27 October 2016
EMA/PRAC/123588/2017
Inspections, Human Medicines Pharmacovigilance and Committees Division

Pharmacovigilance Risk Assessment Committee (PRAC)

Minutes of the meeting on 26-29 September 2016

Chair: June Raine – Vice-Chair: Almath Spooner

Health and safety information

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

Disclaimers

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

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

Note on access to documents

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

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1. Introduction

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

The Chairperson opened the 26-29 September 2016 meeting by welcoming all participants.

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

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

The PRAC Chairperson announced that Marina Dimov Di Giusti and Veerle Verlinden were to step down as member for Croatia and alternate for Belgium respectively after the current PRAC plenary meeting. The PRAC thanked them for their contribution to the work of the Committee.

1.2. Adoption of agenda of the meeting of 26-29 September 2016

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

1.3. Adoption of the minutes of the previous meeting of 30 August–2 September 2016

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 30 August-2 September 2016 were published on the EMA website on 15 November 2016 (EMA/PRAC/693633/2016).

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

2.1. Newly triggered procedures

None

2.2. Ongoing procedures

None

2.3. Procedures for finalisation

None

2.4. Planned public hearings

None

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

3.1. Newly triggered procedures

None

3.2. Ongoing procedures

3.2.1. Gadolinium-containing contrast agents (GdCA): gadobenic acid (NAP); gadobutrol (NAP); gadodiamide (NAP); gadopentetic acid (NAP); gadoteric acid (NAP); gadoteridol (NAP); gadoxetic acid (NAP); gadoversetamide – OPTIMARK (CAP) - EMEA/H/A-31/1437

Applicant: Mallinckrodt Deutschland GmbH (Optimark); various

PRAC Rapporteur: Rafe Suvarna; PRAC Co-rapporteur: Doris Stenver

Scope: Review of the benefit-risk balance following notification by the European Commission 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 gadolinium-containing contrast agents (GdCAs) to review the issue of accumulation of gadolinium in the brain, its clinical consequences and the overall safety profile of GdCAs. For further background, see PRAC minutes March 2016, PRAC minutes June 2016 and PRAC minutes

July 2016.

Summary of recommendation(s)/conclusions

- The PRAC discussed the conclusions reached by the ad-hoc expert group meeting held on 5 September 2016. In addition, the PRAC discussed the joint assessment report of the Rapporteurs and adopted a second list of outstanding issues (LoOI), to be addressed by the MAHs in accordance with a revised timetable (EMA/PRAC/195601/2016 Rev.2).

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

Applicant: Eisai Ltd (Panretin, Targretin), various

PRAC Rapporteur: Leonor Chambel; PRAC Co-rapporteur: Julie Williams

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

Background

A referral procedure under Article 31 of Directive 2001/83/EC is ongoing for retinoid-containing medicines (acitretin; adapalene; alitretinoin; bexarotene; isotretinoin; tazarotene; tretinoin) indicated for the treatment of several conditions mainly affecting the skin such as acne, severe chronic hand eczema unresponsive to corticosteroids, severe forms of psoriasis and keratinisation disorders[1] to evaluate measures currently in place for pregnancy prevention and to minimise the possible risk of neuropsychiatric disorders for oral and topical retinoids. For further background, see PRAC minutes July 2016 and PRAC minutes September 2016.

Summary of recommendation(s)/conclusions

- As agreed at the last PRAC plenary meeting[2], the PRAC discussed the option to conduct a public hearing in the context of the Article 31 procedure on retinoids, according to the pre-defined criteria set out in the rules of procedure[3] (EMA/363479/2015). It was agreed by a majority of the Committee that at this stage in the assessment, due to the currently available data and the need to determine the optimal approach to stakeholder engagement, a public hearing would not be appropriate. The PRAC can come back to reconsider this at a later stage of the procedure as needed.

3.3. Procedures for finalisation

None

[1] Tretinoin may also be used to treat promyelocytic leukaemia
[2] September 2016 PRAC meeting held on 30 August-2 September
[3] Rules of procedure on the organisation and conduct of public hearings at the PRAC

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

None

3.5. Others

None

4. Signals assessment and prioritisation[4]

4.1. New signals detected from EU spontaneous reporting systems

See Annex I.14.1.

4.2. New signals detected from other sources

None

4.3. Signals follow-up and prioritisation

4.3.1. Adalimumab – HUMIRA (CAP) - EMEA/H/C/000481/SDA/092

Applicant: AbbVie Ltd.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of acute febrile neutrophilic dermatosis (Sweet's syndrome)

EPITT 18630 – Follow-up to April 2016

Background

For background information, see PRAC minutes April 2016.

The MAH replied to the request for information on the signal of acute febrile neutrophilic dermatosis (Sweet's syndrome) and the responses were assessed by the Rapporteur.

Discussion

The PRAC discussed the MAH's responses and their assessment. Having considered the data from post-marketing reports, clinical trials and the literature provided by the MAH in its cumulative review, the PRAC concluded that there is currently insufficient evidence to establish a causal relationship between adalimumab and acute febrile neutrophilic dermatosis (Sweet' syndrome) to warrant an update of the product information or any additional risk minimisation measure. Therefore, the PRAC agreed that no further action was necessary at this point in time.

[4] 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

Summary of recommendation(s)

- The MAH for Humira (adalimumab) should continue to monitor acute febrile neutrophilic dermatosis (Sweet's syndrome) as part of routine safety surveillance.

4.3.2. Anakinra - KINERET (CAP) - EMEA/H/C/000363/SDA/027; canakinumab - ILARIS (CAP) - EMEA/H/C/001109/SDA/047

Applicant: Swedish Orphan Biovitrum AB (publ) (Kineret), Novartis Europharm Ltd (Ilaris)

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Signal of weight increase

EPITT 18641 – Follow-up to May 2016

Background

For background information, see PRAC minutes May 2016.

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

Discussion

The PRAC discussed the MAH's responses and their assessment. Having considered the available evidence provided by the MAHs including the pre-clinical and clinical data, post-marketing case reports and the review of the literature, the PRAC agreed, that in light of the current knowledge, there is insufficient evidence to conclude that unintended weight increase is associated with anakinra or canakinumab intake. Therefore, the PRAC considered that MAHs should continue to monitor reports of weight increase and related terms as part of routine safety surveillance.

Summary of recommendation(s)

- The MAHs for Kineret (anakinra) and Ilaris (canakinumab) should continue to monitor reports of weight increase and related terms as part of their routine safety surveillance.

4.3.3. Dexlansoprazole (NAP); lansoprazole (NAP)

Applicant: various

PRAC Rapporteur: Kirsti Villikka

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

EPITT 18645 – Follow-up to May 2016

Background

For background information, see PRAC minutes May 2016.

The MAHs replied to the request for information on the signal of unexpected histopathological findings from a juvenile rat toxicity study and the responses were assessed by the Rapporteur.

Discussion

The PRAC discussed the MAHs' responses and their assessment. Taking into account the

evidence submitted by the MAHs, including a review of clinical trials, post-marketing and literature case reports, the PRAC also reviewed the limited extent of paediatric off-label use in the EU as well as the nonclinical safety data with lansoprazole and dexlansoprazole in juvenile and adult animals, focusing on the histopathological findings in the lung, heart, testis and epididymis. The PRAC agreed that the MAHs should submit responses to a further list of questions.

Summary of recommendation(s)

- The MAH for lansoprazole-containing products should submit to EMA, within 60 days, any existing data regarding inhibition of testosterone synthesis for lansoprazole and all relevant metabolites available in nonclinical data.
- The MAHs for lansoprazole- and dexlansoprazole-containing products should submit to EMA, within 60 days, a detailed discussion on effects potentially mediated via interaction with testosterone metabolism, taking into account any published data. In addition to nonclinical data, the MAHs should provide data on testosterone levels before and after exposure in the paediatric and adult populations from available clinical data.
- The MAHs should provide EMA with the results of the additional nonclinical studies currently conducted (results due Q2 2017) together with a proposal for amending the product information as applicable, as part of the signal procedure.

4.3.4. Fluoroquinolones: Ciprofloxacin (NAP); enoxacin (NAP); flumequine (NAP); levofloxacin – QUINSAIR (CAP), NAP; lomefloxacin (NAP); moxifloxacin (NAP); norfloxacin (NAP); ofloxacin (NAP); pefloxacin (NAP); prulifloxacin (NAP); rufloxacin (NAP)

Applicant: Bayer, Sanofi, Raptor Pharmaceuticals Europe BV (Quinsair), various

PRAC Rapporteur: Valerie Strassmann

Scope: Signal of aortic aneurysm and dissection

EPITT 18651 – Follow-up to May 2016

Background

For background information, see PRAC minutes May 2016.

The MAHs replied to the request for information on the signal of aortic aneurysm and dissection and the responses were assessed by the Rapporteur.

Discussion

The PRAC discussed the MAHs' responses and their assessment. Having considered the studies published by *Daneman et al.*[5] and *Lee et al.*[6] together with the responses from the MAHs of systemic fluoroquinolones, the PRAC agreed that at this stage, there is insufficient evidence of an association between systemic fluoroquinolones and aortic aneurysm or dissection that would warrant an update of the product information. Therefore, the PRAC agreed that the MAHs of systemic fluoroquinolones should continue

[5] Daneman N, Hong L and Redeleier D. A. Fluoroquinolones and collagen associated severe adverse events: a longitudinal cohort study. BMJ Open (2015) 5 (11): e010077 doi:10.1136/bmjopen-2015-010077
[6] Lee C, Lee M, Chen Y, et al. Risk of aortic dissection and aortic aneurysm in patients taking oral fluoroquinolone. JAMA Intern Med. 2015;175(11):1839-1847

to monitor aortic aneurysm or dissection as part of routine safety surveillance.

Summary of recommendation(s)

- The MAHs for fluoroquinolone-containing medicinal products for systemic use should continue to monitor aortic aneurysm or dissection as part of routine safety surveillance.

4.3.5. Levetiracetam (oral solution) – KEPPRA (CAP) – EMEA/H/C/000277/SDA/082, NAP

Applicant: UCB Pharma SA, various

PRAC Rapporteur: Veerle Verlinden

Scope: Signal of medication errors associated with accidental overdose

EPITT 10519 – Follow-up to May 2016

Background

For background information, see PRAC minutes May 2016.

The MAH for Keppra (levetiracetam oral solution) replied to the request for information on the signal of medication errors associated with accidental overdose and the responses were assessed by the Rapporteur.

Discussion

The PRAC discussed the MAH's responses and their assessment. Having considered the available evidence, including the additional information submitted by the MAH on the risk of medication errors associated with accidental overdose with levetiracetam oral solution, the PRAC agreed that all MAHs of levetiracetam-containing products oral solution should amend their package leaflet and enhance the differentiation between presentations by modifying the outer packaging and labels. In addition, the PRAC agreed on the dissemination of an agreed direct healthcare professional communication (DHPC) according to an agreed communication plan to inform relevant healthcare professionals on the risk of medication errors with levetiracetam oral solution formulations and to raise awareness on the fact that information on the administration device should be provided each time a new levetiracetam oral solution presentation is prescribed and dispensed. Finally, the MAH for the originator product Keppra (levetiracetam) should closely monitor, in PSURs, cases of medication error associated with accidental overdoses of levetiracetam oral solution formulation.

Summary of recommendation(s)

- The MAHs for levetiracetam-containing products oral solution formulation should submit to EMA and to National Competent Authorities as applicable, within 60 days, a variation to amend the package leaflet[7] and the outer packaging and labels.
- The MAHs should distribute a DHPC according to an agreed communication plan to inform relevant healthcare professionals of the risk of medication errors with levetiracetam oral solution formulations and to raise awareness on the fact that information on the administration device should be provided each time a new

[7] Update of the package leaflet Section 3. Differentiation of presentations should be enhanced using PRAC recommendations for modification of the outer packaging and labels

levetiracetam oral solution presentation is prescribed and dispensed. All concerned MAHs in each Member State are strongly encouraged to collaborate, so that a single DHPC is prepared and circulated in each Member State.

- Finally, the MAH for Keppra (levetiracetam) should closely monitor, in PSURs, cases of medication error associated with accidental overdoses of levetiracetam oral solution formulation. The evaluation of all new cases received following the implementation of the recommended risk minimisation measures, should aim at assessing the effectiveness of the above mentioned measures and whether or not further actions are needed.

For the full PRAC recommendation, see EMA/PRAC/634818/2016 published on 25/10/2016 on the EMA website.

4.3.6. Metronidazole (NAP)

Applicant: various

PRAC Rapporteur: Martin Huber

Scope: Signal of severe hepatic and neurologic toxicity in patients with Cockayne syndrome

EPITT 18663 – Follow-up to May 2016

Background

For background information, see PRAC minutes May 2016.

The MAH replied to the request for information on the signal of severe hepatic and neurologic toxicity in patients with Cockayne syndrome and the responses were assessed by the Rapporteur.

Discussion

The PRAC discussed the MAH's responses and their assessment. Taking into account the available evidence, the PRAC agreed that a temporal relationship between metronidazole administration and hepatotoxicity could not be excluded and that a possible causal association between metronidazole intake and hepatotoxicity in patients with underlying Cockayne syndrome could not be ruled out. In addition, based on the findings by *Wilson et al.*[8], the PRAC acknowledged there is a biological plausibility between metronidazole and hepatotoxicity. Therefore, the PRAC recommended that the MAHs of metronidazole-containing medicinal products (except those for external use on the skin) should submit a variation to amend the product information to include a warning on cases of severe hepatotoxicity/acute hepatic failure, including cases with a fatal outcome with very rapid onset after treatment initiation in patients with Cockayne syndrome that have been reported with metronidazole-containing products for systemic use.

Summary of recommendation(s)

- The MAH for metronidazole-containing medicinal products (except those for external use on the skin) should submit to the National Competent Authorities of the Member

[8] Wilson BT, Strong A, O'Kelly S, Munkley J, Stark Z. Metronidazole toxicity in Cockayne syndrome: a case series. Pediatrics. 2015 Sep;136(3):e706-8. doi:10.1542/peds.2015-0531. PubMed PMID: 26304821.

States, within 60 days, a variation to amend the product information[9]. Communication[10] of the product information update should be agreed on a national basis, as necessary.

- The MAHs of medicinal products containing a substance belonging to the same group of antibiotics as metronidazole, i.e. nitroimidazole should closely monitor hepatotoxicity in the light of the available evidence associated with metronidazole.

For the full PRAC recommendation, see EMA/PRAC/634818/2016 published on 25/10/2016 on the EMA website.

4.3.7. Paracetamol (NAP)

Applicant: various

PRAC Rapporteur: Veerle Verlinden

Scope: Signal of paracetamol use in pregnancy and child neurodevelopment

EPITT 17796 – Follow-up to May 2014

Background

For background information, see PRAC minutes May 2014.

Since the conclusion of the PRAC in May 2014, results of several epidemiological studies investigating the effect of exposure to paracetamol during pregnancy and neurodevelopmental outcomes in childhood have become available.

Discussion

The PRAC considered the evidence from recently published studies by *Liew et al.*[11] [12], *Avella-Garcia et al.*[13], *Stergiakouli et al.*[14], *Thompson et al.*[15] and *Vlenterie et al.*[16], and agreed that further assessment would be needed taking into account the findings and limitations of the studies (e.g. study design, outcome ascertainment, control of confounding).

Summary of recommendation(s)

- The Rapporteur should further assess the newly available data within 90 days, taking into account the findings and limitations of the studies. The current guidance that paracetamol can be used during pregnancy if clinically needed remains valid. Nevertheless, it should be used at the lowest effective dose for the shortest possible time.

[9] Update of SmPC section 4.4. The package leaflet is to be updated accordingly
[10] Communication was sent by EMA to relevant patients' and HCPs' associations on 21 October 2016 and 24 October 2016 respectively
[11] Liew Z et al. Maternal use of acetaminophen during pregnancy and risk of autism spectrum disorders in childhood: a Danish national birth cohort study. Autism Res. 2016;9:951–958
[12] Liew Z et al. Prenatal use of acetaminophen and child intelligence quotient (IQ): A Danish cohort study. Epidemiology. 2016 Nov;27(6):912-918.
[13] Avella-Garcia C. et al. Acetaminophen use in pregnancy and neurodevelopment: attention function and autism spectrum symptoms. Int. J. Epidemiol. 2016 Jun 28. pii: dyw115.
[14] Stergiakouli E., Thapar A., Smith G.D. Association of acetaminophen use during pregnancy with behavioral problems in childhood: evidence against confounding. JAMA Pediatr. 2016 Aug 15. doi:10.1001/jamapediatrics.2016.1775
[15] Thompson JM et al. Associations between acetaminophen use during pregnancy and attention deficit hyperactivity disorder (ADHD) symptoms measured at ages 7 and 11 years. PLoS One. 2014 Sep 24; 9(9): e108210.
[16] Vlenterie R et al. Neurodevelopmental problems at 18 months among children exposed to paracetamol in utero: a propensity score matched cohort study. Int J Epidemiol. 2016, 1–11 doi: 10.1093/ije/dyw192

4.3.8. Propofol (NAP)

Applicant: various

PRAC Rapporteur: Kristin Thorseng Kvande

Scope: Signal of diabetes insipidus

EPITT 18622 – Follow-up to March 2016

Background

For background information, see PRAC minutes March 2016.

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

Discussion

The PRAC discussed the MAH's responses and their assessment. Having considered the cumulative review provided by the MAH, the PRAC has agreed that there is not enough evidence to establish a causal association between propofol and diabetes insipidus as the number of case reports is low in comparison to the number of patients exposed to propofol. In addition, all cases include confounding factors. Therefore, the PRAC agreed that the MAHs of propofol-containing products should continue to monitor diabetes insipidus in PSURs.

Summary of recommendation(s)

- The MAH for propofol-containing products should continue to monitor diabetes insipidus in PSURs as part of routine safety surveillance.

4.3.9. Regorafenib - STIVARGA (CAP) - EMEA/H/C/002573/SDA/008

Applicant: Bayer Pharma AG

PRAC Rapporteur: Sabine Straus

Scope: Signal of angioedema

EPITT 18656 – Follow-up to May 2016

Background

For background information, see PRAC minutes May 2016.

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

Discussion

The PRAC discussed the MAH's responses and their assessment. Having considered the available evidence from the cumulative review provided by the MAH for Stivarga (regorafenib), the PRAC agreed that there is insufficient evidence supporting a direct causal association between regorafenib and angioedema to warrant an amendment of the product information or the RMP. Therefore, the PRAC agreed that the MAH should monitor angioedema as part of its routine safety surveillance.

Summary of recommendation(s)

- The MAH should continue to monitor cases of angioedema as part of routine safety

surveillance.

5. Risk management plans (RMPs)

5.1. Medicines in the pre-authorisation phase

The PRAC provided advice to the CHMP 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. Baricitinib - EMEA/H/C/004085

Scope: Treatment of moderate to severe active rheumatoid arthritis (RA)

5.1.2. Insulin glargine, lixisenatide - EMEA/H/C/004243

Scope: Treatment of adults with type 2 diabetes mellitus

5.1.3. Prasterone - EMEA/H/C/004138

Scope: Treatment of vulvovaginal atrophy

5.1.4. Rituximab - EMEA/H/C/004112

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

5.1.5. Trientine tetrahydrochloride - EMEA/H/C/004005, Orphan

Applicant: GMP-Orphan SA

Scope: Treatment of Wilson’s disease

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. Ranibizumab - LUCENTIS (CAP) - EMEA/H/C/000715/II/0061

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension of indication to include the treatment of visual impairment due to choroidal neovascularization (CNV) based on 6-month data from the pivotal study CRFB002G2301 (MINERVA). As a consequence, SmPC sections 4.1, 4.2, 4.8 and 5.1 are updated. The Package Leaflet and the RMP (version 16.0) are updated accordingly

Background

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

The CHMP is evaluating an extension of the therapeutic indication for Lucentis, a centrally authorised product containing ranibizumab, to include the treatment of visual impairment due to choroidal neovascularisation (CNV) based on 6-month data from the pivotal study CRFB002G2301[17] (MINERVA). 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 May 2016.

Summary of advice

- The RMP version 16.1 for Lucentis (ranibizumab) in the context of the variation under evaluation by the CHMP is considered acceptable provided that a targeted questionnaire to collect information from spontaneous reports associated with use in children is included as part of routine pharmacovigilance activities before finalisation of the variation procedure by the CHMP.
- With regard to the possibility of conducting a drug utilisation study (DUS) to gain further knowledge on the use of ranibizumab in children and adolescents, the PRAC acknowledged the feasibility issues. In addition, the PRAC agreed that there were no additional safety concerns in relation to potential off label use in children and adolescents beyond the identified and potential risks in adults. Moreover, the PRAC noted that the results of the ongoing study in retinopathy in premature infants that could provide valuable safety data in a sensitive population are expected in 2021. Therefore, the PRAC did not further support the conduct of a DUS in children.

[17] A 12-month, randomized, double-masked, sham-controlled, multicentre study to evaluate the efficacy and safety of 0.5mg ranibizumab intravitreal injections in patients with visual impairment due to VEGF-driven choroidal neovascularization

6. Periodic safety update reports (PSURs)

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

See also annex I.16.1.

6.1.1. Albiglutide - EPERZAN (CAP) - PSUSA/00010175/201603

Applicant: GlaxoSmithKline Trading Services

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

Background

Albiglutide is an acting glucagon-like peptide (GLP)-1 agonist indicated for the treatment of type 2 diabetes mellitus in adults to improve glycaemic control as monotherapy and add-on combination therapy under certain conditions.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Eperzan (albiglutide) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add 'decreased appetite' as an undesirable effect with an unknown frequency. In addition, the package leaflet should further describe the types of possible allergic reaction which are rare side effects. Therefore the current terms of the marketing authorisation(s) should be varied[18].
- In the next PSUR, the MAH should provide a cumulative review of diverticulitis and related terms including data from recently completed clinical trials, and a discussion on the possible biological plausibility of an association. In addition, the MAH should provide further details on the review of Meniere's disease including a discussion on possible biological plausibility. Moreover, the MAH should include a high level summary on medication errors unless changes to the type/nature of errors are received with an impact on patient safety that possibly would require re-evaluation of the additional educational materials.

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.

[18] 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. Alemtuzumab - LEMTRADA (CAP) - PSUSA/00010055/201603

Applicant: Genzyme Therapeutics Ltd

PRAC Rapporteur: Torbjorn Callreus

Scope: Evaluation of a PSUSA procedure

Background

Alemtuzumab is a recombinant immunoglobulin (Ig)G1 kappa monoclonal antibody indicated for adult patients with relapsing remitting multiple sclerosis (RRMS) with active disease defined by clinical or imaging features.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Lemtrada (alemtuzumab) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAH should provide detailed figures relating to patients treated in special population groups. In addition, the MAH should provide a detailed review of bradycardia cases.

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

6.1.3. Apremilast - OTEZLA (CAP) - PSUSA/00010338/201603

Applicant: Celgene Europe Limited

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

Background

Apremilast is an inhibitor of phosphodiesterase 4 (PDE4) indicated alone or in combination with disease modifying antirheumatic drugs (DMARDs) for the treatment of active psoriatic arthritis (PsA) and for the treatment of moderate to severe chronic plaque psoriasis in adult patients under certain conditions.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Otezla (apremilast) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add a warning on use in patients with psychiatric disorders to ensure that the risks and benefits of

starting or continuing treatment with apremilast are carefully assessed if patients report previous or existing psychiatric symptoms or if concomitant treatment with other medicinal products likely to cause psychiatric events is intended. It also includes a recommendation to discontinue the treatment if patients suffer from new or worsening psychiatric symptoms, or suicidal ideation or suicidal attempt. In addition, 'depression' and 'suicidal ideation and behaviour' should be added as undesirable effects with a common and uncommon frequency respectively. Therefore the current terms of the marketing authorisation(s) should be varied[19].

- The PRAC agreed the distribution of a direct healthcare professional communication (DHPC) together with a communication plan to inform prescribers on the potential risk of suicidal ideation and behaviour.
- In the next PSUR, the MAH should provide a detailed review of cases of pneumonia and lower tract respiratory infections together with a proposal to update the product information as applicable. In addition, the MAH should include a detailed review of cases related to glucose metabolism disorder (including diabetes mellitus).

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. Betaine anhydrous[20] - CYSTADANE (CAP) - PSUSA/00000390/201602

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

PRAC Rapporteur: Valerie Strassmann

Scope: Evaluation of a PSUSA procedure

Background

Betaine anhydrous belongs to the pharmacotherapeutic group of 'other' alimentary tract and metabolism products and is indicated as an adjunctive treatment of homocystinuria, involving deficiencies or defects in cystathionine beta-synthase (CBS), 5,10-methylene-tetrahydrofolate reductase (MTHFR) and cobalamin cofactor metabolism (cbl).

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Cystadane (betaine anhydrous) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to change the dosing recommendations to adapt the doses to the patient's body weight for all age groups. Therefore the current terms of the marketing authorisation(s) should be varied[21].

[19] 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
[20] Centrally authorised product only
[21] Update of SmPC section 4.2. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

- In addition, the MAH should submit, to EMA within 90 days, a review regarding dosing in patients with remethylation disorders. The MAH should consider the submission of a variation if product information amendments are considered necessary.

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

6.1.5. Bosutinib - BOSULIF (CAP) - PSUSA/00010073/201603

Applicant: Pfizer Limited

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Bosutinib is a Bcr-Abl tyrosine kinase inhibitor (TKI) indicated for adult patients with relapsing remitting multiple sclerosis (RRMS) with active disease defined by clinical or imaging features.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Bosulif (bosutinib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add a warning on 'severe skin reactions' to ensure that bosutinib treatment is discontinued should such a reaction occur as well as a warning on 'tumour lysis syndrome (TLS)' to recommend correction of clinically significant dehydration and treatment of high uric acid levels prior to initiation of bosutinib. In addition, 'Stevens-Johnson syndrome (SJS)' and 'toxic epidermal necrolysis (TEN)' are added as undesirable effects with an unknown frequency as well as 'TLS' with an uncommon frequency. Therefore the current terms of the marketing authorisation(s) should be varied[22].
- In the next PSUR, the MAH should discuss the need to keep 'patients with background infectious diseases' and 'safety in non-white and non-Asian patients' as missing information based on cumulative clinical data, cumulative post-marketing data and literature and should discuss ways to resolve this. In addition, the MAH should discuss whether immunotoxicity and thyroid disorders should be kept as important potential risks in the RMP or removed based on cumulative data, literature, and non-clinical study findings. Moreover, the MAH should provide an analysis on reasons why Japanese patients might be at increased risk for SJS.
- The MAH should revise the RMP to include SJS/TEN as important identified risks as well as reclassify TLS from an important potential risk to an important identified risk at the next regulatory opportunity.

[22] 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.

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. Cabozantinib - COMETRIQ (CAP) - PSUSA/00010180/201603

Applicant: TMC Pharma Services Ltd

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUSA procedure

Background

Cabozantinib is a multiple receptor tyrosine kinase (RTKs) inhibitor indicated for the treatment of adult patients with progressive, unresectable locally advanced or metastatic medullary thyroid carcinoma.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Cometriq (cabozantinib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning on the risk of drug-drug interaction between cabozantinib and warfarin and the need to monitor the international normalized ratio (INR) with use of this combination. Therefore the current terms of the marketing authorisation(s) should be varied[23].

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.

6.1.7. Cinacalcet - MIMPARA (CAP) - PSUSA/00000756/201602

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Background

Cinacalcet is a calcium homeostasis, anti-parathyroid agent indicated for the treatment of secondary hyperparathyroidism (HPT) in patients with end-stage renal disease (ESRD) on maintenance dialysis therapy and for the reduction of hypercalcaemia in patients with parathyroid carcinoma and in patients with primary HPT for whom parathyroidectomy would be indicated on the basis of serum calcium levels (as defined by relevant treatment guidelines), but in whom parathyroidectomy is not clinically appropriate or is contraindicated.

[23] 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

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Mimpara (cinacalcet) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include information regarding the use of CYP2D6[24] substrates together with cinalcalcet, in particular, multiple doses of 50 mg cinacalcet increased the area under the curve (AUC) of 30 mg dextromethorphan (metabolised primarily by CYP2D6) by 11-fold in CYP2D6 extensive metabolisers. Therefore the current terms of the marketing authorisation(s) should be varied[25].
- The MAH should submit to EMA, within 30 days, a detailed safety assessment of all haemorrhagic events for cinacalcet.
- The MAH should submit to EMA, within 60 days, a variation including the final study report for study PARADIGM (study 20090686[26]).
- The MAH should submit to EMA, within 90 days, a detailed review of cases of drug-related hepatic disorders with all serious cases of drug-related hepatic disorders.
- The MAH should remove myocardial ischemia/myocardial infarction as a potential risk from the RMP at the next regulatory opportunity.

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. Dulaglutide - TRULICITY (CAP) - PSUSA/00010311/201603

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure

Background

Dulaglutide is an acting glucagon-like peptide (GLP)-1 agonist indicated for the treatment of adults with type 2 diabetes mellitus to improve glycaemic control as monotherapy and add-on combination therapy, under certain conditions.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of

[24] Cytochrome P450 2D6
[25] 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
[26] A multicentre, randomized, open-label study to compare the efficacy of cinacalcet versus traditional vitamin D therapy for management of secondary hyperparathyroidism among subjects undergoing haemodialysis. NCT01181531. PARADIGM

Trulicity (dulaglutide) in the approved indication(s) remains unchanged.

- Nevertheless, the package leaflet should be updated to include 'whole body allergic reactions (e.g. swelling, raised itchy skin rash (hives))' as an undesirable effect with an uncommon frequency. Therefore the current terms of the marketing authorisation(s) should be varied[27].
- In the next PSUR, the MAH should provide a cumulative review of cases of anaphylactic shock/anaphylactic reactions, discussing the causality between the effect and the treatment; the MAH should propose to amend the product information as applicable.

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

6.1.9. Fingolimod - GILENYA (CAP) - PSUSA/00001393/201602

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Claire Ferard

Scope: Evaluation of a PSUSA procedure

Background

Fingolimod is a sphingosine 1-phosphate receptor modulator indicated for single disease modifying therapy in highly active relapsing remitting multiple sclerosis under certain conditions.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Gilenya (fingolimod) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add 'thrombocytopenia' and 'Kaposi's sarcoma' as undesirable effects with an uncommon and unknown frequency respectively. Therefore the current terms of the marketing authorisation(s) should be varied[28].
- In the next PSUR, the MAH should provide detailed reviews of cases of sudden unexplained death (SUD) and polymorphic ventricular arrhythmia and discuss the potential role of annual cardiological assessment to minimise the risk of cardiac events as a precautionary measure as well as other cardiologic risk minimisation measures. In addition, the MAH should provide further reviews on cases of bradyarrhythmia including AV Block, hypertension and hypertensive crisis, QT interval prolongation, thromboembolic events, leucopenia/lymphopenia, infections, in particular including specific section for opportunistic infections including progressive

[27] Update of package leaflet section 4. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion
[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

multifocal leukoencephalopathy (PML), haemophagocytic syndrome (HPS), acute disseminated encephalomyelitis-like events, pregnancy and reproduction toxicity cases, other cancers (especially lymphoma) with a discussion on a warning on immunosuppressive effect and potential cancer risk especially lymphoma , atypical or unusual relapses especially tumefactive MS relapses and rebound effect, abuse/misuse and medication errors, accidental exposure in children, and reversible cerebral vasoconstriction syndrome (RCVS) and posterior reversible encephalopathy syndrome (PRES). Moreover, the MAH should submit a detailed review of skin cancer other than basal cell carcinoma (BCC), including a discussion of the possible inclusion of other skin cancer as an important identified risk in the RMP. The MAH should propose to amend the product information as applicable.

- The MAH should submit to EMA, within 60 days, a detailed review on the risk of rebound multiple sclerosis (MS). Based on this review, the MAH should consider the need for risk minimisation measures including identification of any risk factors for rebound MS, appropriate monitoring and treatment of patients post-withdrawal, and reconsideration of the recommended washout period based on the biological activity of the drug after withdrawal. The MAH should propose to amend the product information as applicable.

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

6.1.10. Mepolizumab - NUCALA (CAP) - PSUSA/00010456/201603

Applicant: GlaxoSmithKline Trading Services

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

Background

Mepolizumab is an interleukin-5 (IL-5) inhibitor indicated as an add-on treatment for severe refractory eosinophilic asthma in adult patients.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Nucala (mepolizumab) 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 further evaluate cases of pneumonia as cases of special interest, closely monitor and evaluate cases of 'systemic reactions and local injection site reactions', monitor off-label use of mepolizumab in children as cases of special interest, and evaluate fatal cases in mepolizumab treated patients.

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. Plasmodium falciparum and hepatitis b vaccine (recombinant, adjuvanted) - MOSQUIRIX (Art 58[29]) – EMEA/H/W/002300/PSUV/0011

Applicant: GlaxoSmithKline Biologicals S.A.

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

Background

Mosquirix is a plasmodium falciparum and hepatitis B vaccine (recombinant, adjuvanted) indicated for active immunisation of children aged 6 weeks up to 17 months against malaria caused by Plasmodium falciparum and against hepatitis under certain conditions as per the Scientific Opinion (SO) adopted by the CHMP in the context of the cooperation with the World Health Organisation (WHO) for the evaluation of medicinal products intended exclusively for markets outside the European Community in accordance with Article 58 of Regulation (EC) No 726/2004.

Discussion

- Based on the preliminary assessment of the PSUR for Mosquirix (plasmodium falciparum and hepatitis B vaccine (recombinant, adjuvanted)), the PRAC Rapporteur provided an update on progress to the Committee. Further to this preliminary discussion, a PRAC recommendation will be adopted at the November 2016 PRAC meeting (scheduled on 24-27 October 2016).

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

See Annex I.16.2.

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

See also Annex I.16.3.

6.3.1. Alprostadil[30] (NAP) - PSUSA/00000110/201601

Applicant: various

PRAC Lead: Eva Jirsova

Scope: Evaluation of a PSUSA procedure

Background

Alprostadil is a synthetic prostaglandin E1 indicated for the treatment of male erectile dysfunction of neurogenic, vasculogenic, psychogenic or mixed aetiology, as an adjunct to other diagnostic tests and in the management of erectile dysfunction (ED), for administration by intracavernous and intraurethral route of administration. The topical

[29] Article 58 of Regulation (EC) No 726/2004 allows the Agency's 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)
[30] Erectile dysfunction indication

formulation is only indicated for the treatment of ED.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing alprostadil 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 risk-benefit balance of alprostadil-containing medicinal products for intraurethral, intracavernous and topical use in the approved indications remains unchanged.
- The current terms of the marketing authorisations for alprostadil-containing medicinal products for intraurethral and topical use should be maintained.
- Nevertheless, the product information of alprostadil-containing medicinal products for intracavernous use should be updated to add a warning to use with caution in patients with cardiovascular and cerebrovascular risk factors and to add 'myocardial ischaemia and cerebrovascular accident' as an undesirable effect with a unknown frequency. Therefore the current terms of the marketing authorisations of alprostadil-containing medicinal products for intracavernous use should be varied[31].
- In the next PSUR, the MAHs of alprostadil-containing medicinal products for intraurethral use should closely monitor the risk of myocardial ischaemia.

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. Bilastine (NAP) - PSUSA/00003163/201603

Applicant: various

PRAC Lead: Roxana Stefania Stroe

Scope: Evaluation of a PSUSA procedure

Background

Bilastine is a H1-receptor antagonist indicated for the symptomatic treatment of allergic rhino-conjunctivitis and urticaria.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine containing bilastine, 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 risk-benefit balance of bilastine-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to reflect results from a lactation study in rats[32] showing that available pharmacokinetic data in animals have

[31] 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
[32] Excretion of ^{14}C-bilastine in the milk of lactating rats following a single oral administration at 20 mg/kg

demonstrated excretion of bilastine in milk. Therefore the current terms of the marketing authorisation(s) should be varied[33].

- In the next PSUR, the MAHs should provide cumulative reviews of cases of drug ineffectiveness, cases of off-label use and cases in pregnancy and breast-feeding women. In addition, the MAHs should provide a summary of the results and conclusions of studies ICPCT-2011-UA-FF[34], MEIN/14/Bil-ARU/001[35], MRME/Bil-RAU/2015[36], CHOISIRA[37], DMS/12/Len/HU[38], MRME/BIL-150959/015[39], FIRE[40], MEFR/14/BIL-RAL/001[41], BCHU/14/Bil-AII/001 (LENDIN 2)[42] BUCSU (2014-000181-21)[43] with comments on the possible impact on the safety and efficacy profile of bilastine.

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. Carboplatin (NAP) - PSUSA/00000559/201601

Applicant: various

PRAC Lead: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

Background

Carboplatin is an antineoplastic agent indicated in the treatment of advanced ovarian carcinoma of epithelial origin and small cell lung carcinoma.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing carboplatin, 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 risk-benefit balance of carboplatin-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to add warnings on the occurrence of haemolytic anaemia with the presence of serologic drug-induced antibodies that can be fatal, and warnings on the occurrence of acute promyelocytic leukaemia and myelodysplastic syndrome (MDS)/acute myeloid leukaemia (AML)

[33] Update of SmPC sections 4.6 and 5.3. The package leaflet is not updated. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position
[34] Effects of bilastine on nasal blockage after allergen-induced rhinitis in patients with allergic rhinitis (EUDRACT nb: 2011-004830-32)
[35] Effects of bilastine on F1 simulator driving performance in patients affected by allergic rhinitis and/or urticaria (EUDRACT nb: 2015-001313-26)
[36] A survey in rhinitis and urticarial patients
[37] Criteria for choosing an oral second-generation H1-antihistamine treatment in general medicine and impact on overall patient satisfaction with allergic rhinoconjunctivitis
[38] A study of patient reported improvement in quality of life across age groups
[39] A research of physician usage of antihistamine treatments in the paediatric patients with allergic rhinitis or urticaria
[40] An observational study in patients with poorly controlled allergic rhinitis
[41] Observational survey for the assessment of self-medication
[42] Observational study in allergic rhinitis and urticaria patients
[43] Explorative disease activity controlled, dose escalating, study to assess the efficacy, and safety of treatment with bilastine 20 mg, 40 mg and 80 mg in chronic spontaneous urticaria

reported years after therapy with carboplatin and other antineoplastic treatments. In addition, a warning should be added on veno-occlusive disease advising that patients should be monitored for signs and symptoms of abnormal liver function or portal hypertension, together with a warning on the risk of tumour lysis syndrome (TLS) advising that patients at high risk of TLS should be closely monitored and to ensure appropriate precautions are taken. Finally, 'tumour lysis syndrome' should be added as an undesirable effect with an unknown frequency. Therefore the current terms of the marketing authorisation(s) should be varied[44].

- In the next PSUR, the MAHs should monitor all cases of vascular thromboembolic events (VTEs) and discuss the need for any risk minimisation measures. In addition, the MAHs should monitor cases of intestinal perforation, radiation pneumonitis, progressive multifocal leukoencephalopathy (PML), necrositising fasciitis, Kounis syndrome, inappropriate anti-diuretic hormone secretion, peripheral ischaemia, convulsion, severe hepatotoxicity/hepatic failure, delayed onset hypersensitivity, and interstitial lung disease. The possible risk of carboplatin under-dosing using estimated glomerular filtration rate (GFR) rather than measured standard methods in the Calvert formula for dose calculation should be also monitored.

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

6.3.4. Dexamethasone (NAP) - PSUSA/00000973/201601

Applicant: various

PRAC Lead: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

Background

Dexamethasone is a synthetic corticosteroid indicated in various conditions, including inflammatory and autoimmune diseases, allergic and inflammatory conditions of the conjunctiva, cornea and anterior part of the eye as well as seborrheic dermatitis and atopic eczema in children.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of nationally authorised medicine containing dexamethasone, 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 risk-benefit balance of dexamethasone-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information of dexamethasone-containing medicinal products for ocular and cutaneous use should be updated to include a warning on the risk of Cushing's syndrome and/or adrenal suppression after intensive or long-term continuous therapy in predisposed patients and inform of the interaction with

[44] 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

CYP3A4[45] inhibitors which may increase this risk. In case of occurrence, gradual dose tapering is recommended. In addition, Cushing's syndrome and adrenal suppression should be added as undesirable effects with an unknown frequency. Therefore the current terms of the marketing authorisation(s) should be varied[46].

- The product information of dexamethasone-containing medicinal products for oral and parenteral use should be updated to include a warning on the risk of tumour lysis syndrome (TLS) in patients with haematological malignancies. Patient at high risk of TLS should be monitored closely and appropriate precaution taken. In addition, chorioretinopathy should be added as an undesirable effect with an unknown frequency. Therefore the current terms of the marketing authorisation(s) should be varied[47].
- In the next PSUR, the MAHs of dexamethasone-containing medicinal products for oral and parenteral use should provide a cumulative review of cases of cardiomyopathy in children aged less than one year old as well as a cumulative review of cases of interaction between lapatinib and dexamethasone including relevant available literature.

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. Etoposide (NAP) - PSUSA/00001333/201602

Applicant: various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Etoposide is a topoisomerase inhibitor indicated in chemotherapy for the treatment of cancers such as Kaposi's sarcoma, Ewing's sarcoma, lung cancer, testicular cancer, lymphoma, non-lymphocytic leukaemia, and glioblastoma multiform under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of nationally authorised medicine containing etoposide, 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 risk-benefit balance of etoposide-containing medicinal products in the approved indications remains unchanged.

[45] Cytochrome P450 3A4
[46] Update of SmPC sections 4.4, 4.5 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position
[47] 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

- The current terms of the marketing authorisations should be maintained[48].
- In the next PSUR, the MAHs should closely monitor cases of secondary malignancies, leukoencephalopathy/encephalopathy/posterior reversible encephalopathy syndrome (PRES), acute respiratory distress syndrome, thromboembolic events (TEEs), acute renal failure (ARF) in particular in combination with total body irradiation (TBI) as well as the drug-drug interaction between etoposide and morphine. In addition, MAHs should address questions relating to the use of ethanol and benzyl alcohol as excipients with a calculation of the quantities that may be harmful in children receiving etoposide in the indication of 'remission induction in paediatric acute myeloid leukaemia (AML)' (or for any other paediatric use including potential off label use), or in high dose-chemotherapy with > 200 mg/m2 or ≥ 40 mg/kg etoposide per dose. MAHs[49] should provide a rationale for the use of these excipients in etoposide-containing medicinal products, a discussion on potential consequences according to paediatric age groups as well as a discussion on possible risk minimisation measures to put in place taking into account current guidelines on ethanol and benzyl alcohol excipients.

The frequency of PSUR submission should be revised from three-yearly to 18-monthly 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. In addition, the PRAC agreed that no further PSURs are required for products referred to in Articles 10(1), 10a, 14, 16a of Directive 2001/83/EC. The EURD list is updated accordingly.

6.3.6. Gabapentin (NAP) - PSUSA/00001499/201602

Applicant: various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Gabapentin is an antiepileptic indicated for the treatment of partial seizures under certain conditions and for the treatment of peripheral neuropathic pain such as painful diabetic neuropathy and post-herpetic neuralgia in adults.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing gabapentin, 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 risk-benefit balance of gabapentin-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include a warning on anaphylaxis advising to discontinue gabapentin and seek immediate medical help

[48] This recommendation is without prejudice to the final opinions of the ongoing referral procedure under Article 30 of Directive 2001/83/EC for 'Etopophos and associated names 100/1000mg powder for solution for infusion' containing etoposide phosphate, and for 'Vepesid and associated names 50/100mg capsule, soft' containing etoposide
[49] Including MAHs that do not have a paediatric indication in their marketing authorisation(s)

should patients experience signs or symptoms of anaphylaxis. In addition, anaphylaxis and agitation should be added as undesirable effects with an unknown and uncommon frequency respectively. Therefore the current terms of the marketing authorisation(s) should be varied[50].

- In the next PSUR, the MAHs should provide a cumulative review of cases of 'drug ineffective' taking into account the indication for treatment with gabapentin. In addition, MAHs should provide an updated review on anaemia as well as a review of cases of suicidal ideation. MAHs should propose to update the product information as applicable. MAHs with a RMP in place should update this accordingly as applicable at the next regulatory opportunity.

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. Lenalidomide - REVLIMID (CAP) - EMEA/H/C/000717/LEG 047

Applicant: Celgene Europe Limited

PRAC Rapporteur: Claire Ferard

Scope: Submission of a cumulative review of cases of pulmonary hypertension and a review of cases of viral reactivation as requested in the conclusions of PSUSA/00001838/201512 adopted in July 2016

Background

Lenalidomide, an anti-neoplastic, anti-angiogenic and pro-erythropoietic immunomodulator, is indicated for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for a transplant, and indicated in combination for the treatment of multiple myeloma in adult patients who have received at least one prior therapy. In addition, lenalidomide is indicated for the treatment of patients with transfusion-dependent anaemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate. Finally, lenalidomide is indicated for the treatment of adult patients with relapsed and/or refractory mantle cell lymphoma (MCL).

Following the evaluation of the most recently submitted PSURs for the above mentioned medicine(s), the PRAC requested the MAH to submit further data (for background, see PRAC minutes July 2016). The responses were assessed by the Rapporteur for further PRAC advice.

Summary of advice/conclusion(s)

- The PRAC agreed the distribution[51] of a direct healthcare professional communication

[50] 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
[51] Post-meeting note: by 7 November 2016

(DHPC) together with a communication plan to raise awareness on the risk of viral reactivation amongst specialist HCPs involved in prescribing and dispensing lenalidomide.

- The MAH should submit to EMA, shortly after the dissemination of the DHPC, a variation[52][53] to include a warning on the risk of viral reactivation in the product information. The undesirable effect of 'viral infections, including herpes zoster and hepatitis B virus reactivation' should be added accordingly with an unknown frequency.
- In the next PSUR, the MAH should keep under close monitoring the safety issue of pulmonary hypertension (PAH) and lenalidomide.

7. Post-authorisation safety studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)[54]

See Annex I.17.1.

7.2. Protocols of PASS non-imposed in the marketing authorisation(s)[55]

See Annex I.17.2.

7.3. Results of PASS imposed in the marketing authorisation(s)[56]

None

7.4. Results of PASS non-imposed in the marketing authorisation(s)[57]

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.

[52] Post-meeting note: variation was submitted to EMA on 3 November 2016
[53] Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR is transmitted to the CHMP for adoption of an opinion
[54] In accordance with Article 107n of Directive 2001/83/EC
[55] 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
[56] In accordance with Article 107p-q of Directive 2001/83/EC
[57] In accordance with Article 61a (6) of Regulation (EC) No 726/2004, in line with the revised variations regulation for any submission as of 4 August 2013

7.6. Others

7.6.1. Exenatide - BYDUREON (CAP) - EMEA/H/C/002020/MEA 011.5

Applicant: AstraZeneca AB

PRAC Rapporteur: Qun-Ying Yue

Scope: MAH's responses to MEA 011.4 on a feasibility assessment and proposal for an alternative approach to achieve relevant data on incidence of pancreatic cancer and thyroid neoplasm for study B017, an observational study using one or more European databases to investigate the incidence of pancreatic cancer and thyroid neoplasms among type 2 diabetes mellitus patients who initiate therapy with exenatide once weekly as per the request for supplementary information (RSI) adopted in June 2015

Background

Exenatide is a glucagon-like peptide-1 (GLP-1) receptor agonist indicated in combination for the treatment of type 2 diabetes mellitus under certain conditions. Exenatide is also indicated as adjunctive therapy to basal insulin with or without metformin and/or pioglitazone under certain conditions.

As a post-authorisation measure under additional pharmacovigilance activities in the RMP for Bydureon (exenatide), the MAH committed to conduct an epidemiologic study using one or more European databases to identify possible cases of pancreatic cancer and thyroid neoplasms amongst type 2 diabetes mellitus patients who initiate exenatide once weekly (study BO17; category 3). Annual updates of the progress of the study have been submitted. PRAC previously commented on the slow accrual of Bydureon (exenatide) initiators and adopted a request for supplementary information in June 2015. For further background, see and PRAC minutes July 2014 and PRAC minutes June 2015. The MAH submitted to EMA the results from an updated feasibility assessment including a proposal for an alternative approach to achieve relevant data on incidence of pancreatic cancer and thyroid neoplasms in the actual population by sharing the final study report for a similar study[58] conducted in the USA (estimated by end of 2017).

Summary of advice

- Based on the review of the MAH's updated feasibility assessment and its proposal for an alternative approach to study B017 to achieve relevant data on incidence of pancreatic cancer and thyroid neoplasms in the actual population exposed, the PRAC considered it acceptable to wait for the results of the US study. As part of the submission of the US study final results, the MAH should provide a discussion on the feasibility of including other EU databases as well as the possibility for meta-analytical approaches or other methods to provide a pooled estimate from multiple data sources.
- The MAHs should update the RMP of Bydureon (exenatide) at the next regulatory opportunity, to include the US study as a category 3 study in the RMP pharmacovigilance plan, with defined milestones.
- Finally, the PRAC requested EMA to explore the possibility of an analysis of EU

[58] Incidence of Pancreatic Malignancy and Thyroid Neoplasm in Type 2 Diabetes Mellitus Patients who Initiate Exenatide Compared to Other Antihyperglycemic Drugs—Phase 2 (Extended Accrual and Follow-Up)

relevant data on the incidence of pancreatic cancer and thyroid neoplasms after initiation of treatment with exenatide through the European SAFEGUARD project[59] and submission of such an analysis of EU data at the same time as the submission by the MAH of the US study report (i.e. estimated by end of 2017) so that the PRAC could perform an overall assessment of the data related to pancreatic cancer and thyroid neoplasms after initiation of treatment with exenatide.

7.7. New Scientific Advice

None

7.8. Ongoing Scientific Advice

None

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

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

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

8.1. Annual reassessments of the marketing authorisation

See Annex I.18.1.

8.2. Conditional renewals of the marketing authorisation

See Annex I.18.2.

8.3. Renewals of the marketing authorisation

See Annex I.18.3.

9. Product related pharmacovigilance inspections

9.1. List of planned pharmacovigilance inspections

None

[59] SAFEGUARD: safety evaluation of adverse event reactions in diabetes: http://www.safequard-diabetes.org/?q=content/project

9.2. Ongoing or concluded pharmacovigilance inspections

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

9.3. Others

None

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

10.1. Safety related variations of the marketing authorisation

10.1.1. Guanfacine – INTUNIV (CAP) - EMEA/H/C/003759/II/0004

Applicant: Shire Pharmaceuticals Ireland Ltd

PRAC Rapporteur: Dolores Montero Corominas

Scope: PRAC consultation on a variation to update sections 4.2, 4.4 and 4.8 of the SmPC to include a warning and update the safety information as a result of a post-marketing case of hypertensive encephalopathy upon abrupt discontinuation of Intuniv

Background

Guanfacine is a selective alpha$_{2A}$-adrenergic receptor agonist indicated for the treatment of attention deficit hyperactivity disorder (ADHD) in children and adolescents 6-17 years old for whom stimulants are not suitable, not tolerated or have been shown to be ineffective.

A type II variation proposing to update the product information of Intuniv (guanfacine) to include additional warnings and undesirable effects with regard to down titration and abrupt discontinuation/withdrawal of therapy as a result of a post-marketing case of hypertensive encephalopathy upon abrupt discontinuation of Intuniv (guanfacine) is under evaluation at the CHMP. The procedure includes a proposal to disseminate a direct healthcare professionals communication (DHPC) to physicians. The PRAC was requested to provide advice on this variation.

Summary of advice

- Based on the review of the available information, the PRAC advised that the amendment of the educational material is considered a better approach, rather than the dissemination of a DHPC, to increase the awareness on the risks associated with abrupt discontinuation. The key element list of the educational material should be amended to add information on tapering dosing during withdrawal to avoid risks associated with abrupt discontinuation. The PRAC supported the CHMP proposed amendment to the product information to include a warning on tapering the dosing during withdrawal of therapy.

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

None

10.3. Other requests

None

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

11.1. Safety related variations of the marketing authorisation

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

Applicant: Bioprojet Europe Ltd (Hidrasec)

PRAC Lead: Qun-Ying Yue

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

Background

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

In the framework of the recent renewal procedure for Hidrasec (SE/H/1342/01-03/R/02 finalised in May 2016), the Swedish National Competent Authority (MPA) noted that an interaction between racecadotril and angiotensin-converting-enzyme inhibitor (ACE)-inhibitors leading to angioedema had been added to the French guide on interactions published on the French National Competent Authority (ANSM) website in April 2015. The MAH had submitted a variation in France for its nationally approved product for Tiorfan (racecadotril).

In the context of the evaluation of a type II variation procedure (SE/H/1342/01-03/II/44) on Hidrasec (racecadotril) to update the product information to reflect the interaction between racecadotril and ACE inhibitors, Sweden requested PRAC advice on its assessment.

Summary of advice

- Based on the review of the available information, the PRAC considered further data is necessary before drawing a conclusion on the justification for adding a contraindication regarding concomitant use of racecadotril and an ACE-inhibitor to the product information. Therefore, the PRAC agreed that the MAH should be requested to submit to MPA in the framework of variation SE/H/1342/01-03/II/44 further justification and supporting data as part of the request for supplementary information (RSI) of the ongoing variation procedure.

11.2. Other requests

None

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

12.3.1. Scientific Advice Working Party (SAWP) – consultation procedure: criteria and scheme

As agreed at the last PRAC discussion on the proposed approach for PRAC consultation on scientific advice outside the ongoing pilot for non-imposed post-authorisation studies (see PRAC minutes July 2016), the EMA Secretariat presented to PRAC a revised set of criteria to involve PRAC in the scientific advice procedure when pharmacovigilance (e.g. RMP and PASS planning) questions are posed together with a draft 'aide memoire' including details on procedural aspects. Following discussion, the PRAC considered that instead of establishing specific criteria for its involvement in such scientific advice procedures, the consultation should be fully aligned with the PRAC mandate.

12.3.2. Scientific Advice Working Party (SAWP) – pilot phase on involving the PRAC in non-imposed PASS protocols: objectives and impact

As a follow-up to last month's PRAC discussion (see PRAC minutes September 2016), the PRAC further reflected on the completed 12-month-pilot launched to encourage scientific advice on safety studies focusing on protocols for non-imposed post-authorisation safety studies (PASS). The PRAC agreed to end the pilot phase and considered the involvement of the PRAC in Scientific Advice for non-imposed PASS protocols as a routine procedure. Further adjustments to the process will be discussed in due course once more Scientific Advice procedures on PASS protocols involving PRAC have been handled in light of the experience gained. Accordingly, quantitative and qualitative metrics were agreed to be used in order to capture the impact of the process.

12.4. Cooperation within the EU regulatory network

None

12.5. Cooperation with International Regulators

None

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

None

12.7. PRAC work plan

12.7.1. 2017 PRAC work plan – preparation

PRAC lead: June Raine

At the organisational matters teleconference on 13 October 2016, the PRAC chair provided feedback from the last Scientific Co-ordination Board (SciCoBo) meeting held on 22 September 2016 where the topic of Committee work plans was discussed, including a 2016 mid-year report and general highlights for 2017 objectives. The EMA Secretariat presented to PRAC an overview of key themes based on the SciCoBo discussion as well as on activities carried over from 2016 and new activities identified during the year, in order to develop the draft 2017 PRAC work plan. The list of key areas where the PRAC needs to develop its work plan for 2017 was further refined. Follow-up discussion is scheduled in November 2016.

12.8. Planning and reporting

12.8.1. Marketing authorisation applications (MAA) - planned for the remainder of 2016

The EMA Secretariat presented to the PRAC for information a quarterly updated report on marketing authorisation applications planned for submission (business pipeline). For further background, see PRAC minutes July 2016.

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, Margarida Guimarães

The PRAC was updated on the GPAG September meeting, and on the GPAG activities, focussing on harmonising and streamlining the EURD list. The PRAC welcomed the progress being made.

12.10.3. PSURs repository

None

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

The PRAC endorsed the draft revised EURD list version October 2016 reflecting the PRAC comments impacting on the DLP and PSUR submission frequencies of the substances/combinations. The PRAC endorsed the newly allocated Rapporteurs for upcoming PSUSAs in accordance with the principles previously endorsed by the PRAC (see PRAC minutes April 2013).

Post-meeting note: following the PRAC meeting on 26-29 September 2016, the updated EURD list was adopted by the CHMP and CMDh at their October 2016 meetings and published on the EMA website on 19/10/2016, see:

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

12.11. Signal management

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

PRAC lead: Sabine Straus

The PRAC was updated on the outcome of the October 2016 SMART Working Group (SMART WG) work stream WS1. The WS1 discussed aspects relating to PRAC adoption of signal recommendations outside plenary meetings as part of the pilot exercise in line with the criteria developed in the best practice guidance on using PRAC plenary time efficiently (see PRAC minutes May 2016). This includes the steps for agreement of eligible signals between the Rapporteur, EMA and the Committee prior to any PRAC plenary meeting. The WS1 also discussed the internal EMA guidance on improving the

efficiency of the signal validation process regarding terms related to reactions which are already listed. Finally, the WS1 discussed aspects relating to the handling of signals affecting the outer packaging and how to enhance the information in the signal recommendation.

12.12. Adverse drug reactions reporting and additional reporting

12.12.1. Management and reporting of adverse reactions to medicinal products

None

12.12.2. Additional monitoring

None

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

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

Post-meeting note: The updated additional monitoring list was published on 26/10/2016 on the EMA website (see: Home>Human Regulatory>Human medicines>Pharmacovigilance>Signal management>List of medicines under additional monitoring)

12.13. EudraVigilance database

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

Following the last discussion on the EudraVigilance (EV) auditable requirement project (see PRAC minutes June 2016), the EMA secretariat presented an update, including information relating to the external testing plan. To support stakeholders/partners in preparing for the enhanced EV system, a curriculum of online training has been developed and the first set of EudraVigilance-learning modules is already available on the EudraVigilance training page. In November 2016, EMA will deliver further external testing activities to provide EV stakeholders with the opportunity to use the EV system including the EudraVigilance Data Analysis System (EVDAS) and to give feedback. In addition, the EMA Secretariat informed PRAC that NCA will be able to access Article 57[60] reports via EVDAS as of November 2017. Further updates will be given to PRAC in due course.

12.13.2. EudraVigilance Access Policy – update

The EMA Secretariat presented to PRAC the minor revision made to the EudraVigilance access policy (revision 3) further to the identification of two areas for Level 1 public access

[60] As per the provisions of Article 57 of Regulation (EU) 726/2004

through the European database of suspected adverse drug reaction reports (adrreports.eu portal). This led to the introduction of a minor update to the policy to ensure a coherent approach as regards the disclosure of country information. The PRAC adopted the revised access policy. The policy is planned for adoption by the EMA Management Board on 15-16 December 2016 before coming into force.

12.14. Risk management plans and effectiveness of risk minimisations

12.14.1. Good Pharmacovigilance Practice (GVP) Module V on risk management systems – revision 2

At the organisational matters teleconference held on 13 October 2016, the EMA Secretariat presented to PRAC the consolidated revised GVP module V on 'risk management systems' (Rev.2) following analyses of the comments received via the public consultation that ended on 31 May 2016 (see PRAC minutes September 2015) and further reviewed and agreed at a joint PRAC/CMDh drafting workshop on 15 September 2016. The PRAC welcomed this piece of work and endorsed the revised GVP module V. As next steps, the revised GVP module will be sent to CHMP, CAT, CMDh, and the Pharmacovigilance Inspector Working Group (PhV IWG) for endorsement for final PRAC approval end of 2016/early 2017. The final GVP module V on 'risk management systems' (revision 2) is due for publication early 2017. The PRAC noted that the RMP template for industry was currently being aligned with the revised GVP module V revision. The draft final template will be discussed at PRAC following PRAC approval of GVP module V revision 2.

12.14.2. Risk management systems

None

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

None

12.15. Post-authorisation safety studies (PASS)

12.15.1. Post-authorisation Safety Studies – imposed PASS

None

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

None

12.16. Community procedures

12.16.1. Referral procedures for safety reasons

None

12.17. Renewals, conditional renewals, annual reassessments

None

12.18. Risk communication and transparency

12.18.1. Public participation in pharmacovigilance

None

12.18.2. Safety communication

None

12.19. Continuous pharmacovigilance

12.19.1. Incident management

None

12.20. Others

12.20.1. EMA industry platform on the operation of the EU pharmacovigilance legislation – feedback from the ninth meeting on 21 September 2016

The EMA secretariat reported to PRAC on the Ninth Industry Platform meeting on the operation of pharmacovigilance legislation held on 21 September 2016. The industry platform is held on a three-monthly basis. Discussions at the meeting focussed on GVP module VI on adverse drug reaction (ADR) reporting, GVP module IX on signal management, GVP product- or population-specific considerations P.II for Biologics, PRAC public hearings and feedback from the dry-run exercise run in July 2016 as well as on the 'PRAC strategy on measuring the impact of pharmacovigilance activities' adopted on 11 January 2016.

12.20.2. EMA stakeholders forum on the implementation of the pharmacovigilance legislation – feedback from the tenth meeting on 21 September 2016

The EMA secretariat reported to PRAC on the Tenth EMA stakeholder forum meeting on the implementation of pharmacovigilance legislation held on 21 September 2016. The

EMA stakeholder forum is held on a yearly basis. Discussions at the meeting focussed on the achievements and future priorities of the pharmacovigilance legislation, the use of regulatory science to drive better pharmacovigilance as well aspects relating to lifecycle activities of pharmacovigilance for public health.

12.20.3. Good Pharmacovigilance Practice (GVP) - Guideline on product or population specific considerations III: pregnancy and breastfeeding

At the organisational matters teleconference held on 13 October 2016, the EMA secretariat updated the PRAC on the delayed development of the GVP chapter P III: Product- or population-specific considerations: 'pregnancy and breastfeeding' together with a proposal for revised timelines for the deliverables (for further background, see PRAC minutes October 2015). The aim is to consult the PRAC on the draft GVP chapter P. III in Q2/Q3-2017 and to target PRAC adoption for Q3-Q4 2017 followed by the start of a public consultation by the end of 2017. The PRAC noted the new timelines.

12.20.4. Initial marketing authorisation application (MAA) procedures: early background summaries – review of experience

As a follow-up to the discussion in early 2016 on the assessment process for initial marketing authorisations applications (MAAs) (see PRAC minutes February 2016), the EMA secretariat updated the PRAC on the review of experience with 'early background summaries'. EMA secretariat presented the results of a survey conducted amongst CAT/CHMP/PRAC assessors following the pilot that started at the end of 2014. Data collection and analysis were completed based on a total of more than 100 responses for 21 MAA in the scope of the exercise. The review of the experience with the pilot indicates that 'early background summaries' should be continued with certain adaptations. The EMA secretariat proposed to set up a working group composed of EMA and members of CHMP/CAT/PRAC (ideally two members per Committee) to enhance the 'early background summaries' and elaborate further on criteria for prioritising procedures that qualify for 'early background summaries'. A call for volunteers was launched at PRAC.

13. Any other business

None

14. Annex I – Signals assessment and prioritisation[61]

As per agreed criteria under evaluation for new signal(s), the PRAC adopted without further plenary discussion the recommendation of the Rapporteur to request MAH(s) to submit a cumulative review following standard timetables[62].

[61] 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
[62] Either MAH's submission within 60 days followed by a 60 day-timetable assessment or MAH's submission cumulative review within an ongoing or upcoming PSUR/PSUSA procedure (if the DLP is within 90 days), and no disagreement has been raised before the meeting

14.1. New signals detected from EU spontaneous reporting systems

14.1.1. Lenvatinib – LENVIMA (CAP)

Applicant: Eisai Europe Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of cholecystitis

EPITT 18750 – New signal

Lead Member State: SE

14.1.2. Nivolumab – OPDIVO (CAP)

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Signal of pemphigoid

EPITT 18759 – New signal

Lead Member State: DE

14.2. New signals detected from other sources

None

14.3. Signals follow-up and prioritisation

None

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).

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

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

15.2.1. Defibrotide - DEFITELIO (CAP) - EMEA/H/C/002393/II/0019

Applicant: Gentium S.r.l.

PRAC Rapporteur: Julie Williams

Scope: Updated RMP in order to include information regarding additional risk minimisation measures (i.e. healthcare professionals' material highlighting the existence of the registry) as outlined in Annex II. In addition, the MAH took the opportunity to introduce administrative changes to the protocol of the registry study, to add information about the renal pharmacokinetics study, updated information about off-label use during post-marketing experience and to include further administrative changes to the RMP.

15.2.2. Duloxetine - ARICLAIM (CAP) - EMEA/H/C/000552/WS1015/0065; CYMBALTA (CAP) - EMEA/H/C/000572/WS1015/0069; DULOXETINE LILLY (CAP) - EMEA/H/C/004000/WS1015/0005; XERISTAR (CAP) - EMEA/H/C/000573/WS1015/0072; YENTREVE (CAP) - EMEA/H/C/000545/WS1015/0055

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Dolores Montero Corominas

Scope: Updated RMP to add a new observational study to assess maternal and foetal outcomes following exposure to duloxetine (F1J-MC-B057) and to update the plans for the existing pregnancy registry (F1JMC-B034)

15.2.3. Epoetin alfa - ABSEAMED (CAP) - EMEA/H/C/000727/WS1011/0057; BINOCRIT (CAP) - EMEA/H/C/000725/WS1011/0058; EPOETIN ALFA HEXAL (CAP) - EMEA/H/C/000726/WS1011/0056

Applicant: SANDOZ GmbH

PRAC Rapporteur: Claire Ferard

Scope: Updated RMP as per the outcome of the PSUR single assessment procedure (EMEA/H/C/PSUSA/00001237/201508) dated April 2016 in order to change the risk classification for 'hyperkalemia' and 'hypersensitivity reactions (including anaphylactic reactions)' from important potential risks to important identified risks and to review the table of safety concerns accordingly. Furthermore, the MAH took the opportunity to update the RMP to include changes following the variation approval to add the subcutaneous route of administration in nephrology indications (EMEA/H/C/725-727/WS/0877) dated March 2016. In addition, minor RMP changes were introduced

15.2.4. Etanercept - ENBREL (CAP) - EMEA/H/C/000262/II/0199

Applicant: Pfizer Limited

PRAC Rapporteur: Rafe Suvarna

Scope: Updated RMP (version 6.0) in order to remove 'injection site reactions' as an important potential risk and 'use in pregnant women', 'use in hepatic and renal impaired subjects' and 'use in different ethnic origins' as missing information. In addition, the MAH took the opportunity to amend the due dates of several category 3 studies, to align the

RMP with GVP module V on risk management systems (revision 1), to review the list of studies included in the pharmacovigilance plan and to update the clinical trials and post-marketing experience

15.2.5. Imatinib - GLIVEC (CAP) - EMEA/H/C/000406/II/0103

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Eva Segovia

Scope: Updated RMP (version 9.0) in order to add hepatitis B reactivation as a new important identified risk

15.2.6. Nilotinib - TASIGNA (CAP) - EMEA/H/C/000798/II/0083

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Doris Stenver

Scope: Updated RMP (version 15) in order to add hepatitis B reactivation as a new important identified risk

15.2.7. Posaconazole - NOXAFIL (CAP) - EMEA/H/C/000610/II/0040

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Rafe Suvarna

Scope: Updated RMP (version 12.0) in order to reflect the study results showing a lack of interaction effect of OATP1B1 and OATP1B3 substrates and inhibitors

15.2.8. Roflumilast – DALIRESP (CAP) - EMEA/H/C/002398/WS1037; DAXAS (CAP) - EMEA/H/C/001179/WS1037; LIBERTEK (CAP) - EMEA/H/C/002399/WS1037

Applicant: Takeda GmbH

PRAC Rapporteur: Dolores Montero Corominas

Scope: Updated RMP (version 17.0) in order to reflect the modified availability date, from 'Q3 2016' to 'Q2 2017', for the results of study RO-2455-302-RD (FUM 004) entitled 'A multicentre, randomized, double-blind phase 3 study to evaluate tolerability and pharmacokinetics of 500µg roflumilast once daily with an up-titration regimen in Chronic obstructive pulmonary disease (COPD), including an open-label down-titration period evaluating tolerability and pharmacokinetics of 250µg roflumilast once daily in subjects not tolerating 500µg roflumilast once-daily'

15.2.9. Vardenafil - LEVITRA (CAP) - EMEA/H/C/000475/WS0973; VIVANZA (CAP) - EMEA/H/C/000488/WS0973

Applicant: Bayer Pharma AG

PRAC Rapporteur: Dolores Montero Corominas

Scope: Updated RMP to include a safety concern (identified risk) already assessed and

implemented in the Levitra/Vivanza product information (EMEA/H/C/xxxx/WS/0861) on the contraindication relating to the concomitant use of riociguat and phosphodiesterase type 5 (PDE5) inhibitors including vardenafil

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

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

15.3.1. Arsenic trioxide - TRISENOX (CAP) - EMEA/H/C/000388/II/0058

Applicant: Teva B.V.

PRAC Rapporteur: Claire Ferard

Scope: Extension of indication to include the induction of remission, and the consolidation in adult patients with newly diagnosed low-to-intermediate risk acute promyelocytic leukaemia (APL) (white blood cell count, ≤ 10 x 10^3/µl) characterised by the presence of the t(15;17) translocation and/or the presence of the pro-myelocytic leukaemia/retinoic-acid-receptor-alpha (PML/RAR-alpha) gene for Trisenox. As a consequence, sections 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated regarding the posology, efficacy and safety information and warnings. In addition, a RMP is introduced. The Package Leaflet is updated accordingly

15.3.2. Certolizumab pegol - CIMZIA (CAP) - EMEA/H/C/001037/II/0054

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of the final clinical study report (CSR) for study AS001, a phase 3, multicentre, randomized, double-blind, placebo-controlled study to evaluate efficacy and safety of certolizumab pegol in subjects with active axial spondyloarthritis (axSpA). As a consequence, sections 4.8 and 5.1 of the SmPC are revised in order to update the efficacy and safety information (week 204) for study AS001. The RMP (version 11.0) is updated accordingly. The package leaflet remains unchanged

15.3.3. Certolizumab pegol - CIMZIA (CAP) - EMEA/H/C/001037/II/0055

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of the final clinical study report (CSR) for study PsA001, a phase 3, multicentre, randomized, double-blind, parallel group, placebo-controlled study to evaluate the efficacy and safety of certolizumab pegol in subjects with adult onset active and progressive psoriatic arthritis (PsA), in order to provide data on long-term use of Cimzia in psoriatic arthritis subjects up to 216 weeks of treatment. As a consequence, sections 4.8 and 5.1 of the SmPC are revised in order to update the efficacy and safety information (week 216) for study PsA001. The RMP (version 11) is updated accordingly. The package leaflet remains unchanged

15.3.4. Cinacalcet - MIMPARA (CAP) - EMEA/H/C/000570/X/0055/G

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Line extension to introduce a new pharmaceutical form associated with new strengths (1 mg, 2.5 mg and 5 mg hard capsules) grouped with a type II variation to include paediatric use in the approved indication. As a consequence, sections 4.2 and 4.4 of the SmPC are updated to detail the posology in paediatric patients and to update the safety information respectively. The Package Leaflet and Labelling are updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. Furthermore, the product information is brought in line with the latest QRD template (version 10)

15.3.5. Denosumab - PROLIA (CAP) - EMEA/H/C/001120/II/0057

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of section 4.6 of the SmPC in order to delete references to the pregnancy and lactation surveillance programmes. The Package Leaflet and the RMP are updated accordingly. In addition, the MAH took the opportunity to introduce minor editorial updates to the product information

15.3.6. Denosumab - XGEVA (CAP) - EMEA/H/C/002173/II/0045

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension of indication to include the treatment of hypercalcemia of malignancy refractory to intravenous bisphosphonate. As a consequence, sections 4.2, 4.3, 4.8, 5.1 and 5.3 of the SmPC are updated. The Package Leaflet is updated accordingly

15.3.7. Denosumab - XGEVA (CAP) - EMEA/H/C/002173/II/0046

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of section 4.6 of the SmPC in order to delete references to the pregnancy and lactation surveillance programmes. The Package Leaflet and the RMP are updated accordingly. In addition, the MAH took the opportunity to make minor editorial updates to the product information

15.3.8. Dulaglutide - TRULICITY (CAP) - EMEA/H/C/002825/II/0012

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Carmela Macchiarulo

Scope: Update of sections 4.8 and 5.1 of the SmPC in order to update the safety

information to reflect findings from a recently completed phase 3b study (study H9X-MC-GBDG (GBDG)) concerning the use of dulaglutide in combination with sulphonylurea alone. In addition, the MAH took the opportunity to bring the product information in line with the latest QRD template (version 10)

15.3.9. Dulaglutide - TRULICITY (CAP) - EMEA/H/C/002825/II/0013

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Carmela Macchiarulo

Scope: Update of sections 4.2, 4.7, 4.8 and 5.1 of the SmPC for Trulicity following completion of a phase 3b study (study H9X-MCGBDI (GBDI)) to reflect the study's findings concerning the use of dulaglutide in combination with basal insulin. The Package Leaflet is updated accordingly

15.3.10. Eltrombopag - REVOLADE (CAP) - EMEA/H/C/001110/II/0032

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Eva Segovia

Scope: Update of the SmPC section 4.4 and 4.8 to include new information on drug-induced liver injury. As a consequence, Annex II relating to 'key elements to be included in the educational material' is revised. The RMP (version 39) is updated accordingly

15.3.11. Eltrombopag - REVOLADE (CAP) - EMEA/H/C/001110/II/0035/G

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Eva Segovia

Scope: Submission of the clinical study report (CSR) for study TRC112765 exploring the safety of eltrombopag in subjects with solid tumours receiving gemcitabine monotherapy or gemcitabine plus cisplatin or carboplatin. The RMP (version 40) is updated accordingly. In addition, the MAH took the opportunity to revise due dates for submission of final reports for two studies in the pharmacovigilance plan

15.3.12. Eltrombopag - REVOLADE (CAP) - EMEA/H/C/001110/II/0036/G

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Eva Segovia

Scope: Grouped variations to update Annex II of the product information based on the study assessing the 'effectiveness of the eltrombopag educational materials for hepatitis C associated thrombocytopenia'. The RMP (version 41) is updated by removing the PASS study PLATELET (post-authorisation safety study with eltrombopag: multicentre, prospective, observational cohort study of thromocytopenic hepatitis C virus (HCV) patients receiving eltrombopag) and submission of the final report for ENABLE-TEE study WWE116951/CET115A2404: a prospective observational study to understand later outcome patterns among patients with and without a thromboembolic event

15.3.13. Eslicarbazepine acetate - ZEBINIX (CAP) - EMEA/H/C/000988/X/0050/G

Applicant: Bial - Portela & Cª, S.A.

PRAC Rapporteur: Martin Huber

Scope: Grouping of a line extension application to add a new pharmaceutical form (50 mg/ml oral suspension) and a type II variation (new indication) to add the treatment of children aged 2 years and older. Consequently, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 5.3 of the SmPC, the Package Leaflet and the RMP (version 14.0) are updated accordingly

15.3.14. Fingolimod - GILENYA (CAP) - EMEA/H/C/002202/II/0040

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Claire Ferard

Scope: Update of section 4.6 of the SmPC to add information on the use of fingolimod in pregnancy. In addition, section 5.3 of the SmPC is updated to include information about dose correspondence between human and animal species used for the preclinical tests of teratogenicity. The RMP (version 12.0) is updated accordingly. The MAH took the opportunity to introduce minor editorial changes in sections 4.4, 4.5, 4.6 and 5.2 of the SmPC and in Annex II

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

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Dolores Montero Corominas

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

15.3.16. Golimumab - SIMPONI (CAP) - EMEA/H/C/000992/II/0067

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of sections 4.8 and 5.1 of the SmPC in order to update the safety and efficacy information with the data from the final clinical study reports of studies C0524T18 and P07642 in fulfilment of MEA 031 and MEA 032. In addition, the MAH took the opportunity to combine the SmPC for the pre-filled pen and pre-filled syringe for 50 mg strength and for the pre-filled pen and pre-filled syringe for 100 mg strength

respectively, in line with the latest QRD template (version 9.1). The RMP (version 15) is updated accordingly

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

Applicant: ViiV Healthcare UK Limited

PRAC Rapporteur: Qun-Ying Yue

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

15.3.18. Nilotinib - TASIGNA (CAP) - EMEA/H/C/000798/II/0084/G

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Doris Stenver

Scope: Grouped variations to 1) update of the 150 mg SmPC sections 4.1, 4.2, 4.4, 4.8 and 5.1 and Package Leaflet based on the results from study CAMN107I2201 (ENESTFreedom): a Phase II, single-arm study evaluating nilotinib treatment discontinuation (treatment-free remission (TFR)) in newly-diagnosed patients with Philadelphia chromosome-positive chronic myelogenous leukaemia in chronic phase (Ph+ CML-CP) who achieved a sustained deep molecular response; 2) Update of the 150 mg and 200 mg SmPC sections 4.1, 4.2, 4.4, 4.8 and 5.1 and Package Leaflet based on the results from study CAMN107A2408 (ENESTop): a Phase II, single-arm study evaluating nilotinib treatment discontinuation (treatment-free remission (TFR)) in patients with Ph+ CML-CP who achieved a sustained deep molecular response on nilotinib treatment after switching from imatinib treatment; 3) Update of the 200 mg SmPC sections 4.8 and 5.1, based on the results from study CAMN107A2405 (ENESTcmr): a Phase III open-label, randomised study to evaluate nilotinib or imatinib treatment in patients with Ph+ CML-CP who have not achieved a deep molecular response after previous imatinib therapy. The RMP (version 16) is updated accordingly. Furthermore, the MAH took the opportunity to bring the product information in line with the latest QRD template (version 10)

15.3.19. Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/II/0012

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include the monotherapy treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL): - after autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin, or - after at least two prior therapies in patients who are not candidates for ASCT. As a consequence, sections 4.1, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated in order to add the proposed new indication, add a warning that patients with active autoimmune disease and symptomatic

interstitial lung disease were excluded from clinical trials of cHL, and update the safety and pharmacodynamic information. The Package Leaflet and the RMP (version 5.0) are updated accordingly. Furthermore, the product information is brought in line with the latest QRD template (version 10.0)

15.3.20. Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/II/0017

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include the treatment of recurrent or metastatic squamous cell cancer of the head and neck (SCCHN) after platinum-based therapy in adults. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, of the SmPC are updated in order to add the proposed new indication, add a warning that patients with a baseline performance score ≥ 2, untreated brain metastasis, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the SCCHN clinical trial and update the undesirable effects and safety information. The Labelling and RMP (version 6.0) are updated accordingly

15.3.21. Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/II/0018

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of sections 4.2, 4.4 and 4.8 of the SmPC in order to update the safety information for toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), myositis, myocarditis and rhabdomyolysis based on findings from routine pharmacovigilance activities. The Package Leaflet and RMP (version 4.5) are updated accordingly

15.3.22. Ocriplasmin - JETREA (CAP) - EMEA/H/C/002381/II/0026

Applicant: ThromboGenics NV

PRAC Rapporteur: Julie Williams

Scope: Update of sections 4.4, 4.8 and 5.1 of the SmPC to reflect new long-term safety and efficacy data based on the final clinical study report for study TG-MV-014 in fulfilment of MEA 002. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to implement editorial changes in the annexes, to align the annexes with the latest QRD templates (versions 9.1 and 10). The RMP (version 7) is updated accordingly

15.3.23. Pazopanib - VOTRIENT (CAP) - EMEA/H/C/001141/II/0038

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Doris Stenver

Scope: Update of section 4.6 of the SmPC to add male contraception following a review of pazopanib according to the MAH's guideline on prevention of pregnancies. The Package

Leaflet and the RMP (version 16) are updated accordingly. In addition, the MAH took the opportunity to bring the product information in line with the latest QRD template (version 10) and combine the SmPC of the two tablets strengths

15.3.24. Raltegravir - ISENTRESS (CAP) - EMEA/H/C/000860/X/0059

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Julie Williams

Scope: Line extension to add a new strength of 600mg film coated tablets

15.3.25. Ruxolitinib - JAKAVI (CAP) - EMEA/H/C/002464/II/0031

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of sections 4.8 and 5.1 of the SmPC in order to update the efficacy and safety information for melofibrosis following the completion of two 5-year follow up studies: INCB 18424-351 (randomized, double-blind, placebo-controlled study of the ruxolitinib tablets administered orally to subjects with primary myelofibrosis, post-polycythemia vera myelofibrosis or post-essential thrombocythemia myelofibrosis) and INC424A2352 (randomized study of ruxolitinib tablets compared to best available therapy in subjects with primary myelofibrosis, post-polycythemia vera-myelofibrosis or post-essential thrombocythemia myelofibrosis). Annex II is updated accordingly

15.3.26. Sonidegib - ODOMZO (CAP) - EMEA/H/C/002839/II/0005

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Julie Williams

Scope: Update of sections 4.8 and 5.1 of the SmPC and Annex II to implement the results from the pivotal study CLDE225A2201 (phase II, randomized double-blind study of efficacy and safety of two dose levels of LDE225 in patients with locally advanced or metastatic basal cell carcinoma) and related analyses (correlative analysis of Gli1 data and molecular analysis in tumour material). The RMP (version 4.0) is updated accordingly

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

Applicant: Pfizer Limited

PRAC Rapporteur: Martin Huber

Scope: Final results from study 3066K1-4438-WW (B1771007) entitled 'a randomized phase 4 study comparing two intravenous temsirolimus (TEMSR) regimens in subjects with relapsed, refractory mantle cell lymphoma' and fulfilment of obligation to conduct post authorisation measure ANX 027.2. In addition, submission of the toxic effects of interest (e.g. bleeding, infection- and mucositis-related events0 for study 3066K1-4438-WW (post-marketing commitment MEA 028) together with a review discussing potential new safety concerns arising from the results. The RMP (version3.0) is updated accordingly to add myocardial infarction and cardiovascular events in patient with

coexisting cardiovascular conditions as important potential risks, and anaemia, thrombocytopenia, hypercholesterolemia, and hypertriglyceridemia as important identified risks. Furthermore, the MAH took the opportunity to update the list of local representatives in the Package Leaflet

15.3.28. Vandetanib - CAPRELSA (CAP) - EMEA/H/C/002315/II/0016

Applicant: AstraZeneca AB

PRAC Rapporteur: Claire Ferard

Scope: Extension of indication to include the treatment of paediatric population. As a consequence, sections 4.1, 4.2, 4.6, 4.8, 5.1 and 5.2 of the SmPC are amended. The Package Leaflet is 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 procedures including centrally authorised products only

16.1.1. Alirocumab - PRALUENT (CAP) - PSUSA/00010423/201603

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.2. Bedaquiline - SIRTURO (CAP) - PSUSA/00010074/201603

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

16.1.3. Belimumab - BENLYSTA (CAP) - PSUSA/00009075/201603

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.4. Cangrelor - KENGREXAL (CAP) - PSUSA/00010360/201603

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure

16.1.5. Ceftolozane, tazobactam - ZERBAXA (CAP) - PSUSA/00010411/201603

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.6. Cholic acid[63] - KOLBAM (CAP) - PSUSA/00010182/201603

Applicant: Retrophin Europe Ltd

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of a PSUSA procedure

16.1.7. Cholic acid[64] - ORPHACOL (CAP) - PSUSA/00010208/201603

Applicant: Laboratoires CTRS - Boulogne Billancourt

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of a PSUSA procedure

16.1.8. Ciclosporin[65] - IKERVIS (CAP) - PSUSA/00010362/201603

Applicant: Santen Oy

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.9. Collagenase clostridium histolyticum[66] - XIAPEX (CAP) - PSUSA/00000871/201602

Applicant: Swedish Orphan Biovitrum AB (publ)

[63] Treatment of inborn errors in primary bile acid synthesis: cerebrotendinous xanthomatosis (CTX) deficiency, 2- (or α-) methylacyl-CoA racemase (AMACR) deficiency or cholesterol 7α-hydroxylase (CYP7A1) deficiency indications
[64] Treatment of inborn errors in primary bile acid synthesis: oxosteroid-reductase or hydroxy-steroid dehydrogenase deficiency indications
[65] Topical use only
[66] Treatment of Dupuytren's contracture and treatment of Peyronie's disease

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.10. Dabigatran - PRADAXA (CAP) - PSUSA/00000918/201603

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Torbjorn Callreus

Scope: Evaluation of a PSUSA procedure

16.1.11. Dexmedetomidine - DEXDOR (CAP) - PSUSA/00000998/201603

Applicant: Orion Corporation

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.12. Enfuvirtide - FUZEON (CAP) - PSUSA/00001217/201603

Applicant: Roche Registration Limited

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

16.1.13. Ferric citrate coordination complex - FEXERIC (CAP) - PSUSA/00010418/201603

Applicant: Keryx Biopharma UK Ltd.

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.14. Guanfacine - INTUNIV (CAP) - PSUSA/00010413/201603

Applicant: Shire Pharmaceuticals Ireland Ltd.

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

16.1.15. Influenza vaccine (split virion, inactivated)[67] - IDFLU (CAP); INTANZA (CAP) - PSUSA/00001743/201603

Applicant: Sanofi Pasteur MSD SNC

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

[67] Centrally authorised products only

16.1.16. Influenza vaccine (surface antigen, inactivated, prepared in cell cultures) - OPTAFLU (CAP) - PSUSA/00001745/201603

Applicant: Novartis Influenza Vaccines Marburg GmbH

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUSA procedure

16.1.17. Isavuconazole - CRESEMBA (CAP) - PSUSA/00010426/201603

Applicant: Basilea Medical Ltd

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.18. Lapatinib - TYVERB (CAP) - PSUSA/00001829/201603

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.19. Mifamurtide - MEPACT (CAP) - PSUSA/00002059/201603

Applicant: Takeda France SAS

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUSA procedure

16.1.20. Naloxegol - MOVENTIG (CAP) - PSUSA/00010317/201603

Applicant: AstraZeneca AB

PRAC Rapporteur: Almath Spooner

Scope: Evaluation of a PSUSA procedure

16.1.21. Oritavancin - ORBACTIV (CAP) - PSUSA/00010368/201603

Applicant: The Medicines Company UK Ltd

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.22. Ospemifene - SENSHIO (CAP) - PSUSA/00010340/201602

Applicant: Shionogi Limited

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.23. Pembrolizumab - KEYTRUDA (CAP) - PSUSA/00010403/201603

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUSA procedure

16.1.24. Pirfenidone - ESBRIET (CAP) - PSUSA/00002435/201602

Applicant: Roche Registration Limited

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.25. Riociguat - ADEMPAS (CAP) - PSUSA/00010174/201603

Applicant: Bayer Pharma AG

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.26. Sebelipase alpha - KANUMA (CAP) - PSUSA/00010422/201602

Applicant: Alexion Europe SAS

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

16.1.27. Tedizolid phosphate - SIVEXTRO (CAP) - PSUSA/00010369/201603

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

16.1.28. Teduglutide - REVESTIVE (CAP) - PSUSA/00009305/201602

Applicant: Shire Pharmaceuticals Ireland Ltd

PRAC Rapporteur: Torbjorn Callreus

Scope: Evaluation of a PSUSA procedure

16.1.29. Telaprevir - INCIVO[68] - PSUSA/00009306/201603

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Qun-Ying Yue

[68] MA for Incivo expired on 22 September 2016 following the decision of the MAH not to renew it

Scope: Evaluation of a PSUSA procedure

16.1.30. Telavancin - VIBATIV (CAP) - PSUSA/00002879/201603

Applicant: Clinigen Healthcare Ltd

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.31. Tobramycin (nebuliser solution)[69] - VANTOBRA (CAP) - PSUSA/00010370/201603

Applicant: PARI Pharma GmbH

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

16.1.32. Voriconazole - VFEND (CAP) - PSUSA/00003127/201602

Applicant: Pfizer Limited

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUSA procedure

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

16.2.1. Travoprost - IZBA (CAP); TRAVATAN (CAP); NAP - PSUSA/00003011/201602

Applicant: Alcon Laboratories (UK) Ltd (Izba, Travatan), various

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

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

16.3.1. Acetylsalicylic acid (NAP) - PSUSA/00000039/201602

Applicant: various

PRAC Lead: Julia Pallos

Scope: Evaluation of a PSUSA procedure

[69] Centrally authorised product only

16.3.2. Amitriptyline hydrochloride, chlordiazepoxide (NAP) - PSUSA/00000171/201602

Applicant: various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.3.3. Amlodipine, atorvastatin (NAP) - PSUSA/00000177/201601

Applicant: various

PRAC Lead: Claire Ferard

Scope: Evaluation of a PSUSA procedure

16.3.4. Baclofen[70] (NAP) - PSUSA/00000293/201601

Applicant: various

PRAC Lead: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.3.5. Cilostazol (NAP) - PSUSA/00010209/201602

Applicant: various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.3.6. Cytomegalovirus immunoglobulin (NAP) - PSUSA/00000914/201601

Applicant: various

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.3.7. Erdosteine (NAP) - PSUSA/00001248/201602

Applicant: various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

16.3.8. Ethinylestradiol, gestodene[71] (NAP) - PSUSA/00010145/201602

Applicant: various

[70] Intrathecal route of administration only
[71] Transdermal application only

PRAC Lead: Claire Ferard

Scope: Evaluation of a PSUSA procedure

16.3.9. Exametazime, technetium (^{99m}Tc) exametazime (NAP) - PSUSA/00001344/201601

Applicant: various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

16.3.10. Fluocinolone acetonide[72] (NAP) - PSUSA/00010224/201602

Applicant: various

PRAC Lead: Leonor Chambel

Scope: Evaluation of a PSUSA procedure

16.3.11. Glipizide (NAP) - PSUSA/00001535/201601

Applicant: various

PRAC Lead: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

16.3.12. Human coagulation factor VIII[73] (NAP) - PSUSA/00009174/201602

Applicant: various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.3.13. Hydrochlorothiazide; lisinopril (NAP) - PSUSA/00001654/201602

Applicant: various

PRAC Lead: Margarida Guimaraes

Scope: Evaluation of a PSUSA procedure

16.3.14. Hydroxyethyl starch (NAP) - PSUSA/00001694/201603

Applicant: various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

[72] intravitreal implant in applicator
[73] inhibitor bypassing fraction

16.3.15. Interferon gamma (NAP) - PSUSA/00001760/201601

Applicant: various

PRAC Lead: Sabine Straus

Scope: Evaluation of a PSUSA procedure

16.3.16. Levothyroxine (NAP) - PSUSA/00001860/201601

Applicant: various

PRAC Lead: Claire Ferard

Scope: Evaluation of a PSUSA procedure

16.3.17. Lorazepam (NAP) - PSUSA/00001909/201601

Applicant: various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

16.3.18. Olodaterol (NAP) - PSUSA/00010245/201603

Applicant: various

PRAC Lead: Sabine Straus

Scope: Evaluation of a PSUSA procedure

16.3.19. Propafenone (NAP) - PSUSA/00002550/201601

Applicant: various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.4. Follow-up to PSUR procedures

16.4.1. Atazanavir sulfate - REYATAZ (CAP) - EMEA/H/C/000494/LEG 083

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Claire Ferard

Scope: Submission of a comprehensive review of congenital anomalies reported with atazanavir, including a literature review and a discussion of the data gathered from the antiretroviral pregnancy registry (APR), as requested in the conclusions of PSUSA/00000258/201506 adopted by PRAC and CHMP in February 2016

16.4.2. Memantine - AXURA (CAP) - EMEA/H/C/000378/LEG 041

Applicant: Merz Pharmaceuticals GmbH

PRAC Rapporteur: Dolores Montero Corominas

Scope: Submission of a cumulative review of cases of hyponatremia/syndrome of inappropriate antidiuretic hormone (SIADH) as requested in the conclusions of PSUSA/H/00001967/201509 adopted in April 2016

16.4.3. Memantine - EBIXA (CAP) - EMEA/H/C/000463/LEG 041

Applicant: H. Lundbeck A/S

PRAC Rapporteur: Dolores Montero Corominas

Scope: Submission of a cumulative review of cases of hyponatremia/syndrome of inappropriate antidiuretic hormone (SIADH) as requested in the conclusions of PSUSA/H/00001967/201509 adopted in April 2016

16.4.4. Memantine - MEMANTINE MERZ (CAP) - EMEA/H/C/002711/LEG 005

Applicant: Merz Pharmaceuticals GmbH

PRAC Rapporteur: Dolores Montero Corominas

Scope: Submission of a cumulative review of cases of hyponatremia/syndrome of inappropriate antidiuretic hormone (SIADH) as requested in the conclusions of PSUSA/H/00001967/201509 adopted in April 2016

16.4.5. Tadalafil - ADCIRCA (CAP) - EMEA/H/C/001021/LEG 020

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Dolores Montero Corominas

Scope: Submission of a cumulative analysis of cases of sudden hearing loss as requested in the conclusions of PSUSA/H/00002841/201510 adopted in May 2016

16.4.6. Tadalafil - CIALIS (CAP) - EMEA/H/C/000436/LEG 046

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Dolores Montero Corominas

Scope: Submission of a cumulative analysis of cases of sudden hearing loss as requested in the conclusions of PSUSA/H/00002841/201510 adopted in May 2016

16.4.7. Trastuzumab - HERCEPTIN (CAP) - EMEA/H/C/000278/LEG 098

Applicant: Roche Registration Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Submission of a proposal for a DHPC to treating oncologists and/or oncologists to

ensure awareness of the need to follow the current guidance on cardiac monitoring during and after completion of treatment with Herceptin and to highlight the need for cardiac monitoring during handover of patient management to other physicians as requested in the conclusions of EMEA/H/C/PSUSA/00003010/201509 adopted in April 2016

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)[74]

17.1.1. Autologous CD34^{+} enriched cell fraction that contains CD34+ cells transduced with retroviral vector that encodes for the human ADA cDNA sequence - STRIMVELIS (CAP) - EMEA/H/C/003854/PSP/004

Applicant: GlaxoSmithKline Trading Services, ATMP[75]

PRAC Rapporteur: Sabine Straus

Scope: PASS protocol for study GSK2696273 entitled 'adenosine deaminase severe combined immunodeficiency (ADA-SCID) registry for patients treated with Strimvelis gene therapy: long-term prospective, non-interventional follow-up of safety and effectiveness'

17.1.2. Levonorgestrel (NAP) - EMEA/H/N/PSA/j/0006.1

Applicant: Bayer Pharma AG

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Revised PASS protocol for study EURAS-LCS12: a European active surveillance study of LCS-12, an intra-uterine device (IUD) for Jaydess and Luadei (levonorgestrel) to assess among new users the risks of certain events associated with the use of LCS-12 compared to established IUDs or IUSs (intra-uterine system) during standard clinical practice and to describe drug utilisation patterns as per the request for supplementary information adopted in May 2016

[74] In accordance with Article 107n of Directive 2001/83/EC
[75] Advanced Therapy Medicinal Product

17.2. Protocols of PASS non-imposed in the marketing authorisation(s)[76]

17.2.1. Fenofibrate, simvastatin - CHOLIB (CAP) - EMEA/H/C/002559/MEA 002.4

Applicant: BGP Products Ltd

PRAC Rapporteur: Julie Williams

Scope: MAH's responses to MEA 002.2: Second status report for study ABT285.E.001: a drug utilisation research (DUR) study on the use of fenofibrate and simvastatin fixed combination: a European multinational study using secondary health records databases, as per the request for supplementary information (RSI) adopted in February 2016

17.2.2. Florbetaben (^{18}F) - NEURACEQ (CAP) - EMEA/H/C/002553/MEA 001.4

Applicant: Piramal Imaging Limited

PRAC Rapporteur: Julie Williams

Scope: MAH's responses to MEA. 001.3: revised PASS protocol for study FBB-01_03_13 (PASS2): a non-interventional prospective observational multicentre, multinational registry to observe usage pattern, safety and tolerability of the diagnostic agent NeuraCeq in clinical practice as per the request for supplementary information (RSI) adopted in September 2015

17.2.3. Follitropin alfa - OVALEAP (CAP) - EMEA/H/C/002608/MEA 002.2

Applicant: Teva B.V.

PRAC Rapporteur: Menno van der Elst

Scope: MAH's responses to MEA. 002.2: revised PASS protocol XM17-WH-50005: SOFIA - safety of Ovaleap in infertile women undergoing superovulation for assisted reproductive technologies. A multinational, comparative, prospective, non-interventional, observational cohort study as per the request for supplementary information (RSI) adopted in February 2015

17.2.4. Naltrexone, bupropion - MYSIMBA (CAP) - EMEA/H/C/003687/MEA 003.1

Applicant: Orexigen Therapeutics Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: Revised PASS protocol for a drug utilisation study (DUS): a retrospective chart review and nested naltrexone/bupropion (NB) prescribing physician cross sectional survey to include a multicentre research programme of observational studies to monitor safety and drug utilisation and the MAH's response to the request for supplementary of information (RSI) as adopted in November 2015

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

17.2.5. Naltrexone, bupropion - MYSIMBA (CAP) - EMEA/H/C/003687/MEA 004.1

Applicant: Orexigen Therapeutics Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: Submission of a revised PASS protocol for the naltrexone/bupropion observational database study to include a multicentre research programme of observational studies to monitor safety and drug utilisation with the MAH's response to MEA 003 on naltrexone/bupropion (NB) drug utilisation study (DUS): a retrospective chart review and nested NB prescribing physician cross sectional survey as adopted in November 2015

17.2.6. Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/MEA 008.2

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: MAH's responses to MEA 008 on a protocol for study CA209234: a non-interventional category 3 PASS: pattern of use, safety, and effectiveness of nivolumab in routine oncology practice as per the request for supplementary information (RSI) adopted in March 2016

17.2.7. Selexipag - UPTRAVI (CAP) - EMEA/H/C/003774/MEA 001

Applicant: Actelion Registration Ltd.

PRAC Rapporteur: Rafe Suvarna

Scope: Submission of a protocol for a non-interventional non-imposed PASS: observational cohort study of pulmonary arterial hypertension (PAH) patients exposed and unexposed to selexipag in routine clinical practice

17.3. Results of PASS imposed in the marketing authorisation(s)[77]

None

17.4. Results of PASS non-imposed in the marketing authorisation(s)[78]

17.4.1. Apixaban - ELIQUIS (CAP) - EMEA/H/C/002148/II/0040

Applicant: Bristol-Myers Squibb / Pfizer EEIG

PRAC Rapporteur: Menno van der Elst

Scope: Submission of the final study report of the AEGEAN study (CV185-220) assessing the education and guidance programme for Eliquis (apixaban) adherence in non-valvular atrial fibrillation patients. The RMP is updated accordingly

[77] In accordance with Article 107p-q of Directive 2001/83/EC
[78] In accordance with Article 61a (6) of Regulation (EC) No 726/2004, in line with the revised variations regulation for any submission as of 4 August 2013

17.4.2. Bivalirudin - ANGIOX (CAP) - EMEA/H/C/000562/II/0068

Applicant: The Medicines Company UK Ltd.

PRAC Rapporteur: Julie Williams

Scope: Submission of the final results of the drug utilisation study Eurovision 2. The RMP is amended to refine the additional risk minimisation measures in line with the findings of the study

17.4.3. Fentanyl - INSTANYL (CAP) - EMEA/H/C/000959/II/0040

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Claire Ferard

Scope: Submission of the results for PASS study Instanyl-5001: an evaluation of the effectiveness of risk minimisation measures: a survey among health care professionals to assess their knowledge and attitudes on prescribing conditions of Instanyl in France and the Netherlands included in the RMP

17.4.4. Pioglitazone - ACTOS (CAP) - EMEA/H/C/000285/WS0990/0074; GLUSTIN (CAP) - EMEA/H/C/000286/WS0990/0072 pioglitazone, glimepiride - TANDEMACT (CAP) -EMEA/H/C/000680/WS0990/0050; pioglitazone, metformin - COMPETACT (CAP) - EMEA/H/C/000655/WS0990/0061; GLUBRAVA (CAP) - EMEA/H/C/000893/WS0990/0046

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Almath Spooner

Scope: Submission of the final drug utilisation study report (Pioglitazone_5019) conducted in Denmark designed to assess the utilisation of pioglitazone in Denmark after July 2011 when labelling changes were introduced following the conclusion of an Article 20 procedure

17.4.5. Pioglitazone - ACTOS (CAP) - EMEA/H/C/000285/WS0991/0075; GLUSTIN (CAP) - EMEA/H/C/000286/WS0991/0073 pioglitazone, glimepiride - TANDEMACT (CAP) - EMEA/H/C/000680/WS0991/0051 pioglitazone, metformin - COMPETACT (CAP) - EMEA/H/C/000655/WS0991/0062; GLUBRAVA (CAP) - EMEA/H/C/000893/WS0991/0047

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Almath Spooner

Scope: Submission of the final study report for the Clinical Practice Research Datalink (CPRD) GOLD linkage study (Pioglitazone_5018) conducted to investigate a possible association of the use of pioglitazone with prostate cancer and data on the incidence of adjudicated prostate cancer in patients receiving pioglitazone in the long-term insulin resistance intervention after stroke (IRIS) trial

17.5. Interim results of imposed and non-imposed PASS submitted before the entry into force of the revised variation regulation[79]

17.5.1. Filgrastim - FILGRASTIM HEXAL (CAP) - EMEA/H/C/000918/MEA 006.1

Applicant: Hexal AG

PRAC Rapporteur: Julie Williams

Scope: Fifth annual interim safety report for study EP006-401: safety follow-up of severe chronic neutropenia (SCN) patients included in phase IV study: safety data will be collected via cooperation with the Severe Chronic Neutropenia International Registry and reported annually

17.5.2. Filgrastim - ZARZIO (CAP) - EMEA/H/C/000917/MEA 006.1

Applicant: Hexal AG

PRAC Rapporteur: Julie Williams

Scope: Fifth annual interim safety report for study EP006-401: safety follow-up of severe chronic neutropenia (SCN) patients included in phase IV study: safety data will be collected via cooperation with the Severe Chronic Neutropenia International Registry and reported annually

17.5.3. Filgrastim - ZARZIO (CAP) - EMEA/H/C/000917/MEA 007.2

Applicant: Hexal AG

PRAC Rapporteur: Julie Williams

Scope: Fifth annual interim report for study EP06-501 after four years of treatment: a non-interventional, prospective, long-term observational study to assess the safety and effectiveness of Zarzio/Filgrastim Hexal administered to healthy unrelated stem cell donors for peripheral blood progenitor cell mobilisation

17.5.4. Filgrastim - ZARZIO (CAP) - EMEA/H/C/000917/MEA 007.2

Applicant: Hexal AG

PRAC Rapporteur: Julie Williams

Scope: Fifth annual interim report for study EP06-501 after four years of treatment: a non-interventional, prospective, long-term observational study to assess the safety and effectiveness of Zarzio/Filgrastim Hexal administered to healthy unrelated stem cell donors for peripheral blood progenitor cell mobilisation

17.5.5. Golimumab - SIMPONI (CAP) - EMEA/H/C/000992/MEA 026.2

Applicant: Janssen Biologics B.V.

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

PRAC Rapporteur: Ulla Wändel Liminga

Scope: First progress report for study MRK-2859: ulcerative colitis (UC) Nordic registry: a non-interventional observational longitudinal PASS of Simponi in the treatment of UC using Nordic national health registries

17.5.6. Infliximab - INFLECTRA (CAP) - EMEA/H/C/002778/MEA 008.3

Applicant: Hospira UK Limited

PRAC Rapporteur: Rafe Suvarna

Scope: Annual report for the post marketing surveillance of Inflectra/Remsima 100 mg to evaluate safety and efficacy in Korea

17.5.7. Infliximab - REMSIMA (CAP) - EMEA/H/C/002576/MEA 008.3

Applicant: Celltrion Healthcare Hungary Kft.

PRAC Rapporteur: Rafe Suvarna

Scope: Annual report for the post marketing surveillance of Inflectra/Remsima 100 mg to evaluate safety and efficacy in Korea

17.5.8. Influenza vaccine (surface antigen, inactivated, prepared in cell cultures) - OPTAFLU (CAP) - EMEA/H/C/000758/MEA 041.5

Applicant: Novartis Influenza Vaccines Marburg GmbH

PRAC Rapporteur: Menno van der Elst

Scope: PASS interim results for study V58_30OB: an observational study to investigate the safety of Optaflu vaccination in adults in routine clinical care in the UK using the Health Improvement Network (THIN) database

17.5.9. Nomegestrol, estradiol - ZOELY (CAP) - EMEA/H/C/001213/ANX 011.2

Applicant: Teva B.V.

PRAC Rapporteur: Claire Ferard

Scope: PASS interim results for a prospective observational study (ZEG2013_08) to assess the risk of venous thromboembolic events (VTE) and arterial thromboembolic events (ATE) in nomegestrel/estradiol users compared with the VTE risk in users of combined oral contraceptives containing levonorgestrel (as imposed in accordance with Article 10(a) of Regulation (EC) No 726/2004)

17.5.10. Tenofovir disoproxil - VIREAD (CAP) - EMEA/H/C/000419/MEA 265.6

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Claire Ferard

Scope: Interim results for study GS-EU-174-1403, a pharmacoepidemiology study to

define the long-term safety profile of tenofovir disoproxil fumarate and describe the management of tenofovir-associated renal and bone toxicity in chronic Hepatitis B-infected adolescents aged 12 to <18 years in Europe

17.5.11. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/MEA 022.11

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Julie Williams

Scope: Annual report for study PSOLAR (PSOriasis Longitudinal Assessment and Registry), an international prospective cohort study/registry programme designed to collect data on psoriasis (PSO) patients that are eligible to receive systemic therapies, including generalised phototherapy and biologics

17.6. New Scientific Advice

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

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

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

18.1. Annual reassessments of the marketing authorisation

18.1.1. Clofarabine - EVOLTRA (CAP) - EMEA/H/C/000613/S/0050 (without RMP)

Applicant: Genzyme Europe BV

PRAC Rapporteur: Claire Ferard

Scope: Annual reassessment of the marketing authorisation

18.2. Conditional renewals of the marketing authorisation

18.2.1. Osimertinib - TAGRISSO (CAP) - EMEA/H/C/004124/R/0007 (without RMP)

Applicant: AstraZeneca AB

PRAC Rapporteur: Sabine Straus

Scope: Conditional renewal of the marketing authorisation

18.2.2. Ex vivo expanded autologous human corneal epithelial cells containing stem cells - HOLOCLAR (CAP) - EMEA/H/C/002450/R/0008 (with RMP)

Applicant: Chiesi Farmaceutici S.p.A., ATMP[80]

PRAC Rapporteur: Julie Williams

Scope: Conditional renewal of the marketing authorisation

18.3. Renewals of the marketing authorisation

18.3.1. Capecitabine - ECANSYA (CAP) - EMEA/H/C/002605/R/0018 (without RMP)

Applicant: Krka, d.d., Novo mesto

PRAC Rapporteur: Martin Huber

Scope: 5-year renewal of the marketing authorisation

18.3.2. Pioglitazone - PIOGLITAZONE TEVA (CAP) - EMEA/H/C/002297/R/0016 (without RMP)

Applicant: Teva B.V.

PRAC Rapporteur: Almath Spooner

Scope: 5-year renewal of the marketing authorisation

18.3.3. Pioglitazone - PIOGLITAZONE TEVA PHARMA (CAP) - EMEA/H/C/002410/R/0013 (without RMP)

Applicant: Teva B.V.

PRAC Rapporteur: Almath Spooner

Scope: 5-year renewal of the marketing authorisation

18.3.4. Pioglitazone hydrochloride - PIOGLITAZONE ACCORD (CAP) - EMEA/H/C/002277/R/0011 (without RMP)

Applicant: Accord Healthcare Ltd

PRAC Rapporteur: Almath Spooner

Scope: 5-year renewal of the marketing authorisation

18.3.5. Telbivudine - SEBIVO (CAP) - EMEA/H/C/000713/R/0045 (without RMP)

Applicant: Novartis Europharm Ltd

[80] Advanced Therapy Medicinal Product

PRAC Rapporteur: Claire Ferard

Scope: 5-year renewal of the marketing authorisation

18.3.6. Zoledronic acid - ZOLEDRONIC ACID ACTAVIS (CAP) - EMEA/H/C/002488/R/0017 (without RMP)

Applicant: Actavis Group PTC ehf

PRAC Rapporteur: Doris Stenver

Scope: 5-year renewal of the marketing authorisation

19. Annex II – List of participants

including any restrictions with respect to involvement of members / alternates / experts following evaluation of declared interests for the 26-29 September 2016 meeting.

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
June Munro Raine	Chair	United Kingdom	No interests declared	Full involvement
Jan Neuhauser	Member	Austria	No interests declared	Full involvement
Jean-Michel Dogné	Member	Belgium	No restrictions applicable to this meeting	Full involvement
Veerle Verlinden	Alternate	Belgium	No interests declared	Full involvement
Željana Margan Koletić	Alternate	Croatia	No interests declared	Full involvement
Eva Jirsová	Alternate	Czech Republic	No interests declared	Full involvement
Doris Stenver	Member	Denmark	No interests declared	Full involvement
Torbjörn Callreus	Alternate	Denmark	No interests declared	Full involvement
Maia Uusküla	Member	Estonia	No interests declared	Full involvement
Kirsti Villikka	Member	Finland	No interests declared	Full involvement
Claire Ferard	Alternate	France	No interests declared	Full involvement
Martin Huber	Member	Germany	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Valerie Strassmann	Alternate	Germany	No interests declared	Full involvement
Julia Pallos	Member	Hungary	No interests declared	Full involvement
Guðrún Kristín Steingrímsdóttir	Member	Iceland	No interests declared	Full involvement
Almath Spooner	Member (Vice-Chair)	Ireland	No interests declared	Full involvement
Carmela Macchiarulo	Member	Italy	No interests declared	Full involvement
Amelia Cupelli	Alternate	Italy	No interests declared	Full involvement
Zane Neikena	Member	Latvia	No interests declared	Full involvement
Jolanta Gulbinovic	Member	Lithuania	No interests declared	Full involvement
Amy Tanti	Member	Malta	No interests declared	Full involvement
Sabine Straus	Member - via telephone*	Netherlands	No interests declared	Full involvement
Menno van der Elst	Alternate	Netherlands	No interests declared	Full involvement
Helga Haugom Olsen	Member	Norway	No interests declared	Full involvement
Magdalena Budny	Alternate	Poland	No interests declared	Full involvement
Margarida Guimarães	Member	Portugal	No interests declared	Full involvement
Leonor Chambel	Alternate	Portugal	No interests declared	Full involvement
Roxana Stefania Stroe	Member	Romania	No interests declared	Full involvement
Tatiana Magálová	Member	Slovakia	No interests declared	Full involvement
Gabriela Jazbec	Alternate	Slovenia	No interests declared	Full involvement
Dolores Montero Corominas	Member	Spain	No interests declared	Full involvement
Eva Segovia	Alternate - via telephone*	Spain	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
Ulla Wändel Liminga	Member	Sweden	No interests declared	Full involvement
Qun-Ying Yue	Alternate	Sweden	No interests declared	Full involvement
Julie Williams	Member	United Kingdom	No interests declared	Full involvement
Rafe Suvarna	Alternate	United Kingdom	No interests declared	Full involvement
Marie Louise (Marieke) De Bruin	Member	Independent scientific expert	No interests declared	Full involvement
Stephen J. W. Evans	Member	Independent scientific expert	No interests declared	Full involvement
Brigitte Keller-Stanislawski	Member	Independent scientific expert	No interests declared	Full involvement
Hervé Le Louet	Member	Independent scientific expert	No interests declared	Full involvement
Thierry Trenque	Member	Independent scientific expert	No interests declared	Full involvement
Lennart Waldenlind	Member	Independent scientific expert	No interests declared	Full involvement
Raymond Anderson	Member	Healthcare Professionals' Representative	No restrictions applicable to this meeting	Full involvement
Kirsten Myhr	Alternate	Healthcare Professionals' Representative	No interests declared	Full involvement
Marco Greco	Member	Patients' Organisation Representative	No interests declared	Full involvement
Albert van der Zeijden	Alternate	Patients' Organisation Representative	No restrictions applicable to this meeting	Full involvement
Françoise Wuillaume	Expert - via telephone*	Belgium	No interests declared	Full involvement
Martin Erik Nyeland	Expert - in person*	Denmark	No restrictions applicable to this meeting	Full involvement
Tiina Jaakkola	Expert - via telephone*	Finland	No interests declared	Full involvement
Tiina Palomäk	Expert - via	Finland	No interests	Full

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
	telephone*		declared	involvement
Markku Pasanen	Expert - in person*	Finland	No interests declared	Full involvement
Caroline Laborde	Expert - in person*	France	No interests declared	Full involvement
Thomas Grueger	Expert - via telephone*	Germany	No interests declared	Full involvement
Wiebke Seemann	Expert - via telephone*	Germany	No interests declared	Full involvement
Rhea Fitzgerald	Expert - in person*	Ireland	No restrictions applicable to this meeting	Full involvement
Anouk Neuteboom	Expert - in person*	Netherlands	No interests declared	Full involvement
Johann Lodewijk Hillege	Expert - via telephone*	Netherlands	No interests declared	Full involvement
Charlotte Backman	Expert - in person*	Sweden	No interests declared	Full involvement
Karl-Mikael Kälkner	Expert - via telephone*	Sweden	No interests declared	Full involvement
Kristina Magnusson Lundqvist	Expert - via telephone*	Sweden	No interests declared	Full involvement
Ulf Olsson	Expert - via telephone*	Sweden	No restrictions applicable to this meeting	Full involvement
Elina Rönnemaa	Expert - via telephone*	Sweden	No interests declared	Full involvement
Patrick Batty	Expert - in person*	United Kingdom	No interests declared	Full involvement
Mattia Calissano	Expert - in person*	United Kingdom	No interests declared	Full involvement
John Clements	Expert - in person*	United Kingdom	No restrictions applicable to this meeting	Full involvement
Helen Cross	Expert - via telephone*	United Kingdom	No restrictions applicable to this meeting	Full involvement
A representative from the European Commission attended the meeting				
Meeting run with support from relevant EMA staff				

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

20. Annex III - List of acronyms and abbreviations

For a list of acronyms and abbreviations used in the PRAC minutes, see: Home>Committees>PRAC>Agendas, minutes and highlights

21. Explanatory notes

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

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

(Items 2 and 3 of the PRAC minutes)

A referral is a procedure used to resolve issues such as concerns over the safety or benefit-risk balance of a medicine or a class of medicines. In a referral, 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: www.ema.europa.eu/