cristel Loeb	Expert - in person*	Netherlands	No interests declared	Full involvement
Bianca Mulder	Expert - via telephone*	Netherlands	No restrictions applicable to this meeting	Full involvement
Anouk Neuteboom	Expert - via telephone*	Netherlands	No interests declared	Full involvement
Elizabeth Van Vlijmen	Expert - via telephone*	Netherlands	No interests declared	Full involvement
Maria Vanenburg	Expert - via telephone*	Netherlands	No interests declared	Full involvement
Inge Zomerdijk	Expert - in person*	Netherlands	No interests declared	Full involvement
Joanna Plichta	Expert - in person*	Poland	No interests declared	Full involvement
Sílvia Duarte	Expert - in person*	Portugal	No interests declared	Full involvement
António Lourenço	Expert - via telephone*	Portugal	No interests declared	Full involvement
Pilar Rayón	Expert - in person*	Spain	No interests declared	Full involvement
Maria Jesus Fernandez Cortizo	Expert - via telephone*	Spain	No interests declared	Full involvement
Charlotte Backman	Expert - in person*	Sweden	No interests declared	Full involvement
Kristina Dunder	Expert - via	Sweden	No interests	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
	telephone*		declared	
Mari Thörn	Expert - via telephone*	Sweden	No restrictions applicable to this meeting	Full involvement
Charlotte Welsh	Expert - via telephone*	Sweden	No interests declared	Full involvement
Marta Busana	Expert - via telephone*	United Kingdom	No interests declared	Full involvement
Sarah Mee	Expert - in person*	United Kingdom	No restrictions applicable to this meeting	Full involvement
A representative from the European Commission attended the meeting				
Meeting run with support from relevant EMA staff				

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

20. Annex III - List of acronyms and abbreviations

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

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

21. Explanatory notes

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

[EU Referral procedures for safety reasons: Urgent EU procedures and Other EU referral procedures](#)

(Items 2 and 3 of the PRAC minutes)

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

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000150.jsp&mid=W0b01ac05800240d0

[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/>