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Pharmacovigilance Risk Assessment Committee (PRAC) Minutes of PRAC meeting on 13-16 May 2019

Chair: Sabine Straus – Vice-Chair: Martin Huber

Health and safety information

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

Disclaimers

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

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

Note on access to documents

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



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1. Introduction

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

The Chairperson opened the 13-16 May 2019 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 the Rules of Procedure ([EMA/PRAC/567515/2012 Rev.1](#)). All decisions taken at this meeting were made in the presence of a quorum of members (i.e. 24 or more members were present in the room). All decisions, recommendations and advice were agreed unanimously, unless otherwise specified.

The PRAC Chairperson welcomed Hans Christian Siersted as the new alternate for Denmark. The PRAC Chair also welcomed Sonja Hrabcik, replacing Daniela Philadelphly, as the new alternate for Austria.

1.2. Agenda of the meeting on 13-16 May 2019

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 April 2019

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 April 2019 were published on the EMA website on 27 September 2019 ([EMA/PRAC/527155/2019](#)).

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

2.3.1. Fenspiride (NAP) - EMEA/H/A-107i/1480

Applicant(s): various

PRAC Rapporteur: Julia Pallos; PRAC Co-rapporteur: Adrien Inoubli

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

Background

A referral procedure under Article 107i of Directive 2001/83/EC for fenspiride-containing products is to be concluded. The procedure was initiated following the results of two non-clinical studies¹ showing that fenspiride can induce an inhibition of hERG² tail current *in vitro*, and increase the corrected QT (QTc) intervals in isolated and perfused guinea pig heart. The calculated safety margins between the hERG inhibition concentration and the effective therapeutic plasma concentration are below the acceptable margin proposed in the literature. For further background, see [PRAC minutes February 2019](#). A final assessment of the data submitted was produced by the Rapporteurs according to the agreed timetable.

Discussion

The PRAC discussed the conclusion reached by the Rapporteurs.

The PRAC reviewed the totality of the data available for fenspiride-containing products in relation to the risk of QT prolongation. This included the results of non-clinical studies, published efficacy studies and post-marketing case reports, submitted by the MAHs, by stakeholders and provided by EMA.

The PRAC considered that the use of fenspiride is associated with a risk of QT prolongation, and it has pro-arrhythmic potential and a risk of Torsade de Pointes (TdP). QT prolongation and TdP are unpredictable and potentially life-threatening conditions that constitute a major safety concern, particularly given the benign symptoms for which fenspiride-containing products are used to treat. Taking into account that these medicinal products are only used to treat benign symptoms, the PRAC considered that no feasible and proportionate measures would effectively allow identifying patients with risk factors for QT prolongation and TdP, and that therefore any related risk minimisation measures (RMMs) could not be implemented in clinical practice. No other appropriate measure was identified that would reduce the risk of QT prolongation to an acceptable level. Further, the PRAC could not identify condition(s) to the marketing authorisation(s) which if fulfilled would demonstrate a positive benefit-risk balance for these medicinal products in a defined patient population.

¹ Including a hERG channel binding study requested in the conclusion of periodic safety update report single assessment (PSUSA) procedure PSUSA/00001368/201804 finalised in November 2018. This study was requested following case reports of heart rhythm problems reported in patients who had taken fenspiride-containing product(s) in the past

² Human ether-a-go-go-related gene

As a consequence, the PRAC considered that the benefit-risk balance of fenspiride-containing products is no longer favourable.

Summary of recommendation(s)/conclusions

- The PRAC adopted a recommendation to revoke the marketing authorisation(s) for fenspiride-containing products to be considered by CMDh for a position – see EMA Press Release ([EMA/285298/2019](#)) entitled 'Withdrawal of marketing authorisations for fenspiride medicines' published on 29 May 2019.
- The PRAC agreed on the distribution of a direct healthcare professional communication (DHPC) together with a communication plan.

Post-meeting note: the press release entitled 'Withdrawal of marketing authorisations for fenspiride medicines' ([EMA/285298/2019](#)) representing the position adopted by the CMDh was published on the EMA website on 29 May 2019.

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

3.1. Newly triggered procedures

3.1.1. Tofacitinib - XELJANZ (CAP) - EMEA/H/A-20/1485

Applicant(s): Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan; PRAC Co-rapporteur: Amelia Cupelli

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

Background

The European Commission (EC) sent a letter of [notification](#) dated 15 May 2019 triggering a procedure under Article 20 of Regulation (EC) No 726/2004 for the review of Xeljanz (tofacitinib). Xeljanz is a centrally authorised medicine containing tofacitinib, indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drug (DMARD) therapies, and for the treatment of active psoriatic arthritis (PsA). It is also indicated for the treatment of adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic agent under certain conditions.

During the assessment of a signal on Xeljanz (tofacitinib) of an increased risk of pulmonary embolism and overall mortality arising from study A3921133³ in patients with cardiovascular risk factors treated for rheumatoid arthritis with tofacitinib 10 mg twice daily (BID), the PRAC considered that in view of the seriousness of the emerging data, the findings should be further investigated. Their impact, as well as the impact of the risk

³ A phase 3B/4 randomised safety endpoint study of 2 doses of tofacitinib (tofacitinib 5 mg twice daily (BID) and tofacitinib 10 mg BID) in comparison to a tumour necrosis factor (TNF) inhibitor in subjects with rheumatoid arthritis

of thrombotic events, in particular pulmonary embolism (PE) and deep venous thrombosis should be assessed in the context of the benefit-risk balance of the medicinal product in the authorised indications and doses. See also under 4.3.6.

Therefore, the EC requested the EMA to give its opinion on whether the marketing authorisation(s) for Xeljanz (tofacitinib) should be maintained, varied, suspended or revoked. In addition, the EC requested the EMA to give its opinion, as soon as possible, as to whether provisional measures were necessary to ensure the safe and effective use of the medicinal product.

Discussion

The PRAC noted the notification letter from the EC and appointed Liana Gross-Martirosyan as Rapporteur and Amelia Cupelli as Co-Rapporteur for the procedure.

The PRAC reviewed the available data from study A3921133 on the increased risk of pulmonary embolism and overall mortality in patients with cardiovascular risk factors treated for rheumatoid arthritis with tofacitinib 10 mg BID. The PRAC concluded that a statistically and clinically important difference in the occurrence of pulmonary embolism with the tofacitinib 10 mg BID treatment arm compared to the active TNF inhibitor control was observed. The overall incidence of pulmonary embolism was 6-fold higher in tofacitinib 10 mg BID arm of the study compared with the TNF inhibitor arm and approximately 3-fold higher than tofacitinib in other studies across the tofacitinib programme. An increase in all-cause mortality in the 10 mg BID arm was also noted.

Therefore considering this serious risk, the PRAC considered that until a thorough review is finalised, it is appropriate to limit the number of patients with known risk factors for pulmonary embolism exposed to tofacitinib 10 mg BID. As a result, the PRAC recommended provisional measures to amend the product information to contraindicate the use of tofacitinib 10 mg BID in patients who have known risk factors for pulmonary embolism. The PRAC also introduced warnings regarding the risk of pulmonary embolism in the product information.

The Committee considered that the benefit-risk balance of Xeljanz (tofacitinib) remains favourable subject to the agreed provisional amendments to the product information.

Finally, the PRAC discussed a list of questions (LoQ) to be addressed during the procedure together with a timetable for conducting the review. The PRAC also discussed the need for a public hearing.

Summary of recommendation(s)/conclusions

- The Committee recommended the variation⁴ to the terms of the marketing authorisation(s) for Xeljanz (tofacitinib) as a provisional measure, without prejudice to the final conclusions of the ongoing procedure under Article 20 of Regulation (EC) 726/2004.
- The PRAC also agreed on distribution of a direct healthcare professional communication (DHPC) together with a communication plan.
- The Committee adopted a LoQ for the MAH ([EMA/PRAC/269837/2019](#)) and a timetable for the procedure ([EMA/PRAC/269913/2019](#)).

⁴ Update of SmPC sections 4.3 and 4.4. The package leaflet is updated accordingly

- The PRAC supported the organisation of an ad-hoc expert group meeting during the course of the review.
- The PRAC also discussed the option to conduct a public hearing in the context of the pre-defined criteria set out in the rules of procedure⁵ ([EMA/363479/2015](#)). It was agreed by the Committee that at this stage of the procedure, in light of the currently available data and the need to determine the appropriate approach to stakeholder engagement, a public hearing would not be appropriate. The PRAC can come back to reconsider this at a later stage of the procedure as needed.

See EMA press release ([EMA/267216/2019 Rev.1](#)) entitled 'Restrictions in use of Xeljanz while EMA reviews risk of blood clots in lungs'.

Post-meeting note: On 27 June 2019, the European Commission (EC) granted a Commission Decision on the temporary measures ([C\(2019\) 5007 \(final\)](#)). On 5 July 2019, the PRAC assessment report on provisional measures ([EMA/309456/2019](#)) and [scientific conclusions](#) were published on the EMA website.

3.2. Ongoing procedures

3.2.1. Methotrexate - JYLAMVO (CAP), NORDIMET (CAP); NAP - EMEA/H/A-31/1463

Applicants: Nordic Group B.V. (Nordimet), Therakind Limited (Jylamvo), various

PRAC Rapporteur: Martin Huber; PRAC Co-rapporteur: Željana Margan Koletić

Scope: Review of the benefit-risk balance following notification by Spain 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 methotrexate-containing medicines (oral and parenteral formulations) following reports of overdose toxicity as a consequence of daily intake in error instead of weekly intake. The ongoing review also assesses the risk minimisation measures taken nationally over recent years to fully elucidate the issue and to take appropriate measures. For further background, see [PRAC minutes April 2018](#), [PRAC minutes October 2018](#), [PRAC minutes January 2019](#), [PRAC minutes February 2019](#) and [PRAC minutes March 2019](#).

Summary of recommendation(s)/conclusions

- The PRAC discussed the second joint assessment report by the Rapporteurs.
- The PRAC adopted a third list of outstanding issues (LoOI), to be addressed by the MAHs in accordance with a revised timetable ([EMA/PRAC/199744/2018 Rev 3](#)).

3.3. Procedures for finalisation

None

⁵ Rules of procedure on the organisation and conduct of public hearings at the PRAC

3.4. Re-examination procedures⁶

None

3.5. Others

None

4. Signals assessment and prioritisation⁷

4.1. New signals detected from EU spontaneous reporting systems

See also Annex I 14.1.

4.1.1. Direct-acting antivirals (DAAV): daclatasvir – DAKLINZA (CAP); dasabuvir – EXVIERA (CAP); elbasvir, grazoprevir – ZEPATIER (CAP); glecaprevir, pibrentasvir – MAVIRET (CAP); ledipasvir, sofosbuvir – HARVONI (CAP); ombitasvir, paritaprevir, ritonavir – VIEKIRAX (CAP); sofosbuvir – SOVALDI (CAP); sofosbuvir, velpatasvir – EPCLUSA (CAP); sofosbuvir, velpatasvir, voxilaprevir – VOSEVI (CAP)

Applicant(s): AbbVie Deutschland GmbH & Co. KG (Exviera, Maviret, Viekirax); Bristol-Myers Squibb Pharma (Daklinza); Gilead Sciences Ireland UC (Eplusa, Harvoni, Sovaldi, Vosevi); Merck Sharp & Dohme B.V. (Zepatier)

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Signal of autoimmune hepatitis

EPITT 19395 – New signal

Lead Member State(s): ES, PT, UK

Background

Daclatasvir, dasabuvir, elbasvir/grazoprevir, glecaprevir/pibrentasvir, ledipasvir/sofosbuvir, ombitasvir/paritaprevir/ritonavir, sofosbuvir, sofosbuvir/velpatasvir and sofosbuvir/velpatasvir/voxilaprevir are direct-acting antivirals (DAAV) against hepatitis C virus (HCV).

Daklinza (daclatasvir), Exviera (dasabuvir), Zepatier (elbasvir/grazoprevir), Maviret (glecaprevir/pibrentasvir), Harvoni (ledipasvir/sofosbuvir), Viekirax (ombitasvir/paritaprevir/ritonavir), Sovaldi (sofosbuvir), Eplusa (sofosbuvir/velpatasvir), Vosevi (sofosbuvir/velpatasvir/voxilaprevir) are centrally authorised products indicated for the treatment of chronic hepatitis C virus (HCV) infection in adults or adults and adolescents from the age of 12 years under certain conditions.

The exposure for Daklinza (daclatasvir) is estimated to have been more than 145,428 patients worldwide, in the period from first authorisation in 2014 to 2018. The exposure for Exviera (dasabuvir) is estimated to have been more than 203,000 patient-years

⁶ Re-examination of the PRAC recommendation under Article 32 of Directive 2001/83/EC

⁷ Each signal refers to a substance or therapeutic class. The route of marketing authorisation is indicated in brackets (CAP for Centrally Authorised Products; NAP for Nationally Authorised Products including products authorised via Mutual Recognition Procedures and Decentralised Procedure). Product names are listed for reference Centrally Authorised Products (CAP) only. PRAC recommendations will specify the products concerned in case of any regulatory action required

worldwide, in the period from first authorisation in 2015 to 2019. The exposure for Zepatier (elbasvir/grazoprevir) is estimated to have been more than 30,739 patient-years worldwide, in the period from first authorisation in 2016 to 2018. The exposure for Maviret (glecaprevir/pibrentasvir) is estimated to have been more than 158,322 patient treatment courses worldwide, in the period from first authorisation in 2017 to 2018. The exposure for Harvoni (ledipasvir/sofosbuvir) is estimated to have been more than 210,078 patient-years worldwide, in the period from first authorisation in 2014 to 2018. The exposure for Viekirax (ombitasvir/paritaprevir/ritonavir) is estimated to have been more than 310,150 patient treatment courses worldwide, in the period from first authorisation in 2015 to 2019. The exposure for Sovaldi (sofosbuvir) is estimated to have been more than 212,128 patient-years worldwide, in the period from first authorisation in 2014 to 2018. The exposure for Eplclusa (sofosbuvir/velpatasvir) is estimated to have been more than 64,339 patient-years worldwide, in the period from first authorisation in 2016 to 2018. The exposure for Vosevi (sofosbuvir/velpatasvir/voxilaprevir) is estimated to have been more than 3,677 patient-years worldwide, in the period from first authorisation in 2017 to 2019.

During routine signal detection activities, a signal of autoimmune hepatitis was identified by the EMA for Harvoni (ledipasvir/sofosbuvir), based on 9 cases retrieved from EudraVigilance. Portugal confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

Having considered the evidence from EudraVigilance and the literature, and taking into account that autoimmune hepatitis might result from an imbalance of the immune system following rapid HCV clearance induced by treatment with DAAV rather than direct drug toxicity, the PRAC agreed that the signal warranted further investigation at the class level and agreed to request further information from the MAHs of all DAAV.

The PRAC appointed Ana Sofia Diniz Martins as Rapporteur for the signal.

Summary of recommendation(s)

- The MAHs for Daklinza (daclatasvir), Exviera (dasabuvir), Zepatier (elbasvir/grazoprevir), Maviret (glecaprevir/pibrentasvir), Harvoni (ledipasvir/sofosbuvir), Viekirax (ombitasvir/paritaprevir/ritonavir), Sovaldi (sofosbuvir), Eplclusa (sofosbuvir/velpatasvir), Vosevi (sofosbuvir/velpatasvir/voxilaprevir) should submit to the EMA, within 60 days, a cumulative review of cases of autoimmune hepatitis including spontaneous reports, the literature and non-clinical and clinical trials. Particular attention should be paid to the diagnostic criteria (e.g. type of autoantibody, liver biopsy results), treatment and outcome. The MAHs should also discuss the need for updating the product information and/or the RMP and make a proposal, as appropriate.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.1.2. Ferric carboxymaltose (NAP); iron (NAP); iron dextran (NAP); iron (III) isomaltoside (NAP); iron sucrose (NAP); sodium ferric gluconate (NAP)

Applicant(s): various

PRAC Rapporteur: Zane Neikena

Scope: Signal of arteriospasm coronary

EPITT 19408 – New signal

Lead Member State(s): LV, UK

Background

Ferric carboxymaltose, iron, iron dextran, iron (III) isomaltoside, iron sucrose and sodium ferric gluconate are parenteral iron products indicated for the treatment of iron deficiency anaemia and other types of anaemias.

During routine signal detection activities, a signal of arteriospasm coronary was identified by the MAH Panmedica, based on 35 reports retrieved from EudraVigilance corresponding to the MedDRA HLG⁸ 'coronary artery disorders'. The United Kingdom confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

Based on the assessment of the available evidence from case reports in EudraVigilance and in the literature, as well as a possible biological mechanism, the PRAC considered that further evaluation of the signal of coronary arteriospasm and iron sucrose is warranted and that the signal scope should be extended to include other parenteral iron products including: ferric carboxymaltose, iron (III) isomaltoside 1000, iron dextran and sodium ferric gluconate. The PRAC agreed to request additional data from the MAHs of medicinal products containing these substances.

The PRAC appointed Zane Neikena as Rapporteur for the signal.

Summary of recommendation(s)

- The MAHs of iron sucrose and iron carboxymaltose (Vifor), iron (III) isomaltoside and iron dextran (Pharmacosmos) and sodium ferric gluconate (Sanofi), should submit to the EMA, within 60 days, an in-depth cumulative review of arteriospasm coronary and related terms. This review should include cases where the reactions occurred in the context of hypersensitivity reactions. The MAHs should also discuss possible biological mechanisms and whether the risk of arteriospasm coronary is higher for a specific sub-group. The MAHs should discuss the need for any potential amendments to the product information and/or RMP and make a proposal, as appropriate.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.1.3. Mesalazine (NAP)

Applicant(s): various

PRAC Rapporteur: Martin Huber

Scope: Signal of nephrolithiasis

EPITT 19405 – New signal

Lead Member State(s): DE

⁸ Medical Dictionary for Regulatory Activities – High level group term

Background

Mesalazine is an anti-inflammatory agent indicated for the treatment of mild to moderate ulcerative colitis and for Crohn's disease.

During routine signal detection activities, a signal of nephrolithiasis was identified by the Netherlands, based on 2 cases retrieved from the national database and 4 cases from EudraVigilance. Germany confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the available evidence and considered that there is a possible causal association between mesalazine treatment and the development of kidney stones in patients with inflammatory bowel disease (IBD) based on cases with stones composed of mesalazine, cases with positive dechallenge and similar experience with sulfasalazine. The PRAC agreed that the product information of mesalazine-containing products should be updated and requested the MAHs for mesalazine-containing products to comment on a proposed wording.

The PRAC appointed Martin Huber as Rapporteur for the signal.

Summary of recommendation(s)

- The MAHs for mesalazine-containing products should submit to the EMA, within 30 days, comments on the proposal for amending the product information⁹.
- A 30-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.2. New signals detected from other sources

See also Annex I 14.2.

4.2.1. 5 alfa-reductase inhibitors (5ARIs): finasteride (NAP); dutasteride (NAP)

Applicant(s): various

PRAC Rapporteur: Annika Folin

Scope: Signal of type 2 diabetes mellitus (T2DM)

EPITT 19424 – New signal

Lead Member State(s): HU, SE

Background

Finasteride and dutasteride are 5 alfa-reductase inhibitors, indicated for the treatment of benign prostatic hyperplasia, and finasteride is also indicated (in the 1 mg strength) for the treatment of male pattern hair loss.

The exposure for finasteride-containing products is estimated to have been more than 36.8 million patient-years worldwide (5 mg strength) and more than 12.1 million patient-years worldwide (1 mg strength), in the period from first authorisation in 1998 to 2018.

⁹ Update of SmPC sections 4.4 and 4.8. The package leaflet is to be updated accordingly

The exposure for dutasteride-containing products is estimated to have been more than 18.5 million patient-years worldwide in the period from first authorisation in 2001 to 2017.

Following the publication in the BMJ by *Wei L et al*¹⁰, a signal of type 2 diabetes mellitus (T2DM) was identified by Sweden, suggesting that risk of developing new onset T2DM appears to be higher in men with benign prostatic hyperplasia exposed to 5 α -reductase inhibitors compared with those receiving tamsulosin. Sweden confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the results of the study by *Wei L et al.*, which highlights a higher risk of new onset of T2DM in men with benign prostatic hyperplasia exposed to 5 α -reductase inhibitors (dutasteride and finasteride) than in men receiving tamsulosin. The PRAC agreed that further clarifications were needed from the authors.

The PRAC appointed Annika Folin as Rapporteur for the signal.

Summary of recommendation(s)

- The principal investigators are invited to submit to the EMA, within 90 days, responses to a list of questions (LoQ) as agreed by the PRAC.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.2.2. Amino acid, lipid combinations with vitamins or trace elements^{11 12} (NAP)

Applicant(s): various

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of adverse outcomes in neonates treated with solutions not protected from light

EPITT 19423 – New signal

Lead Member State(s): SE

Background

Amino acid, lipid combinations with vitamins or trace elements are products containing nutrients indicated for the parenteral nutrition of neonates.

The exposure for amino acid combinations, glucose, triglyceride combinations (e.g. olive oil, soya bean oil, fish oil), with or without electrolytes, mineral compounds (intravenous (I.V) application)-containing products is estimated to have been more than 40,800 patients worldwide, in the period from first authorisation in 2011 to 2017.

A signal of adverse outcomes in neonates treated with solutions not protected from light was identified by Sweden based on information received in a variation procedure.

¹⁰ Wei L et al. Incidence of type 2 diabetes mellitus in men receiving steroid 5 α -reductase inhibitors: population based cohort study. *BMJ*. 2019;365:l1204

¹¹ For parenteral nutrition of neonates only

¹² Including amino acid combinations, glucose, triglyceride combinations (e.g. olive oil, soya bean oil, fish oil), with or without electrolytes, mineral compounds (intravenous (I.V) application)

Sweden confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the data regarding the risk of adverse outcomes in neonates treated with parenteral solutions not protected from light, including a meta-analysis of 4 randomised controlled trials which showed reduced mortality at 36 weeks' gestational age resulting from light protection of parenteral nutrition products. The PRAC agreed that toxic degradations when parenteral nutrition solutions containing amino acids and/or lipids with or without admixture of vitamins or trace elements are not protected from light from the point of admixture through administration could result in severe clinical outcomes in premature infants. The PRAC considered it justified to implement a recommendation for light protection in the product information of such parenteral nutrition products.

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

Summary of recommendation(s)

- The MAHs for products containing amino acid, lipid combinations with vitamins or trace elements (for parenteral nutrition of neonates only) should submit to the EMA, within 30 days, responses to a list of questions (LoQ) to discuss the relevance to their particular product, and the proposals for updating of product information regarding the need for protection from light.
- The MAHs should also submit a joint proposal for a direct healthcare professional communication (DHPC) and a communication plan.
- A 30-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.2.3. Ibuprofen (NAP), ketoprofen (NAP) and fixed-dose combinations: chlorphenamine, ibuprofen, phenylephrine (NAP); dimenhydrinate, ibuprofen, caffeine (NAP); ibuprofen, ascorbic acid (NAP); ibuprofen, caffeine (NAP); ibuprofen, codeine (NAP); ibuprofen, hydrocodone (NAP); ibuprofen, paracetamol (NAP); ibuprofen, phenylephrine (NAP); ibuprofen, pseudoephedrine (NAP); ketoprofen, omeprazole (NAP), ketoprofen, sucralfate (NAP)

Applicant(s): various

PRAC Rapporteur: Anette Kirstine Stark

Scope: Signal of serious exacerbation of infections

EPITT 19415 – New signal

Lead Member State(s): DK, FR, IT, PL, SE

Background

Ibuprofen is a non-steroidal anti-inflammatory medicine (NSAID) indicated among others, alone or in combination with other substances, for the treatment of fever and pain of mild to moderate intensity and for treatment of pain and inflammation in chronic inflammatory rheumatic diseases.

Ketoprofen is a NSAID, indicated among others for the treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, acute joint pain, back pain strain, lumbago and sciatica, painful musculoskeletal conditions, acute gout, dysmenorrhoea and control of pain and inflammation following orthopaedic surgery.

During signal detection activities, a signal of serious exacerbation of infections was identified by France, based on 337 cases identified with ibuprofen from a national survey (reported between 2000 and 2018), supplemented by an analysis of disproportionality carried out in WHO¹³, European and French databases and a literature review. Denmark as the lead Member State (LMS) for ibuprofen confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

Having considered the available evidence from the literature and spontaneous case reports, regarding the signal of serious exacerbation of infections with ibuprofen and ketoprofen, the PRAC agreed to further investigate this signal and request further information from the MAHs.

The PRAC appointed Anette Kirstine Stark as Rapporteur for the signal.

Summary of recommendation(s)

- The brand leader MAHs for ibuprofen (Reckitt Benckiser) and ketoprofen (Sanofi-Aventis) as well as the MAH of Pedeia (ibuprofen) should submit to the EMA, within 90 days, a review of literature stating clearly the methodology of the review and excluding the references already mentioned in the signal assessment report as well as available evidence from clinical and pre-clinical studies. The MAHs should also discuss the need for an amendment of the product information and/or the RMP and make a proposal accordingly.
- The PRAC also requested the EMA to provide an analysis of EudraVigilance data related to serious exacerbation of infections reported for ibuprofen and ketoprofen.
- A 90-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.3. Signals follow-up and prioritisation

4.3.1. Clomipramine (NAP); Serotonin and noradrenaline reuptake inhibitors (SNRI)¹⁴: desvenlafaxine (NAP); duloxetine - CYMBALTA (CAP) - EMEA/H/C/000572/SDA/049, DULOXETINE LILLY (CAP) - EMEA/H/C/004000/SDA/005, DULOXETINE MYLAN (CAP), DULOXETINE ZENTIVA (CAP), XERISTAR (CAP) - EMEA/H/C/000573/SDA/050, YENTREVE (CAP) - EMEA/H/C/000545/SDA/045; milnacipran (NAP); venlafaxine (NAP); Selective serotonin reuptake inhibitors (SSRI)¹⁵: citalopram (NAP); escitalopram (NAP); fluoxetine (NAP); fluvoxamine (NAP); paroxetine (NAP); sertraline (NAP); Vortioxetine – BRINTELLIX (CAP) - EMEA/H/C/002717/SDA/006

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

¹³ World Health Organization

¹⁴ Indicated in the treatment of major depressive disorder (MDD)

¹⁵ Indicated in the treatment of major depressive disorder (MDD)

(Duloxetine Zentiva), various

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Signal of persistent sexual dysfunction after drug withdrawal

EPITT 19277 – Follow-up to November 2018

Background

For background information, see [PRAC minutes November 2018 \(29-31 October 2018\)](#).

The MAHs Eli Lilly, Lundbeck, Mylan, Pfizer, GSK, Almirall, Pierre Fabre and Alfasigma replied to the request for information on the signal of persistent sexual dysfunction after drug withdrawal and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence including EudraVigilance, literature, social media and the reviews provided by MAHs for duloxetine, fluoxetine (Eli Lilly), citalopram, vortioxetine, escitalopram (Lundbeck), fluvoxamine (Mylan), sertraline, desvenlafaxine (Pfizer), paroxetine (GSK), venlafaxine (Almirall), milnacipram (Pierre Fabre) and clomipramine (Alfasigma), the PRAC agreed that there is a possible causal association between treatment with serotonin and noradrenaline reuptake inhibitor (SNRI), selective serotonin reuptake inhibitor (SSRI) antidepressants and sexual dysfunction. The PRAC agreed that the product information of products containing these substances should be updated to include a warning on sexual dysfunction that may continue despite discontinuation of these medicinal products. The PRAC agreed that considering that no suggestive cases were identified for clomipramine and vortioxetine, no regulatory action was warranted at this stage for clomipramine- and vortioxetine-containing products.

Summary of recommendation(s)

- The MAHs of citalopram-, escitalopram-, fluvoxamine-, fluoxetine-, paroxetine-, sertraline-containing products (SSRIs) as well as duloxetine-, venlafaxine-, desvenlafaxine-, milnacipram--containing products (SNRIs) should submit to the EMA or relevant National Competent Authorities (NCAs) of the Member States, within 60 days, a variation to update the product information¹⁶.

For the full PRAC recommendation, see [EMA/PRAC/265212/2019](#) published on 11/06/2019 on the [EMA website](#).

4.3.2. Clopidogrel – CLOPIDOGREL APOTEX (CAP), CLOPIDOGREL BGR (CAP), CLOPIDOGREL HCS (CAP), CLOPIDOGREL KRKA (CAP), CLOPIDOGREL KRKA D.D. (CAP), CLOPIDOGREL MYLAN (CAP), CLOPIDOGREL RATIOPHARM (CAP), CLOPIDOGREL RATIOPHARM GMBH (CAP), CLOPIDOGREL TAD (CAP), CLOPIDOGREL TEVA (CAP), CLOPIDOGREL ZENTIVA (CAP), GREPID (CAP), ISCOVER (CAP), PLAVIX (CAP) - EMEA/H/C/000174/SDA/034, ZYLLT (CAP); NAP; clopidogrel/acetylsalicylic acid – CLOPIDOGREL/ACETYLSALICYLIC ACID ZENTIVA (CAP), DUOPLAVIN (CAP); NAP
Lopinavir, ritonavir – KALETRA (CAP), LOPINAVIR/RITONAVIR MYLAN (CAP), NAP; ritonavir – NORVIR (CAP), RITONAVIR (CAP); NAP

Applicant(s): AbbVie Deutschland GmbH & Co. KG (Kaletra, Norvir), Apotex Europe BV

¹⁶ Update of SmPC section 4.4. The package leaflet is to be updated accordingly

(Clopidogrel Apotex), Archie Samuel s.r.o. (Clopidogrel Ratiopharm GmbH), HCS bvba (Clopidogrel HCS), Krka, d.d., Novo mesto (Clopidogrel Krka, Clopidogrel Krka d.d., Zyllt), Laboratoires Biogaran (Clopidogrel BGR), Mylan S.A.S (Clopidogrel Mylan, Lopinavir/Ritonavir Mylan, Ritonavir Mylan), Pharmathen S.A. (Grepid), Sanofi-aventis groupe (Clopidogrel/Acetylsalicylic acid Zentiva, Iscover), Sanofi Clir SNC (Duoplavin, Plavix), TAD Pharma GmbH (Clopidogrel TAD), Teva B.V. (Clopidogrel Ratiopharm, Clopidogrel Teva), Zentiva k.s. (Clopidogrel Zentiva), various

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Signal of interaction with ritonavir boosted antiviral human immunodeficiency virus (HIV) therapy leading to insufficient inhibition of platelet aggregation

EPITT 19325 – Follow-up to December 2018

Background

For background information, see [PRAC minutes December 2018 \(26-29 November 2018\)](#).

The MAHs Sanofi and Zentiva replied to the request for information on the signal of drug interaction with ritonavir boosted antiviral human immunodeficiency virus (HIV) therapy leading to insufficient inhibition of platelet aggregation and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence in EudraVigilance and in the literature as well as the responses from the MAHs, the PRAC agreed that there is sufficient evidence of a drug interaction between clopidogrel and ritonavir boosted antiviral human immunodeficiency virus (HIV) therapy which can result in insufficient inhibition of platelet aggregation. The PRAC agreed that the product information of clopidogrel-containing products should be updated.

Summary of recommendation(s)

- The MAHs of clopidogrel-containing products should submit to the EMA or the relevant National Competent Authorities (NCAs) of the Member States, within 90 days, a variation to amend the product information¹⁷ to include information on this drug interaction.

For the full PRAC recommendation, see [EMA/PRAC/265212/2019](#) published on 11/06/2019 on the [EMA website](#).

4.3.3. Pantoprazole – CONTROLOC CONTROL (CAP) - EMEA/H/C/001097/SDA/017, PANTOLOLOC CONTROL (CAP) - EMEA/H/C/001100/SDA/016, PANTOZOL CONTROL (CAP) - EMEA/H/C/001013/SDA/017, SOMAC CONTROL (CAP) - EMEA/H/C/001098/SDA/022; NAP

Applicant(s): Takeda GmbH (Controloc Control, Pantoloc Control, Pantozol Control, Somac Control), various

PRAC Rapporteur: Rugile Pilviniene

Scope: Signal of colitis microscopic

¹⁷ Update of SmPC section 4.5. The package leaflet is to be updated accordingly

EPITT 19342 – Follow-up to January 2019

Background

For background information, see [PRAC minutes January 2019](#).

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

Discussion

Having considered the available evidence from EudraVigilance, literature and the cumulative review provided by the MAH, as well as the fact that colitis microscopic is a known adverse reaction of other proton pump inhibitors and is a likely class effect, the PRAC agreed that the product information of pantoprazole-containing products should be updated.

Summary of recommendation(s)

- The MAHs for pantoprazole-containing products should submit to EMA or National Competent Authorities (NCAs) of the Member States, within 90 days, a variation to update the product information¹⁸.

For the full PRAC recommendation, see [EMA/PRAC/265212/2019](#) published on 11/06/2019 on the [EMA website](#).

4.3.4. Sertraline (NAP)

Applicant(s): various

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Signal of maculopathy

EPITT 19341 – Follow-up to January 2019

Background

For background information, see [PRAC minutes January 2019](#).

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

Discussion

Based on the review of the available evidence on the risk of maculopathy with sertraline, the PRAC agreed that the product information of sertraline-containing products should be updated.

Summary of recommendation(s)

- The MAHs for sertraline-containing products should submit to National Competent Authorities (NCAs) of the Member States, within 60 days, a variation to update the product information¹⁹.

¹⁸ Update of SmPC section 4.8. The package leaflet is to be updated accordingly

¹⁹ Update of SmPC section 4.8. The package leaflet is to be updated accordingly

For the full PRAC recommendation, see [EMA/PRAC/265212/2019](#) published on 11/06/2019 on the [EMA website](#).

4.3.5. Tocilizumab – ROACTEMRA (CAP) - EMEA/H/C/000955/SDA/054.1

Applicant(s): Roche Registration GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Signal of facial paralysis

EPITT 19295 – Follow-up to February 2019

Background

For background information, see [PRAC minutes February 2019](#).

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

Discussion

Having considered the available evidence from the cumulative review including clinical trials, epidemiological data and post-marketing reports and responses to the additional list of questions provided by the MAH, the PRAC agreed that the data does not support a causal relationship between treatment with tocilizumab and facial paralysis. The PRAC agreed that no further regulatory action is warranted at this stage.

Summary of recommendation(s)

- The MAH for RoActemra (tocilizumab) should continue to monitor facial paralysis as part of routine safety surveillance.

4.3.6. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/SDA/005

Applicant(s): Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Signal of increased risk of pulmonary embolism and overall mortality arising from a post-authorisation safety study in patients with cardiovascular risk factors treated for rheumatoid arthritis with tofacitinib 10 mg twice daily

EPITT 19382 – Follow-up to March 2019

Background

Tofacitinib is a potent, selective inhibitor of the Janus kinase (JAK) family indicated, as Xeljanz, for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying antirheumatic drugs, for the treatment of active psoriatic arthritis (PsA) in adult patients who have had an inadequate response or who have been intolerant to a prior disease-modifying antirheumatic drug (DMARD) therapy and for the treatment of adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic agent. For background information, see [PRAC minutes March 2019](#).

The MAH replied to the request for information on the signal of increased risk of pulmonary embolism and overall mortality and the responses were assessed by the Rapporteur. The MAH provided further clarifications at an oral explanation held on 14 May 2019.

Discussion

Having considered the available evidence from study A3921133, other tofacitinib clinical studies and information from the MAH received during an oral explanation, the PRAC agreed that a benefit-risk assessment should be undertaken within an appropriate regulatory procedure.

As a consequence the European Commission (EC) initiated on 15 May 2019 a referral procedure under Article 20 of Regulation (EC) No 726/2004 and requested the Agency to assess the safety concerns and their impact on the benefit-risk balance of Xeljanz (tofacitinib) including the need for provisional measures to ensure the safe and effective use of this medicinal product. For further information, see under 3.1.1.

Summary of recommendation(s)

- The benefit-risk balance of Xeljanz (tofacitinib) will be further reviewed during the referral procedure initiated under Article 20 of Regulation (EC) No 726/2004.

4.3.7. Vascular endothelial growth factor (VEGF) inhibitors: afibercept – EYLEA (CAP), ZALTRAP (CAP); axitinib – INLYTA (CAP); bevacizumab – AVASTIN (CAP), MVASI (CAP), ZIRABEV (CAP); cabozantinib – CABOMETYX (CAP), COMETRIQ (CAP); lenvatinib – KISPLYX (CAP), LENVIMA (CAP); nintedanib – OFEV (CAP), VARGATEF (CAP); pazopanib – VOTRIENT (CAP); pegaptanib – MACUGEN (CAP); ponatinib – ICLUSIG (CAP); ramucirumab – CYRAMZA (CAP); ranibizumab – LUCENTIS (CAP); regorafenib – STIVARGA (CAP); sorafenib – NEXAVAR (CAP), NAP; sunitinib – SUTENT (CAP); NAP; tivozanib – FOTIVDA (CAP); vandetanib – CAPRELSA (CAP)

Applicant(s): Amgen Europe B.V. (Mvasi), Bayer AG (Eylea, Nexavar, Stivarga), Boehringer Ingelheim (Ofev, Vargatef), Eisai Europe Ltd. (Kispplx, Lenvima), Eli Lilly Nederland B.V. (Cyramza), EUSA Pharma (UK) Limited (Fotivda), Genzyme Europe BV (Caprelsa), Incyte Biosciences Distribution (Iclusig), Ipsen Pharma (Cabometyx, Cometriq), Novartis Europharm Limited (Lucentis, Votrient), Pfizer Europe MA EEIG (Inlyta, Sutent, Zirabev), PharmaSwiss Ceska Republika (Macugen), Roche Registration GmbH (Avastin), Sanofi-aventis groupe (Zaltrap), various

PRAC Rapporteur: Annika Folin

Scope: Signal of artery dissections and aneurysms

EPITT 19330 – Follow-up to December 2018

Background

For background information, see [PRAC minutes December 2018 \(26-29 November 2018\)](#).

The Rapporteur performed the assessment of EudraVigilance cases of artery dissections and aneurysms for vascular endothelial growth factor (VEGF) inhibitors.

Discussion

Having considered the available evidence and following the assessment of the EudraVigilance data, the PRAC agreed that the product information for the VEGF inhibitors for systemic use should be updated to reflect the risk of artery aneurysms and artery dissections. In addition, the PRAC agreed to request further information on this risk from the MAHs of VEGF inhibitor-containing products for intravitreal use.

Summary of recommendation(s)

- The MAHs of Avastin (bevacizumab), Mvasi (bevacizumab), Zirabev (bevacizumab), Cabometyx (cabozantinib), Cometriq (cabozantinib), Caprelsa (vandetanib), Cyramza (ramucirumab), Fotivda (tivozanib), Iclusig (ponatinib), Inlyta (axitinib), Sutent (sunitinib), Kisplyx (lenvatinib), Lenvima (lenvatinib), Nexavar (sorafenib), Stivarga (regorafenib), Ofev (nintedanib), Vargatef (nintedanib), Votrient (pazopanib) and Zaltrap (aflibercept) should submit to the EMA, within 30 days, a proposal to amend the product information. For the medicinal products for which some of these events are already reflected in the product information, the MAHs should review the current warnings in light of this PRAC recommendation. The MAHs should also determine the impact on the RMP.
- A 30-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.
- The MAHs of VEGF inhibitors for intravitreal use, namely for Eylea (aflibercept) and Lucentis (ranibizumab) should submit to the EMA, within 90 days, a cumulative review of all cases of artery dissections and aneurysms.
- A 90-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

5. Risk management plans (RMPs)

5.1. Medicines in the pre-authorisation phase

See also Annex I 15.1.

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

Please refer to the CHMP pages for upcoming information:

<http://www.ema.europa.eu/Committees>CHMP>Agendas, minutes and highlights>.

5.1.1. Dapagliflozin, saxagliptin, metformin hydrochloride - EMEA/H/C/004910

Scope: Treatment in adults aged 18 years and older with type 2 diabetes mellitus (T2DM) to improve glycaemic control in patients who require $\geq 1.5\%$ reduction in HbA1c to reach glycaemic target, where metformin with or without sulphonylurea (SU) does not provide adequate glycaemic control, improve glycaemic control when metformin with or without sulphonylurea (SU) and either saxagliptin or dapagliflozin does not provide adequate glycaemic control when already being treated with saxagliptin and dapagliflozin and metformin

5.1.2. Delafloxacin - EMEA/H/C/004860

Scope: Treatment of acute bacterial skin and skin structure infection (ABSSSI) in adults

5.1.3. Gilteritinib - EMEA/H/C/004752, Orphan

Applicant: Astellas Pharma Europe B.V.

Scope (accelerated assessment): Treatment of patients who have relapsed or refractory acute myeloid leukaemia (AML) with a FMS-like tyrosine kinase 3 (FLT3) mutation

5.1.4. Levodopa - EMEA/H/C/004786

Scope: Treatment of symptoms of 'off' periods in Parkinson's disease

5.1.5. Romosozumab - EMEA/H/C/004465

Scope: Treatment of osteoporosis

Previous PRAC advice was provided in September 2018, see [PRAC minutes September 2018](#).

5.1.6. Siponimod - EMEA/H/C/004712

Scope: Treatment of secondary progressive multiple sclerosis (SPMS)

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. Atezolizumab - TECENTRIQ (CAP) - EMEA/H/C/004143/II/0024

Applicant: Roche Registration GmbH

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Update of sections 4.2, 4.4, and 4.8 of the SmPC in order to add a warning regarding the risk of immune-related myositis identified during a comprehensive analysis of patients treated with Tecentriq (atezolizumab). Annex 2-D on 'conditions or restrictions with regard to the safe and effective use of the medicinal product' are also updated regarding additional risk minimisation(s). Furthermore, a direct healthcare professional communication (DHPC) is proposed to inform healthcare professionals (HCPs) about the risk of immune-related myositis. The package leaflet and the risk management plan (RMP) version 11.0 are updated accordingly

Background

Atezolizumab is a programmed death-ligand 1 (PD-L1) inhibitor indicated, as Tecentriq, for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma (UC) after prior platinum-containing chemotherapy, or who are considered

cisplatin ineligible, and whose tumours have a PD-L1 expression $\geq 5\%$. It is also indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy.

The CHMP is evaluating a type II variation for Tecentriq, a centrally authorised product containing atezolizumab, to add a warning regarding the risk of immune-related myositis and update the additional risk minimisation measures (aRMM). The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this variation.

Summary of advice

- The RMP for Tecentriq (atezolizumab) in the context of the variation procedure under evaluation by the CHMP could be considered acceptable provided that an update to RMP version 11.0 and satisfactory responses to the request for supplementary information (RSI) are submitted.
- The PRAC agreed that 'immune related myositis' should be added to the summary of safety concerns as an important identified risk. With regard to educational material, the PRAC agreed that the 'guide for healthcare professionals (HCPs)' and the 'patient alert card' should be updated to include myositis as an important immune-related risk. As for the proposed direct healthcare professional communication (DHPC), the PRAC did not support its distribution as HCPs are aware of the risk of immune-related adverse drug reactions associated with the class of PD-L1 inhibitors and the guide for HCPs is updated accordingly.

5.3.2. Daratumumab - DARZALEX (CAP) - EMEA/H/C/004077/II/0027, Orphan

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Update of sections 4.4 and 4.8 of the SmPC to add new safety information on the recently identified risk of 'hepatitis B reactivation (HBV)'. The package leaflet and the RMP (version 5) are updated accordingly. In addition, the MAH proposes a direct healthcare professional communication (DHPC) to inform prescribers on the newly identified risk

Background

Daratumumab is an immunoglobulin G1-kappa (IgG1 κ) human monoclonal antibody (mAb) indicated, as Darzalex, in combination with bortezomib, melphalan and prednisone for the treatment of adult patients with newly diagnosed multiple myeloma (MM) who are ineligible for autologous stem cell transplant; as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma (RRMM), whose prior therapy included a proteasome inhibitor and an immunomodulatory agent and who have demonstrated disease progression on the last therapy. It is also indicated in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of adult patients with MM who have received at least one prior therapy.

The CHMP is evaluating a type II variation for Darzalex, a centrally authorised product containing daratumumab, to update the product information with new safety information on the recently identified risk of hepatitis B reactivation (HBV). The PRAC is responsible

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

Summary of advice

- The RMP for Darzalex (daratumumab) in the context of the variation procedure under evaluation by the CHMP could be considered acceptable provided that an update to RMP version 5 and satisfactory responses to the request for supplementary information (RSI) are submitted.
- The PRAC agreed that 'hepatitis B virus (HBV) reactivation' should be added to the summary of safety concerns as an important identified risk.
- The PRAC agreed on the distribution of a direct healthcare professional communication (DHPC) in order to warn healthcare professionals (HCPs) on the risk of HBV reactivation, on the need to screen patients for HBV prior to initiation of daratumumab and on instructions to proceed in case of HBV reactivation. The PRAC agreed the content of the DHPC together with a communication plan.

5.3.3. Deferiprone - FERRIPROX (CAP) - EMEA/H/C/000236/II/0128

Applicant: Apotex Europe BV

PRAC Rapporteur: Ghania Chamouni

Scope: Update of section 4.4 of the SmPC and the patient/carer reminder card in order to update and change the recommended frequency of absolute neutrophil count (ANC) monitoring throughout Ferriprox (deferiprone) treatment from a weekly basis to every week for the first six months of therapy, once every two weeks after six months and to monthly after one year of therapy. The package leaflet and the RMP (version 13.2) are updated accordingly. In addition, the MAH took the opportunity to update minor linguistic amendments in the Hungarian and Maltese product information

Background

Deferiprone is a bidentate ligand which binds to iron. It is indicated, as Ferriprox, for the treatment of iron overload in patients with thalassaemia major when current chelation therapy is contraindicated or inadequate. In combination with another chelator, it is indicated in patients with thalassaemia major when monotherapy with any iron chelator is ineffective, or when prevention or treatment of life-threatening consequences of iron overload (mainly cardiac overload) justifies rapid or intensive correction.

The CHMP is evaluating a type II variation for Ferriprox, a centrally authorised product containing deferiprone, to update the product information and the patient/carer reminder card in order to change the recommended frequency of absolute neutrophil count (ANC) monitoring throughout Ferriprox (deferiprone) treatment. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this variation. For further background, see [PRAC minutes December 2018 \(26-29 November 2018\)](#).

Summary of advice

- The RMP version 13.2 for Ferriprox (deferiprone) in the context of the variation procedure under evaluation by the CHMP is considered acceptable.

- Based on the stable reporting rate of agranulocytosis and neutropenia compared to the increased exposure to deferiprone, and the knowledge gained over the years, the PRAC considered that routine pharmacovigilance is sufficient to further monitor, identify and characterise these risks. In addition, the PRAC agreed with the proposed update of the patient card to ensure that patients seek medical attention in the case of symptoms of infection and a white blood cell count must be checked within 24 hours in order to detect a potential agranulocytosis.

5.3.4. Fingolimod - GILENYA (CAP) - EMEA/H/C/002202/II/0053

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ghania Chamouni

Scope: Update of sections 4.4, 4.6 and 4.8 of the SmPC to add a warning for women stopping treatment for the purpose of becoming pregnant and for pregnant women and to add information to prescribers on 'severe exacerbation of disease after Gilenya (fingolimod) discontinuation', timing of reported events and further recommendations on monitoring of patients. The package leaflet is updated accordingly

Background

Fingolimod is a sphingosine 1-phosphate receptor modulator indicated, as Gilenya, as single disease modifying therapy (DMT) in highly active relapsing remitting multiple sclerosis (RRMS) for adult patients and paediatric patients aged 10 years and older under certain conditions.

The CHMP is evaluating a type II variation for Gilenya, a centrally authorised product containing fingolimod, to update the product information on the timing of reported events and further recommendations on monitoring of patients, to add a warning for women stopping treatment for the purpose of becoming pregnant and for pregnant women as well as to add a new undesirable effect on severe exacerbation of disease after treatment discontinuation with Gilenya (fingolimod). The PRAC is responsible for providing advice to the CHMP on the necessary updates to the risk management plan (RMP) to support this variation.

Summary of advice

- The RMP for Gilenya (fingolimod) in the context of the variation procedure under evaluation by the CHMP could be considered acceptable provided that an update to RMP version 16.0 and satisfactory responses to the request for supplementary information (RSI) are submitted.
- In order to provide patients with the most up-to-date and complete information on their treatment as well as to avoid any confusion for the prescribers on the existence of two patient reminder cards, the PRAC advised to change the current patient/parent/caregiver reminder card into a patient/parent/caregiver guide and to give the name of pregnancy reminder card to the newly agreed pregnancy-related educational material. For further background, see LEG 037 in [PRAC minutes February 2019](#). In addition, the PRAC agreed to amend some key elements for all educational materials that make reference to pregnancy prevention measures.

Applicant: Merck Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Grouped variations consisting of: 1) update of sections 4.3, 4.6 and 5.3 of the SmPC in order to add information about pregnancy and update the statement regarding breast-feeding following the completion of the European interferon beta (IFN- β) pregnancy registry (eighth annual and final report) and the final clinical study report (CSR) of the register-based study in the Nordic countries EUPAS13054: multiple sclerosis pregnancy study - pregnancy outcomes in multiple sclerosis populations exposed and unexposed to interferon beta - a register-based study in the Nordic countries; 2) update of section 4.6 of the SmPC in order to update the statement regarding breast-feeding following a review of studies, case reports and literature articles (fulfilment of MEA 43.2 and 39). The package leaflet is updated accordingly. The RMP (version 10.0) is updated accordingly, including the deletion of the important potential risk 'pregnancy outcomes'. The RMP is also updated to bring it in line with revision 2 of the guidance on the format of RMP in the EU (template)

Background

Interferon beta-1a is a recombinant interferon, glycoproteins endowed with immunomodulatory, antiviral and antiproliferative properties. It is indicated, as Rebif, for the treatment of relapsing multiple sclerosis, as well as in patients with a single demyelinating event with an active inflammatory process, if alternative diagnoses have been excluded, and if they are determined to be at high risk of developing clinically definite multiple sclerosis.

The CHMP is evaluating grouped variations for Rebif, a centrally authorised product containing interferon beta-1a, including the assessment of the final annual report of the EU interferon (IFN)-beta pregnancy registry, the final report for the registry-based study in Nordic countries (EUPAS13054) and update of the product information regarding use in pregnancy and breastfeeding. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this application. For further background, see [PRAC minutes February 2019](#).

Summary of advice

- The RMP for Rebif (interferon beta-1a) in the context of the variation procedure under evaluation by the CHMP could be considered acceptable provided that an update to RMP version 10.0 and satisfactory responses to the request for supplementary information (RSI) are submitted.
- The PRAC considered that the available data did not raise any specific concerns, but the amount of data is limited. Therefore the PRAC agreed that 'use for the second and third trimester' should be included in the RMP as missing information. The feasibility of an additional pharmacovigilance activity (as a category 3 study) should be addressed. It should evaluate in particular whether the pattern of use during pregnancy has changed after the current label change. If the number of pregnancies where exposure has been recorded also during later parts of pregnancy is sufficient, subsequent analyses of pregnancy outcomes should be undertaken. The PRAC advised to undertake these evaluations at least in the same databases as the

register-based pregnancy study (ER-9430²⁰). The MAH should propose an outline for a staggered evaluation, starting with evaluation of drug utilisation, and if the number of exposed pregnancies is meaningful for further review, a subsequent evaluation of outcomes should be undertaken. It should specifically target cases exposed for the duration of pregnancy, and in addition to the outcomes for previous study ER-9430, it should also include the risk of infections in newborns, and address if an optimised estimation of frequency of spontaneous abortions and elective terminations can be made.

5.3.6. Interferon beta-1b - BETAFERON (CAP) - EMEA/H/C/000081/II/0124/G

Applicant: Bayer AG

PRAC Rapporteur: Martin Huber

Scope: Grouped variations consisting of: 1) update of sections 4.3 and 4.6 of the SmPC in order to add information on pregnancy and update the statement regarding breast-feeding following the completion of the European interferon beta (IFN- β) pregnancy registry (eighth annual and final report) and the final clinical study report (CSR) of the register-based study in the Nordic countries EUPAS13054: multiple sclerosis pregnancy study - pregnancy outcomes in multiple sclerosis populations exposed and unexposed to interferon beta - a register-based study in the Nordic countries; 2) update of section 4.6 of the SmPC in order to update the statement regarding breast-feeding following a review of studies, case reports and literature articles (fulfilment of MEA 024.2 and 21). The package leaflet has been updated accordingly. The RMP (version 4.1) is updated accordingly, including the deletion of the important potential risk 'pregnancy outcomes'. The RMP is also updated to bring it in line with revision 2 of the guidance on the format of RMP in the EU (template)

Background

Interferon beta-1b is a recombinant interferon, glycoproteins endowed with antiviral and immunoregulatory properties. It is indicated, as Betaferon, for the treatment of patients with a single demyelinating event with an active inflammatory process, if it is severe enough to warrant treatment with intravenous corticosteroids, if alternative diagnoses have been excluded, and if they are determined to be at high risk of developing clinically definite multiple sclerosis. It is also indicated for the treatment of patients with relapsing-remitting multiple sclerosis (RRMS) and two or more relapses within the last two years as well as for the treatment of patients with secondary progressive multiple sclerosis with active disease, evidenced by relapses.

The CHMP is evaluating grouped variations for Betaferon, a centrally authorised product containing interferon beta-1b, including the assessment of the final annual report of the EU interferon (IFN)-beta pregnancy registry, the final report for the registry-based study in Nordic countries (EUPAS13054) and update of the product information regarding use in pregnancy and breastfeeding. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this application. For further background, see [PRAC minutes February 2019](#).

²⁰ A population-based cohort study conducted with data from Nordic health registers to identify pregnancy outcomes in the multiple sclerosis (MS) population for women exposed to interferon (IFN) beta products and women who were not exposed (EUPAS13054) for reference to the outcomes of patients in the European IFN beta pregnancy registry

Summary of advice

- The RMP for Betaferon (interferon beta-1b) in the context of the variation procedure under evaluation by the CHMP could be considered acceptable provided that an update to RMP version 4.2 and satisfactory responses to the request for supplementary information (RSI) are submitted.
- The PRAC considered that available data did not raise any specific concerns, but the amount of data is limited. Therefore the PRAC agreed that 'use for the second and third trimester' should be included in the RMP as missing information. The feasibility of an additional pharmacovigilance activity (as a category 3 study) should be addressed. It should evaluate in particular whether the pattern of use during pregnancy has changed after the current label change. If the number of pregnancies where exposure has been recorded also during later parts of pregnancy is sufficient, subsequent analyses of pregnancy outcomes should be undertaken. The PRAC advised to undertake these evaluations at least in the same databases as the register-based pregnancy study (ER-9430²¹). The MAH should propose an outline for a staggered evaluation, starting with evaluation of drug utilisation, and if the number of exposed pregnancies is meaningful for further review, a subsequent evaluation of outcomes should be undertaken. It should specifically target cases exposed for the duration of pregnancy, and in addition to the outcomes for previous study ER-9430, it should also include the risk of infections in newborns, and address if an optimised estimation of frequency of spontaneous abortions and elective terminations can be made.

5.3.7. Interferon beta-1b - EXTAVIA (CAP) - EMEA/H/C/000933/II/0096/G

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Martin Huber

Scope: Grouped variations consisting of: 1) update of sections 4.3 and 4.6 of the SmPC in order to add information on pregnancy and update the statement regarding breast-feeding following the completion of the European interferon beta (IFN- β) pregnancy registry (eighth annual and final report) and the final clinical study report (CSR) of the register-based study in the Nordic countries EUPAS13054: multiple sclerosis pregnancy study - pregnancy outcomes in multiple sclerosis populations exposed and unexposed to interferon beta - a register-based study in the Nordic countries; 2) update of section 4.6 of the SmPC in order to update the statement regarding breast-feeding following a review of studies, case reports and literature articles (fulfilment of MEA 022.2 and 019). The package leaflet is updated accordingly. The RMP (version 4.1) is updated accordingly, including the deletion of the important potential risk 'pregnancy outcomes'. The RMP is also updated to bring it in line with revision 2 of the guidance on the format of RMP in the EU (template)

Background

Interferon beta-1b is a recombinant interferon, glycoproteins endowed with antiviral and immunoregulatory properties. It is indicated, as Extavia, for the treatment of patients

²¹ A population-based cohort study conducted with data from Nordic health registers to identify pregnancy outcomes in the multiple sclerosis (MS) population for women exposed to interferon (IFN) beta products and women who were not exposed (EUPAS13054) for reference to the outcomes of patients in the European IFN beta pregnancy registry

with a single demyelinating event with an active inflammatory process, if it is severe enough to warrant treatment with intravenous corticosteroids, if alternative diagnoses have been excluded, and if they are determined to be at high risk of developing clinically definite multiple sclerosis. It is also indicated for the treatment of patients with relapsing remitting multiple sclerosis (RRMS) and two or more relapses within the last two years as well as for the treatment of patients with secondary progressive multiple sclerosis with active disease, evidenced by relapses.

The CHMP is evaluating grouped variations for Extavia, a centrally authorised product containing interferon beta-1b, including the assessment of the final annual report of the EU interferon (IFN)-beta pregnancy registry, the final report for the registry-based study in Nordic countries (EUPAS13054) and update of the product information regarding use in pregnancy and breastfeeding. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this application. For further background, see [PRAC minutes February 2019](#).

Summary of advice

- The RMP for Extavia (interferon beta-1b) in the context of the variation procedure under evaluation by the CHMP could be considered acceptable provided that an update to risk management plan (RMP) version 4.2 and satisfactory responses to the request for supplementary information (RSI) are submitted.
- The PRAC considered that available data did not raise any specific concerns, but the amount of data is limited. Therefore the PRAC agreed that 'use for the second and third trimester' should be included in the RMP as missing information. The feasibility of an additional pharmacovigilance activity (as a category 3 study) should be addressed. It should evaluate in particular whether the pattern of use during pregnancy has changed after the current label change. If the number of pregnancies where exposure has been recorded also during later parts of pregnancy is sufficient, subsequent analyses of pregnancy outcomes should be undertaken. The PRAC advised to undertake these evaluations at least in the same databases as the register-based pregnancy study (ER-9430²²). The MAH should propose an outline for a staggered evaluation, starting with evaluation of drug utilisation, and if the number of exposed pregnancies is meaningful for further review, a subsequent evaluation of outcomes should be undertaken. It should specifically target cases exposed for the duration of pregnancy, and in addition to the outcomes for previous study ER-9430, it should also include the risk of infections in newborns, and address if an optimised estimation of frequency of spontaneous abortions and elective terminations can be made.

5.3.8. Panitumumab - VECTIBIX (CAP) - EMEA/H/C/000741/II/0093

Applicant: Amgen Europe B.V.

PRAC Rapporteur: David Olsen

Scope: Submission of an updated RMP (version 23) brought in line with revision 2 of GVP module V on 'Risk management systems'. In addition, the MAH proposed the removal of

²² A population-based cohort study conducted with data from Nordic health registers to identify pregnancy outcomes in the multiple sclerosis (MS) population for women exposed to interferon (IFN) beta products and women who were not exposed (EUPAS13054) for reference to the outcomes of patients in the European IFN beta pregnancy registry

some additional risk minimisation measures (aRMM). As a result Annex II is updated. The MAH took the opportunity to update sections 4.2 and 4.4 of the SmPC to include the table on dose modification previously located in section 4.4. In addition, section 4.4 is updated to implement the statement on 'sodium' content in accordance with the European Commission (EC) guideline on 'excipients in the labelling and package leaflet of medicinal products for human use'. Furthermore, minor corrections are introduced in section 4.8 of the SmPC and in the list of the local representatives

Background

Panitumumab is a recombinant, fully human immunoglobulin G2 (IgG2) monoclonal antibody, an epidermal growth factor receptor (EGFR) inhibitor. It is indicated, as Vectibix, for the treatment of adult patients with wild-type RAS metastatic colorectal cancer (mCRC) either in first-line in combination with 5-fluorouracil (5FU)/folinic acid (FA)/oxaliplatin (FOLFOX) or 5FU/FA/irinotecan (FOLFIRI); in second-line in combination with FOLFIRI for patients who have received first-line fluoropyrimidine-based chemotherapy (excluding irinotecan) or as monotherapy after failure of fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens.

The CHMP is evaluating a type II variation for Vectibix, a centrally authorised product containing panitumumab, to update the product information on dose modification and to update the RMP in line with revision 2 of GVP module V on 'Risk management systems' and Annex II-D on 'Conditions or restrictions with regard to the safe and effective use of the medicinal product' of the product information. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this variation.

Summary of advice

- The RMP for Vectibix (panitumumab) in the context of the variation procedure under evaluation by the CHMP could be considered acceptable provided that an update to RMP version 23 is submitted.
- In line with revision 2 of GVP module V on 'Risk management systems', the PRAC considered that the removal of the conditions in Annex II-D on additional risk minimisation measures is acceptable. Nevertheless, the MAH should further elaborate on the proposed rationale that no further characterisation of the risk 'interstitial lung disease' is necessary, and whether the risk can be adequately mitigated. In addition, the MAH should comment on how the remaining identified risk of 'dermatologic and soft tissue toxicity' differs from the deleted risks in the RMP, considering that no additional risk minimisation measures or additional pharmacovigilance activities are included in the RMP.

5.3.9. Peginterferon beta-1a - PLEGRIDY (CAP) - EMEA/H/C/002827/II/0052/G

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Grouped variations consisting of: 1) update of sections 4.3 and 4.6 of the SmPC in order to add information on pregnancy and update the statement regarding breast-feeding following the completion of the European interferon beta (IFN- β) pregnancy registry (eighth annual and final report) and the final clinical study report (CSR) of the register-based study in the Nordic countries EUPAS13054: multiple sclerosis pregnancy

study - pregnancy outcomes in multiple sclerosis populations exposed and unexposed to interferon beta - a register-based study in the Nordic countries; 2) update of section 4.6 of the SmPC in order to update the statement regarding breast-feeding following a review of studies, case reports and literature articles (fulfilment of MEA 8.2 and 002). The package leaflet has been updated accordingly. The RMP (version 4.1) is updated accordingly, including the deletion of the important potential risk 'pregnancy outcomes'. The RMP is also updated to bring it in line with revision 2 of the guidance on the format of RMP in the EU (template)

Background

Peginterferon beta-1a is a pegylated recombinant interferon, glycoproteins endowed with immunomodulatory, antiviral and antiproliferative properties. It is indicated, as Plegridy, in adult patients for the treatment of relapsing remitting multiple sclerosis (RRMS).

The CHMP is evaluating grouped variations for Plegridy, a centrally authorised product containing peginterferon beta-1a, including the assessment of the final annual report of the EU interferon (IFN)-beta pregnancy registry, the final report for the registry-based study in Nordic countries (EUPAS13054) and update of the product information regarding use in pregnancy and breastfeeding. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this application. For further background, see [PRAC minutes February 2019](#).

Summary of advice

- The RMP for Plegridy (peginterferon beta-1a) in the context of the variation procedure under evaluation by the CHMP could be considered acceptable provided that an update to RMP version 4.1 and satisfactory responses to the request for supplementary information (RSI) are submitted.
- The PRAC considered that available data did not raise any specific concerns, but the amount of data is limited. Therefore the PRAC agreed that 'use for the second and third trimester' should be included in the RMP as missing information. The feasibility of an additional pharmacovigilance activity (as a category 3 study) should be addressed. It should evaluate in particular whether the pattern of use during pregnancy has changed after the current label change. If the number of pregnancies where exposure has been recorded also during later parts of pregnancy is sufficient, subsequent analyses of pregnancy outcomes should be undertaken. The PRAC advised to undertake these evaluations at least in the same databases as the register-based pregnancy study (ER-9430²³). The MAH should propose an outline for a staggered evaluation, starting with evaluation of drug utilisation, and if the number of exposed pregnancies is meaningful for further review, a subsequent evaluation of outcomes should be undertaken. It should specifically target cases exposed for the duration of pregnancy, and in addition to the outcomes for previous study ER-9430, it should also include the risk of infections in newborns, and address if an optimised estimation of frequency of spontaneous abortions and elective terminations can be made.

²³ A population-based cohort study conducted with data from Nordic health registers to identify pregnancy outcomes in the multiple sclerosis (MS) population for women exposed to interferon (IFN) beta products and women who were not exposed (EUPAS13054) for reference to the outcomes of patients in the European IFN beta pregnancy registry

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Grouped variations consisting of: 1) extension of indication to include a new indication for the vial presentation 'treatment of retinopathy of prematurity (ROP) in preterm infants'. As a consequence, sections 2, 4.1, 4.2, 4.5, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated. The package leaflet, labelling and the RMP (version 18.0) are updated accordingly; 2) introduction of a low volume high accuracy syringe, as a stand-alone medical device for the administration of the Lucentis (ranibizumab) 0.2 mg paediatric dose (corresponding to 0.02 mL of the Lucentis 10 mg/mL solution for injection in vial presentation)

Background

Ranibizumab is a humanised recombinant monoclonal antibody fragment targeted against human vascular endothelial growth factor A (VEGF-A). It is indicated, as Lucentis, in adults for the treatment of neovascular (wet) age-related macular degeneration (AMD), the treatment of visual impairment due to choroidal neovascularisation (CNV), the treatment of visual impairment due to diabetic macular oedema (DME) and the treatment of visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO).

The CHMP is evaluating grouped variations consisting of an extension of the therapeutic indication for Lucentis, a centrally authorised product containing ranibizumab, to include treatment of retinopathy of prematurity (ROP) in preterm infants and to introduce a low volume high accuracy syringe. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this application. For further background, see [PRAC minutes January 2019](#).

Summary of advice

- The RMP for Lucentis (ranibizumab) in the context of the variation procedure under evaluation by the CHMP could be considered acceptable provided that an update to RMP version 18.1 and satisfactory responses to the request for supplementary information (RSI) are submitted.
- The PRAC considered that the MAH should provide a detailed justification regarding the proposed addition of 'impaired bone growth and toxicity' for the proposed indication on retinopathy of prematurity (ROP) and 'impaired vital organ development' for ROP as important potential risks. The MAH should also describe how these are captured in the extension study. In addition, the MAH should further discuss to what extent the proposed important potential risk of 'neurodevelopment impairment' is anticipated to be captured in extension study CRFB002H2301E1 (RAINBOW)²⁴. Moreover, the PRAC concurred that there is no need for additional material for caregivers as long as the package leaflet and the patient information package are adequate. The PRAC supported to include extension study H2301E1 in Annex II-D on 'Conditions or restrictions with regard to the safe and effective use of

²⁴ An extension study to evaluate the long term efficacy and safety of ranibizumab compared with laser therapy for the treatment of infants born prematurely with retinopathy of prematurity

the medicinal product'. The PRAC also confirmed that Lucentis (ranibizumab) does not need to be included in the additional monitoring list.

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

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Ana Sofia Diniz Martins

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

Background

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

The CHMP is evaluating an extension of the therapeutic indication for Xyrem, a centrally authorised medicine containing sodium oxybate, to amend the existing indication to include adolescents and children older than 7 years. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this extension of indication. For further background, see [PRAC minutes November 2018 \(29-31 October 2018\)](#).

Summary of advice

- The RMP for Xyrem (sodium oxybate) in the context of the variation procedure under evaluation by the CHMP could be considered acceptable provided that an update to RMP version 9.1 and satisfactory responses to the request for supplementary information (RSI) are submitted.
- The PRAC considered that proposed part 2 of study JAZZ 13-005²⁵ will not characterise 'long term impact on children and adolescents, including growth and neurocognitive development' as missing information and should be removed from the pharmacovigilance plan. Nevertheless, 'long term impact on children and adolescents, including growth and neurocognitive development' can be further characterised through active surveillance and the MAH should consider suitable registries, such as the ANSM²⁶ monitoring programme. In addition, the MAH should discuss the feasibility of extract exposure information from prescription registries and link that to other health-care and demographic data, including those on educational level/educational results. The evaluation of the effectiveness of the additional risk minimisation measures (aRMMs) agreed for the paediatric population should be performed through the assessment of outcome indicators (routine pharmacovigilance) only. In addition, the PRAC did not support the proposed educational material (EM) regarding the potential for 'medication error' as it is already proposed to update the package leaflet accordingly and this is not included in the RMP as an important safety concern. Finally, the PRAC supported requesting the MAH to consider a PASS to study learning abilities on a patient by patient basis with

²⁵ A multicentre study of the efficacy and safety of Xyrem with an open-label pharmacokinetic evaluation and safety extension in paediatric subjects with narcolepsy with cataplexy

²⁶ Agency Nationale de Sécurité du Médicament et des Produits de Santé (French Medicines Agency)

children of different age range with a 3 month baseline assessment followed by 6 month sodium oxybate treatment on top of the previous best medical treatment.

5.3.12. Tafamidis - VYNDAQEL (CAP) - EMEA/H/C/002294/X/0049/G, Orphan

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Ghania Chamouni

Scope: Grouped application consisting of: extension application to introduce a new strength (61 mg soft capsules, pack-size of 30 and 90 capsules) including an extension of indication to include treatment of transthyretin amyloidosis in adult patients with wild-type or hereditary cardiomyopathy to reduce all-cause mortality and cardiovascular-related hospitalisation (ATTR-CM); update of section 4.6 of the SmPC of 20 mg soft capsules to reflect some wording pertaining to the Tafamidis Enhanced Surveillance for Pregnancy Outcomes (TESPO) programme. The RMP (version 9.0) is updated accordingly, including proposed new dosage/indication, review of the additional data collected from the ATTR-CM clinical programme and post marketing reporting, a reclassification of the safety concerns and the removal of healthcare professional (HCP) educational leaflet. Annex II is updated in accordance. In addition, the MAH proposed to update the information in Braille of Annex III-A on 'Labelling' to differentiate between the dosage forms

Background

Tafamidis meglumine is a specific stabiliser of transthyretin indicated, as Vyndaqel, for the treatment of transthyretin amyloidosis (ATTR) in adult patients with stage 1 symptomatic polyneuropathy to delay peripheral neurologic impairment.

The CHMP is evaluating a grouped application for Vyndaqel, a centrally authorised product containing tafamidis meglumine, consisting of an extension application to introduce a new strength with an extension of indication to include treatment of transthyretin amyloidosis in adult patients with wild-type or hereditary cardiomyopathy to reduce all-cause mortality and cardiovascular-related hospitalisation (ATTR-CM) and an update of the product information in line with the Tafamidis Enhanced Surveillance for Pregnancy Outcomes (TESPO) programme.

The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this application.

Summary of advice

- The RMP for Vyndaqel (tafamidis meglumine) in the context of the variation procedure under evaluation by the CHMP could be considered acceptable provided that an update to RMP version 9.0 and satisfactory responses to the request for supplementary information (RSI) are submitted.
- The PRAC supported maintaining 'reproductive toxicity and lactation' as an important potential risk based on developmental toxicity findings from animal studies, taking into account that the medicinal product is not recommended during pregnancy. In addition, the PRAC considered that 'patients with severe hepatic impairment' should be added as missing information. In addition, the MAH is requested to describe the specific adverse follow-up questionnaires for hepatotoxicity and changes in thyroid function. Moreover, the MAH should propose an adequate post-authorisation study to

monitor the use of tafamidis in patients with NYHA²⁷ class IV disease due to the progressive nature of ATTR amyloidosis including ATTR-CM. Finally, the PRAC supported keeping the healthcare professional education leaflet in addition to the TESPO programme in the product information in order to further encourage healthcare professionals (HCPs) to report any cases of pregnancy captured as missing information.

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. Adefovir dipivoxil - HEPSERA (CAP) - PSUSA/00000060/201809

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

Background

Adefovir dipivoxil is an oral prodrug of adefovir, an acyclic nucleotide phosphonate analogue of adenosine monophosphate. It is indicated, as Hepsera, for the treatment of chronic hepatitis B in adults with compensated liver disease with evidence of active viral replication, persistently elevated serum alanine aminotransferase (ALT) levels and histological evidence of active liver inflammation and fibrosis. It is also indicated for the treatment of chronic hepatitis B in adults with decompensated liver disease in combination with a second agent without cross-resistance to Hepsera (adefovir dipivoxil).

Based on the assessment of the periodic safety update report (PSUR), the PRAC reviewed the benefit-risk balance of Hepsera, a centrally authorised medicine containing adefovir dipivoxil 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 Hepsera (adefovir dipivoxil) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to combine the wording of the existing undesirable effects 'proximal renal tubulopathy' and 'Fanconi syndrome' to a single undesirable effect as 'proximal renal tubulopathy (including Fanconi syndrome)' with a change in frequency from 'not known' to 'uncommon'. Therefore, the current terms of the marketing authorisation(s) should be varied²⁸.

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 New York Heart Association

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

6.1.2. Ceftaroline fosamil - ZINFORO (CAP) - PSUSA/00010013/201810

Applicant: Pfizer Ireland Pharmaceuticals

PRAC Rapporteur: Maia Uusküla

Scope: Evaluation of a PSUSA procedure

Background

Ceftaroline fosamil is an antibacterial agent for systemic use. It is indicated, as Zinforo, for the treatment of complicated skin and soft tissue infections (cSSTI) and community-acquired pneumonia (CAP) in adults and children from the age of 2 months.

Based on the assessment of the periodic safety update report (PSUR), the PRAC reviewed the benefit-risk balance of Zinforo, a centrally authorised medicine containing ceftaroline fosamil 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 Zinforo (ceftaroline fosamil) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAH should continue monitoring the current knowledge of use of ceftaroline fosamil in both adult and paediatric patients with cystic fibrosis. The MAH should provide a detailed cumulative review and provide a pooled population pharmacokinetic (PK) report based on the recently published studies. Based on this review, the MAH should propose updates to the current product information as appropriate.

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. Cobicistat, elvitegravir, emtricitabine, tenofovir alafenamide - GENVOYA (CAP) - PSUSA/00010449/201811

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

Background

Cobicistat is a selective, mechanism-based inhibitor of cytochrome P450 (CYP) enzymes of the CYP3A subfamily and elvitegravir is a human immunodeficiency virus-1 (HIV-1) integrase strand transfer inhibitor. Emtricitabine is a nucleoside reverse transcriptase inhibitor (NRTI) and tenofovir alafenamide is a nucleotide reverse transcriptase inhibitor (NtRTI). In combination, cobicistat/elvitegravir/emtricitabine/tenofovir alafenamide is indicated, as Genvoya, for the treatment of HIV-1 infection without any known mutations associated with resistance to the integrase inhibitor class, emtricitabine or tenofovir, in adults and adolescents aged from 12 years with body weight at least 35 kg and children aged from 6 years and with body weight at least 25 kg for whom alternative regimens are unsuitable due to toxicities. Based on the assessment of the periodic safety update report

(PSUR), the PRAC reviewed the benefit-risk balance of Genvoya, a centrally authorised medicine containing cobicistat/elvitegravir/emtricitabine/tenofovir alafenamide 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 Genvoya (cobicistat/elvitegravir/emtricitabine/tenofovir alafenamide) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include 'suicidal ideation and suicide attempt (in patients with a pre-existing history of depression or psychiatric illness)' as an undesirable effect with a frequency 'uncommon'. Therefore, the current terms of the marketing authorisation(s) should be varied²⁹.
- In the next PSUR, the MAH should address the issues of viral resistance, hyperuricemia, pancreatitis and cardiac disorders. The MAH should closely monitor any new medication errors occurring following confusion between Genvoya (cobicistat/elvitegravir/emtricitabine/tenofovir alafenamide) and cobicistat/elvitegravir/emtricitabine/tenofovir disoproxil-containing product with a discussion on the critical steps identified in the process leading to any mix-up.

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. Dapagliflozin - EDISTRIDE (CAP); FORXIGA (CAP) - PSUSA/00010029/201810

Applicant: AstraZeneca AB

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

Background

Dapagliflozin is a sodium-glucose co-transporter-2 (SGLT2) inhibitor indicated, as Edistride and Forxiga, in adults for the treatment of insufficiently controlled type 2 diabetes mellitus (T2DM) as an adjunct to diet and exercise, to improve glycaemic control, alone or in combination with other medicinal products for the treatment of T2DM. It is also indicated for the treatment of type 1 diabetes mellitus (T1DM) as an adjunct to insulin in patients with BMI ≥ 27 kg/m², when insulin alone does not provide adequate glycaemic control.

Based on the assessment of the periodic safety update report (PSUR), the PRAC reviewed the benefit-risk balance of Edistride and Forxiga, centrally authorised medicines containing dapagliflozin 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 Edistride and Forxiga (dapagliflozin) in the approved indication(s) remains unchanged.

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

- Nevertheless, the product information should be updated to include 'angioedema' as an undesirable effect with a frequency 'very rare'. Therefore, the current terms of the marketing authorisation(s) should be varied³⁰.
- In the next PSUR, the MAH should present the periodic reporting rate and an analysis of post-marketing cases of nephritis, and include a cumulative review with information relevant for causality assessment for all cases of severe cutaneous reactions. In addition, the MAH should provide a cumulative review on cases of muscle atrophy, muscular weakness, myositis and myopathy.

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

6.1.5. Deferasirox - EXJADE (CAP) - PSUSA/00000939/201810

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

Background

Deferasirox is an orally active chelator that is highly selective for iron (III). It is indicated as Exjade for the treatment of chronic iron overload due to frequent blood transfusions in patients with beta thalassaemia major aged 6 years and older. It is also indicated for the treatment of chronic iron overload due to blood transfusions in paediatric patients with beta thalassaemia major with iron overload subject to certain conditions and in adult and paediatric patients with other anaemias aged 2 years and older and for the treatment of chronic iron overload in patients with non-transfusion-dependent thalassaemia syndromes.

Based on the assessment of the periodic safety update report (PSUR), the PRAC reviewed the benefit-risk balance of Exjade, a centrally authorised medicine containing deferasirox and issued a recommendation on its marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the safety and efficacy, the benefit-risk balance of Exjade (deferasirox) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include information on posology recommendations and extra information in an existing warning related to over-chelation and to modify information on overdose, respectively. Therefore, the current terms of the marketing authorisation(s) should be varied³¹.
- In the next PSUR, the MAH should provide information on the development of the granules formulation (for patients who have difficulty swallowing film-coated tablets, especially paediatric patients), discuss cases of metabolic acidosis as a subsection

³⁰ 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

³¹ Update of SmPC sections 4.2, 4.4 and 4.9. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

included in the corresponding identified risks 'hepatic failure/TA elevations' and 'renal disorders', or separately if occurring on their own. The MAH should also discuss whether any additional risk minimisation measures are needed. The MAH should provide an updated analysis with the data on cases of hepatic failure and whether the majority of patients had pre-existing liver injury/cirrhosis, continue to monitor safety during pregnancy and collect data regarding the outcomes of pregnancy exposures, and merge the two identified risks of 'increased liver transaminases' and 'hepatic failure' into a single safety concern. Furthermore, the MAH should closely monitor cases of colic inflammation, ulcerative colitis and colic haemorrhage, provide and interval review of cases of medication errors and should provide an interval review from post-marketing cases, clinical trials and literature regarding fatal cases, cerebral haemorrhage, hyperammonaemia, off-label use and over-chelation.

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. Delamanid - DELTYBA (CAP) - PSUSA/00010213/201810

Applicant: Otsuka Novel Products GmbH

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

Background

Delamanid is an anti-mycobacterial agent indicated, as Delytba, as part of an appropriate combination regimen for the treatment of pulmonary multi-drug resistant tuberculosis (MDR-TB) in adult patients.

Based on the assessment of the periodic safety update report (PSUR), the PRAC reviewed the benefit-risk balance of Delytba, a centrally authorised medicine containing delamanid 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 Delytba (delamanid) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include bedaquiline in the list of concomitant drugs known to prolong the QTc interval. Therefore, the current terms of the marketing authorisation(s) should be varied³².
- In the next PSUR, the MAH should provide a cumulative review of the important potential risk liver disorders and an updated review of cases potentially associated with the signal covalent binding.

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.

³² 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

6.1.7. Nintedanib³³ - VARGATEF (CAP) - PSUSA/00010318/201810

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Agni Kapou

Scope: Evaluation of a PSUSA procedure

Background

Nintedanib is a triple angiokinase inhibitor blocking vascular endothelial growth factor receptors (VEGFR 1-3), platelet-derived growth factor receptors (PDGFR α and β) and fibroblast growth factor receptors (FGFR 1-3) kinase activity. It is indicated, as Vargatef, in combination with docetaxel for the treatment of adult patients with locally advanced, metastatic or locally recurrent non-small cell lung cancer (NSCLC) of adenocarcinoma tumour histology after first-line chemotherapy.

Based on the assessment of the periodic safety update report (PSUR), the PRAC reviewed the benefit-risk balance of Vargatef, a centrally authorised medicine containing nintedanib 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 Vargatef (nintedanib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include pulmonary embolism within the existing warnings on venous thromboembolism and to include colitis as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied³⁴.
- In the next PSUR, the MAH should closely monitor and provide an interval and cumulative review of cases of colitis, fatal cases and cases of nephrotic syndrome.

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

6.1.8. Nintedanib³⁵ - OFEV (CAP) - PSUSA/00010319/201810

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

Background

Nintedanib is a small molecule tyrosine kinase inhibitor including the receptors platelet-derived growth factor receptor (PDGFR) α and β , fibroblast growth factor receptor (FGFR) 1-3, and VEGFR 1-3. It is indicated, as Ofev, for the treatment of Idiopathic Pulmonary Fibrosis (IPF).

³³ Oncology indication(s) only

³⁴ Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

³⁵ Respiratory indication(s) only

Based on the assessment of the periodic safety update report (PSUR), the PRAC reviewed the benefit-risk balance of Ofev, a centrally authorised medicine containing nintedanib 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 Ofev (nintedanib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include colitis as an undesirable effect with a frequency 'uncommon'. Therefore, the current terms of the marketing authorisation(s) should be varied³⁶.
- In the next PSUR, the MAH should provide cumulative reviews of diverticulitis, medication errors, pulmonary thromboembolism and cases of drug-induced liver injury (DILI), as well as assess the effectiveness of product information update regarding DILI in light of the observed cases of liver enzymes and bilirubin elevations (including DILI) during this interval period.

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

6.1.9. Sofosbuvir, ledipasvir - HARVONI (CAP) - PSUSA/00010306/201810

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

Background

Ledipasvir is a hepatitis C virus (HCV) inhibitor targeting the HCV non-structural 5A (NS5A) protein and sofosbuvir is a nucleotide prodrug that undergoes intracellular metabolism to form the pharmacologically active uridine analogue triphosphate. Ledipasvir/sofosbuvir are indicated, as Harvoni, for the treatment of chronic hepatitis C (CHC) in adults and in adolescents.

Based on the assessment of the periodic safety update report (PSUR), the PRAC reviewed the benefit-risk balance of Harvoni, a centrally authorised medicine containing ledipasvir/sofosbuvir 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 Harvoni (ledipasvir/sofosbuvir) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include new information on the impact of direct-acting antiviral (DAAV) therapy on drugs metabolised by the liver and on the potential need for dose adjustment of those drugs when they are co-

³⁶ 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

administered with DAAV therapy. Therefore, the current terms of the marketing authorisation(s) should be varied³⁷.

- In the next PSUR, the MAH should provide a review of the risk of acute kidney injury in patients treated with ledipasvir/sofosbuvir, including and not limited to the publications by *Brown PR et al.*³⁸, and *Michal JL et al.*³⁹.

The PRAC considered that the above recommendation for updating the product information to reflect the risk of DAAV therapy affecting other drugs metabolised by the liver is also relevant for other medicinal products within the same therapeutic class (DAAV therapy for HCV). Therefore, the MAHs of centrally authorised products of the same class should update their product information accordingly. Further consideration should be given at the level of CHMP.

The PRAC also considered that the information regarding the impact of DAAV therapy on tacrolimus and ciclosporin would also be relevant for tacrolimus and ciclosporin. Therefore, the MAHs of tacrolimus- and ciclosporin-containing products, should review the need to update their product information in an upcoming regulatory procedure or at the latest within 60 days of the European Commission (EC) decision. Further consideration should be given at the level of CHMP and CMDh.

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

6.1.10. Thalidomide - THALIDOMIDE CELGENE (CAP) - PSUSA/00002919/201810

Applicant: Celgene Europe BV

PRAC Rapporteur: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

Background

Thalidomide is an immunomodulatory drug indicated, as Thalidomide Celgene, in combination with melphalan and prednisone as first line treatment of patients with untreated multiple myeloma, aged ≥ 65 years or ineligible for high dose chemotherapy.

Based on the assessment of the periodic safety update report (PSUR), the PRAC reviewed the benefit-risk balance of Thalidomide Celgene, a centrally authorised medicine containing thalidomide 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 Thalidomide Celgene (thalidomide) in the approved indication(s) remains unchanged.

³⁷ Update of SmPC section 4.5. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

³⁸ Brown PR, Sadiq O, Weick A, Lenhart A, Elbatta M, Fernandez C, Kutait A, Pompa R, Jafri SM. Acute kidney injury in patients undergoing chronic hepatitis C virus treatment with ledipasvir/sofosbuvir. *hepatol commun.* 2018;2(10):1172-1178

³⁹ Michal JL, Rab S, Patel M, Kyle AW, Miller LS, Easley KA, Kalapila AG. Incidence of acute kidney injury in patients coinfecting with human immunodeficiency virus (HIV) and hepatitis C virus receiving tenofovir disoproxil fumarate and ledipasvir/sofosbuvir in a real-world, Urban, Ryan White Clinic. *AIDS Res Hum Retroviruses.* 2018;34(8):690-698

- Nevertheless, the product information should be updated to include a warning and recommendations regarding the risk of severe skin reactions including drug reaction with eosinophilia and systemic symptoms (DRESS) and to add DRESS as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied⁴⁰.
- In the next PSUR, the MAH should perform cumulative reviews of cases of diarrhoea, migraine, off-label use, fatal cases, progressive multifocal leukoencephalopathy, reactivation of Epstein-Barr virus (EBV), graft versus host disease (GvHD), increased intracranial pressure and solid organ transplant rejection. The MAH should provide a description and status for the implementation of the pregnancy prevention programme (PPP) in each Member State, the monitoring methodology and timelines for available data as well as the results of monitoring programmes. An estimate of usage in each member state should also be provided. The MAH should also provide a stand-alone characterisation of the risk of off-label use.
- The MAH should evaluate, in a separate variation⁴¹, whether any changes to existing risk minimisation measures concerning use of protective equipment, handling procedure training and monitoring, or reporting are warranted to minimise the risk of unintended occupational exposures in pregnant female healthcare professionals.

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

6.1.11. Trastuzumab - HERCEPTIN (CAP); HERZUMA (CAP); KANJINTI (CAP); ONTRUZANT (CAP); TRAZIMERA (CAP) - PSUSA/00003010/201809

Applicant(s): Roche Registration GmbH (Herceptin), Celltrion Healthcare Hungary Kft. (Herzuma), Amgen Europe B.V., Breda (Kanjinti), Samsung Bioepis NL B.V. (Ontruzant), Pfizer Europe MA EEIG (Trazimera)

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

Background

Trastuzumab is a monoclonal antibody which binds to the extracellular domain of human epidermal growth factor receptors 2 (HER2). It is indicated, as Herceptin, Herzuma, Kanjinti, Ontruzant and Trazimera for the treatment of adult patients with HER2 positive metastatic breast cancer, as monotherapy or in combination with paclitaxel or docetaxel or an aromatase inhibitor, subject to certain conditions. It is also indicated for the treatment of adult patients with HER2 positive early breast cancer following surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy, subject to certain conditions; and in combination with capecitabine or 5-fluorouracil and cisplatin for the treatment of adult patients with HER2 positive metastatic adenocarcinoma of the stomach or gastroesophageal junction.

⁴⁰ Update of SmPC section 4.2, 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

⁴¹ Expected to be submitted to the EMA by the end of Q2 2019

Based on the assessment of the periodic safety update report (PSUR), the PRAC reviewed the benefit-risk balance of Herceptin, Herzuma, Kanjinti, Ontruzant and Trazimera, centrally authorised medicines containing trastuzumab, 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 Herceptin, Herzuma, Kanjinti, Ontruzant and Trazimera (trastuzumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include tumour lysis syndrome as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisations should be varied⁴².

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

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

See also Annex I 16.2.

6.2.1. Carbidopa, entacapone, levodopa - CORBILTA (CAP); LEVODOPA/CARBIDOPA/ENTACAPONE ORION (CAP); STALEVO (CAP); NAP - PSUSA/00000547/201810

Applicant(s): Orion Corporation (Corbilta, Levodopa/Carbidopa/Entacapone Orion, Stalevo), various

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

Background

Corbilta, Levodopa/Carbidopa/Entacapone Orion and Stalevo are centrally authorised products containing carbidopa/entacapone/levodopa, a fixed-dose combination of anti-Parkinson's medicines, and are indicated for the treatment of adult patients with Parkinson's disease and end-of-dose motor fluctuations not stabilised on levodopa/dopa decarboxylase inhibitor treatment.

Based on the assessment of the periodic safety update report (PSUR), the PRAC reviewed the benefit-risk balance of Corbilta, Levodopa/Carbidopa/Entacapone Orion and Stalevo, centrally authorised medicines containing carbidopa/entacapone/levodopa, and nationally authorised medicines containing carbidopa/entacapone/levodopa and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

⁴² Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

- Based on the review of the data on safety and efficacy, the benefit-risk balance of carbidopa/entacapone/levodopa-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include dopamine dysregulation syndrome (DDS) as an undesirable effect with a frequency 'not known' and to add a warning with relevant precautions. Therefore, the current terms of the marketing authorisations should be varied⁴³.

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

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

See also Annex I 16.3.

6.3.1. Baclofen⁴⁴ (NAP) - PSUSA/00000294/201809

Applicant(s): various

PRAC Lead: Ronan Grimes

Scope: Evaluation of a PSUSA procedure

Background

Baclofen is a muscle relaxant indicated for the treatment of spasticity of voluntary muscle resulting from disorders such as multiple sclerosis, spinal lesions, cerebral palsy, cerebrovascular accidents, traumatic head injury and meningitis.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of baclofen-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning on suicide and suicide-related events and a warning on misuse, abuse and dependence. Therefore, the current terms of the marketing authorisation(s) should be varied⁴⁵.
- In the next PSUR, the MAHs should provide a cumulative review of all cases of completed suicide, attempted suicide, suicidal ideation and all related events using the MedDRA⁴⁶ SMQ⁴⁷ 'depression and suicide/self-injury'. A review of all data

⁴³ Update of SmPC section 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

⁴⁴ For oral use only

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

⁴⁶ Medical Dictionary for Regulatory Activities

⁴⁷ Standardised MedDRA queries

regarding severe cutaneous adverse reactions (SCARs) with baclofen as well as a review of the safety profile of baclofen in off-label use in alcohol use disorders should be also provided. In addition, The MAHs should conduct an updated critical analysis of all cases of mania and hypomania with baclofen both at therapeutic doses and at doses higher than recommended in the current product information, in view of the literature case reports published by *Ghosh et al.*⁴⁸, *Geoffroy et al.*⁴⁹, and *Rivollier et al.*⁵⁰.

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

6.3.2. Carmustine⁵¹ (NAP) - PSUSA/00010348/201809

Applicant(s): various

PRAC Lead: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

Background

Carmustine is a nitrosourea antineoplastic agent indicated as an implant for the treatment of newly-diagnosed high-grade malignant glioma patients as an adjunct to surgery and radiation, and as an adjunct to surgery in patients with recurrent glioblastoma multiforme for whom surgical resection is indicated.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of carmustine-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include pneumocephalus sometimes associated with neurological symptoms as an undesirable effect with a frequency 'uncommon' and to include a corresponding warning on the occurrence of pneumocephalus. Therefore, the current terms of the marketing authorisation(s) should be varied⁵².
- In the next PSUR, the MAH should provide detailed reviews of cases of changes in the local blood vessels, implant site necrosis, cases of severe cutaneous adverse reactions (SCARs) and cases with fatal outcome. The MAH should also cumulatively review cases of non-infective meningitis (including eosinophilic meningitis, aseptic

⁴⁸ Ghosh S and Bhuyan D. Baclofen abuse due to its hypomanic effect in patients with alcohol dependence and comorbid major depressive disorder. *Clinical Psychopharmacology and Neuroscience* 2017;15(2):187-189

⁴⁹ Geoffroy PA et al. Baclofen-induced manic symptoms: case report and systematic review. *Psychosomatics*. 2014;55:326-332

⁵⁰ Rivollier F and Masson M. Manic symptoms induced by high doses of baclofen: A case report. *L'Encephale*. 2016;42:382-3

⁵¹ Implant only

⁵² 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

meningitis and chemical meningitis) and provide information about off label use of carmustine wafer implant.

- The PRAC considered that the MAH should be requested to review all relevant available clinical and preclinical data addressing the risks of embryotoxicity, genotoxicity and teratogenicity, including a cumulative review of cases of pregnancy (female patients and female partners of male patients) and discuss the need to update the product information including the need for recommending the use of contraception in patients treated with carmustine. Further consideration should be given at the level of CMDh.

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. Clenbuterol (NAP) - PSUSA/00000794/201809

Applicant(s): various

PRAC Lead: Julia Pallos

Scope: Evaluation of a PSUSA procedure

Background

Clenbuterol is an adrenergic agonist with predominant β_2 -activity indicated for the prophylaxis and symptomatic bronchodilatory treatment of asthma and other conditions with reversible airway narrowing in adults and children.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of clenbuterol-containing medicinal product(s) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAHs should change the important potential risk of 'off label use' to 'misuse/abuse/overdose' in the baseline summary of safety concerns. The MAHs should further explore the extent and potential serious consequences of clenbuterol misuse, abuse, overdose and illicit use and associated risks based on all available data (including the scientific literature, post-marketing case safety reports, data from poison control centres or any national or international bodies) and provide a cumulative review of cases of misuse, abuse, overdose and illicit use. The review should include the purpose of such use, its duration, risks/reactions and their outcome and the details on the source of obtaining clenbuterol. The MAHs should perform a cumulative analysis of serious reactions reported in association with clenbuterol use within the terms of the marketing authorisation(s) as well as discuss relevant differences in the safety profile of clenbuterol when used outside the terms of the marketing authorisation. The MAHs should also discuss the clinical benefits of clenbuterol, its therapeutic place and medical need in approved indications and

target patient populations and whether data presented on the risk profile of clenbuterol either used within or outside the terms of the marketing authorisation impacts on the benefit-risk balance of clenbuterol-containing medicinal product(s).

The frequency of PSUR submission should be revised from five-yearly to yearly and the next PSUR should be submitted to the EMA within 90 days of the data lock point. The data lock point (DLP) should be aligned with the ambroxol/clenbuterol entry. Submission of PSURs for products referred to in Articles 10(1), 10a, 14, 16a of Directive 2001/83/EC is required and the EURD list should be updated accordingly. The list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC is updated accordingly.

6.3.4. Diclofenac⁵³ (NAP) - PSUSA/00001048/201809

Applicant(s): various

PRAC Lead: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

Background

Diclofenac is a non-steroidal anti-inflammatory medicine indicated in patients with, but not limited to inflammatory and degenerative forms of rheumatism, post-traumatic and post-operative pain, inflammation, and swelling, painful and/or inflammatory conditions in gynaecology, painful conditions such as headache, dental pain, period pain, rheumatic pain, muscular pain and backache, relief of symptoms of colds and flu, including aches and pains and sore throat, and reduction of fever.

Based on the assessment of the periodic safety update report PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing diclofenac for systemic use and issued a recommendation on their marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of diclofenac-containing medicinal product(s), systemic formulations in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning on anastomotic leak and Kounis syndrome as well as include Kounis syndrome as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied⁵⁴.
- In the next PSUR, the MAH(s) should perform a cumulative review regarding the risk of venous thrombosis, including and not limited to the publications by *Lee et al*⁵⁵, *Biere-Rafi et al*⁵⁶ and *Schmidt M et al*⁵⁷. The MAHs should consider the relevance of a

⁵³ Systemic formulation(s) only

⁵⁴ 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

⁵⁵ Lee et al. Use of non-steroidal anti-inflammatory drugs correlates with the risk of venous thromboembolism in knee osteoarthritis patients: a UK population-based case-control study. *Rheumatology (Oxford)*; 2016

⁵⁶ Biere-Rafi et al. Non-steroidal anti-inflammatory drugs and risk of pulmonary embolism. *Pharmacoepidemiol Drug Saf*; 2011

⁵⁷ Schmidt M. Cardiovascular risks associated with non-aspirin non-steroidal antiinflammatory drug use. *Dan Med J*. 2015;62

warning in the product information, to recommend caution in using of diclofenac in patients with underlying diseases or concomitant medication, where diclofenac induced ototoxicity could potentially result in deafness. MAHs should also discuss the risk of spontaneous abortion in relation to diclofenac and consider the relevance of including a warning in the product information.

- The PRAC considered the risk of anastomotic leakage and concluded that Kounis syndrome would also be relevant to be included in all fixed dose combinations of diclofenac (systemic formulations). This is due to the indications and administration route in the mono-substance and the fixed dose combinations being very similar, and so are the concentrations of diclofenac. Further consideration should be given at the level of CMDh.

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

6.3.5. Diclofenac⁵⁸ (NAP) - PSUSA/00010342/201809

Applicant(s): various

PRAC Lead: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

Background

Diclofenac is a non-steroidal anti-inflammatory medicine indicated, as topical formulations, for the relief of pain in inflammation and swelling: soft-tissue injuries: trauma of the tendons, ligaments, muscles and joints, e.g. due to sprains, strains, bruises and backache (sports injuries), and localized forms of soft tissue rheumatism: tendonitis (e.g. tennis elbow), bursitis, shoulder-hand syndrome and periarthropathy, and for the relief of pain of non-serious arthritis of the knee or fingers. Diclofenac (topical formulations) is also used for cutaneous treatment of actinic keratosis.

Based on the assessment of the periodic safety update report - PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing diclofenac for topical use and issued a recommendation on their marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of diclofenac-containing medicinal products (topical formulations) in the approved indications remains unchanged.
- Nevertheless, the product information of cutaneous topical products that do not currently include 'rash, eczema, erythema, dermatitis (including dermatitis contact), pruritus', 'application site burn' or 'burning sensation' should be updated to include burning sensation at the application site and dry skin as undesirable effects with a frequency 'not known'. The product information of ophthalmic topical products that do not currently include eye pain, application site burn or burning sensation should

⁵⁸ Topical formulation(s) only

be updated to include burning sensation in the eye as an undesirable effect with a frequency 'not known'. The product information of oromucosal topical products that do not currently include 'irritation of the oral cavity' or 'application site burn' should be updated to include burning sensation in the mouth as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied⁵⁹.

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

6.3.6. Indoramin (NAP) - PSUSA/00001740/201809

Applicant(s): various

PRAC Lead: Ronan Grimes

Scope: Evaluation of a PSUSA procedure

Background

Indoramin is an alpha adrenoceptor blocking agent indicated for the management of urinary outflow obstruction due to benign prostatic hyperplasia.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of indoramin-containing medicinal product(s) in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include a warning on the risk of QTc interval prolongation in overdose and its management. Therefore, the current terms of the marketing authorisation(s) should be varied⁶⁰.

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

6.3.7. Levofloxacin⁶¹ (NAP) - PSUSA/00001854/201810

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

⁵⁹ 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

⁶⁰ Update of SmPC section 4.9. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

⁶¹ Except for centrally authorised product(s)

Background

Levofloxacin is the S-enantiomer of ofloxacin, a fluoroquinolone antibacterial agent indicated for the treatment of bacterial infections with consideration given to the official guidance on the appropriate use of antibacterial agents.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of levofloxacin-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information of levofloxacin-containing products for systemic use should be updated to include a warning on drug reaction with eosinophilia and systemic symptom (DRESS), and to add DRESS, fixed drug eruption, and syndrome of inappropriate antidiuretic hormone (SIADH) as undesirable effects with a frequency 'rare'. The product information of levofloxacin-containing products for topical ophthalmic use should be updated to include a warning on tendon inflammation and rupture and to include, as undesirable effects, ruptures of the shoulder, hand, achilles, or other tendons that required surgical repair or resulted in prolonged disability. Therefore, the current terms of the marketing authorisation(s) should be varied⁶².

In the next PSUR, the MAHs of levofloxacin for topical ophthalmic use should provide a cumulative review of cases of drug induced lung injury (DILI) from company's database, EudraVigilance, and literature. The MAHs should also provide a cumulative review evaluating the risk of tendon-related disorders associated with the use of levofloxacin in ophthalmic formulations.

- The PRAC considered that the update of the product information to reflect tendon-related disorders would also be relevant for ofloxacin (of which levofloxacin is the S-enantiomer) for topical ophthalmic use. Further consideration should be given at the level of CMDh.

The list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC should be updated to separate levofloxacin according to the following route of administration: levofloxacin for systemic use and levofloxacin for topical ophthalmic use respectively. The next PSUR for levofloxacin for systemic use should be submitted in accordance with the requirements set out in the EURD list. The frequency of PSUR submission for levofloxacin for topical ophthalmic use should be revised from three-yearly to five-yearly and the next PSUR should be submitted to the EMA within 90 days of the data lock point. The EURD list is updated accordingly.

6.3.8. Permethrin (NAP) - PSUSA/00002355/201808

Applicant(s): various

⁶² 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

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Permethrin is an anti-parasitic agent indicated for the treatment of head lice (*Pediculus capitis*), scabies (caused by *Sarcoptes scabiei*) and crab lice (caused by *Pthirus pubis*).

Based on the assessment of the periodic safety update report - PSURs, the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing permethrin and issued a recommendation on their marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of permethrin-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information of permethrin-containing products (head lice indication) should be updated to include information about avoiding the use during pregnancy unless alternatives were ineffective and/or treatment with permethrin is required. The product information should also be updated to include information on treatment failure and resistance development. Therefore, the current terms of the marketing authorisation(s) should be varied⁶³. Additionally, the product information of permethrin-containing products (head lice indication) that do not currently include alopecia in the product information should be updated to include alopecia as an undesirable effect with a frequency 'not known'. Further consideration should be given at the level of CMDh.

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

6.3.9. Phloroglucinol (NAP); phloroglucinol, trimethylphloroglucinol (NAP) - PSUSA/00010355/201809

Applicant(s): various

PRAC Lead: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

Background

Phloroglucinol is an antispasmodic used alone or in combination with trimethylphloroglucinol for the treatment of spasms of the smooth muscles in the gastrointestinal, biliary, and genitourinary tract.

Based on the assessment of the periodic safety update report PSUR(s), the PRAC reviewed the benefit-risk balance of phloroglucinol-, and

⁶³ Update of SmPC section 4.2, 4.4 and 4.6. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

phloroglucinol/trimethylphloroglucinol- containing nationally authorised medicine(s) and issued a recommendation on their marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of phloroglucinol and phloroglucinol/trimethylphloroglucinol-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include acute generalized exanthematous pustulosis (AGEP) as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied⁶⁴.
- In the next PSUR, the MAHs should discuss all cases with a fatal outcome and should provide a cumulative review and detailed analysis of all medication error cases in paediatric population with separate analysis of errors related to 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.

6.4. Follow-up to PSUR/PSUSA procedures

See also Annex I 16.4.

6.4.1. Tocilizumab - ROACTEMRA (CAP) - EMEA/H/C/000955/LEG 055

Applicant: Roche Registration GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Cumulative hepatotoxicity drug safety reports (DSR), as requested in the conclusions of PSUSA/00002980/201804 adopted at the November 2018 PRAC

Background

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

⁶⁴ 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

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

Summary of advice/conclusion(s)

- The MAH should submit to the EMA, within 30 days, a variation to update the product information to include a warning on the occurrence of hepatotoxicity as well as to include drug-induced liver injury, hepatitis and jaundice as undesirable effects with a frequency 'rare' and hepatic failure with a frequency 'very rare'.
- The PRAC also agreed on distribution of a direct healthcare professional communication (DHPC) together with a communication plan.

7. Post-authorisation safety studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)⁶⁵

7.1.1. Axicabtagene ciloleucel - YESCARTA (CAP) - EMEA/H/C/PSP/S/0079

Applicant: Kite Pharma EU B.V., ATMP⁶⁶

PRAC Rapporteur: Anette Kirstine Stark

Scope: Protocol for a long-term, non-interventional study in patients taking Yescarta (axicabtagene ciloleucel) for the treatment of relapsed or refractory diffuse large B-cell lymphoma and primary mediastinal B-cell lymphoma to evaluate the safety of patients, including secondary malignancies, cytokine release syndrome (CRS), neurologic events, serious infections, prolonged cytopenias, hypogammaglobulinaemia and pregnancy outcomes in female patients of childbearing potential

Background

Axicabtagene ciloleucel is a an anti-CD19 chimeric antigen receptor (CAR) T-cell advanced therapy, indicated as Yescarta a centrally authorised medicine, for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma (PMBCL), after two or more lines of systemic therapy.

The obligation to conduct a post authorisation safety study (PASS) for the MAH of Yescarta (axicabtagene ciloleucel) was imposed as a condition of the initial marketing authorisation on 26 June 2018 in order to address the long-term safety of the medicine focussing on secondary malignancies, cytokine release syndrome (CRS), neurologic events, serious infections, prolonged cytopenias, hypogammaglobulinemia and pregnancy outcome. In order to fulfil the obligation to conduct a PASS imposed in accordance with Article 107n(3) of Directive 2001/83/EC, the MAH submitted PASS protocol version 1.0 for a PASS entitled: 'long term, non-interventional study of recipients of Yescarta for treatment of relapsed or refractory diffuse large B-cell lymphoma and primary mediastinal B-cell lymphoma'. The PRAC is responsible for evaluating the PASS protocol.

⁶⁵ In accordance with Article 107n of Directive 2001/83/EC

⁶⁶ Advanced therapy medicinal product

Endorsement/Refusal of the protocol

- The PRAC, having reviewed PASS protocol version 1.0 and in accordance with Article 107n of Directive 2001/83/EC, considered that the PASS is non-interventional but the study design does not fulfil the study objectives at this stage as several minor objections remain to be resolved before the protocol can be considered adequate. The protocol for Yescarta (axicabtagene ciloleucel) PASS could be acceptable provided that satisfactory responses are provided regarding the rate/frequency of loss of target antigen in patients relapsing after Yescarta therapy. Details on how the MAH intends to follow patients after the initial 5 years after Yescarta therapy and on study time period should also be provided. In addition, the MAH should provide a description of the European Society for Blood and Marrow Transplantation (EBMT) as part of the protocol, including a description of how data is translated from the primary medical records into the EBMT forms. Moreover, the MAH is requested to provide a detailed description of how missing data will be handled in the data analysis and elaborate on the specific measures in place to ensure data integrity.
- The MAH should submit a revised PASS protocol within 60 days to the EMA. A 60 day-assessment timetable will be followed.

7.2. Protocols of PASS non-imposed in the marketing authorisation(s)⁶⁷

See also Annex I 17.2.

7.2.1. Radium (Ra²²³) dichloride - XOFIGO (CAP) - EMEA/H/C/2653/MEA 014

Applicant: Bayer AG

PRAC Rapporteur: Rugile Pilviniene

Scope: Protocol for a drug utilisation study (DUS) of Xofigo (radium-223) under routine clinical practice in Europe to investigate the risk of off-label use, as requested in the conclusions of the referral procedure on Xofigo (radium-223) under Article 20 of Regulation (EC) No 726/2004 (EMA/H/A-20/1459) finalised in 2018

Background

Radium (Ra²²³) dichloride is a radiopharmaceutical centrally authorised medicine, indicated as Xofigo, in monotherapy or in combination with luteinising hormone releasing hormone analogue for the treatment of castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastases.

As part of the risk management plan (RMP) for Xofigo (radium (Ra²²³) dichloride), the MAH was required to conduct a PASS entitled: 'a drug utilisation study (DUS) of radium ²²³ under routine clinical practice in Europe (DIRECT)' aiming at investigating the potential off-label use of radium (Ra²²³) dichloride regarding its use in combination with abiraterone acetate.

⁶⁷ In accordance with Article 107m of Directive 2001/83/EC, supervised by the PRAC in accordance with Article 61a (6) of Regulation (EC) No 726/2004

The MAH submitted protocol version 1.0 for Xofigo (radium (Ra²²³) dichloride) for the evaluation of the DUS which was assessed by the Rapporteur. The PRAC is requested to provide advice to CHMP on the protocol submitted by the MAH.

Summary of advice

- The PRAC confirmed that the proposed study is non-interventional but does not meet its objectives at this stage. Therefore, the MAH should submit a revised protocol and satisfactory responses to the request for supplementary information (RSI) agreed by the PRAC. The MAH should refine the research questions and objectives of the DUS, reconsider the primary and secondary objectives by in particular characterising the population of patients receiving Xofigo (radium (Ra²²³) dichloride) and by characterising off-label use. In addition, the MAH should provide further details on the study size and consider including patients who are not at their first prescription/dispensing of Xofigo and include further European databases to increase the sample size. The MAH should also refine the proposed inclusion criteria and details regarding the enrollment phase and follow-up period.

7.3. Results of PASS imposed in the marketing authorisation(s)⁶⁸

7.3.1. Valproate (NAP) - EMEA/H/N/PSR/J/0021

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

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Results for a joint drug utilisation study (DUS) of valproate and related substances, in Europe, using databases to describe the prescribing practices before and after the dissemination of risk minimisations measures (RMMs) (i.e. educational materials and direct healthcare professional communication (DHPC) between December 2014 and June 2015) and to assess the effectiveness of these measures, as imposed in the outcome of the referral procedure on valproate and related substances (EMEA/H/A-31/1387) concluded in 2014

Background

Sodium valproate is indicated for the treatment of epilepsy and for the treatment of manic episodes when lithium is contraindicated or not tolerated. Valproate is also indicated in some EU Member States in prophylaxis of migraine attacks.

In line with the conclusions reached in 2014 of the referral procedure under Article 31 of Directive 2001/83/EC ([EMEA/H/A-31/1387](#)) conducted by the PRAC for valproate-containing medicines, MAHs were required as a condition to the marketing authorisations ([Annex IV](#)) to conduct a PASS to describe the prescribing practices before and after the dissemination of risk minimisations measures (RMMs) (i.e. educational materials and direct healthcare professional communication (DHPC) between December 2014 and June 2015) and to assess the effectiveness of these measures.

The final study report version 1.0 was submitted to the EMA by the MAH Sanofi-aventis Recherche & Development (on behalf of a consortium) on 30 January 2019. For further background, see [PRAC minutes October 2014](#). The PRAC discussed the final study results

⁶⁸ In accordance with Article 107p-q of Directive 2001/83/EC

and agreed to request the MAH's answers to a request for supplementary information (RSI).

Summary of recommendation(s) and conclusions

- Based on the review of the final report of the non-interventional post authorisation safety studies (PASS) entitled 'a joint drug utilisation study (DUS) of valproate and related substances, in Europe, using databases', as well as the MAH's responses to the RSI, the PRAC considered that a further RSI was necessary before a recommendation could be made on the benefit-risk balance of medicinal products containing valproate concerned by the PASS final report.
- The MAH should submit responses to the RSI within 30 days to the EMA. A 30 day-assessment timetable will be followed.

7.4. Results of PASS non-imposed in the marketing authorisation(s)⁶⁹

See Annex I 17.4.

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

See Annex I 17.5.

7.6. Others

See also Annex I 17.6.

7.6.1. Ocrelizumab - OCREVUS (CAP) - EMEA/H/C/004043/MEA 005.2

Applicant: Roche Registration GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: MAH's response to MEA 005.1 [protocol for study WA40404 (listed as category 3 study in the RMP): a phase 3b multicentre, randomised, double-blind, placebo controlled study to evaluate the efficacy and safety of ocrelizumab in adults with primary progressive multiple sclerosis later in their disease course] as per the request for supplementary information (RSI) adopted in December 2018

Background

Ocrelizumab is a recombinant humanised monoclonal antibody that selectively targets CD20-expressing B cells. It is indicated, as Ocrevus, for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features and for the treatment of adult patients with early primary progressive multiple sclerosis (PPMS) in terms of disease duration and level of disability, and with imaging features characteristic of inflammatory activity.

The MAH submitted responses to a request for supplementary information (RSI) and the responses were assessed by the Rapporteur. For background information, see [PRAC](#)

⁶⁹ 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

[minutes December 2018 \(26-29 November 2018\)](#).

Summary of recommendation(s) and conclusions

- Based on the PRAC Rapporteur's review of amended post authorisation safety study (PASS) protocol (WA40404) version 1 as well as the MAH's responses to the RSI, the PRAC considered that the PASS protocol and study design meets the objectives set out in the RMP in order to fulfil the post approval commitment of Ocrevus (ocrelizumab) in primary progressive multiple sclerosis (PPMS).

7.7. New Scientific Advice

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

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

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

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

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

8.1. Annual reassessments of the marketing authorisation

None

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. Acclidinium, formoterol fumarate dihydrate - BRIMICA GENUAIR (CAP) - EMEA/H/C/003969/R/0026 (without RMP)

Applicant: AstraZeneca AB

PRAC Rapporteur: Adam Przybylkowski

Scope: 5-year renewal of the marketing authorisation

Background

Acclidinium is a competitive, selective muscarinic receptor antagonist and formoterol a potent selective β_2 -adrenoceptor agonist. In combination, acclidinium/formoterol fumarate

dihydrate is indicated, as Brimica Genuair, as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).

Brimica Genuair, a centrally authorised medicine containing acclidinium/formoterol fumarate dihydrate, was authorised in 2014.

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 Brimica Genuair (acclidinium/formoterol fumarate dihydrate) and the CHMP Rapporteur's assessment report, the PRAC considered that the renewal of the marketing authorisation could be granted with unlimited validity.
- The PRAC supported removing 'safety in patients with important concomitant diseases who were not included in clinical trials', 'symptomatic benign prostatic hypertrophy, urinary retention', 'safety in patients with hepatic or severe renal impairment' and 'use in pregnancy and lactation' from missing information of the risk management plan (RMP) list of safety concerns as these are not linked to any pharmacovigilance activities or risk minimisation measures.

8.3.2. Acclidinium, formoterol fumarate dihydrate - DUAKLIR GENUAIR (CAP) - EMEA/H/C/003745/R/0026 (without RMP)

Applicant: AstraZeneca AB

PRAC Rapporteur: Adam Przybylkowski

Scope: 5-year renewal of the marketing authorisation

Background

Acclidinium is a competitive, selective muscarinic receptor antagonist and formoterol a potent selective β_2 -adrenoceptor agonist. In combination, acclidinium/formoterol fumarate dihydrate is indicated, as Duaklir Genuair, as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).

Duaklir Genuair, a centrally authorised medicine containing acclidinium/formoterol fumarate dihydrate, was authorised in 2014.

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 Duaklir Genuair (acclidinium/formoterol fumarate dihydrate) and the CHMP Rapporteur's assessment report, the PRAC considered that the renewal of the marketing authorisation could be granted with unlimited validity.
- The PRAC supported removing 'safety in patients with important concomitant diseases who were not included in clinical trials', 'symptomatic benign prostatic hypertrophy, urinary retention', 'safety in patients with hepatic or severe renal

impairment' and 'use in pregnancy and lactation' from missing information of the risk management plan (RMP) list of safety concerns as these are not linked to any pharmacovigilance activities or risk minimisation measures.

8.3.3. Ketoconazole - KETOCONAZOLE HRA (CAP) - EMEA/H/C/003906/R/0014 (with RMP)

Applicant: Laboratoire HRA Pharma

PRAC Rapporteur: Željana Margan Koletić

Scope: 5-year renewal of the marketing authorisation

Background

Ketoconazole is an imidazole derivative, a steroidogenesis inhibitor. It is indicated, as Ketoconazole HRA, for the treatment of endogenous Cushing's syndrome in adults and adolescents above the age of 12 years.

Ketoconazole HRA, a centrally authorised medicine containing ketoconazole, was authorised in 2014.

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 Ketoconazole HRA (ketoconazole) and the CHMP Rapporteur's assessment report, the PRAC considered that the renewal of the marketing authorisation could be granted with unlimited validity.

9. Product related pharmacovigilance inspections

9.1. List of planned pharmacovigilance inspections

None

9.2. Ongoing or concluded pharmacovigilance inspections

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

9.3. Others

None

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

10.1. Safety related variations of the marketing authorisation

10.1.1. Febuxostat - ADENURIC (CAP) - EMEA/H/C/000777/II/0051

Applicant: Menarini International Operations Luxembourg S.A.

PRAC Rapporteur: Jan Neuhauser

Scope: PRAC follow-up consultation in a variation to update section 5.1 of the SmPC in order to include the results of the clinical safety study CARES (TMX-67_301) to compare the cardiovascular outcomes of febuxostat and allopurinol in subjects with gout and cardiovascular comorbidities. This is a multicentre, randomised, active-control, phase 3B study. In addition, the MAH took the opportunity to provide a consolidated Module 2.7.6 in order to list all the synopsis of individual studies in a unique tabular format

Background

Febuxostat is a non-purine selective inhibitor of xanthine oxidase (NP-SIXO). Adenuric (febuxostat) is a centrally authorised product indicated in adults for the treatment of chronic hyperuricaemia in conditions where urate deposition has already occurred (including a history, or presence of, tophus and/or gouty arthritis) and for the prevention and treatment of hyperuricaemia in adult patients undergoing chemotherapy for haematologic malignancies at intermediate to high-risk of tumour lysis syndrome (TLS).

A type II variation is under evaluation at the CHMP proposing to update the product information of Adenuric (febuxostat) with the results of the clinical post-authorisation safety study CARES (TMX-67_301)⁷⁰ to evaluate the cardiovascular safety of Adenuric (febuxostat) and allopurinol in subjects with gout and cardiovascular comorbidities. The PRAC was requested to provide advice on the possible need, in the context of this variation, for a direct healthcare professional communication (DHPC) to inform the prescriber of the results of the post-approval safety study CARES. For further background, see [PRAC minutes December 2018 \(26-29 November 2018\)](#).

Summary of advice

- The PRAC agreed on the distribution of a direct healthcare professional communication (DHPC) in order to warn healthcare professionals (HCPs) that treatment with febuxostat in patients with pre-existing major cardiovascular (CV) disease should be avoided, unless no other therapy options are appropriate. The PRAC agreed the content of the DHPC together with a communication plan.

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

None

⁷⁰ Performed in USA, Canada and Mexico by the Sponsor Takeda (MAH of febuxostat registration in US) in order to fulfil a post-approval commitment for Uloric (febuxostat) requested by the US FDA

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

11.1.1. Azithromycin (NAP) - FI/H/xxxx/WS/035

Applicant(s): Pfizer (Zithromax)

PRAC Lead: Kimmo Jaakkola

Scope: PRAC consultation on a national worksharing variation assessing the final study report of study A0661209: a registry based study estimating the relative and absolute cardiovascular risk amongst adult azithromycin users compared to amoxicillin users, within 5 days and within 6-10 days of dispensed prescription, using the Kaiser Permanente in Northern California (KPNC) and Kaiser Permanente in Southern California (KPSC) databases, on request of Finland

Background

Azithromycin is a macrolide antibiotic indicated for the treatment of bacterial infections with consideration given to the official guidance on the appropriate use of antibacterial agents.

Based on the evaluation of a signal of potentially fatal heart events for azithromycin-containing products in 2013, the MAH Pfizer committed to conduct a pharmacoepidemiological study to estimate the relative and absolute risk of cardiovascular (CV) death and sudden cardiac death for adult azithromycin users as compared to amoxicillin users, within 5 days and within 6-10 days of dispensed prescription, including in patients with a diagnosis of prior CV disease and patients with high baseline CV risk. For background, see [PRAC minutes January 2015](#), [PRAC minutes March 2015](#) and [PRAC minutes July 2015](#).

In the context of the evaluation of a national worksharing variation procedure on the results of the final study report A0661209 investigating the cardiovascular risk in azithromycin users, Finland, as the Reference Member State (RMS), requested PRAC advice on its assessment.

Summary of advice

- Based on the review of the available information, the PRAC supported the conclusions of the RMS and concurred that the results, taken individually, do not warrant a change of warnings in the product information, given the limitations of the study, in

particular potential for confounding by indication. The PRAC agreed that the proposed pharmacovigilance follow-up is also considered adequate.

- The PRAC considered that the MAH(s) should discuss the possible association with adverse cardiovascular outcomes taking into account all available evidence for azithromycin as well as for the macrolides class and its impact on the azithromycin benefit-risk balance, and discuss whether an update to the product information is warranted. The evidence should include the upcoming results from the study in the Veteran Affairs database and results from meta-analyses by *Cheng et al.*⁷¹ and *Wong et al.*⁷².

11.1.2. Leuprorelin (NAP) - DE/H/0580/001-003/II/077, DE/H/0580/001-003/II/078

Applicant(s): Astellas Pharma (Eligard)

PRAC Lead: Martin Huber

Scope: PRAC follow-up consultation on national variations on RMP updates proposing the removal of additional risk minimisation measure (aRMM) on the development of a new product presentation, the addition of new risk minimisation measures and pharmacovigilance activities updating the product information with monitoring the response to Eligard (leuprorelin) by measuring the serum concentrations of testosterone, on request of Germany

Background

Leuprorelin is a gonadotrophin-releasing hormone (GnRH) analogue indicated for the treatment of advanced hormone-dependent prostate cancer.

In 2014, a signal of 'wrong technique in drug usage process' (EPITT 17753) leading to lack of efficacy for Eligard (leuprorelin) with a new safety needle was concluded at the PRAC. Since 2014, several risk minimisation measures (RMMs) have been introduced to reduce the number of handling errors. The current device was modified to reduce handling errors due to a stopper remaining in the device, educational materials (poster, video, website) were introduced and the product information updated. Although the number of cases of handling errors was reduced, cases were still reported. Therefore, further measures were put in place, i.e. update of the existing educational materials and the introduction of QR⁷³ codes into the product information and poster. For further background, see [PRAC minutes November 2014](#) and [PRAC minutes November 2017 \(23-26 October 2017\)](#) and [PRAC minutes February 2019](#).

In the context of the evaluation of the variation procedures on updating the risk management plan (RMP), recommending monitoring of testosterone levels as well as further risk minimisation measures and pharmacovigilance activities (including an interventional PASS and a non-interventional PASS), Germany requested PRAC advice on its assessment. As requested by the PRAC in February 2019, the MAH provided the data regarding the nature of medication errors leading to lack of efficacy from 2015 to 2018.

Summary of advice

⁷¹ Cheng YJ et al. The Role of Macrolide Antibiotics in Increasing Cardiovascular Risk. *J Am Coll Cardiol.* 2015;66(20):2173-2184

⁷² Wong AYS et al. Managing Cardiovascular Risk of Macrolides: Systematic Review and Meta-Analysis. *Drug Saf.* 2017;40(8):663-677

⁷³ Quick Response

- Based on the review of the available information, the PRAC supported the conclusions of the assessment by the PRAC lead and noted with concern the high number of medication errors still occurring with Eligard, based on the data provided by the MAH.
- The PRAC expressed a number of concerns regarding the proposed design of the interventional post-authorisation study, such as being focused on efficacy, lack of blinding and the resulting risk of bias, limited generalisability of the results to everyday use and concurred that the proposed study is not supported. The PRAC also considered that the proposed non-interventional post authorisation safety study (PASS) design -retrospective chart review - was inadequate as it was regarded as unlikely that the handling errors are systematically recorded. The PRAC agreed that the proposed recommendation for intensified monitoring of serum testosterone was of limited value to prevent medication errors and it would be difficult to implement, would create issues with compliance and ultimately create an unnecessary burden for health systems and patients. Consequently, the PRAC did not support the distribution of a direct healthcare professional communication (DHPC) due to its focus on intensified monitoring of serum testosterone. The PRAC did not endorse changes to the other risk minimisation measures (educational material, QR codes leading to training video, retraining of healthcare professionals (HCPs) with a placebo device in case of reported handling errors (HE) and noted that reports of medication errors continued despite risk minimisation measures being already implemented.
- The PRAC agreed to collect information from Member States in order to obtain an overview of alternative products containing leuprorelin and other substances from the same therapeutic class available in each Member State.

11.2. Other requests

11.2.1. Ulipristal acetate - AT/H/0862/001/DC, AT/H/0863/001/DC

PRAC Lead: Jan Neuhauser

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

Background

Ulipristal acetate is an orally-active synthetic selective progesterone receptor modulator used, amongst other indications, in emergency contraception within 120 hours (5 days) of unprotected sexual intercourse or contraceptive failure.

In the context of ongoing evaluations for initial marketing authorisation applications for generic medicinal products containing ulipristal acetate, assessed in accordance with Article 10(1) of Directive 2001/83/EC under the decentralised procedure, Austria, as reference Member State (RMS) requested a second PRAC advice. For further background, see [PRAC minutes January 2019](#).

Summary of advice

- Based on the review of the available information and the lead Member State (LMS)'s assessment, the PRAC supported to ensure that MAHs of generic ulipristal-containing medicinal products assess pregnancy outcomes and address the safety concerns of

'effects on pregnancy/off-label use', 'risk of incomplete abortion and heavy bleeding', 'risk of ectopic pregnancy and 'effects on foetus and newborn'. The PRAC supported to update the EURD list for ulipristal (female emergency contraceptive) to require MAHs of generic fingolimod-containing products to submit PSURs.

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 – extension of the period under Article 50 of Treaty on the European Union (EU)

The EMA Secretariat updated the PRAC on the practical arrangements for cooperation within the EU regulatory network including the participation of the UK during the extension of the period under Article 50 of Treaty on the European Union.

12.4.2. European Commission (EC) report on pharmacovigilance tasks from the European Union (EU) Member States and the European Medicines Agency (EMA) - 2015-2018

The European Commission is required⁷⁴ to make a report on the pharmacovigilance activities of EMA and the Member States every 3 years. The PRAC was informed of the current report which covers 2015-2018 and includes an overview of the impact of the legislation (public health, simplification and process improvement and transparency and stakeholder engagement), and a summary of key pharmacovigilance activities conducted by the Member States as well as by the EMA. PRAC comments on the report are invited by 24 May 2019.

⁷⁴ Article 108b of Directive 2001/83/EC and Article 29 of Regulation (EC) 726/2004 (as amended)

12.5. Cooperation with International Regulators

12.5.1. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)-E19 on 'optimisation of safety data collection' – draft guideline

The PRAC was informed of the draft guideline [ICH E19 - Optimisation of safety data collection](#). This new guideline is proposed to provide harmonised guidance on when it would be appropriate to use a targeted approach to safety data collection in late-stage pre-marketing or post-marketing studies, and how such an approach would be implemented. The protection of patient welfare during drug development is critically important and unnecessary data collection may be burdensome to patients. Optimisation of safety data collection using a selective approach may improve the efficiency of clinical studies while reducing the burden to study participants. PRAC members were invited to send comments until 15 July 2019.

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.

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 May 2019, 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 in May 2019, the updated EURD list was adopted by the CHMP and CMDh at their May 2019 meetings and published on the EMA website on 05 June 2019, see:

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

12.11. Signal management

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

PRAC lead: Menno van der Elst

The May 2019 SMART meeting was cancelled.

12.12. Adverse drug reactions reporting and additional monitoring

12.12.1. Management and reporting of adverse reactions to medicinal products

None

12.12.2. Additional monitoring

None

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

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

Post-meeting note: The updated additional monitoring list was published on the EMA website on 29 May 2019, see: [Home>Human Regulatory>Post-](#)

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

12.15.3. Post-authorisation Safety Studies - Guidance for assessors to request the conduct of a PASS

PRAC lead: Ulla Wändel Liminga

The topic was postponed to June 2019.

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

None

12.20. Others

12.20.1. Strategy on measuring the impact of pharmacovigilance - draft technical specifications for EMA funded impact research

The PRAC was presented with two draft technical specifications for EMA funded impact research for comments on the proposed topic for impact research, the draft timelines and the study objectives. PRAC comments are invited by 29 May 2019.

13. Any other business

None

14. Annex I – Signals assessment and prioritisation⁷⁵

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 timetables⁷⁶.

14.1.1. Febuxostat – ADENURIC (CAP); FEBUXOSTAT MYLAN (CAP); NAP

Applicant(s): Menarini International (Adenuric); Mylan S.A.S. (Febuxostat Mylan), various

PRAC Rapporteur: Jan Neuhauser

Scope: Signal of gynaecomastia

EPITT 19412 – New signal

⁷⁵ 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

⁷⁶ 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

Lead Member State(s): AT

- 14.1.2. Ibuprofen (NAP) and fixed-dose combinations: chlorphenamine, ibuprofen, phenylephrine (NAP); dimenhydrinate, ibuprofen, caffeine (NAP); ibuprofen, ascorbic acid (NAP); ibuprofen, caffeine (NAP); ibuprofen, codeine (NAP); ibuprofen, hydrocodone (NAP); ibuprofen, paracetamol (NAP); ibuprofen, phenylephrine (NAP); ibuprofen, pseudoephedrine (NAP)
-

Applicant(s): various

PRAC Rapporteur: Anette Kirstine Stark

Scope: Signal of acute generalised exanthematous pustulosis (AGEP)

EPITT 19409 – New signal

Lead Member State(s): DK, FR, PL

- 14.1.3. Sebelipase alfa – KANUMA (CAP)
-

Applicant(s): Alexion Europe SAS

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of nephrotic syndrome

EPITT 19410 – New signal

Lead Member State(s): SE

- 14.1.4. Tigecycline – TYGACIL (CAP); NAP
-

Applicant(s): Pfizer Europe MA EEIG, various

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Signal of bradycardia

EPITT 19394 – New signal

Lead Member State(s): ES

14.2. New signals detected from other sources

- 14.2.1. Lithium (NAP)
-

Applicant(s): various

PRAC Rapporteur: Martin Huber

Scope: Signal of drug induced lichenoid reaction

EPITT 19389 – New signal

Lead Member State(s): DE

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. Deferasirox - EMEA/H/C/005014

Scope: Treatment of chronic iron overload

15.1.2. Erlotinib - EMEA/H/C/005071

Scope: Treatment of non-small cell lung cancer (NSCLC) and pancreatic cancer

15.1.3. Etanercept - EMEA/H/C/004711

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

15.1.4. Tigecycline - EMEA/H/C/005114

Scope: Treatment of complicated skin and soft tissue infections (cSSTI) excluding diabetic foot infections, complicated intra-abdominal infections (cIAI)

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

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

15.2.1. Aliskiren - RASILEZ (CAP) - EMEA/H/C/000780/WS1581/0123; Aliskiren, hydrochlorothiazide - RASILEZ HCT (CAP) - EMEA/H/C/000964/WS1581/0093

Applicant: Noden Pharma DAC

PRAC Rapporteur: Amelia Cupelli

Scope: Submission of an updated RMP (version 14) in order to reflect changes in the categorisation of safety concerns in line with revision 2 of GVP module V on 'Risk management systems' and in line with revision 2 of the guidance on the format of RMP in the EU (template). The update also includes the addition of the new important potential risk of non-melanoma skin cancer (related to Rasilez HCT (aliskiren/hydrochlorothiazide) only) as per the final recommendation of the signal on hydrochlorothiazide-containing products and skin cancer (EPITT 19138) adopted in September 2018

15.2.2. Darvadstrocel - ALOFISEL (CAP) - EMEA/H/C/004258/II/0006, Orphan

Applicant: Takeda Pharma A/S, ATMP⁷⁷

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Submission of an updated RMP (version 7) in order to propose the replacement of the existing observational PASS (listed as category 3 study: 'a study to evaluate the long term safety of Alofisel (darvadstrocel (Cx601)) in patients treated and retreated (i.e. repeated dosing and immunogenicity) and to assess the effectiveness of Alofisel (darvadstrocel) in patients treated and retreated (i.e. repeated dosing) in routine clinical practice (for treatment of complex perianal fistulas in adult patients with non-active/mildly active luminal Crohn's disease, when fistulas have shown an inadequate response to at least one conventional or biologic therapy)' with two separate studies: 1) a long-term safety extension of the ADMIRE-CD II study: a phase 3 randomised, double-blind, parallel-group, placebo-controlled, multicentre study to assess efficacy and safety of darvadstrocel (Cx601), allogeneic expanded adipose-derived stem cells for complex perianal fistula(s) in Crohn's disease; and 2) a retreatment PASS. The European multi-database linkage study is added for the assessment of the potential risk of tumourgenicity

15.2.3. Filgrastim - FILGRASTIM HEXAL (CAP) - EMEA/H/C/000918/WS1608/0049; ZARZIO (CAP) - EMEA/H/C/000917/WS1608/0050

Applicant: Sandoz GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Submission of an updated RMP (version 12.0) in order to align the due dates and deliverables for post-authorisation measure MEA 007 relating to study EP06-501: a non-interventional, prospective, long-term safety data collection of Zarzio/Filgrastim Hexal (filgrastim) in healthy unrelated stem cell donors undergoing peripheral blood progenitor cell mobilisation. The due date is extended from December 2019 to March 2020, to combine the annual safety report (ASR) with the 5-year interim clinical study report (CSR) in 2020 and the final CSR in 2024 and for the MEA to cover the entire duration of study EP06-501

15.2.4. Human papillomavirus vaccine [types 6, 11, 16, 18] (recombinant, adsorbed) - GARDASIL (CAP) - EMEA/H/C/000703/II/0081

Applicant: MSD Vaccins

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of an updated RMP (version 13.1) in order to update the list of safety concerns by removing all remaining important identified and potential risks and missing information in line with revision 2 of GVP module V on 'Risk management systems' and revision 2 of the guidance on the format of RMP in the EU (template)

⁷⁷ Advanced therapy medicinal product

15.2.5. [Icatibant - FIRAZYR \(CAP\) - EMEA/H/C/000899/II/0047, Orphan](#)

Applicant: Shire Pharmaceuticals Ireland Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of an updated RMP (version 7.0) to reflect the completion of paediatric study HGT-FIR-086: a multicentre, open-label, non-randomised study to assess the pharmacokinetics, tolerability, and safety of a single subcutaneous administration of icatibant in children and adolescents with hereditary angioedema, to update the list of safety concerns accordingly and to remove the study as an additional pharmacovigilance activity. In addition, the RMP is updated in line with revision 2 of the guidance on the format of RMP in the EU (template)

15.2.6. [Measles, mumps, rubella and varicella vaccine \(live\) - PROQUAD \(CAP\) - EMEA/H/C/000622/II/0134](#)

Applicant: MSD Vaccins

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Submission of an updated RMP (version 6.1) in order to reflect changes in the categorisation of safety concerns in line with revision 2 of the guidance on the format of RMP in the EU (template)

15.2.7. [Octocog alfa - KOVALTRY \(CAP\) - EMEA/H/C/003825/II/0022](#)

Applicant: Bayer AG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of the RMP (version 2.0) in line with revision 2 of GVP module V on 'Risk management systems' and in line with revision 2 of the guidance on the format of RMP in the EU (template)

15.2.8. [Pazopanib - VOTRIENT \(CAP\) - EMEA/H/C/001141/II/0054](#)

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Anette Kirstine Stark

Scope: Submission of an updated RMP (version 17.0) in order to postpone the submission due date for the clinical study report (CSR) for study VEG108844 (COMPARZ): a study of pazopanib versus sunitinib in the treatment of subjects with locally advanced and/or metastatic renal cell carcinoma, and its sub-studies. In addition, the RMP is updated to reflect PRAC recommendations for additional assessments of some risks and to revise the categorisation of the safety concerns in line with revision 2 of the guidance on the format of RMP in the EU (template)

15.2.9. [Pembrolizumab - KEYTRUDA \(CAP\) - EMEA/H/C/003820/II/0068](#)

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Update of the RMP (version 23.1) in order to discuss the effectiveness of the

educational materials put in place for Keytruda (pembrolizumab) at the time of the initial marketing authorisation, to provide a proposal to update these materials and to revise the safety specification as requested in the outcome of the PSUR single assessment procedure (PSUSA/00010403/201803) finalised in October 2018

15.2.10. Pregabalin - PREGABALIN MYLAN (CAP) - EMEA/H/C/004078/WS1603/0013; PREGABALIN MYLAN PHARMA (CAP) - EMEA/H/C/003962/WS1603/0011

Applicant: Mylan S.A.S

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Submission of an updated RMP (version 6) to get adjusted to the RMP of the originator medicinal product containing pregabalin. In addition, the RMP is updated in line with revision 2 of the guidance on the format of RMP in the EU (template)

15.2.11. Sunitinib - SUTENT (CAP) - EMEA/H/C/000687/II/0073

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Amelia Cupelli

Scope: Update of the RMP (version 17.0) in order to reflect changes in the categorisation of safety concerns in line with revision 2 of the guidance on the format of RMP in the EU (template)

15.2.12. Umeclidinium, vilanterol - ANORO ELLIPTA (CAP) - EMEA/H/C/002751/WS1586/0028; LAVENTAIR ELLIPTA (CAP) - EMEA/H/C/003754/WS1586/0031

Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Amelia Cupelli

Scope: Submission of an updated RMP (version 8.0) following the completion of the annual renewal procedures (R/0022 and R/0025) in November 2018 concluding on the commitments to remove the important identified risks of 'hypersensitivity' and 'paradoxical bronchospasm' from the list of safety concerns and to update all relevant sections of the RMP in line with revision 2 of GVP module V on 'Risk management systems' and revision 2 of the guidance on the format of RMP in the EU (template). In addition, the MAH proposed to remove some additional risks ('narrow angle glaucoma', 'bladder outflow obstruction and urinary retention', safety in pregnancy and lactation', 'safety in long-term use' and 'safety in severe hepatic impairment')

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

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

15.3.1. Atezolizumab - TECENTRIQ (CAP) - EMEA/H/C/004143/X/0017

Applicant: Roche Registration GmbH

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Extension application to add a new strength of 840 mg (60 mg/mL) for Tecentriq (atezolizumab) concentrate for solution for infusion in a vial and to add a new indication for the treatment of metastatic triple-negative breast cancer (TNBC). The new indication applies only to the 840 mg strength. The RMP (version 7.0) is updated accordingly

15.3.2. Avelumab - BAVENCIO (CAP) - EMEA/H/C/004338/II/0009/G, Orphan

Applicant: Merck Europe B.V.

PRAC Rapporteur: Anette Kirstine Stark

Scope: Grouped variations consisting of: 1) extension of indication to include a new indication as the first-line combination treatment with avelumab and axitinib in adult patients with advanced renal cell carcinoma (aRCC). 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 1.7) are updated accordingly; 2) change in section 4.2 of the SmPC to support the switch of the avelumab dosing regimen from 10 mg/kg every two weeks (weight-based) to a flat dose of 800 mg every two weeks applicable to the new proposed indication aRCC and the existing one on Merkel cell carcinoma (MCC). The MAH took the opportunity to introduce some editorial changes in the product information

15.3.3. Bedaquiline - SIRTURO (CAP) - EMEA/H/C/002614/II/0033/G, Orphan

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Grouped variations consisting of: 1) extension of indication to include patients 12 years of age and older based on week 24 analysis of cohort 1 (adolescent subjects aged ≥ 12 to < 18 years) for study TMC207-TIDP59-C211: a phase 2, open-label, multicentre, single-arm study to evaluate the pharmacokinetics, safety, tolerability and anti-mycobacterial activity of bedaquiline (TMC207) in combination with a background regimen (BR) of multidrug resistant tuberculosis (MDR-TB) medications for the treatment of children and adolescents 0 months to < 18 years of age who have confirmed or probable pulmonary MDR-TB. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 3.2) are updated accordingly; 2) update of section 4.9 of the SmPC to remove reference to the use of activated charcoal as an aid to remove unabsorbed bedaquiline in case of overdose

15.3.4. Belimumab - BENLYSTA (CAP) - EMEA/H/C/002015/II/0065

Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of sections 4.4 and 4.8 of the SmPC in order to add a warning on suicidality and depression based on interim results from study BEL115467 (listed in Annex II): a randomised, double-blind, placebo-controlled 52-week study to assess adverse events of special interest in adults with active, autoantibody-positive systemic lupus erythematosus receiving belimumab. The package leaflet and the RMP (version 30) are updated accordingly

15.3.5. Benralizumab - FASENRA (CAP) - EMEA/H/C/004433/II/0014/G

Applicant: AstraZeneca AB

PRAC Rapporteur: David Olsen

Scope: Grouped variations consisting of: 1) addition of an auto-injector delivery device, Fasentra 30 mg solution for injection in pre-filled pen, 2) update of sections 4.2, 6.4, 6.5 and 6.6 of the SmPC in order to update the information for self-administration for Fasentra 30 mg solution for injection in pre-filled syringe. The labelling and the package leaflet are updated accordingly. In addition, the RMP (version 2.0) is updated to reflect the information about the new presentation, to include additional information on completed studies, namely: study ALIZE: 'a multicentre, randomized, double-blind, parallel group, placebo-controlled, phase 3b study to evaluate the potential effect of benralizumab on the humoral immune response to the seasonal influenza vaccination in adolescent and young adult patients with severe asthma'; study GREGALE: 'a multicentre, open-label, functionality, reliability, and performance study of an accessorized pre-filled syringe with home-administered subcutaneous benralizumab in adult patients with severe asthma'; study AMES: 'a multicentre, randomised, open-label, parallel group, phase 1 study designed to compare benralizumab pharmacokinetics exposure in healthy subjects following single subcutaneous administration of a fixed 30 mg dose of benralizumab when using an autoinjector and accessorised pre-filled syringe'; study GRECO: 'a multicentre, open-label, functionality, reliability and performance study of a single-use auto-injector with home-administered subcutaneous benralizumab in adult patients with severe asthma'. The RMP is also updated with exposure data post marketing authorisation (MA) approval, and additional details on the following post-authorisation safety studies: study D3250R00026 (pregnancy registry): benralizumab pregnancy exposure study: a Vaccines and Medications in Pregnancy Surveillance System (VAMPSS) post marketing surveillance study, and study D3250R00042 (malignancy PASS): 'a descriptive study of the incidence of malignancy in patients with severe asthma overall and among those receiving benralizumab and other biologic therapy'. Furthermore, the RMP is brought in line with revision 2 of the guidance on the format of RMP in the EU (template)

15.3.6. Bosutinib - BOSULIF (CAP) - EMEA/H/C/002373/II/0037

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Martin Huber

Scope: Update of sections 4.6 and 5.3 of the SmPC based on final results from study 17GR319 (00655202) (listed as a category 3 study in the RMP): an oral (gavage) study of the effects of bosulif (PF-05208763) on pre- and postnatal development, including maternal function in rats. The package leaflet and the RMP (version 4.5) are updated accordingly

15.3.7. Ceftolozane, tazobactam - ZERBAXA (CAP) - EMEA/H/C/003772/II/0020

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Extension of indication to include treatment of nosocomial pneumonia, including

ventilator associated pneumonia for Zerbaxa (ceftolozane/tazobactam) based on results from study CXA-NP-11-04 (PN008): a prospective, randomised, double-blind, phase 3 study to assess the safety and efficacy of intravenous ceftolozane/tazobactam compared to meropenem in adult patients with ventilated nosocomial pneumonia. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2, 5.3 and 6.6 of the SmPC are updated. The package leaflet and the RMP (version 2.1) are updated accordingly. The MAH took the opportunity to implement editorial changes in sections 5.2 of the SmPC and to bring section 4.4 of the SmPC and section 2 of the package leaflet in line with the latest Annex to the European Union (EC) guideline on 'excipients in the labelling and package leaflet of medicinal products for human use'

15.3.8. [Ciclosporin - IKERVIS \(CAP\) - EMEA/H/C/002066/WS1490/0014; VERKAZIA \(CAP\) - EMEA/H/C/004411/WS1490/0001](#)

Applicant: Santen Oy

PRAC Rapporteur: Jan Neuhauser

Scope: Update of the RMP (version 7.0) in order to bring the RMP in line with revision 2 of the guidance on the format of RMP in the EU (template). The milestones for Verkazia (ciclosporin) PASS on 'quantification of the risk of periocular skin cancer, conjunctival or corneal neoplasia in children treated with Verkazia (ciclosporin) for vernal keratoconjunctivitis (VKC)' have also been updated. In addition, the MAH proposed to align Ikervis (ciclosporin) SmPC section 4.4 on concomitant therapy and effects on immune system with Verkazia (ciclosporin) SmPC in order to harmonise the routine risk minimisation measures for both medicinal products. The MAH took this opportunity to implement the latest quality review of documents (QRD) template and the safety features for Ikervis (ciclosporin)

15.3.9. [Cinacalcet - MIMPARA \(CAP\) - EMEA/H/C/000570/II/0062/G](#)

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Grouped variations consisting of: 1) update of section 4.4 of the SmPC to provide additional information on switching from etelcalcetide to Mimpara (cinacalcet) as requested by PRAC in the conclusions of the PSUR single assessment procedure for etelcalcetide (PSUSA/00010533/201711) adopted in May 2018; 2) update of section 6.1 of the SmPC to replace the term 'silica, dental type' by 'amorphous silicon dioxide'. The RMP is updated (version 9.0) in order to reflect changes in the categorisation of safety concerns in line with revision 2 of the guidance on the format of RMP in the EU (template)

15.3.10. [Darunavir, cobicistat, emtricitabine, tenofovir alafenamide - SYMTUZA \(CAP\) - EMEA/H/C/004391/II/0017/G](#)

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Grouped variations consisting of an update of sections 4.8, 5.1 and 5.2 of the SmPC in order to update the safety information based on week-96 results from two

studies (listed as category 3 studies in the RMP): 1) study TMC114FD2HTX3001 (AMBER): a phase 3, randomised, active-controlled, double-blind study to evaluate 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 fixed dose combination (DRV/COBI FDC) co-administered with emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) FDC in antiretroviral (ARV) treatment-naïve human immunodeficiency virus type 1 (HIV-1) infected subjects, 2) study TMC114IFD3013 (EMERALD): a phase 3, randomised, active-controlled, open-label study to evaluate 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 package leaflet is updated accordingly. The RMP (version 5.0) is also updated accordingly and brought in line with revision 2 of the guidance on the format of RMP in the EU (template). In addition, the MAH took the opportunity to update section 4.2 of the SmPC and package leaflet to include advice in the event of vomiting in line with the approved SmPC for elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide-containing product. The MAH also introduced some minor editorial changes in the SmPC and updated the list of local representatives in the package leaflet in line with the latest quality review of documents (QRD) template (version 10.0)

15.3.11. Fidaxomicin - DIFICLIR (CAP) - EMEA/H/C/002087/X/0034/G

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Grouped application consisting of: 1) extension application to introduce a new pharmaceutical form associated with new strength (40 mg/mL granules for oral suspension); 2) extension of indication to include paediatric use of Dificlir (fidaxomicin) in children from birth to less than 18 years of age. The RMP (version 11.0) is updated accordingly. The SmPC of Dificlir (fidaxomicin) 200 mg film-coated tablet, labelling and package leaflet are updated accordingly. In addition, the MAH took the opportunity to update the package leaflet with the statement on 'sodium-free' in accordance with the European Commission (EC) guideline on 'excipients in the labelling and package leaflet of medicinal products for human use'. Furthermore, the MAH updated the details of the local representative in Czech Republic

15.3.12. Insulin human (rDNA⁷⁸) - ACTRAPANE (CAP) - EMEA/H/C/000427/WS1582/0076; ACTRAPID (CAP) - EMEA/H/C/000424/WS1582/0070; INSULATARD (CAP) - EMEA/H/C/000441/WS1582/0073; MIXTARD (CAP) - EMEA/H/C/000428/WS1582/0077; PROTAPANE (CAP) - EMEA/H/C/000442/WS1582/0072

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Hans Christian Siersted

Scope: Submission of an updated RMP (version 3.0) for insulin human-containing products to reclassify the risk of 'medication errors' from an important potential risk to

⁷⁸ Recombinant deoxyribonucleic acid

an important identified risk as requested in the outcome of the PSUR single assessment procedure (PSUSA/00001753/201710) finalised in June 2018 and in line with the 'Good practice guide on risk minimisation and prevention of medication errors' dated 2015. In addition, the RMP is brought in line with revision 2 of GVP module V on 'Risk management systems' and revision 2 of the guidance on the format of RMP in the EU (template). As a consequence, the MAH proposed to remove this risk as it is fully characterised and managed through routine pharmacovigilance. Section 4.4 of the SmPC is updated in order to add a warning on accidental mix-ups/medication. The package leaflet is updated accordingly. Furthermore, the MAH took the opportunity to include minor updates to Annex III-A on 'labelling' and to bring the package leaflet in line with the latest quality review document (QRD) template (version 10.0)

15.3.13. Lenalidomide - REVLIMID (CAP) - EMEA/H/C/000717/II/0107, Orphan

Applicant: Celgene Europe BV

PRAC Rapporteur: Ghania Chamouni

Scope: Extension of indication to include Revlimid (lenalidomide) in combination with rituximab for the treatment of adult patients with previously treated follicular lymphoma or marginal zone lymphoma. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 36.2) are updated accordingly

15.3.14. Letermovir - PREVYMIS (CAP) - EMEA/H/C/004536/II/0011, Orphan

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Kirsti Villikka

Scope: Update of sections 4.4 and 4.5 of the SmPC in order to update the safety information following the final results of clinical pharmacology trial MK-8228-038 (listed as a category 3 study in the RMP): a study to assess the effect of rifampin on the single-dose and steady-state pharmacokinetics of letermovir (MK-8228) in healthy adult subjects. The package leaflet and the RMP (version 2.1) are updated accordingly

15.3.15. Mepolizumab - NUCALA (CAP) - EMEA/H/C/003860/II/0021

Applicant: GlaxoSmithKline Trading Services Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of sections 4.8 and 5.1 of the SmPC in order to update the safety information based on the final results from study 200363 part B and two open label extension (OLE) studies namely study 201312 and study MEA115666 (listed as category 3 studies in the RMP). These are interventional PASS conducted to assess the long-term (52 weeks) safety and tolerability of mepolizumab when administered subcutaneously to patients aged 6 to 11 years old with severe eosinophilic asthma (study 200363 part B), to describe the long-term safety profile of mepolizumab (MEA115666), and to provide extended treatment to subjects from study MEA115661 and further describe long-term safety in these subjects (study 201312). The RMP (version 5.0) is updated accordingly and brought in line with revision 2 of the guidance on the format of RMP in the EU (template)

15.3.16. Mepolizumab - NUCALA (CAP) - EMEA/H/C/003860/X/0018

Applicant: GlaxoSmithKline Trading Services Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension application to introduce a new pharmaceutical form, solution for injection (in pre-filled syringe or in pre-filled pen). The RMP (version 4.0) is updated accordingly

15.3.17. Moroctocog alfa - REFACTO AF (CAP) - EMEA/H/C/000232/II/0151

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Anette Kirstine Stark

Scope: Update of sections 4.8 and 5.1 of the SmPC based on the final results from study 3082B2-313 (B1831001) (listed as a category 3 study in the RMP): an open-label study to evaluate prophylaxis treatment, and to characterize the efficacy, safety, and pharmacokinetics of b-domain deleted recombinant factor VIII albumin free (moroctocog alfa [AF_CC]) in children with haemophilia A (MEA 116). The RMP (version 13.0) is updated accordingly. In addition, the SmPC is brought in line with revision 3 of the 'Guideline on core SmPC for human plasma derived and recombinant coagulation factor VIII products' (EMA/CHMP/BPWP/1619/1999 rev. 3)

15.3.18. Nalotimagene carmaleucel - ZALMOXIS (CAP) - EMEA/H/C/002801/II/0016, Orphan

Applicant: MolMed S.p.A, ATMP⁷⁹

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Proposal to terminate study TK008 (listed as a category 2 study, specific condition to the conditional marketing authorisation): a phase 3, randomised trial of haploidentical hematopoietic cell transplantation (HCT) with or without an add back strategy of human herpes simplex virus thymidine kinase type 1 gene (HSV-Tk) donor lymphocytes in patients with high risk acute leukaemia, and replace it with study TK013: a two-step study consisting in an initial feasibility study, followed by a single-arm trial with matched-pair controls from the European Society for Blood and Marrow Transplantation (EBMT) registry. The RMP (version 8.1) is updated accordingly

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

Applicant: Orexigen Therapeutics Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: Grouped variations consisting of: 1) update of section 4.8 to adjust the list of adverse drug reactions and their corresponding frequencies in line with the outcome of the PSUSA procedure (PSUSA/00010366/201709) finalised in April 2018; 2) update of sections 4.2, 4.4 and 5.2 of the SmPC to add results from a phase 1 open label parallel

⁷⁹ Advanced therapy medicinal product

study to evaluate the pharmacokinetics of a single oral dose of extended-release combination of naltrexone and bupropion in subjects with normal hepatic function or varying degrees of impaired hepatic function and remove the recommendation to not use naltrexone/bupropion in patients with mild hepatic impairment. The existing warning is updated accordingly. The warning related to contraindications is aligned to section 4.3 to add end-stage renal failure patients. As a consequence, the RMP is updated accordingly (version 11). In addition, the MAH took the opportunity to update the warning on lactose in accordance with the European Commission (EC) guideline on 'excipients in the labelling and package leaflet of medicinal products for human use'

15.3.20. Obinutuzumab - GAZYVARO (CAP) - EMEA/H/C/002799/II/0034, Orphan

Applicant: Roche Registration GmbH

PRAC Rapporteur: Annika Folin

Scope: Submission of the final results of the pivotal study BO21005/GOYA: a phase 3, multicentre, open-label randomised trial comparing the efficacy of obinutuzumab (GA101 (RO5072759)) in combination with cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP) (G-CHOP) versus rituximab and CHOP (R-CHOP) in previously untreated patients with CD20-positive diffuse large B-cell lymphoma (DLBCL), to address the additional pharmacovigilance activities required in the EU RMP. The RMP (version 5.0) is updated accordingly

15.3.21. Pegfilgrastim - PELGRAZ (CAP) - EMEA/H/C/003961/II/0005

Applicant: Accord Healthcare S.L.U.

PRAC Rapporteur: Menno van der Elst

Scope: Change in the immediate packaging of Pelgraz (pegfilgrastim) finished product solution for injection 6 mg/0.6 mL to add an additional presentation as a solution for injection in pre-filled injector in addition to the existing approved solution for injection in Pre-filled syringe. The RMP (version 1.4) is updated accordingly

15.3.22. Pembrolizumab - KEYTRUDA (CAP) - EMEA/H/C/003820/II/0072

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to include a new indication for Keytruda (pembrolizumab) as monotherapy for the treatment of recurrent locally advanced or metastatic oesophageal cancer in adults whose tumours express programmed death-ligand 1 (PD-L1) with a combined positive score (CPS) ≥ 10 and who have received prior systemic therapy, based on the results from study KEYNOTE-181: an international, randomised, open-label phase 3 trial of pembrolizumab versus the investigator's choice of paclitaxel, docetaxel, or irinotecan in participants with advanced/metastatic adenocarcinoma or squamous cell carcinoma of the oesophagus, or advanced/metastatic Siewert type I adenocarcinoma of the oesophagogastric junction. As a consequence, sections 4.1, 4.2, and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 25.1) are updated accordingly

15.3.23. Propranolol - HEMANGIOL (CAP) - EMEA/H/C/002621/II/0019

Applicant: Pierre Fabre Dermatologie

PRAC Rapporteur: Eva Segovia

Scope: Submission of the results of a drug utilisation study (DUS) performed in Germany and France to evaluate off-label use and effectiveness of risk minimisation measures (RMM) in a real-life clinical setting (MEA 002). As a consequence, the package leaflet is updated to strengthen the warning on hypoglycaemia and bronchospasm. The RMP (version 3.1) is updated accordingly. In addition, the MAH took the opportunity to introduce some editorial changes in section 4.4 of the SmPC as well as changes in the package leaflet in accordance with the latest quality review document (QRD) template (version 10.0)

15.3.24. Rituximab - MABTHERA (CAP) - EMEA/H/C/000165/II/0162

Applicant: Roche Registration GmbH

PRAC Rapporteur: Anette Kirstine Stark

Scope: Extension of indication to include the treatment of paediatric patients (aged ≥ 2 to <18 years old) with active polyangiitis (Wegener's) (GPA) and microscopic polyangiitis (MPA) for the 100 mg and 500 mg concentrate for solution based on efficacy and safety data from study WA25615: a phase 2A, international, multicentre, open-label, uncontrolled study to evaluate the safety and pharmacokinetics of 4×375 mg/m² intravenous rituximab in paediatric patients with severe granulomatosis with polyangiitis (Wegener's) or microscopic polyangiitis (PePRS). As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC is updated. The package leaflet and the RMP (version 20.0) are updated accordingly. In addition, the product information is brought in line with the latest quality review document (QRD) template (version 10) and the opportunity is taken to combine the SmPC and package leaflet for the 100 mg and 500 mg concentrate for solution presentations. Furthermore, the MAH took the opportunity to implement minor editorial changes in the SmPC

15.3.25. Rituximab - RIXATHON (CAP) - EMEA/H/C/003903/WS1599/0020; RIXIMYO (CAP) - EMEA/H/C/004729/WS1599/0020

Applicant: Sandoz GmbH

PRAC Rapporteur: Anette Kirstine Stark

Scope: Submission of the final report from study GP13-301 (listed as a category 3 study in the RMP): a randomised, controlled double-blind phase 3 trial to compare the efficacy, safety and pharmacokinetics of Rixathon/Riximyo (GP2013 – rituximab biosimilars) plus cyclophosphamide, vincristine, prednisone vs. MabThera (rituximab) plus cyclophosphamide, vincristine, prednisone, followed by Rixathon/Riximyo (GP2013 - rituximab biosimilars) or MabThera (rituximab) maintenance therapy in patients with previously untreated advanced stage follicular lymphoma. The RMP (version 4.0) is updated accordingly

15.3.26. Ruxolitinib - JAKAVI (CAP) - EMEA/H/C/002464/II/0040

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Annika Folin

Scope: Update of section 5.3 of the SmPC in order to update the preclinical safety information based on the final results from juvenile toxicity studies 1570143 (dose range finding juvenile study) and 157014 (juvenile development study). The RMP (version 10) is updated accordingly. Furthermore, the RMP is updated to revise the safety specification as requested in the outcome of the PSUR single assessment procedure (PSUSA/00010015/201802) finalised in September 2018 as well as in line with revision 2 of GVP module V on 'Risk management systems' and revision 2 of the guidance on the format of RMP in the EU (template)

15.3.27. Ruxolitinib - JAKAVI (CAP) - EMEA/H/C/002464/II/0041

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Annika Folin

Scope: Submission of the final results of drug-drug interaction (DDI) study INC4242A2106: an open-label, crossover study evaluating the effect of multiple doses of fluconazole on the pharmacokinetics (PK) of ruxolitinib administered as a single dose in healthy subjects (fulfilment of post-authorisation measures (PAM) MEA 016). The RMP (version 10) is updated accordingly and brought in line with revision 2 of GVP module V on 'Risk management systems' and in line with revision 2 of the guidance on the format of RMP in the EU (template)

15.3.28. Trastuzumab emtansine - KADCYLA (CAP) - EMEA/H/C/002389/II/0045

Applicant: Roche Registration GmbH

PRAC Rapporteur: Anette Kirstine Stark

Scope: Extension of indication to include the adjuvant treatment of adult patients with human epidermal growth factor receptor 2 (HER2)-positive early breast cancer. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 9.0) are updated accordingly. In addition, the MAH took the opportunity to introduce editorial changes

15.3.29. Varenicline - CHAMPIX (CAP) - EMEA/H/C/000699/II/0074

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Anette Kirstine Stark

Scope: Update of sections 4.2, 5.1 and 5.2 of the SmPC in order to reflect results of paediatric study A3051073 (MEA 047): a phase 4, twelve-week, randomised, double-blind, placebo-controlled, parallel-group, dose-ranging study with follow-up, evaluating the safety and efficacy of varenicline for smoking cessation in healthy adolescent smokers. The package leaflet and the RMP (version 11.0) are updated accordingly

15.3.30. Venetoclax - VENCLYXTO (CAP) - EMEA/H/C/004106/II/0020, Orphan

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Eva Jirsová

Scope: Update of sections 4.2 and 5.2 of the SmPC in order to include that a 50% dose reduction of venetoclax is recommended in patients with severe hepatic impairment, based on the final results from study M15-342 (listed as a category 3 study in the RMP): a study to evaluate the safety and pharmacokinetics of a single dose of venetoclax in female subjects with mild, moderate, or severe hepatic impairment. The package leaflet and the RMP (version 3.4) 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. Axicabtagene ciloleucel - YESCARTA (CAP) - PSUSA/00010703/201810

Applicant: Kite Pharma EU B.V., ATMP⁸⁰

PRAC Rapporteur: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

16.1.2. Bezlotoxumab - ZINPLAVA (CAP) - PSUSA/00010576/201810

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.3. Cariprazine - REAGILA (CAP) - PSUSA/00010623/201810

Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Ana Sofia Diniz Martins

⁸⁰ Advanced therapy medicinal product

Scope: Evaluation of a PSUSA procedure

16.1.4. Ceritinib - ZYKADIA (CAP) - PSUSA/00010372/201810

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

16.1.5. Cerliponase alfa - BRINEURA (CAP) - PSUSA/00010596/201810

Applicant: BioMarin International Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.6. Conestat alfa - RUCONEST (CAP) - PSUSA/00000873/201810

Applicant: Pharming Group N.V

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.1.7. Daclizumab - ZINBRYTA⁸¹ - PSUSA/00010518/201811

Applicant: Biogen Idec Ltd

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

16.1.8. Defibrotide - DEFITELIO (CAP) - PSUSA/00010086/201810

Applicant: Gentium S.r.l.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.9. Durvalumab - IMFINZI (CAP) - PSUSA/00010723/201810

Applicant: AstraZeneca AB

PRAC Rapporteur: David Olsen

Scope: Evaluation of a PSUSA procedure

16.1.10. Edoxaban - LIXIANA (CAP); ROTEAS (CAP) - PSUSA/00010387/201810

Applicant: Daiichi Sankyo Europe GmbH

PRAC Rapporteur: Adrien Inoubli

⁸¹ European Commission (EC) decision on the marketing authorisation (MA) withdrawal dated 27 March 2018

Scope: Evaluation of a PSUSA procedure

16.1.11. Flutemetamol (¹⁸F) - VIZAMYL (CAP) - PSUSA/00010293/201810

Applicant: GE Healthcare AS

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.12. Gemtuzumab ozogamicin - MYLOTARG (CAP) - PSUSA/00010688/201810

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Evaluation of a PSUSA procedure

16.1.13. Granisetron⁸² - SANCUSO (CAP) - PSUSA/00010101/201810

Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Rugile Pilviniene

Scope: Evaluation of a PSUSA procedure

16.1.14. Hepatitis A (inactivated), hepatitis B (rDNA) vaccine (adsorbed) - AMBIRIX (CAP); TWINRIX ADULT (CAP); TWINRIX PAEDIATRIC (CAP) - PSUSA/00001593/201809

Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

16.1.15. Herpes zoster vaccine (recombinant, adjuvanted) - SHINGRIX (CAP) - PSUSA/00010678/201810

Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Sonja Hrabcik

Scope: Evaluation of a PSUSA procedure

16.1.16. Idarucizumab - PRAXBIND (CAP) - PSUSA/00010435/201810

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

⁸² Transdermal patch only

16.1.17. Insulin detemir - LEVEMIR (CAP) - PSUSA/00001750/201810

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

16.1.18. Irinotecan⁸³ - ONIVYDE (CAP) - PSUSA/00010534/201810

Applicant: Les Laboratoires Servier

PRAC Rapporteur: David Olsen

Scope: Evaluation of a PSUSA procedure

16.1.19. Letemovir - PREVYMIS (CAP) - PSUSA/00010660/201811

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

16.1.20. Lopinavir, ritonavir - ALUVIA (Art 58⁸⁴); KALETRA (CAP) - PSUSA/00001905/201809

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

16.1.21. Macitentan - OPSUMIT (CAP) - PSUSA/00010115/201810

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

16.1.22. Measles, mumps, rubella, varicella vaccines (live) - PROQUAD (CAP) - PSUSA/00001936/201809

Applicant: MSD Vaccins

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

⁸³ Liposomal formulations only

⁸⁴ Article 58 of Regulation (EC) No 726/2004 allows the Committee for Medicinal Products for Human Use (CHMP) to give opinions, in co-operation with the World Health Organisation (WHO) on medicinal products for human use that are intended exclusively for markets outside of the European Union (EU)

16.1.23. Meningococcal group B vaccine (recombinant, adsorbed) - TRUMENBA (CAP) - PSUSA/00010607/201810

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

16.1.24. Micafungin - MYCAMINE (CAP) - PSUSA/00002051/201810

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.25. Midostaurin - RYDAPT (CAP) - PSUSA/00010638/201810

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Evaluation of a PSUSA procedure

16.1.26. Miglustat - ZAVESCA (CAP) - PSUSA/00002062/201810

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.27. Netupitant, palonosetron - AKYNZEO (CAP) - PSUSA/00010393/201810

Applicant: Helsinn Birex Pharmaceuticals Limited

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.1.28. Obinutuzumab - GAZYVARO (CAP) - PSUSA/00010279/201810

Applicant: Roche Registration GmbH

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

16.1.29. Ocriplasmin - JETREA (CAP) - PSUSA/00010122/201810

Applicant: Oxurion NV

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.30. Ofatumumab - ARZERRA⁸⁵ - PSUSA/00002202/201810

Applicant: Novartis Europharm Limited
PRAC Rapporteur: Anette Kirstine Stark
Scope: Evaluation of a PSUSA procedure

16.1.31. Olaratumab - LARTRUVO (CAP) - PSUSA/00010541/201810

Applicant: Eli Lilly Nederland B.V.
PRAC Rapporteur: Menno van der Elst
Scope: Evaluation of a PSUSA procedure

16.1.32. Oseltamivir - TAMIFLU (CAP) - PSUSA/00002225/201809

Applicant: Roche Registration GmbH (Tamiflu)
PRAC Rapporteur: Kirsti Villikka
Scope: Evaluation of a PSUSA procedure

16.1.33. Pandemic influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) - FOCLIVIA (CAP); prepandemic influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) - AFLUNOV (CAP) - PSUSA/00010008/201810

Applicant: Seqirus S.r.l
PRAC Rapporteur: Amelia Cupelli
Scope: Evaluation of a PSUSA procedure

16.1.34. Para-aminosalicylic acid⁸⁶ - GRANUPAS (CAP) - PSUSA/00010171/201810

Applicant: Eurocept International B.V.
PRAC Rapporteur: Ulla Wändel Liminga
Scope: Evaluation of a PSUSA procedure

16.1.35. Parathyroid hormone - NATPAR (CAP) - PSUSA/00010591/201810

Applicant: Shire Pharmaceuticals Ireland Limited
PRAC Rapporteur: Rhea Fitzgerald
Scope: Evaluation of a PSUSA procedure

16.1.36. Pasireotide - SIGNIFOR (CAP) - PSUSA/00009253/201810

Applicant: Novartis Europharm Limited
PRAC Rapporteur: Annika Folin

⁸⁵ European Commission (EC) decision on the marketing authorisation (MA) withdrawal dated 25 February 2019

⁸⁶ Centrally authorised product(s) only

Scope: Evaluation of a PSUSA procedure

16.1.37. Patisomer - VELTASSA (CAP) - PSUSA/00010618/201810

Applicant: Vifor Fresenius Medical Care Renal Pharma France

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

16.1.38. Pazopanib - VOTRIENT (CAP) - PSUSA/00002321/201810

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

16.1.39. Stiripentol - DIACOMIT (CAP) - PSUSA/00002789/201811

Applicant: Biocodex

PRAC Rapporteur: Maia Uusküla

Scope: Evaluation of a PSUSA procedure

16.1.40. Talimogene laherparepvec - IMLYGIC (CAP) - PSUSA/00010459/201810

Applicant: Amgen Europe B.V., ATMP⁸⁷

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.41. Tofacitinib - XELJANZ (CAP) - PSUSA/00010588/201811

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.42. Turoctocog alfa - NOVOEIGHT (CAP) - PSUSA/00010138/201810

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.43. Vinflunine - JAVLOR (CAP) - PSUSA/00003123/201809

Applicant: Pierre Fabre Medicament

PRAC Rapporteur: Eva Segovia

⁸⁷ Advanced therapy medicinal product

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. Chenodeoxycholic acid - CHENODEOXYCHOLIC ACID LEADIANT (CAP); NAP - PSUSA/00010590/201810

Applicant(s): Leadiant GmbH (Chenodeoxycholic acid Leadiant), various

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.2.2. Enoxaparin⁸⁸ - INHIXA (CAP); THORINANE (CAP); NAP - PSUSA/00010553/201810

Applicant(s): Techdow Europe AB (Inhixa), Techdow Pharma Netherlands B.V. (Thorinane), various

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.2.3. Epoetin alfa - ABSEAMED (CAP); BINOCRIT (CAP); EPOETIN ALFA HEXAL (CAP); NAP - PSUSA/00001237/201808

Applicant(s): Medice Arzneimittel Pütter GmbH & Co. KG (Abseamed), Sandoz GmbH (Binocrit), Hexal AG (Epoetin alfa Hexal), various

PRAC Rapporteur: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

16.2.4. Filgrastim - ACCOFIL (CAP); FILGRASTIM HEXAL (CAP); GRASTOFIL (CAP); NIVESTIM (CAP); RATIOGRASTIM (CAP); TEVAGRASTIM (CAP); ZARZIO (CAP); NAP - PSUSA/00001391/201809

Applicant(s): Accord Healthcare S.L.U. (Accofil), Hexal AG (Filgrastim Hexal), Apotex Europe BV (Grastofil), Pfizer Europe MA EEIG (Nivestim), ratiopharm GmbH (Ratiograstim), TEVA GmbH (Tevagrastim), Sandoz GmbH (Zarzio), various

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

16.2.5. Memantine - AXURA (CAP); EBIXA (CAP); MEMANTINE MERZ (CAP); NAP - PSUSA/00001967/201809

Applicant(s): Merz Pharmaceuticals GmbH (Axura, Memantine Merz), H. Lundbeck A/S (Ebixa)

PRAC Rapporteur: Maria del Pilar Rayon

⁸⁸ Biosimilar(s) only

Scope: Evaluation of a PSUSA procedure

16.2.6. Sodium oxybate⁸⁹ - XYREM (CAP); NAP - PSUSA/00010612/201810

Applicant(s): UCB Pharma S.A. (Xyrem), various

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.2.7. Teriparatide - FORSTEO (CAP); MOVYMIA (CAP); TERROSA (CAP); NAP - PSUSA/00002903/201809

Applicant(s): Eli Lilly Nederland B.V. (Forsteo), Stada Arzneimittel AG (Movymia), Gedeon Richter Plc. (Terrosa), various

PRAC Rapporteur: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

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

16.3.1. Acetylcysteine (NAP) - PSUSA/00000034/201809

Applicant(s): various

PRAC Lead: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.3.2. Alfentanil (NAP) - PSUSA/00000082/201809

Applicant(s): various

PRAC Lead: Ronan Grimes

Scope: Evaluation of a PSUSA procedure

16.3.3. Asparaginase⁹⁰ (NAP), crisantaspase (NAP), pegaspargase⁹¹ (NAP) - PSUSA/00003161/201808

Applicant(s): various

PRAC Lead: Roxana Stefania Stroe

Scope: Evaluation of a PSUSA procedure

⁸⁹ For oral use only

⁹⁰ Nationally authorised product(s) only

⁹¹ Nationally authorised product(s) only

16.3.4. Dermatophagoides pteronyssinus, dermatophagoides farina^{92 93} (NAP) - PSUSA/00010582/201809

Applicant(s): various

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.3.5. Diclofenac, omeprazole (NAP) - PSUSA/00010461/201809

Applicant(s): various

PRAC Lead: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

16.3.6. Dienogest, estradiol⁹⁴ (NAP) - PSUSA/00010444/201809

Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.3.7. Etonogestrel (NAP) - PSUSA/00001331/201809

Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.3.8. Isotretinoin⁹⁵ (NAP); isotretinoin, erythromycin (NAP) - PSUSA/00010487/201808

Applicant(s): various

PRAC Lead: Tatiana Magalova

Scope: Evaluation of a PSUSA procedure

16.3.9. Meropenem (NAP) - PSUSA/00001989/201808

Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.3.10. Mirtazapine (NAP) - PSUSA/00002068/201808

Applicant(s): various

⁹² Allergen for therapy for oromucosal use only

⁹³ Mutual recognition procedure (MRP) and decentralised procedure (DCP) only

⁹⁴ Contraception indication(s) only

⁹⁵ Topical formulation(s) only

PRAC Lead: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

16.3.11. Sodium oxybate⁹⁶ (NAP) - PSUSA/00010613/201810

Applicant(s): various

PRAC Lead: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.3.12. Zidovudine (NAP) - PSUSA/00003143/201809

Applicant(s): various

PRAC Lead: Jana Lukačičinová

Scope: Evaluation of a PSUSA procedure

16.4. Follow-up to PSUR/PSUSA procedures

16.4.1. Fluticasone furoate - AVAMYS (CAP) - EMEA/H/C/000770/LEG 027

Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Adam Przybylkowski

Scope: Cumulative review of cases of respiratory, thoracic and mediastinal disorders together with a cumulative review of lower respiratory tract infections, as requested in the conclusions of PSUSA/009154/201804 adopted in December 2018

16.4.2. Fluticasone furoate - AVAMYS (CAP) - EMEA/H/C/000770/LEG 028

Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Adam Przybylkowski

Scope: Cumulative review of cases of drug dependence, as requested in the conclusions of PSUSA/009154/201804 adopted in December 2018

16.4.3. Natalizumab - TYSABRI (CAP) - EMEA/H/C/000603/LEG 066.2

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: MAH's response to LEG 066.1 [detailed study report of the retrospective analysis of extended interval dosing (EID) versus standard interval dosing (SID), a proposal for further investigation of efficacy and safety in terms of progressive multifocal leukoencephalopathy (PML) risk reduction with EID relative to SID, and updated pharmacokinetic/pharmacodynamic (PK/PD) modelling taking into account body weight and extended dosing intervals, as requested in the conclusions of PSUSA/00002127/201708 adopted by PRAC in March 2018] as per the request for

⁹⁶ For intravenous use only

17. Annex I – Post-authorisation safety studies (PASS)

Based on the assessment of the following PASS protocol(s), result(s), interim result(s) or feasibility study(ies), and following endorsement of the comments received, the PRAC adopted the conclusion of the Rapporteurs on their assessment for the medicines listed below without further plenary discussion.

17.1. Protocols of PASS imposed in the marketing authorisation(s)⁹⁷

None

17.2. Protocols of PASS non-imposed in the marketing authorisation(s)⁹⁸

17.2.1. Brigatinib - ALUNBRIG (CAP) - EMEA/H/C/004248/MEA 002

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Protocol for study Brigatinib-5007: a cohort study to describe the occurrence of early-onset pulmonary events in patients with anaplastic lymphoma kinase-positive (ALS+) advance non-small cell lung cancer (NSCLC) treated with brigatinib

17.2.2. Brodalumab - KYNTHEUM (CAP) - EMEA/H/C/003959/MEA 002.3

Applicant: LEO Pharma A/S

PRAC Rapporteur: Eva Segovia

Scope: MAH's response to MEA 002.2 [protocol for study NIS-KYNTHEUM-1345: an observational PASS of suicidal behaviour, serious infections, major adverse cardiovascular events (MACE) and malignancy in psoriasis patients treated with brodalumab. The brodalumab assessment of hazards: a multinational safety (BRAHMS) study in electronic healthcare databases [final report expected in Q3 2030]] as per the request for supplementary information (RSI) adopted in December 2018

17.2.3. Emicizumab - HEMLIBRA (CAP) - EMEA/H/C/004406/MEA 001.2

Applicant: Roche Registration GmbH

PRAC Rapporteur: Amelia Cupelli

Scope: MAH's response to MEA 001.1 [protocol for study GO40162: a PASS based on the European Haemophilia Safety Surveillance (EUHASS) registry to characterise the safety profile of patients with haemophilia A exposed to emicizumab under real-world conditions, including an estimate of event rates of the following important risks:

⁹⁷ In accordance with Article 107n of Directive 2001/83/EC

⁹⁸ 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

thromboembolic events, thrombotic microangiopathy, systemic hypersensitivity, anaphylaxis and anaphylactoid events [final clinical study report: (CSR) expected in June 2024] as per the request for supplementary information (RSI) adopted in December 2018

17.2.4. Mexiletine - NAMUSCLA (CAP) - EMEA/H/C/004584/MEA 001

Applicant: Lupin Europe GmbH

PRAC Rapporteur: Eva Jirsová

Scope: Protocol for a registry study to determine the long-term safety and tolerability of Namuscla (mexiletine) for the symptomatic treatment of myotonia in adult patients with non-dystrophic myotonic disorder (from the initial opinion/MA)

17.2.5. Niraparib - ZEJULA (CAP) - EMEA/H/C/004249/MEA 003.2

Applicant: Tesaro Bio Netherlands B.V.

PRAC Rapporteur: Jan Neuhauser

Scope: MAH's response to MEA 003.1 [protocol and statistical analysis plan for a non-interventional non-imposed PASS: a pooled analysis of the incidence of acute myelogenous leukaemia, myelodysplastic syndrome, and other secondary primary malignancies in patients treated with niraparib] as per the request for supplementary information (RSI) adopted in December 2018

17.2.6. Sirolimus - RAPAMUNE (CAP) - EMEA/H/C/000273/MEA 054.1

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Ulla Wändel Liminga

Scope: MAH's response to MEA 054 [protocol for study B1741224: a non-interventional observational PASS to present additional long-term safety and effectiveness data on patients with sporadically lymphangioliomyomatosis (S-LAM) treated with sirolimus], as per the request for supplementary information (RSI) adopted in January 2019

17.2.7. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/MEA 007.3

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: MAH's response to MEA 007.2 [protocol for a non-interventional PASS study A3921298 (listed as a category 3 study in the RMP) evaluating the effectiveness of additional risk minimisation measures (aRMM) for Xeljanz (tofacitinib) in the European Union via a survey of healthcare professionals (HCPs) considered as an additional pharmacovigilance activity in the RMP] as per the request for supplementary information (RSI) adopted in January 2019

17.3. Results of PASS imposed in the marketing authorisation(s)⁹⁹

None

17.4. Results of PASS non-imposed in the marketing authorisation(s)¹⁰⁰

17.4.1. Certolizumab pegol - CIMZIA (CAP) - EMEA/H/C/001037/II/0074/G

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Grouped variations consisting of: 1) submission of the final report from study RA0021 (Anti-Rheumatic Therapies in Sweden (ARTIS) registry) (listed as a category 3 study in the RMP): registry to gather short- and long-term safety data from the use of certolizumab pegol (CZP) in Sweden for rheumatoid arthritis (RA) patients; 2) submission of the final report from study RA005 (NBD registry) (listed as a category 3 study in the RMP): registry to gather safety and outcome data in RA patients receiving CZP and other RA treatments. In addition, the MAH submitted interim results for two ongoing registries studies, namely: study RA0020 - Rheumatoide Arthritis: Beobachtung der Biologika-Therapie (RABBIT): a German long-term observation of biologics/disease-modifying antirheumatic drugs (DMARD) in RA; and study RA0022 - British Society of Rheumatology Biologics Register for Rheumatoid Arthritis (BSRBR): a longitudinal observational study of patients with RA treated with biologic agents, and prospective surveillance study for adverse events

17.4.2. Exenatide - BYDUREON (CAP) - EMEA/H/C/002020/II/0059

Applicant: AstraZeneca AB

PRAC Rapporteur: Annika Folin

Scope: Submission of the final clinical study report (CSR) for study H80-MC-B016: a modified prescription-event monitoring programme (modified PEM) to be conducted in the UK enrolling patients with type 2 diabetes mellitus (T2DM) to quantify the incidence of acute pancreatitis in the first 12 months after initiating treatment with prescription exenatide once weekly. The RMP (version 33) is updated accordingly (fulfilment of post-authorisation measures (PAM) MEA 010.5)

17.4.3. Florbetaben (¹⁸F) - NEURACEQ (CAP) - EMEA/H/C/002553/II/0028

Applicant: Life Radiopharma Berlin GmbH

PRAC Rapporteur: Martin Huber

Scope: Submission of the final report from non-interventional PASS study FBB-01_02_13 (listed as a category 3 study in the RMP): a prospective observational study to assess the effectiveness of the training and risk minimisation measures recommended for the usage of NeuraCeq (florbetaben (¹⁸F)) in the post-authorisation clinical settings. The RMP (version 3.9) is updated accordingly

⁹⁹ In accordance with Article 107p-q of Directive 2001/83/EC

¹⁰⁰ 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

17.4.4. [Idelalisib - ZYDELIG \(CAP\) - EMEA/H/C/003843/II/0046](#)

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Martin Huber

Scope: Submission of the final clinical study report (CSR) for study GS-EU-313-4226 (listed as a category 3 study in the RMP): a cross-sectional PASS to assess healthcare provider awareness of risks associated with Zydelig (idelalisib) in the European Union (EU). The study assesses the effectiveness of additional risk minimisation measures (RMM) by determining the level of knowledge of haematologists and oncologists on the infection risks associated with Zydelig (idelalisib) treatment and the corresponding recommendation to minimise these risks (fulfilment of post-authorisation measures (PAM) MEA 016)

17.4.5. [Indacaterol, glycopyrronium - ULTIBRO BREEZHALER \(CAP\) - EMEA/H/C/002679/WS1543/0029; ULUNAR BREEZHALER \(CAP\) - EMEA/H/C/003875/WS1543/0029; XOTERNA BREEZHALER \(CAP\) - EMEA/H/C/003755/WS1543/0033](#)

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Anette Kirstine Stark

Scope: Submission of the final study report of study CQVA149A2402 (listed as a category 1 study): a multinational database cohort study in Europe in chronic obstructive pulmonary disease (COPD) patients to assess the incidence rates and hazard ratios of various safety outcomes in new users of indacaterol/glycopyrronium compared to new users of comparator drugs (at the drug-class level). The product information is updated to remove the black triangle and reflect the relevant amendments in Annex II.D on 'Conditions or restrictions with regard to the safe and effective use of the medicinal product'. The RMP (version 5.0) is updated accordingly

17.4.6. [Insulin lispro - HUMALOG \(CAP\) - EMEA/H/C/000088/WS1596/0172; LIPROLOG \(CAP\) - EMEA/H/C/000393/WS1596/0133](#)

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Annika Folin

Scope: Submission of the final report from an on-going review of adverse drug events related to Humalog (insulin lispro) (MEA 028) and Liprolog (insulin lispro) (MEA 021) (listed as a category 3 study in the RMP): a post approval safety surveillance programme for lot-specific adverse event review to evaluate any potential change in frequency of hypersensitivity, immunogenicity, and lack of drug effect (LODE) events for insulin lispro synthesized via streamlined lispro drug substance process (sKPB)

17.4.7. [Teriparatide - FORSTEO \(CAP\) - EMEA/H/C/000425/II/0050/G](#)

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Adrien Inoubli

Scope: Grouped variations consisting of the submission of the final study reports of the European Union (EU) components of two PASS; namely study B3DMC-GHBX (2.2) and

study B3D-MC-GHBX (2.3b) both US population-based comparative cohort studies undertaken to evaluate a potential association between teriparatide and adult osteosarcoma. The RMP (version 7.0) is updated accordingly

17.4.8. Vardenafil - LEVITRA (CAP) - EMEA/H/C/000475/WS1536/0064; VIVANZA (CAP) - EMEA/H/C/000488/WS1536/0060

Applicant: Bayer AG

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Submission of the final clinical study report (CSR) for study 12912: (listed as category 3 study in the RMP) a non-interventional PASS to investigate the risk of non-arteritic anterior ischemic optic neuropathy (NAION) associated with phosphodiesterase type 5 (PDE5) inhibitors. The RMP (version 6.0) is updated accordingly

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

17.5.1. Abatacept - ORENCIA (CAP) - EMEA/H/C/000701/MEA 048.7

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Kimmo Jaakkola

Scope: Annual update report on recruitment for study IM101240: an observational registry of abatacept in patients with juvenile idiopathic arthritis (JIA registry) to explore the long-term safety of abatacept treatment for JIA in routine clinical practice by quantifying the incidence rates of serious infections, autoimmune disorders and malignancies [final registry report expected by 2029]

17.5.2. Adalimumab - HUMIRA (CAP) - EMEA/H/C/000481/MEA 065.9

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Tenth interim annual report for study P10-023, a psoriasis patient registry: a 10-year, post-marketing observational study to assess the long term safety of Humira (adalimumab) in adult patients with chronic plaque psoriasis (PS) [final registry report expected in February 2023]

17.5.3. Bazedoxifene - CONBRIZA (CAP) - EMEA/H/C/000913/MEA 012.13

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Martin Huber

Scope: Sixth annual report for PASS B1781044: a cohort study of venous thromboembolism and other clinical endpoints among osteoporotic women prescribed bazedoxifene, bisphosphonates or raloxifene in Europe [final clinical study report (CSR) expected in April 2020]

[17.5.4. Dolutegravir - TIVICAY \(CAP\) - EMEA/H/C/002753/MEA 001.4](#)

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Martin Huber

Scope: Fourth annual interim report for EuroSIDA PASS study 201177 (listed as a category 3 study in the RMP): a prospective observational cohort study in patients receiving dolutegravir to investigate the risk of hypersensitivity reactions (HSR), hepatotoxicity and serious rash (division of acquired immune deficiency syndrome (DAIDS) grading scale category 3 or 4)

[17.5.5. Dolutegravir, abacavir, lamivudine - TRIUMEQ \(CAP\) - EMEA/H/C/002754/MEA 007.4](#)

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Martin Huber

Scope: Fourth annual interim report for EuroSIDA PASS study 201177 (listed as a category 3 study in the RMP): a prospective observational cohort study in patients receiving dolutegravir to investigate the risk of hypersensitivity reactions (HSR), hepatotoxicity and serious rash (division of acquired immune deficiency syndrome (DAIDS) grading scale category 3 or 4)

[17.5.6. Golimumab - SIMPONI \(CAP\) - EMEA/H/C/000992/MEA 007.4](#)

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Fourth annual report for study CNTO148ART4001: a pregnancy research initiative to study the exposure to golimumab during pregnancy in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis: a review and analysis of birth outcomes from the Swedish, Danish, and Finnish medical birth registers; together with the study summary reports for study CNTO148ART4001 and for study CNTO148ART4002: a pregnancy research initiative to study the exposure to golimumab during pregnancy using a US health insurance claims database

[17.5.7. Lesinurad - ZURAMPIC \(CAP\) - EMEA/H/C/003932/ANX 002.2](#)

Applicant: Grunenthal GmbH

PRAC Rapporteur: Eva Segovia

Scope: Annual progress report for an observational PASS of lesinurad patients (SATURATES) to further assess cardiovascular (CV) safety with a focus on major adverse cardiovascular events (MACE) in gout patients treated with Zurampic (lesinurad) in combination with a xanthine oxidase inhibitor (XOI)

[17.5.8. Levofloxacin - QUINSAIR \(CAP\) - EMEA/H/C/002789/ANX 004.3](#)

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Maria del Pilar Rayon

Scope: First interim report for a post-marketing, open-label, observational safety study of Quinsair (nebulised levofloxacin hemihydrate) in patients with cystic fibrosis and chronic *Pseudomonas aeruginosa* infection, using data collected through European cystic fibrosis registries

17.6. Others

17.6.1. Febuxostat - ADENURIC (CAP) - EMEA/H/C/000777/MEA 005.12

Applicant: Menarini International Operations Luxembourg S.A.

PRAC Rapporteur: Jan Neuhauser

Scope: Seventh interim annual report for the FAST study: a prospective, randomised, comparative, open-label phase 4 cardiovascular safety study in patients exposed to febuxostat or allopurinol in the clinical settings [final clinical study report (CSR) expected in Q4 2019]

17.6.2. Indacaterol, glycopyrronium - ULTIBRO BREEZHALER (CAP) - EMEA/H/C/002679/LEG 007

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Anette Kirstine Stark

Scope: MAH's clarification following the temporary halt of study CIDD001D2402: a 24-week randomised, controlled, multicentre, open-label study to evaluate the effect of reminder notifications and motivational/adaptive messaging on treatment adherence of chronic obstructive pulmonary disease (COPD) subjects receiving Ultibro Breezhaler (indacaterol/glycopyrronium) treatment using the concept 2 inhaler for dose administration and tracking

17.6.3. Prucalopride - RESOLOR (CAP) - EMEA/H/C/001012/REC 022

Applicant: Shire Pharmaceuticals Ireland Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Report from the FDA¹⁰¹ on study SPD555-802: a retrospective cohort (observational) study measuring the incidence of major adverse cardiovascular events (MACE; non-fatal acute myocardial infarction, non-fatal stroke, or in-hospital cardiovascular death) in five European data sources, as requested in the conclusions of variation II/42 concluded in September 2018

17.7. New Scientific Advice

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

¹⁰¹ US Food & Drug Administration

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

None

18.2. Conditional renewals of the marketing authorisation

18.2.1. Nalotimagene carmaleucel - ZALMOXIS (CAP) - EMEA/H/C/002801/R/0015 (with RMP)

Applicant: MolMed S.p.A, ATMP¹⁰²

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Conditional renewal of the marketing authorisation

18.3. Renewals of the marketing authorisation

18.3.1. Ataluren - TRANSLARNA (CAP) - EMEA/H/C/002720/R/0051 (with RMP)

Applicant: PTC Therapeutics International Limited

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: 5-year renewal of the marketing authorisation

¹⁰² Advanced therapy medicinal product

18.3.2. [Darunavir, cobicistat - REZOLSTA \(CAP\) - EMEA/H/C/002819/R/0031 \(without RMP\)](#)

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Amelia Cupelli

Scope: 5-year renewal of the marketing authorisation

18.3.3. [Dronedarone - MULTAQ \(CAP\) - EMEA/H/C/001043/R/0042 \(with RMP\)](#)

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Menno van der Elst

Scope: 5-year renewal of the marketing authorisation

18.3.4. [Duloxetine - DULOXETINE LILLY \(CAP\) - EMEA/H/C/004000/R/0015 \(without RMP\)](#)

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Maria del Pilar Rayon

Scope: 5-year renewal of the marketing authorisation

18.3.5. [Flutemetamol \(¹⁸F\) - VIZAMYL \(CAP\) - EMEA/H/C/002557/R/0017 \(without RMP\)](#)

Applicant: GE Healthcare AS

PRAC Rapporteur: Martin Huber

Scope: 5-year renewal of the marketing authorisation

18.3.6. [Insulin glargine - ABASAGLAR \(CAP\) - EMEA/H/C/002835/R/0023 \(without RMP\)](#)

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Amelia Cupelli

Scope: 5-year renewal of the marketing authorisation

18.3.7. [Ledipasvir, sofosbuvir - HARVONI \(CAP\) - EMEA/H/C/003850/R/0080 \(without RMP\)](#)

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: 5-year renewal of the marketing authorisation

18.3.8. [Naloxegol - MOVENTIG \(CAP\) - EMEA/H/C/002810/R/0028 \(without RMP\)](#)

Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Ronan Grimes

Scope: 5-year renewal of the marketing authorisation

18.3.9. Nintedanib - OFEV (CAP) - EMEA/H/C/003821/R/0025 (without RMP)

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: 5-year renewal of the marketing authorisation

18.3.10. Pandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) - ADJUPANRIX (CAP) - EMEA/H/C/001206/R/0062 (with RMP)

Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Menno van der Elst

Scope: 5-year renewal of the marketing authorisation

18.3.11. Ramucirumab - CYRAMZA (CAP) - EMEA/H/C/002829/R/0031 (without RMP)

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: 5-year renewal of the marketing authorisation

18.3.12. Tadalafil - TADALAFIL MYLAN (CAP) - EMEA/H/C/003787/R/0014 (without RMP)

Applicant: Mylan S.A.S

PRAC Rapporteur: Maria del Pilar Rayon

Scope: 5-year renewal of the marketing authorisation

18.3.13. Tilmanocept - LYMPHOSEEK (CAP) - EMEA/H/C/002085/R/0016 (with RMP)

Applicant: Norgine B.V.

PRAC Rapporteur: Rugile Pilviniene

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 13-16 May 2019 meeting.

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Sabine Straus	Chair	The Netherlands	No interests declared	Full involvement
Jan Neuhauser	Member	Austria	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Sonja Hrabcik	Alternate	Austria	No interests declared	Full involvement
Jean-Michel Dogné	Member	Belgium	No interests declared	Full involvement
Laurence de Fays	Alternate - via telephone*	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
Jana Lukacisinova	Alternate	Czech Republic	No interests declared	Full involvement
Anette Kristine Stark	Member	Denmark	No interests declared	Full involvement
Hans Christian Siersted	Alternate	Denmark	No restrictions applicable to this meeting	15.3.15. Mepolizumab - NUCALA (CAP); 15.3.16. Mepolizumab - NUCALA (CAP)
Maia Uusküla	Member	Estonia	No interests declared	Full involvement
Kirsti Villikka	Member	Finland	No interests declared	Full involvement
Kimmo Jaakkola	Alternate	Finland	No interests declared	Full involvement
Ghania Chamouni	Member	France	No restrictions applicable to this meeting	17.5.8. Levofloxacin - QUINSAIR (CAP)
Adrien Inoubli	Alternate	France	No interests declared	Full involvement
Martin Huber	Member (Vice-Chair)	Germany	No interests declared	Full involvement
Brigitte Keller-Stanislawski	Alternate	Germany	No interests declared	Full involvement
Sophia Trantz	Alternate	Greece	No restrictions applicable to this meeting	4.3.2. Clopidogrel – CLOPIDOGREL APOTEX (CAP), CLOPIDOGREL BGR (CAP), CLOPIDOGREL HCS (CAP), CLOPIDOGREL KRKA (CAP), CLOPIDOGREL KRKA D.D. (CAP), CLOPIDOGREL MYLAN (CAP), CLOPIDOGREL RATIOPHARM (CAP),

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				CLOPIDOGREL RATIOPHARM GMBH (CAP), CLOPIDOGREL TAD (CAP), CLOPIDOGREL TEVA (CAP), CLOPIDOGREL ZENTIVA (CAP), GREPID (CAP), ISCOVER (CAP), PLAVIX (CAP), ZYLLT (CAP); NAP; clopidogrel/acetylsalicylic acid – CLOPIDOGREL/ACETYLSALICYLIC ACID ZENTIVA (CAP), DUOPLAVIN (CAP); NAP; Lopinavir, ritonavir – KALETRA (CAP), LOPINAVIR/RITONAVIR MYLAN (CAP), NAP; ritonavir – NORVIR (CAP), RITONAVIR (CAP); NAP
Julia Pallos	Member	Hungary	No interests declared	Full involvement
Guðrún Stefánsdóttir	Member	Iceland	No restrictions applicable to this meeting	5.1.3. Gilteritinib (CAP MAA); 15.3.11. Fidaxomicin - DIFICLIR (CAP); 16.1.24. Micafungin - MYCAMINE (CAP) 11.1.2. Leuprorelin (NAP) 4.1.3. Mesalazine (NAP)
Rhea Fitzgerald	Member	Ireland	No restrictions applicable to this meeting	Full involvement
Amelia Cupelli	Member	Italy	No interests declared	Full involvement
Zane Neikena	Member	Latvia	No interests declared	Full involvement
Rugile Pilviniene	Member	Lithuania	No interests declared	Full involvement
Marcel Bruch	Member	Luxembourg	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
John Joseph Borg	Member	Malta	No interests declared	Full involvement
Menno van der Elst	Member	Netherlands	No interests declared	Full involvement
Liana Gross-Martirosyan	Alternate	Netherlands	No interests declared	Full involvement
David Olsen	Member	Norway	No restrictions applicable to this meeting	4.1.2. Ferric carboxymaltose (NAP); iron (NAP); iron dextran (NAP); iron (III) isomaltoside (NAP); iron sucrose (NAP); sodium ferric gluconate (NAP) 4.2.3. Ibuprofen (NAP), ketoprofen(NAP) and fixed-dose combinations: chlorphenamine, ibuprofen, phenylephrine (NAP); dimenhydrinate, ibuprofen, caffeine (NAP); ibuprofen, ascorbic acid (NAP); ibuprofen, caffeine (NAP); ibuprofen, codeine (NAP); ibuprofen, hydrocodone (NAP); ibuprofen, paracetamol (NAP); ibuprofen, phenylephrine (NAP); ibuprofen, pseudoephedrine (NAP); ketoprofen, omeprazole(NAP), ketoprofen, sucralfate (NAP) 4.3.2. Clopidogrel – CLOPIDOGREL APOTEX (CAP), CLOPIDOGREL BGR (CAP), CLOPIDOGREL HCS (CAP), CLOPIDOGREL KRKA (CAP), CLOPIDOGREL KRKA D.D. (CAP), CLOPIDOGREL

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				MYLAN (CAP), CLOPIDOGREL RATIOPHARM (CAP), CLOPIDOGREL RATIOPHARM GMBH (CAP), CLOPIDOGREL TAD (CAP), CLOPIDOGREL TEVA (CAP), CLOPIDOGREL ZENTIVA (CAP), GREPID (CAP), ISCOVER (CAP), PLAVIX (CAP), ZYLLT (CAP); NAP; clopidogrel/acetylsalicylic acid – CLOPIDOGREL/ACE TYLSALICYLIC ACID ZENTIVA (CAP), DUOPLAVIN (CAP); NAP; Lopinavir, ritonavir – KALETRA (CAP), LOPINAVIR/RITONAVIR MYLAN (CAP), NAP; ritonavir – NORVIR (CAP), RITONAVIR (CAP); NAP
Karen Pernille Harg	Alternate	Norway	No interests declared	Full involvement
Katarzyna Ziolkowska	Alternate	Poland	No interests declared	Full involvement
Ana Diniz Martins	Member	Portugal	No interests declared	Full involvement
Marcia Silva	Alternate	Portugal	No interests declared	Full involvement
Roxana Stefania Stroe	Member	Romania	No interests declared	Full involvement
Michal Radik	Member	Slovakia	No restrictions applicable to this meeting	Full involvement
Jasmina Klopčič	Alternate	Slovenia	No interests declared	Full involvement
Eva Segovia	Member	Spain	No interests declared	Full involvement
Maria del Pilar Rayon	Alternate	Spain	No interests declared	Full involvement
Ulla Wändel Liminga	Member	Sweden	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Annika Folin	Alternate	Sweden	No interests declared	Full involvement
Julie Williams	Member	United Kingdom	No interests declared	Full involvement
Birgitta Grundmark	Member	Independent scientific expert	No interests declared	Full involvement
Daniel Morales	Member	Independent scientific expert	No interests declared	Full involvement
Hedvig Nordeng	Member	Independent scientific expert	No interests declared	Full involvement
Antoine Pariente	Member	Independent scientific expert	No restrictions applicable to this meeting	4.2.3. Ibuprofen (NAP), ketoprofen(NAP) and fixed-dose combinations: chlorphenamine, ibuprofen, phenylephrine (NAP); dimenhydrinate, ibuprofen, caffeine (NAP); ibuprofen, ascorbic acid (NAP); ibuprofen, caffeine (NAP); ibuprofen, codeine (NAP); ibuprofen, hydrocodone (NAP); ibuprofen, paracetamol (NAP); ibuprofen, phenylephrine (NAP); ibuprofen, pseudoephedrine (NAP); ketoprofen, omeprazole(NAP), ketoprofen, sucralfate (NAP)
Livia Puljak	Member	Independent scientific expert	No interests declared	Full involvement
Stefan Weiler	Member	Independent scientific expert	No restrictions applicable to this meeting	11.2.1. Ulipristal acetate
Raymond Anderson	Member	Healthcare Professionals' Representative	No interests declared	Full involvement
Cathalijne van Doorne	Member	Patients' Organisation Representative	No interests declared	Full involvement
Virginie Hivert	Alternate	Patients' Organisation Representative	No restrictions applicable to this meeting	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Els Beghein	Expert - via telephone*	Belgium	No interests declared	Full involvement
Ane Blicher Schelde	Expert - via telephone*	Denmark	No restrictions applicable to this meeting	Full involvement
Martin Zahle Larsen	Expert - in person*	Denmark	No interests declared	Full involvement
Mette Juul Wikkelsø	Expert - in person*	Denmark	No interests declared	Full involvement
Laura Andreoli	Expert - via telephone*	France	No interests declared	Full involvement
Alice Aribaud	Expert - via telephone*	France	No interests declared	Full involvement
Anissa Benlazar	Expert - in person*	France	No restrictions applicable to this meeting	Full involvement
Badis-Lakhdar Bensaad	Expert - via telephone*	France	No interests declared	Full involvement
Benjamin Burrus	Expert - in person*	France	No interests declared	Full involvement
Milou-Daniel Drici	Expert - in person*	France	No restrictions applicable to this meeting	Full involvement
Sylvain Perriot	Expert - in person*	France	No restrictions applicable to this meeting	Full involvement
Marie-Caroline Pesquidous	Expert - via telephone*	France	No restrictions applicable to this meeting	Full involvement
Christine Diesinger	Expert - via telephone*	Germany	No interests declared	Full involvement
Claudia Kayser	Expert - via telephone*	Germany	No interests declared	Full involvement
Nils Lilienthal	Expert - via telephone*	Germany	No interests declared	Full involvement
Kerstin Loeschcke	Expert - via telephone*	Germany	No interests declared	Full involvement
Martin Mengel	Expert - in person*	Germany	No interests declared	Full involvement
Karin Seifert	Expert - in person*	Germany	No restrictions applicable to this meeting	Full involvement
Valerie Strassmann	Expert - in person*	Germany	No interests declared	Full involvement
Niamh Buckley	Expert - via telephone*	Ireland	No interests declared	Full involvement
Grainne Kirwan	Expert - in person*	Ireland	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
Aine McKenna	Expert - via telephone*	Ireland	No restrictions applicable to this meeting	Full involvement
Marianne Klanker	Expert - in person*	Netherlands	No interests declared	Full involvement
Dolores Montero Corominas	Expert - via telephone*	Spain	No interests declared	Full involvement
Charlotte Backman	Expert - in person*	Sweden	No interests declared	Full involvement
Rolf Gedeberg	Expert - via telephone*	Sweden	No interests declared	Full involvement
A representative from the European Commission attended the meeting				
Meeting run with support from relevant EMA staff				

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

20. Annex III - List of acronyms and abbreviations

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

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

21. Explanatory notes

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

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

(Items 2 and 3 of the PRAC minutes)

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

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

Signals assessment and prioritisation

(Item 4 of the PRAC minutes)

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

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

relationship between the medicine and the reported adverse event.

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

Risk Management Plans (RMPs)

(Item 5 of the PRAC minutes)

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

Assessment of Periodic Safety Update Reports (PSURs)

(Item 6 of the PRAC minutes)

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

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

Post-authorisation Safety Studies (PASS)

(Item 7 of the PRAC minutes)

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

Product related pharmacovigilance inspections

(Item 9 of the PRAC minutes)

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

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

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