15 March 2016
EMA/PRAC/251925/2016
Procedure Management and Committees Support Division

Pharmacovigilance Risk Assessment Committee (PRAC)

Minutes of the PRAC meeting on 08-11 February 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 scopes 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 8-11 February 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 18. 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 Chair noted the nomination of Željana Margan Koletić, as the new alternate for Croatia, in replacement of Viola Macolić Šarinić. The PRAC noted that Corinne Féchant, will step down as alternate for France after the current PRAC plenary meeting. The PRAC thanked her for her contribution to the work of the PRAC and wished her all the best for any future appointment.

1.2. Agenda of the meeting of 08-11 February 2016

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

1.3. Minutes of the previous meeting on 11-14 January 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 11-14 January 2016 were published on the EMA website on 3 March 2016 (EMA/PRAC/92676/2016).

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

None

3.3. Procedures for finalisation

3.3.1. Fusafungine (NAP), nasal and oral solution - EMEA/H/A-31/1420

Applicant: Les Laboratoires Servier, various

PRAC Rapporteur: Julia Pallos; PRAC Co-rapporteur: Jana Mladá

Scope: Review of the benefit-risk balance following notification by Italy 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 for fusafungine-containing products reviewing the benefit-risk of fusafungine following an increase in the reporting rate of serious allergic reactions and its potential role in promoting antibiotic resistance is to be concluded. A final assessment of the data was produced by the Rapporteurs according to the agreed timetable. For background information, see PRAC minutes September 2015, PRAC minutes December 2015 and PRAC minutes January 2016.

Discussion

The PRAC discussed the conclusions reached by the Scientific Advisory Group in Anti-infectives (SAG-AI) held on 21 January 2016. Together with the responses from the Paediatric Committee (PDCO) and the SAG-AI conclusions, the PRAC reviewed the totality of the data submitted in support of the safety and efficacy of fusafungine-containing products for oromucosal and nasal use. An oral explanation with the MAH for the originator medicinal product also took place at the meeting.

In the context of use in minor self-limiting disease, the PRAC considered that fusafungine is associated with an increased risk of serious hypersensitivity adverse reactions including anaphylactic reactions which can be life threatening and fatal. In addition, the aetiology of the disease (including common cold) is primarily viral and although there is insufficient evidence to conclude on the potential risk of inducing bacterial resistance, the risk of cross-

resistance cannot be excluded. Moreover, based on the available efficacy data, the PRAC concurred that the evidence for beneficial effects of fusafungine in all approved indications is weak and such effects were not clinically meaningful. The PRAC considered that the risk minimisation measures discussed during the assessment, including further restriction of the indication and additional contra-indications, limitation of treatment duration, addition of special warnings and precautions for use, limitation of excipients, distribution of a Direct Healthcare Professional Communication (DHPC) and restriction to prescription only, would not outweigh the risk of serious hypersensitivity (including allergic) reactions. Furthermore, the PRAC could not identify any potential measure or condition, the fulfilment of which would demonstrate a positive benefit-risk balance for fusafungine in any of the current indications.

Summary of recommendation(s)/conclusions

The PRAC adopted, by majority, a recommendation to be considered by the CMDh, to revoke the marketing authorisations for all fusafungine-containing-medicinal products for oromucosal and nasal use. See EMA press release (EMA/91073/2016) entitled 'PRAC recommends that fusafungine nose and mouth sprays are no longer marketed'.

Twenty-nine members voted in favour of the recommendation whilst five members had divergent views[1]. The Icelandic PRAC member agreed with the recommendation while the Norwegian member agreed with the divergent views.

The PRAC also agreed the distribution of a DHPC together with a communication plan.

Post-meeting note: the press release entitled 'CMDh endorses revocation of authorisations for fusafungine sprays used to treat airway infections' (EMA/227560/2016) representing the position of the CMDh was published on the EMA website on 1 April 2016.

3.3.2. Natalizumab – TYSABRI (CAP) - EMEA/H/A-20/1416

Applicant: Biogen Idec Ltd

PRAC Rapporteur: Brigitte Keller-Stanislawski; PRAC Co-rapporteur: Carmela Macchiarulo

Scope: Review of the benefit-risk balance following notification by the European Commission of a referral under Article 20(8) of Regulation (EC) No 726/2004, based on pharmacovigilance data

Background

A referral procedure under Article 20 of Regulation (EC) No 726/2004 for Tysabri (natalizumab) reviewing the risk estimates and diagnosis of progressive multifocal leukoencephalopathy (PML) before the development of clinical symptoms and anti-JCV (John Cunningham virus) antibodies in the light of further evidence and scientific progress is to be concluded. A final assessment of the data submitted was produced by the Rapporteurs according to the agreed timetable. For background information, see PRAC minutes May 2015, PRAC minutes September 2015, PRAC minutes October 2015, PRAC minutes November 2015, PRAC minutes December 2015 and PRAC minutes January 2016.

Discussion

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

The PRAC reviewed the totality of the data presented by the MAH on the risk of PML in association with Tysabri, as well as other data made available during the procedure and the views expressed by the Scientific Advisory Group in Neurology (SAG-N).

The PRAC concluded that PML which is clinically asymptomatic at diagnosis more frequently represents localised disease in a magnetic resonance image (MRI), with a higher survival rate and better clinical outcome as compared to symptomatic PML. Early diagnosis of PML appears to be associated with improved outcomes. As a consequence, the PRAC recommended that more frequent MRI screening for PML (e.g. every 3-6 months) using an abbreviated MRI protocol should be considered in patients at higher risk of development of PML. In addition, the PRAC concluded that, in patients who have not received prior immunosuppressant therapy and are anti-JCV antibody positive, the level of the anti-JCV antibody response (index) is associated with the risk of developing PML. Current evidence suggests that the risk increases with increasing antibody index but there is no clear cut-off value. In patients who have not received prior immunosuppressant therapy, that are anti-JCV antibody positive and treated for longer than 2 years, the risk of PML is low at index values of 0.9 or less, and increases substantially at values above 1.5. The PRAC recommended that patients with low anti-JCV antibody index who have not received prior immunosuppressant therapy should be retested every six months once they reach the 2-year treatment point. The PRAC also considered it necessary to update the existing educational material, particularly in relation to the risk estimates for development of PML in Tysabri-treated patients. The PRAC considered that the benefit-risk balance of Tysabri remains favourable subject to the agreed amendments to the product information and additional risk minimisation measures.

Summary of recommendation(s)/conclusions

The PRAC adopted, by consensus, the variation of the marketing authorisation(s) for Tysabri (natalizumab) and adopted a recommendation to be considered by the CHMP for an opinion. See EMA press release (EMA/85655/2016) entitled 'Updated recommendations to minimise the risk of the rare brain infection PML with Tysabri'.

The PRAC also agreed the distribution of a DHPC together with a communication plan.

Post-meeting note: the press release entitled 'EMA confirms recommendations to minimise risk of brain infection PML with Tysabri' (EMA/137488/2016) representing the opinion adopted by the CHMP was published on the EMA website on 26 February 2016. The PRAC assessment report (EMA/762033/2015) taken into account by the CHMP in its opinion was published on 26 February 2016.

3.3.3. Sodium-glucose co-transporter-2 (SGLT2) inhibitors: canagliflozin – INVOKANA (CAP); canagliflozin, metformin – VOKANAMET (CAP); dapagliflozin – FORXIGA (CAP); dapagliflozin, metformin – XIGDUO (CAP); empagliflozin - JARDIANCE (CAP); empagliflozin, metformin – SYNJARDY (CAP) - EMEA/H/A-20/1419

Applicant: AstraZeneca AB (Forxiga, Xigduo), Boehringer Ingelheim International GmbH (Jardiance, Synjardy), Janssen-Cilag International N.V. (Invokana, Vokanamet)

PRAC Rapporteur: Menno van der Elst; PRAC Co-rapporteurs: Valerie Strassmann, Qun-Ying Yue

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

Background

A referral procedure under Article 20 of Regulation (EC) No 726/2004 reviewing the risk of diabetic ketoacidosis (DKA) and its impact on the benefit-risk balance of sodium-glucose co-transporter-2 (SGLT2) inhibitor medicinal products-containing canagliflozin, dapagliflozin or empagliflozin alone or in combination with metformin, is to be concluded. For background information, see PRAC minutes June 2015 and PRAC minutes October 2015.

Discussion

The PRAC reviewed the totality of the data submitted by the MAHs in relation to the risk of DKA in association with SGLT2 inhibitor-containing products and in support of the efficacy of SGLT2 inhibitor-containing products.

The PRAC considered that the efficacy of SGLT2 inhibitor-containing products had been adequately demonstrated in their currently authorised indications in monotherapy and in combination as an adjunct to diet and exercise to improve glycaemic control in adult patients with type 2 diabetes mellitus (T2DM). The PRAC concluded that a small excess risk of DKA associated with SGLT2 inhibitors treatment in patients with T2DM could not be excluded. Importantly, DKA with atypical presentation may occur in association with SGLT2 inhibitors, the PRAC concluded that the risk of DKA should be minimised by its inclusion in the product information with a warning highlighting to healthcare professionals and patients that the possible atypical presentation of DKA should be considered if non-specific symptoms occur, together with a description of the identified risk factors, and recommendations regarding treatment discontinuation. Furthermore, the PRAC concluded that a risk of DKA, including with atypical presentation, is also associated with the use of SGLT2 inhibitors in patients with type 1 diabetes mellitus (T1DM). Notwithstanding that SGLT2 inhibitors-containing products are currently not authorised for T1DM, the PRAC considered that healthcare professionals should be warned of this risk and reminded that patients with T1DM should not be treated with SGLT2 inhibitors. The PRAC also recommended updates to the risk management plans (RMPs) of SGLT2 inhibitors-containing products (inclusion of DKA with atypical presentation as an important identified risk and corresponding activities to further characterise this risk).

Overall, the PRAC considered that the benefit-risk balance of SGLT2 inhibitors-containing products remains favourable subject to the agreed amendments to the product information.

Summary of recommendation(s)/conclusions

The PRAC adopted, by consensus, the variations of the marketing authorisation(s) for Forxiga (dapagliflozin), Xigduo (dapagliflozin/metformin), Invokana (canagliflozin), Vokanamet (canagliflozin/metformin), Jardiance (empagliflozin) and Synjardy (empagliflozin/metformin) and adopted a recommendation to be considered by the CHMP for an opinion. See EMA press release (EMA/100751/2016) entitled 'SGLT2 inhibitors: PRAC makes recommendations to minimise risk of diabetic ketoacidosis'.

The PRAC also agreed the distribution of a DHPC together with a communication plan.

Post-meeting note: the press release entitled 'EMA confirms recommendations to minimise ketoacidosis risk with SGLT2 inhibitors for diabetes' (EMA/142655/2016) representing the

opinion adopted by the CHMP was published on the EMA website on 26 February 2016. The PRAC assessment report (EMA/PRAC/50218/2016) taken into account by the CHMP in its opinion was published 10 March 2016.

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

None

3.5. Others

None

4. Signals assessment and prioritisation[2]

4.1. New signals detected from EU spontaneous reporting systems

4.1.1. Rivaroxaban - XARELTO (CAP)

Applicant: Bayer Pharma AG

PRAC Rapporteur: Qun-Ying Yue

Scope: Signal of spontaneous spinal haematoma

EPITT 18606 – New signal
Lead Member State: SE

Background

Rivaroxaban is a highly selective direct factor Xa inhibitor indicated for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) under certain conditions, for the prevention of venous thromboembolism in adult patients undergoing elective hip or knee replacement surgery, for the prevention of stroke and systemic embolism in adult patients under certain conditions and for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.

The post-marketing exposure for Xarelto, a centrally authorised medicine containing rivaroxaban, is estimated to have been more than 7,137,901 patient-years worldwide, in the period from first authorisation in 2008 until September 2015.

During routine signal detection activities, a signal of spontaneous spinal haematoma was identified by the EMA, based on 6 supportive cases retrieved from EudraVigilance. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the available evidence from case reports in EudraVigilance. Taking into account that all patients experienced some type of pain in the 6 reported cases with no

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

concurrent or medical history of spinal anaesthetic or puncture procedures, trauma or injuries, and that there was a positive de-challenge in one patient, the PRAC agreed to request the MAH of Xarelto to provide a cumulative review of all cases of 'spinal epidural haematoma', 'spinal cord haematoma', 'spinal cord haemorrhage', 'spinal epidural haemorrhage', 'spinal subarachnoid haemorrhage', 'spinal subdural haemorrhage', and 'spinal subdural haematoma' MedDRA[3] preferred terms (PTs) associated with rivaroxaban.

Summary of recommendation(s)

- The MAH for Xarelto (rivaroxaban) should submit to the EMA, in the next PSUR (DLP: 15/09/2016) (PSUSA/00002653/201609), a cumulative review of all cases of 'spinal epidural haematoma', 'spinal cord haematoma', 'spinal cord haemorrhage', 'spinal epidural haemorrhage', 'spinal subarachnoid haemorrhage', 'spinal subdural haemorrhage', and 'spinal subdural haematoma' MedDRA preferred terms associated with rivaroxaban. The cumulative review should include a review of published literature, post-marketing experience and clinical trials focusing on cases reported with the above mentioned PTs and with no medical history or concurrent spinal anaesthetic/puncture procedures/trauma and injuries. The MAH should also discuss the need for any potential amendment to the product information and/or the risk RMP and make accordingly a proposal for the changes to the relevant sections within this discussion.

4.1.2. Sofosbuvir – SOVALDI (CAP)

Applicant: Gilead Sciences International Ltd polymerase indicated

PRAC Rapporteur: Rafe Suvarna

Scope: Signal of hepatitis B reactivation

EPITT 18607 – New signal
Lead Member State: UK

Background

Sofosbuvir is a pan-genotypic inhibitor of the hepatitis C virus (HCV) NS5B RNA[4]-dependent RNA in combination with other antiviral treatment for the treatment of chronic hepatitis C (CHC) in adults.

The post-marketing exposure for Sovaldi, a centrally authorised medicine containing sofosbuvir, is estimated to have been more than 74,096 patient-years worldwide, in the period from first authorisation in 2014 until June 2015.

During routine signal detection activities, a signal of hepatitis B reactivation was identified by the EMA, based on 4 supportive cases retrieved from EudraVigilance. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the available evidence from case reports in EudraVigilance and from the literature. Taking into account the well documented cases, that the increase in HBV (hepatitis B virus) viral load was associated with worsening of hepatic state in two cases

[3] Medical Dictionary for Regulatory Activities
[4] Non-structural protein 5B ribonucleic acid

(leading to transplant in one case), that there is a biological plausibility for HBV reactivation with all interferon-free direct acting anti-viral (DAAV) therapies and that a small number of cases of HBV reactivation have been reported with several other direct acting anti-viral therapies for the treatment of hepatitis C, the PRAC agreed that a thorough evaluation of the issue within a formal procedure with appropriate expert consultation should be considered.

Summary of recommendation(s)

- The PRAC agreed that a thorough evaluation of the issue within a formal procedure with appropriate expert consultation with clinical experts should be considered.

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/089

Applicant: AbbVie Ltd.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of autoimmune haemolytic anaemia (AIHA) and haemolytic anaemia (HA) EPITT 18447 – Follow-up to October 2015

Background

For background information, see PRAC minutes October 2015. The MAH replied to the request for information on the signal of autoimmune haemolytic anaemia (AIHA) and haemolytic anaemia (HA) and the responses were assessed by the Rapporteur.

Discussion

The PRAC discussed the MAH's responses. Taking into account the data from spontaneous reports, clinical trials and the literature provided by the MAH in its cumulative review, the PRAC has concluded that there is not enough evidence of an association between adalimumab and autoimmune haemolytic anaemia. Therefore, no further action is deemed necessary at this time. The MAH for Humira should however continue to monitor this event as part of routine safety surveillance.

Summary of recommendation(s)

- The MAH for Humira (adalimumab) should continue to closely monitor cases of autoimmune haemolytic anaemia as part of routine safety surveillance.

4.3.2. Alogliptin – VIPIDIA (CAP) - EMEA/H/C/0002182/SDA/010; alogliptin, metformin – VIPDOMET (CAP); alogliptin, pioglitazone – INCRESYNC (CAP); linagliptin – TRAJENTA (CAP) - EMEA/H/C/002110/SDA/015; linagliptin, metformin – JENTADUETO (CAP) - EMEA/H/C/002279/SDA/009

Applicant: Boehringer Ingelheim International (Jentadueto, Trajenta), Takeda Pharma A/S (Incresync, Vipdomet, Vipidia)

PRAC Rapporteur: Menno van der Elst

Scope: Signal of arthralgia
EPITT 18489 – Follow-up to October 2015

Background

For background information, see PRAC minutes October 2015. The MAHs replied to the request for information on the signal of arthralgia and the responses were assessed by the Rapporteur.

Discussion

The PRAC discussed the MAHs' responses. Taking into account the available evidence from the cumulative review provided by the MAHs, the PRAC agreed that the likelihood of a causal relationship between treatment with alogliptin or linagliptin and arthralgia was not sufficiently robust to warrant changes in the product information at this stage. The PRAC recommended that the MAHs for alogliptin- and linagliptin-containing products should include arthralgia in the RMP as an important potential risk at the next regulatory opportunity and should closely monitor arthralgia in future PSURs.

Summary of recommendation(s)

- The MAHs for Vipidia (alogliptin) and Trajenta (linagliptin) should include arthralgia in the RMP as an important potential risk at the next regulatory opportunity and should closely monitor arthralgia in future PSURs.

4.3.3. Carbidopa, levodopa (NAP)

Applicant: AbbVie Ltd, various

PRAC Rapporteur: Qun-Ying Yue

Scope: Signal of intussusception
EPITT 18424 – Follow-up to October 2015

Background

For background information, see PRAC minutes October 2015. The MAH replied to the request for information on the signal of associated intussusception with the carbidopa/levodopa intestinal gel delivered via small bowel feeding tube and the responses were assessed by the Rapporteur.

Discussion

The PRAC discussed the MAHs' responses. Based on the cumulative review of cases of intussusception in association with carbidopa/levodopa including data from clinical trials, literature and post-marketing experience as well as the MAH's conclusions, the PRAC agreed that the product information for carbidopa/levodopa-containing intestinal gel should be updated to reflect the risk associated with the use of small bowel feeding tubes and the development of intussusception.

Summary of recommendation(s)

- The MAH for Duodopa (carbidopa/levodopa) should submit to the relevant EU national competent authorities, within 60 days, a variation to include a warning on intussusception and on bezoar formation leading to intestinal obstruction and/or intussusception and to include intussusception as a new undesirable effect.

For the full PRAC recommendations, see EMA/PRAC/87046/2016 published on 07/03/2016 on the EMA website.

4.3.4. Mitotane – LYSODREN (CAP) – EMEA/H/C/000521/SDA/023

Applicant: Laboratoire HRA Pharma, SA

PRAC Rapporteur: Dolores Montero Corominas

Scope: Signal of sex hormone disturbances and development of ovarian macrocysts
EPITT 18301 – Follow-up to October 2015

Background

For background information, see PRAC minutes May 2015 and PRAC minutes October 2015. The MAH replied to the request for information on the signal of sex hormone disturbances and development of ovarian macrocysts and the responses were assessed by the Rapporteur.

Discussion

The PRAC discussed the MAH's responses. Having considered the responses submitted from the MAH for Lysodren, the evidence from post-marketing data and the scientific literature, the PRAC agreed that the product information for Lysodren should be updated to include a new warning on ovarian macrocysts in premenopausal women and to include new undesirable effects related to sex hormone disturbances and the development of ovarian macrocysts.

Summary of recommendation(s)

- The MAH for Lysodren (mitotane) should submit to the EMA, within 60 days, a variation to include a new warning on ovarian macrocysts in premenopausal women and to include new undesirable effects related to sex hormone disturbances and the development of ovarian macrocysts.

For the full PRAC recommendations, see EMA/PRAC/87046/2016 published on 07/03/2016 on the EMA website.

4.3.5. Peginterferon alfa-2a – PEGASYS (CAP) - EMEA/H/C/000395/SDA/055

Applicant: Roche Registration Limited

PRAC Rapporteur: Qun-Ying Yue

Scope: Signal of acquired haemophilia
EPITT 18476 – Follow-up to October 2015

Background

For background information, see PRAC minutes October 2015. The MAH replied to the request for information on the signal of acquired haemophilia and the responses were assessed by the Rapporteur.

Discussion

The PRAC discussed the MAH's responses. Taking into consideration the data from spontaneous reports, clinical trials and the literature provided by the MAH in the cumulative

review, the PRAC concluded that there is insufficient evidence of a causal relationship between peginterferon alfa-2a and acquired haemophilia to warrant an update of the product information. The PRAC therefore agreed that the MAH should monitor acquired haemophilia in future PSURs.

Summary of recommendation(s)

- The MAH for Pegasys (peginterferon alfa-2a) should carefully monitor acquired haemophilia in future PSURs. When known, the type of factor VIII inhibitor involved should be specified.

4.3.6. Tyrosine kinase inhibitors (TKI): bosutinib – BOSULIF (CAP) -EMEA/H/C/002373/SDA/012; dasatinib - SPRYCEL (CAP) - EMEA/H/C/000709/SDA/042; imatinib – GLIVEC (CAP) - EMEA/H/C/000406/SDA/196; nilotinib – TASIGNA (CAP) - EMEA/H/C/000798/SDA/049; ponatinib – ICLUSIG (CAP) - EMEA/H/C/002695/SDA/013

Applicant: Bristol-Myers Squibb Pharma EEIG (Sprycel), Novartis Europharm Ltd (Glivec, Tasigna), Pfizer Limited (Bosulif), Ariad Pharma Ltd (Iclusig)

PRAC Rapporteur: Dolores Montero Corominas

Scope: Signal of hepatitis B virus (HBV) reactivation
EPITT 18405 – Follow-up to September 2015

Background

For background information, see PRAC minutes September 2015. The MAHs replied to the request for information on the signal of hepatitis B virus (HBV) reactivation and the responses were assessed by the Rapporteur.

Discussion

The PRAC discussed the MAHs' responses and detailed analysis of non-clinical, clinical and post-marketing data, as well as the medical literature. Although the mechanism of HBV reactivation is not known at this time, the PRAC concluded that there is convincing evidence of a class-effect among 'breakpoint cluster region' (BCR)-Abelson murine leukaemia viral oncogene homolog (ABL) tyrosine kinase inhibitors (TKIs) with documented cases of HBV reactivation in patients taking BCR-ABL TKIs in the literature. The PRAC agreed that the product information of BCR-ABL TKIs should be updated to include HBV reactivation.

Summary of recommendation(s)

- The MAHs for Glivec (imatinib), Sprycel (dasatinib), Tasigna (nilotinib), Bosulif (bosunitib) and Iclusig (ponatinib) should submit to the EMA, within 60 days, a variation to amend the product information (warnings and precautions for use and undesirable effects sections of the SmPC and the package leaflet).
- The MAHs should distribute a joint direct healthcare professional communication (DHPC) according to the text and communication plan agreed with the PRAC and CHMP.

For the full PRAC recommendations, see EMA/PRAC/87046/2016 published on 07/03/2016 on the EMA website.

4.3.7. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/SDA/043

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Julie Williams

Scope: Signal of pemphigoid
EPITT 18469 – Follow-up to October 2015

Background

For background information, see PRAC minutes October 2015. The MAH replied to the request for information on the signal of pemphigoid and the responses were assessed by the Rapporteur.

Discussion

The PRAC discussed the MAH's response. Taking into account the review of the available data from clinical trials, the Psoriasis Longitudinal Assessment and Registry (PSOLAR) and post-marketing cases on bullous pemphigoid and bullous conditions, the PRAC considered that the data currently available do not provide sufficient evidence to support a causal association. Therefore, the PRAC agreed that no updates to the product information are necessary at present. Nevertheless, the MAH should continue to closely monitor the risk of bullous pemphigoid and bullous conditions as part of routine pharmacovigilance.

Summary of recommendation(s)

- The MAH for Stelara (ustekinumab) should closely monitor cases of bullous pemphigoid and bullous conditions 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).

See also Annex I 14.1.

5.1.1. Chenodeoxycholic acid - EMEA/H/C/004061, Orphan

Applicant: Sigma-Tau Arzneimittel GmbH

Scope (accelerated assessment): Treatment of inborn errors of primary bile acid synthesis

5.1.2. Chlorhexidine - EMEA/H/W/003799

Scope (accelerated assessment): Prophylaxis of omphalitis

5.1.3. Ceftazidime, avibactam - EMEA/H/C/004027

Scope: Treatment of complicated intra-abdominal infections (cIAI), complicated urinary-tract infections (cUTI) and nosocomial pneumonia

5.1.4. Irinotecan - EMEA/H/C/004125, Orphan

Applicant: Baxter Innovations GmbH

Scope: Treatment of pancreatic cancer

5.1.5. Lutetium (^{177}Lu) chloride - EMEA/H/C/003999

Scope: Radiolabelling of carrier molecules specifically developed for radiolabelling with this radionuclide

5.1.6. Palonosetron - EMEA/H/C/004129

Scope: Prevention of nausea and vomiting associated with cancer chemotherapy

5.1.7. Palonosetron - EMEA/H/C/004069

Scope: Prevention of nausea and vomiting associated with cancer chemotherapy

5.1.8. Saxagliptin, dapagliflozin - EMEA/H/C/004057

Scope: Treatment of type 2 diabetes mellitus

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

See also Annex I 14.2.

5.2.1. Velaglucerase alfa – VPRIV (CAP) - EMEA/H/C/001249/II/0029

Applicant: Shire Pharmaceuticals Ireland Ltd.

PRAC Rapporteur: Valerie Strassmann

Scope: Revised RMP (version 9.0) in order to include an additional risk minimisation measure to mitigate the risk of serious infusion related reactions and hypersensitivity reactions in the home setting, such as educational material for healthcare professionals and patients/caregivers and questionnaire (testing request form)

Background

Velaglucerase alfa is a glycoprotein that supplements or replaces beta-glucocerebrosidase and is indicated for long-term enzyme replacement therapy (ERT) in patients with type 1 Gaucher disease.

The PRAC is evaluating a type II variation procedure for Vpriv, a centrally authorised medicine containing velaglucerase alfa, to update the RMP. The proposed changes include the introduction of additional risk minimisation measures such as educational material for healthcare professionals and patients/caregivers to mitigate the risk of serious infusion-related reactions and hypersensitivity reactions associated with Vpriv administration in the home setting. For further background, see PRAC minutes September 2015. The PRAC is

responsible for producing an assessment report to be further considered at the level of the CHMP, responsible for adopting an opinion on this variation.

Summary of advice

- The RMP version 9.0 for Vpriv (velaglucerase alfa) in the context of the variation under evaluation by the PRAC and CHMP is considered acceptable provided that satisfactory responses to a request for supplementary information (RSI) are submitted by the MAH.
- The PRAC considered that the proposed key elements for educational materials for the home infusion setting, consisting of a manual for patients, a guide for healthcare professionals, an infusion diary as well as an 'emergency plan´, should be revised. With regard to the proposed category 3 PASS, to assess the effectiveness of the educational material, the protocol should be submitted to the EMA for review by PRAC, within 90 days, following finalisation of the variation procedure.

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

See also Annex I 14.3.

5.3.1. Evolocumab – REPATHA (CAP) - EMEA/H/C/003766/X/0002

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Kimmo Jaakkola

Scope: Addition of a new strength of 420 mg (120 mg/mL) for evolocumab solution for injection in cartridge, for subcutaneous (SC) administration by an automated mini-doser device

Background

Evolocumab is a monoclonal immunoglobulin (Ig)G2 antibody indicated in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet under certain conditions and also indicated in adults and adolescents aged 12 years and over with homozygous familial hypercholesterolaemia in combination with other lipid-lowering therapies.

The CHMP is evaluating a line extension for Repatha, a centrally authorised product containing evolocumab, to add a new strength of 420 mg (120 mg/mL) for evolocumab solution for injection in a cartridge, for subcutaneous (SC) administration by an automated mini-doser (AMD) device to reduce the need for three injections at one time. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this line extension procedure.

Summary of advice

- The RMP version 1.3 for Repatha (evolocumab) in the context of the line extension under evaluation by the CHMP is considered acceptable provided that satisfactory responses to a request for supplementary information (RSI) are submitted by the MAH.
- The PRAC considered that the MAH should discuss the need to include 'device failure associated with the use of the AMD' in the RMP as an important identified risk. The MAH should present measures to minimize the risks of device failure and discuss the observed and expected effectiveness of the proposed strategy.

6. Periodic safety update reports (PSURs)

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

See also Annex I 15.1.

6.1.1. Aflibercept – ZALTRAP (CAP) - PSUSA/10019/201508

Applicant: Sanofi-Aventis Groupe

PRAC Rapporteur: Ulla Wändel Liminga

Scope of procedure: Evaluation of a PSUSA procedure

Background

Aflibercept is a recombinant fusion protein consisting of vascular endothelial growth factor (VEGF)-binding portions from the extracellular domains of human VEGF receptors 1 and 2, indicated in adult patients in combination with irinotecan/5-fluorouracil/folinic acid (FOLFIRI) chemotherapy for the treatment of metastatic colorectal cancer (MCRC) that is resistant to or has progressed after an oxaliplatin-containing regimen.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Zaltrap, a centrally authorised medicine containing aflibercept, 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 Zaltrap (aflibercept) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to revise the current warning on proteinuria and to include a new warning on osteonecrosis of the jaw and to add osteonecrosis of the jaw as a new undesirable effect with an uncommon frequency. Therefore the current terms of the marketing authorisation(s) should be varied[5].
- The MAH should inform the relevant healthcare professionals about the risk of osteonecrosis of the jaw and appropriate measures to be taken via a Direct Healthcare Professional Communication (DHPC), in accordance with the agreed communication plan.
- In the next PSUR, the MAH should provide a cumulative review and analysis of cardiac failure/left ventricular ejection fraction (LVEF) decreased, including a discussion on the mechanism. The MAH should also discuss the need to update the product information and/or the RMP accordingly.
- The MAH should be requested to submit an updated RMP at the next regulatory opportunity requiring an RMP update to re-categorise osteonecrosis of the jaw as an important identified risk.

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

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

6.1.2. Aripiprazole – ABILIFY (CAP); ABILIFY MAINTENA (CAP) - PSUSA/00234/201507

Applicant: Otsuka Pharmaceutical Europe Ltd

PRAC Rapporteur: Leonor Chambel

Scope of procedure: Evaluation of a PSUSA procedure

Background

Aripiprazole is an antipsychotic indicated for the treatment of schizophrenia, moderate to severe manic episodes in bipolar I disorder and for the prevention of a new manic episode under certain conditions. The solution for injection is indicated for the rapid control of agitation and disturbed behaviours in patients with schizophrenia or in patients with manic episodes in bipolar I disorder, when oral therapy is not appropriate. The suspension for injection pharmaceutical form is indicated for maintenance treatment of schizophrenia in adult patients stabilised with oral aripiprazole.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Abilify and Abilify Maintena, centrally authorised medicines containing aripiprazole, 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 Abilify and Abilify Maintena (aripiprazole) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include hiccups as a new undesirable effect with an uncommon frequency. Therefore the current terms of the marketing authorisation(s) should be varied[6].
- In the next PSUR, the MAH should provide a complete review and analysis of the cases related to thyroid disorders.
- The MAH should submit to the EMA, within 60 days, a detailed review of serious adverse events under the MedDRA SOC[7] eye disorder. Regarding the signal of pulmonary embolism, the MAH should submit a cumulative review and analysis of all related events. The MAH should also review the reported cases of interaction between aripiprazole and other antipsychotics, including a discussion on this potential pharmacodynamic interaction and the possibility to submit a study proposal to assess this interaction.
- The MAH should be requested, when submitting the results of PASS study 31-12-300 in November 2016, to provide a revised RMP to update the pharmacovigilance plan. Based on the outcome of this study, the MAH should make a proposal on whether or not the educational materials could be stopped. Additionally, the MAH should review all the

[6] 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
[7] Medical dictionary for regulatory activities system organ class

safety concerns stated in the current RMP, as well as consider the inclusion of 'diplopia', 'aggression', 'hyperprolactinaemia' and 'acute renal failure' as new safety concerns, as requested in the previous PSUR (PSUSA/00234/201407). Also, taking into account the ongoing safety evaluations, in particular on extrapyramidal symptom-related adverse reactions from study 270 for Abilify Maintena, the MAH should reflect on the validity of including these safety concerns in the updated RMP.

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. Atazanavir – REYATAZ (CAP) - PSUSA/00258/201506

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Isabelle Robine

Scope of procedure: Evaluation of a PSUSA procedure

Background

Atazanavir is an azapeptide human immunodeficiency virus (HIV-1) protease inhibitor indicated in combination for the treatment of HIV-1 infected adults and paediatric patients of 6 years of age and older in combination with other antiretroviral medicinal products.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Reyataz, a centrally authorised medicine containing atazanavir, 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 Reyataz (atazanavir) 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 an updated review of sialolithiasis and discuss the relevance of including 'sialolithiasis' as a possible undesirable effect in the product information. The MAH should also provide an updated review of renal disorders/failure reported with atazanavir and any new data collected for each safety specification identified with atazanavir.
- The MAH should submit to the EMA, within 90 days, a comprehensive review of congenital anomalies reported with atazanavir. This review should include an estimated incidence of congenital anomalies in the offspring after the first trimester of exposure to atazanavir from the prospectively reported pregnancies with a known outcome, a specific literature review and a discussion of the data gathered from the Antiretroviral Pregnancy Registry (APR).

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. Dasabuvir – EXVIERA (CAP) - PSUSA/10363/201507

Applicant: AbbVie Ltd.

PRAC Rapporteur: Miguel-Angel Macia

Scope of procedure: Evaluation of a PSUSA procedure

Background

Dasabuvir is a non-nucleoside inhibitor of the hepatitis C virus (HCV) ribonucleic acid (RNA)-dependent RNA polymerase, indicated in combination with other medicinal products for the treatment of chronic hepatitis C (CHC) in adults.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Exviera, a centrally authorised medicine containing dasabuvir, 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 Exviera (dasabuvir) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include angioedema as a new undesirable effect with a rare frequency. Therefore the current terms of the marketing authorisation(s) should be varied[8].
- In the next PSUR, the MAH should evaluate the signal related to drug-drug interaction (DDI) with angiotensin receptor blockers (ARBs) identified during the late-breaking information. With regard to a drug-drug interaction (DDI) with colchicine, a DDI with statins, a DDI with voriconazole and a DDI with calcium channel blockers, the MAH should clarify the sources of data reviewed to consider these as signals and consider whether amendments to the product information are warranted. In addition, the MAH should provide detailed reviews of hypersensitivity cases and cases of hepatic decompensation as well as cases of pneumonia. The MAH should also closely monitor reported cases related to bradycardia, heart block, concomitant treatment with amiodarone, and a possible drug interaction with mammalian target of rapamycin (mTOR) inhibitors.

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. Ingenol mebutate – PICATO (CAP) - PSUSA/10035/201507

Applicant: Leo Pharma A/S

PRAC Rapporteur: Julie Williams

Scope of procedure: Evaluation of a PSUSA procedure

Background

[8] 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

Ingenol mebutate induces local lesion cell death and promotes an inflammatory response characterised by local production of pro-inflammatory cytokines and chemokines and infiltration of immunocompetent cells. It is indicated for the cutaneous treatment of non-hyperkeratotic, non-hypertrophic actinic keratosis in adults.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Picato, a centrally authorised medicine containing ingenol mebutate, 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 Picato (ingenol mebutate) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the current warning to minimise the risk of accidental exposure to the eye and include a warning on chemical conjunctivitis and corneal burn on accidental eye exposure. In addition the product information should be updated to include as new undesirable effects application site pigmentation change and hypersensitivity (including angioedema) with an uncommon frequency. Therefore the current terms of the marketing authorisation(s) should be varied[9].
- The MAH should submit to the EMA, within 60 days, a variation to update the product information to reflect the findings of the large treatment area study LP0105-1020.
- The MAH should also submit to the EMA, within 60 days, a detailed analysis of the findings of study LP0105-1020 with regard to squamous cell carcinoma and consider the need to update the product information accordingly to inform healthcare professionals. The MAH should also provide an update relating to study LP0105-1032, an ongoing controlled study on the use of ingenol mebutate in larger treatment areas, and discuss the findings relating to skin malignancies (both within and outside the treatment areas). In addition, the MAH should present interim results from studies LP0041-63 and LP0105-1120, particularly focussing on the findings for skin tumours, both within and outside the treatment area, for the ingenol mebutate group versus those in the vehicle group.

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. Ombitasvir, paritaprevir, ritonavir – VIEKIRAX (CAP) - PSUSA/10367/201507

Applicant: AbbVie Ltd.

PRAC Rapporteur: Miguel-Angel Macia

Scope of procedure: Evaluation of a PSUSA procedure

Background

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

Ombitasvir and paritaprevir are inhibitors of the hepatitis C virus (HCV). Ritonavir, which is not active against HCV, is a CYP3A inhibitor that increases the systemic exposure of the CYP3A substrate paritaprevir. The combination ombitasvir, paritaprevir and ritonavir is indicated in combination with other medicinal products for the treatment of chronic hepatitis C (CHC) in adults.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Viekirax, a centrally authorised medicine containing ombitasvir, paritaprevir and ritonavir, 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 Viekirax (ombitasvir, paritaprevir, ritonavir) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include angioedema as a new undesirable effect with a rare frequency. Therefore the current terms of the marketing authorisation(s) should be varied[10].
- In the next PSUR, the MAH should evaluate the signal related to drug-drug interaction (DDI) with angiotensin receptor blockers (ARBs) identified during the late-breaking information. With regard to DDI with colchicine, DDI with statins, DDI with voriconazole and DDI with calcium channel blockers, the MAH should clarify the sources of data reviewed to consider these as signals and consider whether amendments to the product information are warranted. In addition, the MAH should provide detailed reviews of hypersensitivity cases, and cases of hepatic decompensation as well as cases of pneumonia. The MAH should also closely monitor reported cases related to bradycardia, heart block, concomitantly treated with amiodarone, and a possible drug interaction with mammalian target of rapamycin (mTOR) inhibitors. Taking into account a possible risk of increased plasma concentrations of sildenafil due to a decrease of its liver metabolism as a result of an interaction between sildenafil and ombitasvir/paritaprevir, the MAH should evaluate the possibility to include this contraindication in the product information.

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. Romiplostim – NPLATE (CAP) - PSUSA/02660/201507

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Dolores Montero Corominas

Scope of procedure: Evaluation of a PSUSA procedure

Background

Romiplostim is a crystallisable fragment (Fc)-peptide fusion protein that signals and activates intracellular transcriptional pathways via the TPO receptor (also known as cMpl) to

[10] 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

increase platelet production. It is indicated for adult chronic immune (idiopathic) thrombocytopenic purpura (ITP) splenectomised patients who are refractory to other treatments (e.g. corticosteroids, immunoglobulins).

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Nplate, a centrally authorised medicine containing romiplostim, 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 Nplate (romiplostim) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a table clarifying the issue of vial overfill in the 'special precautions for disposal and other handling' section of the SmPC. Therefore the current terms of the marketing authorisation(s) should be varied[11].
- In the next PSUR, the MAH should closely monitor cases of eosinophilia and systemic symptoms, agranulocytosis, polycythemia, non-haematological malignancies, cataracts, retinal haemorrhage, interstitial lung disease and pulmonary fibrosis.

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

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

6.2.1. Ibandronic acid monosodium salt, monohydrate – BONDRONAT (CAP); BONVIVA (CAP); NAP - PSUSA/01702/201506

Applicant: Roche Registration Limited, various

PRAC Rapporteur: Doris Stenver

Scope of procedure: Evaluation of a PSUSA procedure

Background

Ibandronic acid is a highly potent bisphosphonate belonging to the nitrogen-containing group of bisphosphonates indicated in adults for the prevention of skeletal events in patients with breast cancer and bone metastases, for the treatment of tumour-induced hypercalcaemia with or without metastases as well as for the treatment of osteoporosis in postmenopausal women at increased risk of fracture.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Bondronat and Bonviva, centrally authorised medicines containing ibandronic acid, and nationally authorised medicines containing ibandronic acid, and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

[11] Update of SmPC section 6.6. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

- Based on the review of the data on safety and efficacy, the risk-benefit balance of ibandronic acid-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include in the posology and method of administration section that patients treated with ibandronic acid should be given the package leaflet and the patient reminder card, to reflect the current knowledge on osteonecrosis of the jaw (ONJ) as set out in the warnings and undesirable effects sections. Therefore the current terms of the marketing authorisation(s) should be varied[12]. See 'PRAC recommends further measures to minimise risk of osteonecrosis of the jaw with bisphosphonate medicine' EMA/169618/2015.
- In the next PSUR, the MAHs should monitor closely the incidence of osteonecrosis and pain in the jaw in patients receiving combinations of several bisphosphonates. In addition, cancer patients should be included in the next review unless duly justified. The MAHs should provide a review of safety in men using ibandronic acid. The MAHs should also provide a review of the signal of venous thrombo-embolism in the oncology indication even though confounding factors might make conclusions difficult.
- The MAH of Bonviva should provide information on the use of Bonviva in Germany and compare the ratio of use of Bonviva intravenous (i.v.) in patient-years and the number of reported cases in Germany with extravascular injection versus the use of Bonviva i.v. overall and the number of cases with extravascular injection overall. If there is a difference, the MAH should provide a justification or a proposal for adequate risk minimisation measures. Furthermore, the MAH for Bonviva should provide a discussion on cases of medication error (paravenous application) with concomitantly reported adverse events.
- The MAH should be requested to submit to EMA, within 60 days, a revised RMP to reflect the addition of a new additional risk minimisation measure (introduction of the reminder card on osteonecrosis of the jaw) as well as to propose indicators to measure the effectiveness of this new measure.

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

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

See also Annex I 15.3.

6.3.1. Bemetizide, triamterene (NAP) - PSUSA/00009076/201506

Applicant: various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

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

Background

Bemetizide is a benzothiadiazide and triamterene is a potassium-sparing diuretic. Used in combination it is indicated for the treatment of hypertension and oedema.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing bemetizide and triamterene, 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 medicinal products containing bemetizide and triamterene in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include new warnings on acute myopia and secondary angle-closure glaucoma, and on exacerbation or activation of systemic lupus erythematosus. In addition the product information should be updated to include hypersensitivity reactions as a new undesirable effect with a rare frequency. Therefore the current terms of the marketing authorisation(s) should be varied[13].
- In the next PSUR, the MAHs should closely monitor cases of exfoliative/bullous dermatitis, Stevens-Johnson syndrome (SJS) and pancytopenia. The MAHs should strengthen their efforts to estimate patient exposure based on average treatment duration and average daily dose (e.g. via a drug utilisation study or other market research activities) and present such data within the next PSUR.

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. Daunorubicin (NAP) - PSUSA/00000936/201506

Applicant: various

PRAC Lead: Marianne Lunzer

Scope: Evaluation of a PSUSA procedure

Background

Daunorubicin is a cytostatic antineoplastic agent belonging to the anthracycline family (antibiotics), indicated in the treatment of acute myelogenous leukemia (AML) and acute lymphocytic leukemia (ALL) in combination with other antineoplastic agents, of erythroleukemia, of chronic myelogenous leukemia (CML), of non-Hodgkin's lymphoma and Hodgkin's lymphoma, under certain conditions.

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

Summary of recommendation(s) and conclusions

[13] 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

- Based on the review of the data on safety and efficacy, the risk-benefit balance of daunorubicin-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include as new undesirable effects colitis with an unknown frequency and bone marrow failure with a very common frequency. Therefore the current terms of the marketing authorisation(s) should be varied[14].
- In the next PSUR, the MAHs should closely monitor and discuss any new information with details on cases reported of posterior reversible encephalopathy syndrome, fatal infection, febrile neutropenia, secondary malignancies, hepatitis and hepatic failure.

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

6.3.3. Glibenclamide, metformin hydrochloride (NAP) - PSUSA/00002002/201506

Applicant: various

PRAC Lead: Corinne Fechant

Scope: Evaluation of a PSUSA procedure

Background

Glibenclamide is a second generation sulfonylurea and metformin is a biguanide. The combination is indicated for the treatment of type 2 diabetes mellitus (T2DM) in adults.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing glibenclamide and metformin hydrochloride, and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of medicinal products containing glibenclamide and metformin hydrochloride in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include a new warning that older age is a risk factor for hypoglycaemia in patients treated with sulfonylureas in the 'posology and methods of administration' and 'special warnings and precautions for use' sections of the SmPC. Therefore the current terms of the marketing authorisation(s) should be varied[15].
- In the next PSUR, the MAHs should closely monitor the risk during pregnancy and in utero exposure, keep under close monitoring the following signals: hypoglycaemia, interaction with levothyroxine, phenprocoumin, and pyrimethamine, haemolytic anemia, encephalopathy, cardiac arrhythmia, acute renal failure, dystonia, cancer risk, photosensitivity and tendinitis. Finally the MAHs should provide a critical analysis of the

[14] Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position
[15] 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

following events: haemolytic anaemia, hepatic failure, encephalopathy, pemphigoid/pemphigus/angioedema.

- It was highlighted that new epidemiological studies and a recent meta-analysis have become available during the period covered assessing the risk of glibenclamide compared to metformin or other sulfonylureas in terms of cardiovascular (CV) mortality and/or all-cause mortality. The PRAC noted that the originator MAH (Sanofi) updated the SmPC of glibenclamide containing-products in some Member States with a new warning about cardiovascular mortality. The PRAC considered that a broader and more in depth analysis of available data on the cardiovascular mortality and/or all-cause mortality risk of glibenclamide compared with other sulfonylureas was needed. In this context, as there is an ongoing variation addressing CV mortality risk of glibenclamide in Belgium, Belgium will seek PRAC advice. The PRAC advice would serve as a platform for a more in depth review of the issue.

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 15.4.

6.4.1. Botulinum b toxin – NEUROBLOC (CAP) - EMEA/H/C/000301/LEG 062.1

Applicant: Eisai Ltd

PRAC Rapporteur: Leonor Chambel

Scope: MAH's responses to LEG 062 [MAH's response to PSUSA/00000428/201406 following PRAC outcome in February 2015] as adopted in September 2015

Background

Botulinum toxin type B is a muscle relaxant (peripherally acting agent) indicated for the treatment of cervical dystonia (torticollis).

Following the evaluation of the most recently submitted PSURs for NeuroBloc, the PRAC requested the MAH to submit further data on the effectiveness of the educational materials for botulinum toxin B and the need to keep these educational materials as a condition to the marketing authorisation (see PRAC minutes February 2015 and PRAC minutes September 2015). The responses were assessed by the Rapporteur for further PRAC advice.

Summary of advice/conclusion(s)

- The MAH concluded that its website where approved education materials are published had not been demonstrated to be effective in reaching EU physicians and patients. The MAH therefore proposed to discuss with relevant national competent authorities the replacement of the website with an alternative suitable dissemination method. In order to measure the effectiveness of the educational materials disseminated, the MAH proposed to send HCPs a questionnaire. The PRAC considered this proposal acceptable, considering that the questionnaire would be delivered to all HCPs in each of the EU countries, to whom the educational materials have been previously delivered. The assessment of the effectiveness of the educational materials should also take into

account any change in the frequency and severity of adverse reactions related to the risks of the product that the educational materials aim to address.

- The MAH should submit to EMA, within the next PSUR (DLP: 30/06/2017), an updated table with data on the approval status and ways of dissemination of the NeuroBloc educational materials to the HCPs in all EU countries where the product is marketed, some feedback regarding the proposed questionnaires as well as an assessment of the effectiveness of the educational materials, the frequency and severity of any adverse reactions related to the risks of the product that the educational materials aim to address. Taking this evaluation into account, the MAH should reflect on the usefulness of the distribution of the educational materials. Finally these measures should be reflected in an updated RMP.

6.4.2. Repaglinide – NOVONORM (CAP) - EMEA/H/C/000187/LEG 018; PRANDIN (CAP) - EMEA/H/C/000362/LEG 018

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Menno van der Elst

Scope: MAH's responses to the request included in the recommendation of PSUSA/00002618/201412 adopted in September 2015 on the interaction between repaglinide and clopidogrel

Background

Repaglinide is a short-acting oral secretagogue indicated in adults with type 2 diabetes mellitus under certain conditions.

Following the evaluation of the most recently submitted PSUR for NovoNorm and Prandin, the PRAC requested the MAH to submit further data regarding concomitant use of repaglinide with clopidogrel and to discuss whether advice that concomitant use of clopidogrel and repaglinide should be avoided needs to be included in the product information (see PRAC minutes September 2015). The responses were assessed by the Rapporteur for further PRAC advice.

Summary of advice/conclusion(s)

- The PRAC discussed the MAH's responses and concluded that there is no conclusive evidence in the data provided by the MAH supporting that concomitant treatment of clopidogrel and repaglinide leads to a higher risk of hypoglycaemia in patients with type 2 diabetes. However, since the safety profile of the co-treatment has not been established in these patients, the concomitant use of clopidogrel and repaglinide should be avoided and in case concomitant use is necessary, monitoring of blood glucose and close clinical monitoring should be performed. The PRAC concluded that the product information should be updated accordingly.
- The MAH should submit to EMA, within 60 days, a variation to reflect in the product information that concomitant use of clopidogrel with repaglinide should be avoided.

7. Post-authorisation safety studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)[16]

See also Annex I 16.1.

7.1.1. Dinutuximab – UNITUXIN (CAP) - EMEA/H/C/PSP/0035

Applicant: United Therapeutics Europe Limited

PRAC Rapporteur: Sabine Straus

Scope: Protocol for a PASS registry to evaluate the long-term safety outcomes of dinutuximab in high-risk neuroblastoma patients (including central and peripheral nervous system, prevalence of organ dysfunction, long-term effects on growth and endocrine development, hearing loss, cardiac toxicity and survival data)

Background

Dinutuximab is a monoclonal chimeric antibody indicated for the treatment of high-risk neuroblastoma in patients aged 12 months to 17 years, under certain conditions, in combination with granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-2 (IL-2), and isotretinoin.

A protocol for a PASS registry to evaluate the long-term safety outcomes of dinutuximab in high-risk neuroblastoma patients (including central and peripheral nervous system, prevalence of organ dysfunction, long-term effects on growth and endocrine development, hearing loss, cardiac toxicity and survival data) was submitted by the MAH in accordance with the conditions to the marketing authorisation(s).

Endorsement/Refusal of the protocol

- The PRAC, having considered the draft protocol version 1 in accordance with Article 107n of Directive 2001/83/EC, objected to the draft protocol for the above listed medicinal product(s), as the Committee considered that that the design of the study did not fulfil the study objectives. A number of concerns regarding the study objectives, the study design, the milestones, the study participants and setting, the variables, the data sources, the study size and the data analysis should be resolved before the final approval of the study protocol.
- The MAH should submit a revised PASS protocol within 60 days to the EMA. A 60 days-assessment timetable will be applied

7.1.2. Sebelipase alfa – KANUMA (CAP) - EMEA/H/C/PSP/0036

Applicant: Alexion Europe SAS

PRAC Rapporteur: Qun-Ying Yue

Scope: Protocol for a PASS: a non-interventional, multicentre, prospective disease and clinical outcome registry of patients with lysosomal acid lipase deficiency (LAL-D) to further understand the disease, its progression and any associated complication, and to evaluate the long-term efficacy (normalisation of hepatic function) and safety of Kanuma (in

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

particular hypersensitivity reactions, including anaphylaxis, and anti-drug antibodies development potentially impacting response to drug)

Background

Sebelipase alfa is a recombinant human lysosomal acid lipase (rhLAL) indicated for long-term enzyme replacement therapy (ERT) in patients of all ages with lysosomal acid lipase (LAL) deficiency.

A protocol for a non-interventional, multicentre, prospective disease and clinical outcome registry of patients with lysosomal acid lipase deficiency (LAL-D) to further understand the disease, its progression and any associated complication, and to evaluate the long-term efficacy (normalisation of hepatic function) and safety of Kanuma (in particular hypersensitivity reactions, including anaphylaxis, and development of anti-drug antibodies potentially impacting on the response to the drug was submitted by the MAH in accordance with the conditions to the marketing authorisation(s).

Endorsement/Refusal of the protocol

- The PRAC, having considered the draft protocol version 2.0 in accordance with Article 107n of Directive 2001/83/EC, objected to the draft protocol for the above listed medicinal product(s), as the Committee considered that that the design of the study did not fulfil the study objectives. A number of concerns regarding the milestones, the study objectives, the variables, and data collection should be resolved before the final approval of the study protocol.
- The MAH should submit a revised PASS protocol within 60 days to the EMA. A 60 days-assessment timetable will be applied

7.2. Protocols of PASS non-imposed in the marketing authorisation(s)[17]

See also Annex I 16.2.

7.2.1. Rituximab – MABTHERA (CAP) - EMEA/H/C/000165/MEA/093.1

Applicant: Roche Registration Limited

PRAC Rapporteur: Doris Stenver

Scope: Revised PASS registry protocol for a long-term surveillance study of rituximab (Mabthera)-treated patients with granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA) following MAH's responses to MEA 093 request for supplementary information (RSI)

Background

Mabthera is a centrally authorised medicine containing rituximab, a genetically engineered chimeric mouse/human monoclonal antibody, indicated for non-Hodgkin's lymphoma (NHL), chronic lymphocytic leukaemia (CLL), and rheumatoid arthritis as well as for granulomatosis with polyangiitis and microscopic polyangiitis under certain conditions.

As part of the RMP for Mabthera, the MAH was required to conduct a PASS to determine the long-term safety of rituximab for the treatment of granulomatosis with polyangiitis (GPA) or

[17] 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

microscopic polyangiitis (MPA). The aim was to better characterize the risk profile of rituximab by collecting safety-focused data in patients with GPA/MPA who have been treated with rituximab or other available therapies. The MAH therefore submitted a draft protocol for such a PASS, using data submitted to the UKIVAS[18] registry as the data source for the RItuximab surveillance study in VASculitis (RIVAS), which has been assessed by the Rapporteur. The PRAC was requested to provide advice to CHMP on the protocol submitted by the MAH. A request for supplementary information was adopted in September 2015 (see PRAC minutes September 2015). The responses were assessed by the Rapporteur for further PRAC advice.

Summary of advice

- The MAH submitted a revised PASS protocol along with responses to the list of questions. Most of the issues raised in the previous round of assessment are now considered resolved. However there are a number of outstanding issues remaining on how switchers will be handled in the statistical model, on the exclusion criteria, the variables and the statistical analysis plan.
- The revised study protocol for this PASS could be acceptable provided an updated protocol and satisfactory responses to a list of questions agreed by the PRAC is submitted to the EMA within 30 days.

7.3. Results of PASS imposed in the marketing authorisation(s)[19]

7.3.1. Trimetazidine (NAP) - EMEA/H/N/PSR/0001

Applicant: Les Laboratoires Servier

PRAC Rapporteur: Dolores Montero Corominas

Scope: Results of a drug utilisation study (DUS) in five European countries, using cross sectional analysis, to assess the extent of prescriptions of trimetazidine for its withdrawn ophthalmological and/or ear, nose and throat (ENT) indications among general practitioners, ophthalmologists and ENT specialists

Background

Trimetazidine is a metabolic agent indicated as add-on therapy for the symptomatic treatment of adults with stable angina pectoris who are inadequately controlled by or intolerant to first-line antianginal therapies.

In line with the conclusions of a referral under Article 31 of Directive 2001/83/EC conducted by the CHMP in 2012 for trimetazidine-containing medicines (EMEA/H/A-31/1305), MAHs were required to conduct a post-authorisation safety study (drug utilisation study) to verify the compliance of prescribers with respect to the restricted indication following the referral. The draft protocol for this study was assessed by the PRAC, followed by the submission of the final study results for assessment by the PRAC. For background information, see PRAC minutes February 2014 and PRAC minutes October 2015.

[18] UK and Ireland Vasculitis Rare Disease Group
[19] In accordance with Article 107p-q of Directive 2001/83/EC

Based on the assessment of the final report of the non-interventional PASS conducted by MAH Servier, the PRAC issued a recommendation on the marketing authorisation(s) of the concerned nationally authorised medicine containing trimetazidine.

Summary of advice

- Based on the review of the final report of the non-interventional PASS, the PRAC considered that the risk-benefit balance of trimetazidine-containing products concerned by the PASS final report remains unchanged.
- Nevertheless, the current terms of the marketing authorisation(s) should be varied[20] in order to remove the condition of the marketing authorisation(s) to conduct a non-interventional PASS.
- In addition, based on the final study results, the following Member States: France, Greece and Spain may consider the need to reinforce the message to HCPs about the removing the indications of the referral related to ear, nose and throat (ENT) conditions.

7.3.2. Trimetazidine (NAP) - EMEA/H/N/PSR/J/0002

Applicant: Lupin (Europe) Limited (on behalf of consortium)

PRAC Rapporteur: Dolores Montero Corominas

Scope: Results of a drug utilisation study (DUS): a joint PASS survey among healthcare professionals to assess knowledge and attitudes on prescribing conditions of trimetazidine in Bulgaria, Czech Republic, Estonia, France, Hungary, Latvia, Lithuania, Poland, Portugal, Romania, Slovakia, and Spain; results of a database DUS: trimetazidine drug utilization study in European countries using databases – analysis for France, Hungary, Romania and Spain

Background

Trimetazidine is a metabolic agent indicated as add-on therapy for the symptomatic treatment of adults with stable angina pectoris who are inadequately controlled by or intolerant to first-line antianginal therapies.

In line with the conclusions of a referral under Article 31 of Directive 2001/83/EC conducted by the CHMP in 2012 for trimetazidine-containing medicines (EMEA/H/A-31/1305), MAHs were required to conduct a post-authorisation safety study (drug utilisation study) to verify the compliance of prescribers with respect to the restricted indication following the referral. A consortium of MAHs submitted a draft protocol for this study for assessment by the PRAC. The consortium now submitted the final study results for assessment by the PRAC.

Based on the assessment of the final report of the joint non-interventional PASS, the PRAC issued a recommendation on the marketing authorisations of the concerned nationally authorised medicines containing trimetazidine.

Summary of advice

[20] Update of the conditions of the marketing authorisation(s). The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

- Based on the review of the final report of the joint non-interventional PASS, the PRAC considered that the risk-benefit balance of trimetazidine-containing products concerned by the PASS final report remains unchanged.
- Nevertheless, the current terms of the marketing authorisation(s) should be varied[21] in order to remove the condition of the marketing authorisation(s) to conduct a non-interventional PASS.
- In addition, based on the final study results, the following member states: France, Portugal and Spain may consider the need to reinforce the message to HCPs about the conclusions of the referral removing the indications related to ear, nose and throat (ENT) conditions.

7.4. Results of PASS non-imposed in the marketing authorisation(s)[22]

See also Annex I 16.4.

7.4.1. Ipilimumab – YERVOY (CAP) - EMEA/H/C/002213/II/0038

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Sabine Straus

Scope: Submission of the final study report for study CA184242: risk minimisation tool effectiveness evaluation survey. The RMP (version 12) is updated accordingly

Background

Ipilimumab is a cytotoxic T-lymphocyte antigen-4 (CTLA-4) indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults.

The MAH had committed to perform the following non-interventional PASS: study CA18424, a patients and HCPs survey, as listed in the RMP. The Rapporteur assessed the final results of study CA18424, a PASS to assess the effectiveness of the additional risk minimisation measures agreed at the time of granting of the marketing authorisation.

Summary of advice

- The PRAC discussed the final results from study CA18424, a patients and HCPs survey conducted in 10 countries that evaluated the effectiveness of the additional risk minimisation measures agreed at the time of granting of the marketing authorisation. The PRAC noted that the response rate of this survey was very low (only 4.6% of the invited HCPs participated in the survey). While awareness and usage of the HCP tool (HCP brochure) and the patient information brochure were quite high among HCPs, knowledge of the management of immune-related adverse reactions was low. With regard to patients, approximately one–third of the patients was not aware of/stated they had not received the patient tools (patient information brochure and patient alert card). When aware of the existence, patients seemed to use the patient information brochure. However, almost half the patients who had received the patient alert card

[21] Update of the conditions of the marketing authorisation(s). The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position
[22] 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

reported not using it (7 of 16 patients). More than half of the patients were lacking knowledge on the details of the specific syndromes.

- Considering these results, the PRAC agreed on a list of questions to the MAH. As part of the request for supplementary information, the MAH should discuss the usefulness of the additional risk minimisation tools (for HCPs and patients) and if appropriate, the need to revise the RMP with proposals for better approaches. The PRAC agreed in addition to consult the Scientific Advisory Group in Oncology (SAG-O) on the need to maintain the HCP brochure and on whether the patient information brochure (including the alert card) can be considered a useful additional risk minimisation measure.

Post-meeting note: In relation to the PRAC advice to consult the SAG-O on the educational materials, the CHMP considered that instead, the EMA should coordinate the collection of data through learned societies.

7.4.2. Pioglitazone – ACTOS (CAP) - EMEA/H/C/000285/WS/0827; GLUSTIN (CAP) - EMEA/H/C/000286/WS/0827 pioglitazone, glimepiride – TANDEMACT (CAP) - EMEA/H/C/000680/WS/0827 pioglitazone, metformin – COMPETACT (CAP) - EMEA/H/C/000655/WS/0827; GLUBRAVA (CAP) - EMEA/H/C/000893/WS/0827

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Almath Spooner

Scope: Submission of the final results from observational study PROactive together with post-hoc analysis of Kaiser Permanente Northern California (KPNC) and comprehensive review of the data on prostate cancer risk. The RMP is updated accordingly

Background

Actos and Glustin are centrally authorised medicines containing pioglitazone, a thiazolidinedione (TZD) with hypoglycemic (antihyperglycemic, antidiabetic) action indicated as second or third line treatment of type 2 diabetes mellitus as monotherapy, dual therapy or triple oral therapy under certain conditions. Tandemact is a centrally authorised medicine containing pioglitazone and glimepiride, a TZD and a sulfonylurea respectively, indicated as second line treatment of adult patients with type 2 diabetes mellitus who show intolerance to metformin or for whom metformin is contraindicated and who are already treated with a combination of pioglitazone and glimepiride. Competact and Glubrava are centrally authorised medicines containing pioglitazone and metformin, a TZD and a biguanide respectively, indicated as second line treatment of type 2 diabetes mellitus adult patients, particularly overweight patients, who are unable to achieve sufficient glycaemic control at their maximally tolerated dose of oral metformin alone.

The MAH had committed to perform the following non-interventional PASS: the PROactive extension study, an observational study of patient cohorts who previously received long-term treatment with pioglitazone or placebo in addition to existing antidiabetic medications (study AD-4833-EC445), as listed in the RMP. In addition the MAH also committed to perform post-hoc analyses of the Kaiser Permanente North Carolina (KPNC) non-bladder cancer malignancy study: a pharmacoepidemiological study using the KPNC database to explore the risk of other (non-bladder) neoplasia based on comparative incidence of non-bladder malignancy in type 2 diabetes I pioglitazone and non-pioglitazone users (study AD4833-403), as listed in the RMP. The Rapporteur the MAH's responses (see PRAC minutes October 2015).

Summary of advice

- The PRAC discussed the MAH's responses to the request for supplementary information. The PRAC noted that an observed small increased risk of prostate cancer still remains in the observational KPNC non-bladder malignancy study (HR=1.13, [95% CI 1.02-1.26]) and an imbalance in the PROactive extension study (HR=1.50, [95% CI 0.98-2.29]). However, in the absence of supportive evidence from other data sources including the meta-analysis of clinical trials conducted by the MAH and the MAH's non-clinical studies, the PRAC concluded that the possible association of prostate cancer and pioglitazone should remain a signal warranting further investigation. The results of a further epidemiological study designed to evaluate this signal are anticipated in Q3 2016 and will be evaluated by the PRAC. The MAH should continue to monitor and integrate knowledge from any relevant and available data streams in its ongoing evaluation of the issue.

7.5. Interim results of imposed and non-imposed PASS submitted before the entry into force of the revised variation regulation[23]

See also Annex I 16.5.

7.5.1. Strontium ranelate – OSSEOR (CAP) - EMEA/H/C/000561/ANX/039; PROTELOS (CAP) - EMEA/H/C/000560/ANX/039

Applicant: Les Laboratoires Servier

PRAC Rapporteur: Ulla Wändel Liminga

Scope: First annual report for an imposed non-interventional safety study to evaluate the effectiveness of the applied risk minimisation measures, including a description of the treated patient population in everyday clinical practice (reference to EMEA/H/C/PSP/j/0013.1– ANX 034)

Background

Strontium ranelate is indicated for the treatment of severe osteoporosis in postmenopausal women at high risk for fracture to reduce the risk of vertebral and hip fractures and the treatment of severe osteoporosis in adult men at increased risk of fracture.

A protocol for a PASS to evaluate the effectiveness of the applied risk minimisation measures, including a description of the treated patient population in everyday clinical practice was submitted by the MAH in accordance with the conditions to the marketing authorisation and was endorsed by the PRAC in January 2015 (see PRAC minutes January 2015). The MAH has now submitted interim results (the first annual report) of this PASS which were assessed by the PRAC Rapporteur for PRAC review.

Summary of advice

- The PRAC discussed the interim results of the PASS which provided preliminary partial results for the first two objectives (to characterize utilisation patterns of strontium ranelate in three periods and to estimate the prevalence of contraindications in strontium ranelate users during the same three periods). The PRAC noted that these preliminary results indicate that the additional risk minimisation measures, imposed as

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

part of the outcome of the Article 20 referral (EMA/235924/2014), disseminated in March 2014 have had a substantial impact. The incidence and the prevalence of use of strontium ranelate have both decreased in the combined analysis as well as in the individual analyses from 5 countries: Denmark, Italy, Netherlands, Spain, and the UK. These have decreased by more than 40 % amongst prevalent users of strontium renalate and by almost 30% amongst incident users, while no changes in the prevalence of peripheral arterial disease (PAD) has been observed. No further action based on these interim results was considered needed by the PRAC. The final PASS study report is expected by Q4 2017.

7.6. Others

See also Annex I 16.6.

7.6.1. Pegaptanib sodium – MACUGEN (CAP) - EMEA/H/C/000620/LEG 049

Applicant: PharmaSwiss Ceska Republika s.r.o

PRAC Rapporteur: Jean-Michel Dogné

Scope: Cumulative review of the available data for systemic exposure and adverse events with Macugen [from R/62]

Background

Pegaptanib is a pegylated modified oligonucleotide indicated for the treatment of neovascular (wet) age-related macular degeneration (AMD) in adults.

As part of the renewal of the marketing authorization, the MAH was requested to provide a cumulative review of the available data for systemic exposure and systemic adverse events with Macugen and based on these data discuss the applicability of the warning for Macugen.

Summary of advice

- The PRAC discussed the cumulative review of the available data for systemic exposure and adverse events with pegaptanib provided by the MAH. Considering the relatively low exposure of pagaptanib, the PRAC considered that it is not possible to exclude the potential risk of arterial thromboembolic events linked to systemic exposure. However, also considering that at present, a class labelling exists for all vascular endothelial growth factor (VEGF) inhibitors, the PRAC recommended that a class warning about the systemic effects of anti-VEGF should also be implemented for pegaptanib. The MAH should therefore submit to the EMA, within 60 days, a variation to update the product information accordingly as appropriate.

7.7. New Scientific Advice

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

7.8. Ongoing Scientific Advice

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

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

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

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

8.1. Annual reassessments of the marketing authorisation

See also Annex I 17.1.

8.1.1. Antithrombin alfa – ATRYN (CAP) - EMEA/H/C/000587/S/00026 (without RMP)

Applicant: GTC Biotherapeutics UK Limited

PRAC Rapporteur: Isabelle Robine

Scope: Annual reassessment of the marketing authorisation

Background

Antithrombin alfa is a serine protease inhibitor indicated for the prophylaxis of venous thromboembolism in surgery of adult patients with congenital antithrombin deficiency.

ATryn, a centrally authorised medicine containing antithrombin alfa, was authorised in 2006 under exceptional circumstances. The benefit-risk of ATryn is reviewed on a yearly basis by the CHMP and PRAC based on the submission and assessment of additional post-authorisation data (i.e. specific obligations). The PRAC is responsible for providing advice to the CHMP on this annual re-assessment with regard to safety and risk management aspects.

Summary of advice

- Based on the review of the available information on the status of the fulfilment of specific obligations and safety data submitted, the PRAC considered that the MAH should submit satisfactory responses to a request for supplementary information (RSI) before the annual re-assessment procedure for ATryn (antithrombin alfa) can be concluded.
- The PRAC considered that the MAH should provide further information relating to the low patient recruitment for the study under specific obligation SOB 002[24]. The MAH should also provide a proposal to promote the enrolment of hereditary deficient patients when ATryn is available in the EU to address the immunological safety concerns. The MAH should submit an RMP updated accordingly.

See also under 8.3.1.

8.2. Conditional renewals of the marketing authorisation

None

[24] Post-marketing surveillance program in EU and US including an immunosurveillance programme (collection of efficacy and safety data and detection of antibodies, if any, against endogenous antithrombin, goat antithrombin and goat milk proteins)

8.3. Renewals of the marketing authorisation

See also Annex I 17.3.

8.3.1. Antithrombin alfa – ATRYN (CAP) - EMEA/H/C/000587/R/0024 (without RMP)

Applicant: GTC Biotherapeutics UK Limited

PRAC Rapporteur: Isabelle Robine

Scope: 5-year renewal of the marketing authorisation

Background

Antithrombin alfa is a serine protease inhibitor indicated for the prophylaxis of venous thromboembolism in surgery of adult patients with congenital antithrombin deficiency.

ATryn, a centrally authorised medicine containing antithrombin alfa, was authorised in 2006.

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

Summary of advice

- Based on the review of the available pharmacovigilance data for ATryn (antithrombin alfa), the PRAC considered that the MAH should submit satisfactory responses to a request for supplementary information (RSI) before this procedure can be concluded.

- The PRAC considered that the MAH should provide further information relating to the low patient recruitment for the study under specific obligation SOB 002[25]. See also under 8.1.1.

8.3.2. Nomegestrol, estradiol – ZOELY (CAP) - EMEA/H/C/001213/R/0032 (without RMP)

Applicant: Teva B.V.

PRAC Rapporteur: Corinne Fechant

Scope: 5-year renewal of the marketing authorisation

Background

Nomegestrol acetate is a selective progestogen and estradiol is an estrogen. In combination, nomegestrol/estradiol is indicated for oral contraception.

Zoely, a centrally authorised medicine containing nomegestrol/estradiol, was authorised in 2011.

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

Summary of advice

[25] Post-marketing surveillance program in EU and US including an immunosurveillance programme (collection of efficacy and safety data and detection of antibodies, if any, against endogenous antithrombin, goat antithrombin and goat milk proteins)

- Based on the review of the available pharmacovigilance data for Zoely (nomegestrol/estradiol) the PRAC considered that an additional 5-year renewal is necessary. Further characterisation of the risk of venous thromboembolism (VTE) in women taking Zoely compared to women taking an oral combined contraceptive containing levonorgestrel is warranted through the ongoing PASS[26] imposed following the conclusions of the referral procedure under Article 31 of Directive 2001/83/EC for combined hormonal contraceptives (CHCs) (EMEA/H/A-31/1356) which concluded in 2013, and for which the final report is anticipated in October 2017.

9. Product related pharmacovigilance inspections

9.1. List of planned pharmacovigilance inspections

None

9.2. Ongoing or concluded pharmacovigilance inspections

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

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

10.1. Safety related variations of the marketing authorisation

None

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

None

10.3. Other requests

None

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

11.1. Safety related variations of the marketing authorisation

None

[26] Prospective observational study to assess in particular the risk of venous thromboembolic events (VTE) and arterial thromboembolic events (ATE) in nomegestrol/estradiol users compared with the VTE risk in users of combined oral contraceptives containing levonorgestrel

11.2. Other requests

11.2.1. Bosentan - NL/H/3407/001-2/DC, NL/H/3421/001-2/DC, NL/H/3422/001-2/DC

PRAC Lead: Menno van der Elst

Scope: PRAC consultation on the evaluation of initial marketing authorisation applications under the decentralised procedure for a generic medicinal product in order to consider the need for additional pharmacovigilance activities to reduce the number of new digital ulcers in patients with systemic sclerosis and ongoing digital ulcer disease

Disclosure of information related to this section on a medicinal product in the pre-authorisation phase cannot be released at the present time as it is deemed to contain commercially confidential information.

11.2.2. Iron for intravenous (IV) use (NAP)

Applicant: various

PRAC Lead: Corinne Fechant

Scope: PRAC consultation on the evaluation of a PASS feasibility study: evaluation of European databases for studies evaluating the risk of hypersensitivity reactions in users of intravenous iron compounds (database feasibility evaluation report), literature review of ferumoxytol and other IV iron-containing medicinal products and hypersensitivity reactions, annual cumulative reviews of hypersensitivity reactions for IV iron-containing medicinal products

Background

Intravenous (IV) iron-containing products, nationally authorised medicinal products, are indicated in the treatment of iron deficiency when the oral route is insufficient or poorly tolerated especially in CKD patients (hemodialysis), but also in pre- or post-operative situations, or in case of intestinal absorption disorders.

As part of the outcome of the Article 31 referral procedure on intravenous iron-containing medicinal products (EMEA/H/A-31/1322) finalised at the level of CHMP in 2013, the MAHs were requested to conduct a post-authorisation safety study (PASS) to further characterise the safety concerns relating to serious hypersensitivity reactions. To address this request, a consortium of MAHs of IV iron compounds has been established with the objective of assessing the feasibility of conducting a European multinational PASS on the utilisation of IV iron compounds and the risk of serious hypersensitivity reactions among users of IV iron compounds, to be conducted in several existing population-based automated health care data sources. Following PRAC advice to the Member States on a common protocol synopsis for the PASS feasibility assessment, the consortium of MAHs was requested to provide an updated feasibility study. For background information, see PRAC minutes March 2015..

For the current PRAC meeting, France, requested the advice of the PRAC on the assessment of the updated feasibility study report.

Summary of advice

- Based on the review of the available data, the PRAC considered that there are limitations when evaluating the risk of anaphylaxis in the identified databases and

advised on the need to consider further other databases. The PRAC supported the new anticipated sample size, taking into consideration the article by *Auerbach et al.*[27] in NEJM as well as the need for another IV-iron classification similar to that described in the article by *Wang et al.*[28] in JAMA.

- The PRAC agreed with the conclusions of the Rapporteur that should be duly taken into account by the consortium of MAHs in order to submit a PASS protocol to the EMA, within 30 days, in line with the provisions of Article 107n of Directive 2001/83/EC.

11.2.3. Trimetazidine (NAP)

Applicant: Les Laboratoires Servier (Vastarel)

PRAC Lead: Dolores Montero Corominas

Scope: PRAC consultation on 1) evaluation of interim study results for a nested case-control study based on data from the registry of the European Society of Cardiology to evaluate of the risk of extrapyramidal syndrome (EPS) in patients with a chronic ischemic cardiovascular disease (CICD) taking trimetazidine; 2) feasibility study report using the SIDIAP[29] database to assess the feasibility for a PASS on the potential association of extrapyramidal symptoms with trimetazidine

As per the conclusions of the referral procedure under Article 31 of Directive 2001/83/EC finalised by the CHMP in 2012 for trimetazidine-containing medicines (EMEA/H/A-31/1305), a PASS was imposed to the MAHs to assess and estimate, in routine medical practice, the risk of extrapyramidal symptoms (EPS) including Parkinsonism associated with trimetazidine, particularly its incidence, severity, relationship to trimetazidine and outcome after treatment withdrawal. The PASS was requested to be performed using a case-control design nested within the long-term European Society of Cardiology (ESC) chronic ischemic cardiovascular disease (CICD) registry. For background information, see PRAC minutes February 2014. Later on, the MAH was also requested to investigate other data sources such as databases of electronic primary healthcare records. The MAH proposed an overview of the potential European data sources, in which SIDIAP[30] was retained for a more in-depth feasibility evaluation.

As the appointed Rapporteur for the evaluation of the protocol and results of the PASS, Spain requested PRAC advice on the assessment of the interim study results submitted at national level and the report of the feasibility study using the SIDIAP database to assess the feasibility for a PASS on the potential association of extrapyramidal symptoms with trimetazidine.

Summary of advice

- Based on the review of the interim results, and taking into consideration the trend of decreasing trimetazidine exposure in the EU, the PRAC concurred that the nested case-control study using the ESC registry will be unlikely to further reduce any outstanding uncertainties on the safety profile of trimetazadine in a timely manner. Considering that risk of Parkinsonian symptoms is adequately reflected in the current product information of trimetazidine-containing products and that the use of trimetazidine is contraindicated

[27] Auerbach M, Rodgers GM. Intravenous iron. New England Journal of Medicine. 2007;357(1):93–94
[28] Wang C et al., Comparative risk of anaphylactic reactions associated with intravenous iron products. Journal of the American Medical Association. JAMA. 2015;314(19):2062-2068. doi:10.1001/jama.2015.15572
[29] Information system for the development of primary care research
[30] Information system for the improvement of research in primary care

in patients with Parkinson's disease and related symptoms, the PRAC considered that the nested case-control study using the ESC registry, which is an obligation included as a condition of the marketing authorisation, could be replaced by continuing monitoring of risk minimisation activities through routine pharmacovigilance measures and followed-up within PSURs, within a specific section for extrapyramidal symptoms.

- With reference to the feasibility study using the SIDIAP database, the PRAC noted the results provided by the MAH and acknowledged the difficulties in retrieving reliable information in patients with EPS using this source of information. The PRAC agreed with the conclusions from Spain that this would not provide meaningful results.

12. Organisational, regulatory and methodological matters

12.1. Mandate and organisation of the PRAC

None

12.2. Coordination with EMA Scientific Committees or CMDh

None

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

12.3.1. EMA workshop on the role of pharmacokinetic and pharmacodynamic measurements in the use of direct oral anticoagulants (DOAC) held on 23 November 2015 – feedback

PRAC lead: Jean-Michel Dogné

The PRAC was updated on the EMA workshop on the role of pharmacokinetic (PK) and pharmacodynamic (PD) measurements in the use of direct oral anticoagulants (DOAC) held on 23 November 2015 and its conclusions. The EMA secretariat also provided feedback on the discussion held at the CHMP in January 2016 during which an agreement in principle was reached to finalise the ongoing legally binding post-authorisation measures (LEGs) as per timelines agreed for individual products. The possibility to evaluate further PK/PD data as part of a research project will be explored.

12.3.2. Enhanced early dialogue to foster development and facilitate accelerated assessment: PRIME project

The EMA secretariat presented to the PRAC an update on the PRIME project designed to facilitate the development and accelerated assessment of innovative medicines of major public health interest, in particular from the viewpoint of therapeutic innovation. Following the end of the public consultation in December 2015, the draft reflection paper has been revised and will be adopted by the CHMP during its February 2016 meeting with the aim of launching the PRIME scheme in March 2016 (EMA/89921/2016). An oversight group is being set up with the objective to discuss the eligibility requests received every month with the SAWP and EMA officers that are conducting the reviews, prior to their discussion at SAWP and CHMP. The aim of the group, to be convened on a monthly basis, is to build and ensure consistency, particularly as this new activity is being implemented. It will also support any

change of general guidance as experience on PRIME is gained. In addition to SAWP and CHMP members, a call for participation of chairs or alternate representative from PDCO, COMP, CAT and PRAC is being launched. PRAC delegates were invited to send their nominations by 26 February 2016.

12.3.3. Scientific Advice Working Party (SAWP) – consultation procedure: criteria and process

The EMA secretariat presented to the PRAC a proposal for PRAC consultation on scientific advice (outside the ongoing pilot for non-imposed post-authorisation studies). This consultation procedure would be considered when requests for scientific advice include questions falling under the expertise of the PRAC (e.g. RMP), excluding PASS protocols. Draft criteria for PRAC consultation on scientific advice requests and a proposed process were presented to the PRAC. Follow-up discussion is scheduled in March 2016.

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

12.6.1. Innovative Medicines Initiative (IMI)2 Patient Preferences in benefit-risk assessment during the life cycle – potential for PRAC participation

The EMA secretariat presented to the PRAC the Innovative Medicines Initiative (IMI)2 Patient Preferences in benefit-risk assessment during the life cycle project and its key research questions. As part of the IMI2 call 5, the PRAC was invited to be involved. PRAC delegates were invited to send nominations by 15 March 2016.

12.7. PRAC work plan

12.7.1. PRAC work plan 2016

The EMA secretariat presented a revised draft of the 2016 PRAC work plan which was adopted by the PRAC.

Post-meeting note: on 24 February 2016, the 2016 PRAC work plan (EMA/148594/2016) was published on the EMA website.

12.8. Planning and reporting

None

12.9. Pharmacovigilance audits and inspections

12.9.1. Pharmacovigilance systems and their quality systems

None

12.9.2. Pharmacovigilance inspections

None

12.9.3. Pharmacovigilance audits

None

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

12.10.1. Periodic safety update reports

None

12.10.2. Granularity and Periodicity Advisory Group (GPAG)

PRAC lead: Menno van der Elst; Margarida Guimarães

The PRAC was updated on the activities of the GPAG, focussing on harmonising and streamlining the EURD list, and 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 February 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 in February 2016, the updated EURD list was adopted by the CHMP and CMDh at their February 2016 meetings and published on the EMA website on 04/03/2016, 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)

12.10.5. Project and Maintenance Group (PMG) 2 - common understanding on EU PSUR single assessment: Joint PRAC/CMDh recommendation paper - draft

PRAC lead: Margarida Guimarães; Menno van der Elst; Jolanta Gulbinovic

The EMA secretariat presented to the PRAC the draft joint PRAC/CMDh recommendation paper on a common understanding on the EU PSUR single assessment for nationally authorised products prepared following the workshop held on 14-15 January 2016 composed of EMA staff, PRAC and CMDh delegates. PRAC delegates were invited to send their comments in advance of the PRAC Strategic Review and Learning Meeting in Utrecht, Netherlands organised on 3-4 March 2016.

12.11. Signal management

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

PRAC lead: Sabine Straus

At the organisational matters teleconference held on 25 February 2016, the PRAC was updated on the outcome of the January 2016 SMART Working Group (SMART WG) work stream WS1. The SMART WS1 discussed communication on nationally authorised products (NAPs) signals/safety issues from other regulatory authorities (follow-up from July 2015, see PRAC minutes July 2015). Since September 2015, the EMA circulates monthly a cumulative table with the issues communicated by other regulatory authorities to the national competent authorities. This tool has been piloted for 6 months as agreed in July 2015. The feedback received was that it was beneficial to have all the safety issues compiled together even if Member States normally subscribe to safety alerts from other international agencies. It was agreed to continue the monthly communication without any changes. As a follow-up from January 2016 (see PRAC minutes January 2016), the EMA presented an update on homeopathic products and PRAC recommendations for signals in the context of the thioctic acid signal follow-up. It was highlighted that the proposal for a request for supplementary information to the MAH of thioctic acid was not supported by the PRAC as some Member States may consider that actions for such products should be taken at national level. Several options to move forward were presented by EMA and discussed. No agreement was reached as divergent positions were expressed during the meeting. This topic will be re-discussed in March 2016.

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 24/02/2016 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 – external testing plan

The EMA secretariat presented to the PRAC the external testing plan for the EudraVigilance (EV) auditable requirement project. To provide an opportunity to EV stakeholders to use the EV system including EudraVigilance Data Analysis System (EVDAS) and provide feedback, external testing activities will be organised by EMA in June and July 2016. A closed group of national competent authorities and MAHs will be invited to participate through a call for volunteers to be launched in March 2016. PRAC delegates were invited to send their nominations by 15 March 2016. The final list of participants will be confirmed in April/May 2016.

12.13.1. EudraVigilance – annual report 2015

The EMA secretariat presented to the PRAC the 2015 EudraVigilance annual report for the European Parliament, the Council and the Commission. Following the next EMA Management Board meeting organised in March 2016, the report will be submitted to the EU institutions and published on the EMA website in Q2 2016.

12.14. Risk management plans and effectiveness of risk minimisations

12.14.1. Risk management systems

None

12.14.2. Risk Management Plan (RMP) revised assessment process for initial marketing authorisation(s) - performance indicators

The importance of documenting the experience gained so far with the RMP revised assessment process for initial marketing authorisations applications (MAAs) was highlighted to the PRAC. The EMA secretariat presented to the PRAC the proposed approach which includes setting performance indicators covering the three phases of the MAAs based on the key principles of the revised RMP review process. In a first stage, the EMA secretariat would collect simple quantitative metrics and in a second stage, informed by the results of the first stage, the CHMP and PRAC Rapporteurs would be requested to fill in surveys on the content and on qualitative aspects for each MAA started between May and December 2015. As the outcome of this review of the experience gained with the revised RMP process, a report would be prepared and presented to both the CHMP and the PRAC by Q3 2016. Some comments and suggestions were raised by the PRAC on how to make this revised RMP process as clear and smooth as possible. The PRAC endorsed the proposal to start collecting the quantitative metrics to be collected by the EMA secretariat. However, the PRAC advised to come back on the qualitative metrics by the end of 2016.

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

None

12.15. Post-authorisation safety studies (PASS)

12.15.1. Direct oral anticoagulants(DOACs)– proposal for an EMA funded study on the risk of major bleeding

See also under 12.3.1.

The EMA Secretariat presented to the PRAC a proposal for an EMA-funded non-interventional study to assess the safety and effectiveness of direct oral anticoagulants (DOAC) and warfarin in EU patients with non-valvular atrial fibrillation, with particular focus on high-risk patients. An outline of the methods was presented. The proposal will be further refined taking into account the comments made by the PRAC.

12.15.2. Post-authorisation Safety Studies – imposed PASS

None

12.15.3. 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. Effects tables in selected important benefit-risk reviews

PRAC lead: Rafe Suvarna

As part of the ongoing benefit-risk project, over the last year, a small group of PRAC members have been discussing options on how to utilise the effects tables in pharmacovigilance procedures. Some information on the effects tables (objectives, some guidance, their practical use and an example) was presented to the PRAC along with an update on the mandate of the 'PRAC benefit-risk task force' and its activities to date. The draft principles developed so far on the effects tables by the task force were also highlighted to the PRAC. In terms of the next steps and in line with the 2016 PRAC work plan, the PRAC agreed to pilot the use of the effects tables prospectively in a small number of selected important benefit-risk reviews in 2016. PRAC delegates and their assessors were invited to send their nominations to join the task force by 25 February 2016.

12.19.2. Incident management

None

12.20. Others

12.20.1. Initial marketing authorisation(s) - revised accelerated assessment procedural timetables – follow up

PRAC lead: Ulla Wändel Liminga

The topic was deferred to the March 2016 PRAC meeting.

12.20.2. Pharmacovigilance operation and implementation - streamlined governance structure - finalisation

The EMA Secretariat presented to the PRAC a revised proposal to review and streamline the EU network governance structure for pharmacovigilance implementation and operation and outlined the role of the PRAC on the proposed governance of operational aspects following the discussion held at the PRAC in January 2016 (see PRAC minutes January 2016) and the feedback received from the European Risk Management Strategy Facilitation Group (ERMS-FG). Considering that the points raised in January 2016 have been satisfactorily addressed, the PRAC adopted the revised proposal which was presented at Heads of Medicines Agencies (HMA) later in February 2016 for agreement. The revised EU network governance structure for pharmacovigilance implementation and operation is planned to be in operation as of April 2016.

12.20.3. Strategy on impact of pharmacovigilance - PRAC interest group (IG) mandate

The EMA secretariat presented to the PRAC the draft mandate of the PRAC interest group on measuring the impact of pharmacovigilance activities following the adoption and publication of the strategy in January 2016 (see PRAC minutes January 2016). The PRAC adopted the draft mandate.

13. Any other business

None

14. Annex I – Risk management plans

14.1. 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).

14.1.1. Albutrepenonacog alfa - EMEA/H/C/003955, Orphan

Applicant: CSL Behring GmbH

Scope: Prophylaxis and treatment of bleeding in all patients with haemophilia B5.1 RMP - Medicines in pre-authorisation phase

14.1.2. Amikacin - EMEA/H/C/003936, Orphan

Applicant: Insmed Limited

Scope: Treatment of nontuberculous mycobacterial lung infection

14.1.3. Autologous CD34$^+$ enriched cell fraction that contains CD34$^+$ cells transduced with retroviral vector that encodes for the human adenosine deaminase (ADA) cDNA sequence - EMEA/H/C/003854, Orphan

Applicant: GlaxoSmithKline Trading Services, ATMP[31]

Scope: Treatment of severe combined immunodeficiency

14.1.4. Daclizumab - EMEA/H/C/003862

Scope: Treatment of multiple sclerosis

14.1.5. Grazoprevir, elbasivir - EMEA/H/C/004126

Scope: Treatment of chronic hepatitis C (CHC) in adults

14.1.6. Infliximab - EMEA/H/C/004020

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

14.1.7. Opicapone - EMEA/H/C/002790

Scope: Treatment of Parkinson’s disease and motor fluctuations

[31] Advanced-therapy medicinal product

14.1.8. Pancreas powder - EMEA/H/C/002070

Scope: Treatment in exocrine pancreatic insufficiency

14.1.9. Trifluridine, tipiracil - EMEA/H/C/003897

Scope: Treatment of colorectal cancer

14.2. 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).

14.2.1. Bosentan – STAYVEER (CAP) - EMEA/H/C/002644/WS/0899/G; TRACLEER (CAP) - EMEA/H/C/000401/WS/0899/G

Applicant: Marklas Nederlands BV (Stayveer), Actelion Registration Ltd (Tracleer)

PRAC Rapporteur: Isabelle Robine

Scope: Revised RMP in order to align the additional risk minimisation measures of three safety concerns ('pulmonary oedema associated with veno-occlusive disease', 'interaction with sildenafil' and 'interaction with antiretrovirals'), with the requirements defined in Annex II of the Marketing Authorisation. In addition, the RMP is updated in line with the outcome of previous procedures and other corrections

14.2.2. Efavirenz, emtricitabine, tenofovir disoproxil – ATRIPLA (CAP) - EMEA/H/C/000797/WS/0860/G emtricitabine – EMTRIVA (CAP) - EMEA/H/C/000533/WS/0860/G emtricitabine, rilpivirine, tenofovir disoproxil – EVIPLERA (CAP) - EMEA/H/C/002312/WS/0860/G

Applicant: Bristol-Myers Squibb and Gilead Sciences Ltd (Atripla), Gilead Sciences International Ltd (Emtriva, Eviplera)

PRAC Rapporteur: Rafe Suvarna

Scope: Revised RMP following the PRAC review on the 'comprehensive analysis of existing data on lipodystrophy (updated literature data on non-clinical and clinical aspects)' and 'comprehensive analysis of existing data on lactic acidosis (updated literature data on non-clinical and clinical aspects)'

14.2.3. Emtricitabine, tenofovir disoproxil – TRUVADA (CAP) - EMEA/H/C/000594/WS/0903/G tenofovir disoproxil – VIREAD (CAP) - EMEA/H/C/000419/WS/0903/G

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Julie Williams

Scope: Revised RMP to remove 'lactic acidosis with severe hepatomegaly with steatosis' as an important identified risk following the PRAC outcome whereby the warning statements regarding lactic acidosis have been removed from the product information for emtricitabine and tenofovir disoproxil-containing products. In addition, the RMP is revised to remove 'lipodystophy' as an important identified risk following the PRAC outcome on lipodystrophy whereby the warning statements regarding lipodystrophy have been removed from the product information for antiretroviral products. Furthermore, the RMP is amended with the

due date for submission of GS-US-236-0103 Week 192 clinical study report from 'Q3 2015' to 'Q1 2016'

14.2.4. Liraglutide – SAXENDA (CAP) - EMEA/H/C/003780/WS/0892; VICTOZA (CAP) - EMEA/H/C/001026/WS/0892

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Menno van der Elst

Scope: Revised RMP to change the due date submission of the final study report for the Optum database study (study NN2211-3784) from 'January 2016' to 'August 2016'

14.2.5. Orlistat – ALLI (CAP) - EMEA/H/C/000854/II/0052

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Rafe Suvarna

Scope: Revised RMP in order to update the safety concerns, pharmacovigilance plan and risk minimisations measures and replace PASS study RH01159 (survey based on the use of a questionnaire handed out by pharmacists at the point of sale) with PASS study 204675 (study comprising an online questionnaire on a series of virtual customers to include both customers who are suitable and unsuitable for alli)

14.2.6. Pertuzumab – PERJETA (CAP) - EMEA/H/C/002547/II/0021/G

Applicant: Roche Registration Limited

PRAC Rapporteur: Doris Stenver

Scope: Revised RMP in order to update the length of the follow-up period of the PERUSE study from 45 to 60 months. Consequently, the due date for study completion is amended to September 2020. Annex II of the product information is updated accordingly. In addition, further to the outcome of PSUSA/10125/201412 procedure concluding on the inclusion of diarrhoea management in the product information, the RMP is updated accordingly

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

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Rafe Suvarna

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

14.2.8. Zoledronic acid – ACLASTA (CAP) - EMEA/H/C/000595/II/0056

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Revised RMP (version 11.0) in order to introduce a patient reminder card as an additional risk minimisation measure for the existing identified risk of osteonecrosis of the jaw (ONJ) and to propose indicators to measure the effectiveness of this new measure. Furthermore, the clinical trial exposure data from the Aclasta study ZOL446H2301E2 has been updated

14.2.9. Zoledronic acid – ZOMETA (CAP) - EMEA/H/C/000336/II/0069

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Doris Stenver

Scope: Revised RMP in order to reflect the PSUR data approved in procedure EMEA/H/C/PSUSA/00003149/201408 and to introduce a patient reminder card in osteonecrosis of the jaw (ONJ) as an additional risk minimisation measure as well as to propose indicators to measure its effectiveness . The MAH has also taken the opportunity to add to the RMP the targeted follow-up checklist for the identified risk of hypocalcaemia

14.3. 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).

14.3.1. Abatacept – ORENCIA (CAP) - EMEA/H/C/000701/II/0097

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Kirsti Villikka

Scope: Extension of indication in combination with methotrexate (MTX) in the treatment of adults with rheumatoid arthritis (RA) who have highly active disease with poor prognostic factors not previously treated with MTX. As a consequence, sections 4.1 and 5.1 of the SmPC are updated based on results from the AVERT study (IM101226). The Package Leaflet is updated accordingly. Moreover, the updated RMP version 20 has been submitted

14.3.2. Afatinib – GIOTRIF (CAP) - EMEA/H/C/002280/II/0012

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension of indication to include patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) of squamous histology progressing on or after platinum-based chemotherapy for Giotrif. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet and RMP are updated accordingly

14.3.3. Aflibercept – EYLEA (CAP) - EMEA/H/C/002392/II/0027/G

Applicant: Bayer Pharma AG

PRAC Rapporteur: Isabelle Robine

Scope: Grouped variations to include: 1) 3-year data of the pivotal trials VIVID-DME and VISTA-DME; 2) protocol T data with a consequential update to section 5.1 of the SmPC . Furthermore, the MAH took the opportunity to condense the SmPC section 4.8 text relating to antiplatelet trialists' collaboration (APTC) as recommended by EMA during II/0018 variation (diabetic macular oedema (DME) 2 year data), to shorten SmPC section 5.1 as committed by the MAH during II/0021 variation (indication myopic choroidal neovascularisation (mCNV)), to align the annexes with the latest QRD templates (version 9.1, June 2015) and to implement minor changes within age-related macular degeneration (AMD) and DME posology sections

14.3.4. Brentuximab vedotin – ADCETRIS (CAP) - EMEA/H/C/002455/II/030/G

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Sabine Straus

Scope: Update of section 4.4 of the SmPC in order to add a warning on hepatotoxicity, further to the outcome of PSUSA/00010039/201502. The Package Leaflet and RMP are updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. Update of section 4.4 of the SmPC in order to add a warning on gastrointestinal complications. The Package Leaflet and RMP are updated accordingly. Update of section 4.4 of the SmPC in order to update a warning on pulmonary toxicity, providing examples of pulmonary toxicity diagnoses. The Package Leaflet and RMP are updated accordingly. Update of section 4.8 of the SmPC in order to implement data from the pivotal phase II studies. The RMP is updated accordingly

14.3.5. Cobimetinib – COTELLIC (CAP) - EMEA/H/C/003960/II/0001/G

Applicant: Roche Registration Limited

PRAC Rapporteur: Sabine Straus

Scope: Update of sections 4.2, 4.8, 5.2 of the SmPC to reflect the results of GP29342, with recommendations for patients with hepatic impairment. In addition, the MAH took the opportunity to correct an alternative use of 'CYP3A' and 'CYP3A4' in sections 4.4, 4.5 of the SmPC in line with previous recommendations. The Package Leaflet is updated accordingly. Furthermore, the MAH submitted results of the in vitro CYP time-dependent inhibition study (study 15-1983)

14.3.6. Conestat alfa – RUCONEST (CAP) - EMEA/H/C/001223/II/0032

Applicant: Pharming Group N.V

PRAC Rapporteur: Rafe Suvarna

Scope: Update of sections 4.2 and 4.4 of the SmPC in order to remove the requirement for testing all new patients for immunoglobulin E (IgE) antibodies against rabbit epithelium (dander) prior to initiation of treatment and the requirement for repeat testing of IgE antibodies to rabbit dander. The Package Leaflet is updated accordingly. Annex II is updated to reflect changes to the educational material. Furthermore, the RMP is updated accordingly

14.3.7. Empagliflozin – JARDIANCE (CAP) - EMEA/H/C/002677/II/0014

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Miguel-Angel Macia

Scope: Extension of indication to include the prevention of cardiovascular events, based on the final data of the cardiovascular safety phase III clinical trial EMPA-REG OUTCOME. As a consequence, section 4.1 of the SmPC is updated in order to add safety information on this study. The Package Leaflet is updated accordingly

14.3.8. Epoetin alfa – ABSEAMED (CAP) - EMEA/H/C/000727/WS/0877; BINOCRIT (CAP) - EMEA/H/C/000725/WS/0877; EPOETIN ALFA HEXAL (CAP) - EMEA/H/C/000726/WS/0877

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

PRAC Rapporteur: Isabelle Robine

Scope: Update of sections 4.2 and 4.4 of the SmPC in order to add a subcutaneously (SC) route of administration in addition to the intravenous route in the treatment of anaemia in patients with chronic renal failure based on clinical study HX575-308 (SENSE) to address MEA 024.1. The Package Leaflet is updated accordingly. In addition, the Worksharing applicant (WSA) took the opportunity to make minor editorial changes in the SmPC and to update the list of local representatives in Greece in the Package Leaflet and to bring the product information in line with the latest QRD template version 9.1. Moreover, the RMP (version 15) is updated accordingly

14.3.9. Everolimus – AFINITOR (CAP) - EMEA/H/C/001038/II/0048

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Martin Huber

Scope: Extension of indication to include the treatment of unresectable or metastatic, well-differentiated non-functional neuroendocrine tumours of gastrointestinal or lung origin in adults with progressive disease for Afinitor. As a consequence, sections 4.1, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated accordingly. Furthermore, the product information is brought in line with the latest QRD template version 9.1

14.3.10. Everolimus – VOTUBIA (CAP) - EMEA/H/C/002311/II/0039

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Martin Huber

Scope: Update of section 4.8 (for dispersible tablets) and section 4.8 and 5.2 (for tablets) of the SmPC in order to update the safety and efficacy information with the data from the final clinical study report (CSR) comprising the extension phase of study M2302 in fulfilment of ANX 027. The Annex II and Package Leaflet are updated accordingly. In addition, update of section 4.2 and 4.4 of the SmPC in order to align the wording with the product information of Afinitor. Furthermore, the MAH took the opportunity to bring the PI in line with the latest QRD template version 9.1. Moreover, the RMP (version 11.0) is updated accordingly

14.3.11. Human papillomavirus vaccine [types 6, 11, 16, 18] (recombinant, adsorbed) – GARDASIL (CAP) - EMEA/H/C/000703/WS/0908; SILGARD (CAP) - EMEA/H/C/000732/WS/0908

Applicant: Sanofi Pasteur MSD SNC (Gardasil), Merck Sharp & Dohme Limited (Silgard)

PRAC Rapporteur: Qun-Ying Yue

Scope: Update of section 5.1 of the SmPC with long-term data based on the final clinical study report (CSR) for study P018-11, in fulfilment of Article 46 and post-authorisation measures MEA 020.6 and MEA 020.7, as well as interim reports for studies P015-21, P019-21 and P020-21. In addition, the MAH took the opportunity to implement changes related to the latest QRD template v 9.1, in particular, the MAH has combined the SmPC of the pre-filled syringe and the vial presentations, Annex II and labelling. The RMP (version 10.0) is updated accordingly

14.3.12. Ibrutinib – IMBRUVICA (CAP) - EMEA/H/C/003791/II/0013

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Julie Williams

Scope: Update of SmPC sections 4.8 and 4.9 of the SmPC with information on hepatic failure and hepatotoxicity. The Package Leaflet and RMP are updated accordingly

14.3.13. Ibrutinib – IMBRUVICA (CAP) - EMEA/H/C/003791/II/0017/G

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Julie Williams

Scope: Update of sections 4.8 and 5.1 of the SmPC in order to update the safety and efficacy information following the conclusion of studies MCL 3001 and CLL 3001. Annex II has been updated to remove the obligation to submit the final clinical study report (CSR) of study MCL 3001. The Package Leaflet and RMP are updated accordingly. In addition, the final CSRs for studies MCL 2001 and 1117 are provided in fulfilment of post-authorisation measures. Furthermore, data from two other trials are included in support of the use of ibrutinib in combination with other agents in subjects with relapsed/refractory chronic lymphocytic leukaemia (CLL)

14.3.14. Idelalisib – ZYDELIG (CAP) - EMEA/H/C/003843/II/0011

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Rafe Suvarna

Scope: Extension of indication to include the combination of idelalisib with ofatumumab. As a consequence, sections 4.1, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated accordingly

14.3.15. Idelalisib – ZYDELIG (CAP) - EMEA/H/C/003843/II/0018

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Rafe Suvarna

Scope: Update of sections 4.4 and 4.8 of the SmPC in order to update the safety information regarding Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) based on post marketing experience. The Package Leaflet and the RMP (version 1.5) are updated accordingly

14.3.16. Iloprost – VENTAVIS (CAP) - EMEA/H/C/000474/II/0051/G

Applicant: Bayer Pharma AG

PRAC Rapporteur: Isabelle Robine

Scope: Grouped variations to introduce an additional nebulizer 'FOX Bavent' for application of Ventavis 10 µg/ mL and Ventavis 20 µg/mL solution, a change of pack sizes within the range of current approved pack sizes as well as consequential changes to SmPC sections 4.2, 4.4, 6.5 and 8, to the labelling and Package Leaflet. In addition, the MAH took the opportunity to delete reference in the product information to nebulizers which are no longer available by the device manufacturer (ProDose and HaloLite), to merge the texts for Ventavis 10 µg/ mL and Ventavis 20 µg/ mL,nebulizer solution into one SmPC and one Package Leaflet text, to update the list of local representatives in the Package Leaflet, to implement minor editorial changes in the annexes and to bring the annexes in line with the latest QRD template version 9.1. The RMP (version 7.0) is updated accordingly

14.3.17. Lumacaftor, ivacaftor – ORKAMBI (CAP) - EMEA/H/C/003954/II/0002

Applicant: Vertex Pharmaceuticals (Europe) Ltd.

PRAC Rapporteur: Almath Spooner

Scope: Update of sections 4.4, 4.8 and 5.1 of SmPC to add information regarding increase of blood pressure and decrease of heart rate following the review of clinical safety data. The Package Leaflet is updated accordingly

14.3.18. Maraviroc – CELSENTRI (CAP) - EMEA/H/C/000811/II/0045/G

Applicant: ViiV Healthcare Uk Limited

PRAC Rapporteur: Qun-Ying Yue

Scope: Submission of the 148 week final clinical study report (CSR) for study A4001098, a multicentre, randomized, blinded, placebo-controlled study to evaluate the safety of maraviroc in combination with other antiretroviral agents in HIV-1-infected subjects co-infected with Hepatitis C and/or Hepatitis B virus. The RMP (version 10.0) is updated to add information related to study A4001098 and to include modifications requested during variation II/41 (i.e. to remove the associations between study A4001098 and the safety concern 'potential to alter immune function: infection since this concern is not addressed by the study). Moreover, the RMP contains also information on ongoing studies (studies A4001067, POEM and WS324148/CRT115653, CADIRIS). In addition, the due dates for A4001067 (category 3 study) are amended in the RMP

14.3.19. Olaparib – LYNPARZA (CAP) - EMEA/H/C/003726/II/0001/G

Applicant: AstraZeneca AB

PRAC Rapporteur: Carmela Macchiarulo

Scope: Update of sections 4.4, 4.5 and 4.6 of the SmPC in order to include further information related to pharmacokinetic interactions based on the in vivo interaction study D0816C00008, three in vitro interaction studies (studies ADME-AZS-Wave3-140714, ADME-AZS-Wave3-140725 and 140483) and data from previously submitted interaction studies. The provision of the final clinical study report (CSR) for study D0816C00008 addresses the post-authorisation measure MEA 004. Furthermore, the MAH provided the study report of in vitro study 8305083. In addition, the MAH took the opportunity to add the published ATC code in section 5.1 of the SmPC, and to implement minor editorial changes in the SmPC, labelling and Package Leaflet. The RMP (version 6) is updated accordingly. Further, the MAH is taking the opportunity to update the due dates for the provision of the final study reports of the category 3 studies D0816C00005 and D0816C00006, and to add the new category 3 study D0816C00010

14.3.20. Panobinostat – FARYDAK (CAP) - EMEA/H/C/003725/II/0001

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Julie Williams

Scope: Update of section 5.1 of the SmPC in order to update the safety information with regards to the key secondary endpoint of overall survival in study D2308 to fulfil a post authorisation measure (ANX 001). The Annex II of the product information is updated accordingly to remove the specific obligations. The RMP (version 2.2) is updated accordingly

14.3.21. Panobinostat – FARYDAK (CAP) - EMEA/H/C/003725/II/0003

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Julie Williams

Scope: Update of section 4.6 of the SmPC in order to update the safety information with a recommendation for pregnancy testing prior to treatment with Farydak, as a cautionary measure. The RMP (version 2.3) is updated accordingly

14.3.22. Pembrolizumab – KEYTRUDA (CAP) - EMEA/H/C/003820/II/0002

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Sabine Straus

Scope: Update of sections 4.8, 5.1 and 5.2 of the SmPC with safety and pharmacokinetic (PK) data based on the clinical study report (CSR) of study P006v01. Furthermore, the adverse drug reaction (ADR) Guillain-Barré Syndrome (GBS) is added to sections 4.4 and 4.8 of the SmPC. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to revise the text referring to fatal cases of pneumonitis in section 4.4 of the SmPC, to implement minor editorial changes in the annexes, to align the SmPC, Annex II, labelling and Package Leaflet with the latest QRD template version 9.1, and to update the contact details of the local representative in Luxemburg in the Package Leaflet. The RMP (version 2.0) is updated accordingly

14.3.23. Regorafenib – STIVARGA (CAP) - EMEA/H/C/002573/II/0015/G

Applicant: Bayer Pharma AG

PRAC Rapporteur: Sabine Straus

Scope: Update of SmPC section 5.1 based on the results from study 15967 (CONSIGN), a phase 3b trial in patients with metastatic colorectal cancer. In addition, the MAH took the opportunity to provide long-term results from study 14874 (GRID addendum clinical study report (CSR)), a pivotal phase 3 trial in patients with gastrointestinal stromal tumour (GIST). The RMP (version 4.0) is updated accordingly

14.3.24. Thiotepa – TEPADINA (CAP) - EMEA/H/C/001046/II/0026

Applicant: Adienne S.r.l. S.U.

PRAC Rapporteur: Corinne Fechant

Scope: Update of section 4.8 of the SmPC in order to update the safety information on leukoencephalopathy. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to make editorial changes in the Product Information

14.3.25. Trastuzumab emtansine – KADCYLA (CAP) - EMEA/H/C/002389/II/0019/G

Applicant: Roche Registration Limited

PRAC Rapporteur: Doris Stenver

Scope: Grouped variation to amend Annex II of the product information to delete the obligation regarding the EMILIA (TDM4370g/BO21977) study (ANX 006). Furthermore, update of section 4.8 of the SmPC in order to update frequency of adverse drug reaction as a result of a pool data analysis from several clinical studies. The RMP is updated accordingly, including also changes related to inclusion and deletion of safety concerns in the RMP (enhanced pregnancy programme, evaluation of cardiac safety in patients with baseline left ventricular ejection fraction and efficacy of monotherapy versus trastuzumab associated to docetaxel). In addition, changes of the final clinical study report (CSR) due dates for the KRISTINE study (study BO28408) and the KAMILLA study (study mo28231) have been introduced. The MAH also took the opportunity to update the RMP following requests from previously assessed procedures (MEA 011.1 and ANX 007)

15. 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).

15.1. PSUR procedures including centrally authorised products only

15.1.1. Aclidinium bromide – BRETARIS GENUAIR (CAP); EKLIRA GENUAIR (CAP) - PSUSA/09005/201507

Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

Scope of procedure: Evaluation of a PSUSA procedure

15.1.2. Agalsidase alfa – REPLAGAL (CAP) - PSUSA/00069/201508

Applicant: Shire Human Genetic Therapies AB

PRAC Rapporteur: Sabine Straus

Scope of procedure: Evaluation of a PSUSA procedure

15.1.3. Ataluren – TRANSLARNA (CAP) - PSUSA/10274/201507

Applicant: PTC Therapeutics International Limited

PRAC Rapporteur: Sabine Straus

Scope of procedure: Evaluation of a PSUSA procedure

15.1.4. Catridecacog – NOVOTHIRTEEN (CAP) - PSUSA/10034/201507

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Isabelle Robine

Scope of procedure: Evaluation of a PSUSA procedure

15.1.5. Dapagliflozin, metformin – XIGDUO (CAP) - PSUSA/10294/201507

Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

Scope of procedure: Evaluation of a PSUSA procedure

15.1.6. Dolutegravir – TIVICAY (CAP); dolutegravir, abacavir, lamivudine - TRIUMEQ (CAP) - PSUSA/10075/201507

Applicant: ViiV Healthcare (Tivicay), ViiV Healthcare UK Limited (Triumeq)

PRAC Rapporteur: Julie Williams

Scope of procedure: Evaluation of a PSUSA procedure

15.1.7. Efavirenz, emtricitabine, tenofovir – ATRIPLA (CAP) - PSUSA/01201/201507

Applicant: Bristol-Myers Squibb and Gilead Sciences Ltd.

PRAC Rapporteur: Martin Huber

Scope of procedure: Evaluation of a PSUSA procedure

15.1.8. Eliglustat – CERDELGA (CAP) - PSUSA/10351/201507

Applicant: Genzyme Europe BV

PRAC Rapporteur: Dolores Montero Corominas

Scope of procedure: Evaluation of a PSUSA procedure

15.1.9. Icatibant – FIRAZYR (CAP) - PSUSA/01714/201507

Applicant: Shire Orphan Therapies GmbH

PRAC Rapporteur: Qun-Ying Yue

Scope of procedure: Evaluation of a PSUSA procedure

15.1.10. Idursulfase – ELAPRASE (CAP) - PSUSA/01722/201507

Applicant: Shire Human Genetic Therapies AB

PRAC Rapporteur: Rafe Suvarna

Scope of procedure: Evaluation of a PSUSA procedure

15.1.11. Infliximab – INFLECTRA (CAP), REMSIMA (CAP) - PSUSA/10106/201507

Applicant: Hospira UK Limited (Inflectra), Celltrion Healthcare Hungary Kft. (Remsima)

PRAC Rapporteur: Rafe Suvarna

Scope of procedure: Evaluation of a PSUSA procedure

15.1.12. Lipegfilgrastim – LONQUEX (CAP) - PSUSA/10111/201507

Applicant: Sicor Biotech UAB

PRAC Rapporteur: Julie Williams

Scope of procedure: Evaluation of a PSUSA procedure

15.1.13. Lomitapide – LOJUXTA (CAP) - PSUSA/10112/201507

Applicant: Aegerion Pharmaceuticals Limited

PRAC Rapporteur: Menno van der Elst

Scope of procedure: Evaluation of a PSUSA procedure

15.1.14. Modified vaccinia ankara virus – IMVANEX (CAP) - PSUSA/10119/201507 (with RMP)

Applicant: Bavarian Nordic A/S

PRAC Rapporteur: Rafe Suvarna

Scope of procedure: Evaluation of a PSUSA procedure

15.1.15. Peginterferon beta-1a – PLEGRIDY (CAP) - PSUSA/10275/201507

Applicant: Biogen Idec Ltd

PRAC Rapporteur: Julie Williams

Scope of procedure: Evaluation of a PSUSA procedure

15.1.16. Perampanel – FYCOMPA (CAP) - PSUSA/09255/201507

Applicant: Eisai Europe Ltd.

PRAC Rapporteur: Julie Williams

Scope of procedure: Evaluation of a PSUSA procedure

15.1.17. Rotavirus vaccine live oral monovalent – ROTARIX (CAP) - PSUSA/02665/201507

Applicant: GlaxoSmithKline Biologicals S.A.

PRAC Rapporteur: Jean-Michel Dogné

Scope of procedure: Evaluation of a PSUSA procedure

15.1.18. Simoctocog alfa – NUWIQ (CAP) - PSUSA/10276/201507

Applicant: Octapharma AB

PRAC Rapporteur: Ulla Wändel Liminga

Scope of procedure: Evaluation of a PSUSA procedure

15.1.19. Telithromycin – KETEK (CAP) - PSUSA/02881/201507

Applicant: Aventis Pharma S.A.

PRAC Rapporteur: Qun-Ying Yue

Scope of procedure: Evaluation of a PSUSA procedure

15.1.20. Tocofersolan – VEDROP (CAP) - PSUSA/02981/201507 (with RMP)

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

PRAC Rapporteur: Julie Williams

Scope of procedure: Evaluation of a PSUSA procedure

15.1.21. Vismodegib – ERIVEDGE (CAP) - PSUSA/10140/201507

Applicant: Roche Registration Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope of procedure: Evaluation of a PSUSA procedure

15.1.22. Vorapaxar – ZONTIVITY (CAP) - PSUSA/10357/201507

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Carmela Macchiarulo

Scope of procedure: Evaluation of a PSUSA procedure

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

None

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

15.3.1. Aciclovir (NAP) - PSUSA/00000048/201506

Applicant: various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

15.3.2. Alanine, arginine, aspartic acid, cysteine, glucose anhydrous, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, olive oil refined, ornithine, phenylalanine, proline, serine, sodium chloride, sodium glycerophosphate hydrated, soya bean oil refined, taurine, threonine, tryptophan, tyrosine, valine, potassium acetate, calcium chloride dihydrate, magnesium acetate tetrahydrate (NAP) - PSUSA/00010190/201506

Applicant: various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

15.3.3. Cefepime (NAP) - PSUSA/00000593/201506

Applicant: various

PRAC Lead: Margarida Guimarães

Scope: Evaluation of a PSUSA procedure

15.3.4. Clonazepam (NAP) - PSUSA/00000812/201506

Applicant: various

PRAC Lead: Maia Uusküla

Scope: Evaluation of a PSUSA procedure

15.3.5. Dexchlorpheniramine (NAP) - PSUSA/00000989/201506

Applicant: various

PRAC Lead: Leonor Chambel

Scope: Evaluation of a PSUSA procedure

15.3.6. Dihydroergocryptine (NAP) - PSUSA/00001074/201507

Applicant: various

PRAC Lead: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure

15.3.7. Ethinylestradiol, etonogestrel (NAP) - PSUSA/00001307/201507

Applicant: various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

15.3.8. Human fibrinogen (NAP) - PSUSA/00001624/201506

Applicant: various

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

15.3.9. Ibuprofen, pseudoephedrine (NAP) - PSUSA/00001711/201507

Applicant: various

PRAC Lead: Isabelle Robine

Scope: Evaluation of a PSUSA procedure

15.3.10. Magnesium sulfate (NAP) - PSUSA/00009225/201506

Applicant: various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

15.3.11. Manidipine (NAP) - PSUSA/00001932/201506

Applicant: various

PRAC Lead: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure

15.3.12. Misoprostol (gastrointestinal indication) (NAP) - PSUSA/00010291/201506

Applicant: various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

15.3.13. Nimesulide (systemic formulations) (NAP) - PSUSA/00009236/201506

Applicant: various

PRAC Lead: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

15.3.14. Nimesulide (topical formulations) (NAP) - PSUSA/00002165/201506

Applicant: various

PRAC Lead: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

15.3.15. Rabbit anti-human thymocyte (concentrate for solution for infusion) (NAP) - PSUSA/00010252/201506

Applicant: various

PRAC Lead: Maia Uusküla

Scope: Evaluation of a PSUSA procedure

15.3.16. Rabbit anti-human thymocyte (powder for solution for infusion) (NAP) - PSUSA/00010184/201506

Applicant: various

PRAC Lead: Maia Uusküla

Scope: Evaluation of a PSUSA procedure

15.3.17. Rupatadine (NAP) - PSUSA/00002673/201506

Applicant: various

PRAC Lead: Miguel-Angel Macia

Scope: Evaluation of a PSUSA procedure

15.3.18. Salmon calcitonin, synthetic analogue of eel calcitonin (NAP) - PSUSA/00000494/201506

Applicant: various

PRAC Lead: Miguel-Angel Macia

Scope: Evaluation of a PSUSA procedure

15.3.19. Sertindole (NAP) - PSUSA/00002695/201507

Applicant: various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

15.3.20. Solifenacin, tamsolusin (NAP) - PSUSA/00010285/201507

Applicant: various

PRAC Lead: Sabine Straus

Scope: Evaluation of a PSUSA procedure

15.3.21. Tiagabine (NAP) - PSUSA/00002942/201506

Applicant: various

PRAC Lead: Isabelle Robine

Scope: Evaluation of a PSUSA procedure

15.3.22. Tianeptine (NAP) - PSUSA/00002943/201506

Applicant: various

PRAC Lead: Isabelle Robine

Scope: Evaluation of a PSUSA procedure

15.3.23. Urapidil (NAP) - PSUSA/00003078/201507

Applicant: various

PRAC Lead: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

15.4. Follow-up to PSUR procedures

15.4.1. Pregabalin – LYRICA (CAP) - EMEA/H/C/000546/LEG 050; PREGABALIN PFIZER (CAP) - EMEA/H/C/003880/LEG 003

Applicant: Pfizer Limited

PRAC Rapporteur: Sabine Straus

Scope: MAH's responses to the request included in the recommendation of PSUSA/00002511/201501 adopted in September 2015: on positive de-challenge or re-challenge and temporal association between pregabalin use and the occurrence of hyponatraemia/syndrome of inappropriate antidiuretic hormone (SIADH)

16. 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.

16.1. Protocols of PASS imposed in the marketing authorisation(s)[32]

16.1.1. Dexamfetamine (NAP) - EMEA/H/N/PSP/0018.2

Applicant: Medice Arzneimittel Pütter GmbH & Co. KG.

PRAC Rapporteur: Julie Williams

Scope: Revised protocol for a PASS to evaluate the long-term safety profile of dexamfetamine in children with attention deficit hyperactivity disorder (ADHD), specifically targeting key issues such as cardiovascular events, growth and psychiatric related adverse events

16.2. Protocols of PASS non-imposed in the marketing authorisation(s)[33]

16.2.1. Alemtuzumab – LEMTRADA (CAP) - EMEA/H/C/003718/MEA/005.1

Applicant: Genzyme Therapeutics Ltd

PRAC Rapporteur: Torbjorn Callreus

Scope: Updated PASS protocol for a knowledge survey to assess the effectiveness of educational materials among healthcare professionals who prescribe alemtuzumab

16.2.2. Alglucosidase alfa – MYOZYME (CAP) - EMEA/H/C/000636/MEA/053.2

Applicant: Genzyme Europe BV

PRAC Rapporteur: Isabelle Robine

Scope: MAH's responses to MEA 053.1 [PASS study ALGMYC07390 protocol 'prevalence of immunology testing in patients treated with alglucosidase alfa with significant hypersensitivity/anaphylactic reaction'] as per the request for supplementary information (RSI) as adopted in December 2015

16.2.3. Apremilast – OTEZLA (CAP) - EMEA/H/C/003746/MEA/006.1

Applicant: Celgene Europe Limited

PRAC Rapporteur: Dolores Montero Corominas

[32] In accordance with Article 107n of Directive 2001/83/EC
[33] 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

Scope: MAH's response to MEA 006 [revised PASS protocol for CPRD (UK) data analysis for PsA and psoriasis] as per the request for supplementary information (RSI) as adopted in September 2015

16.2.4. Eliglustat – CERDELGA (CAP) - EMEA/H/C/003724/MEA/005.2

Applicant: Genzyme Europe BV

PRAC Rapporteur: Dolores Montero Corominas

Scope: MAH's revised protocol and responses to MEA 005.1 [PASS protocol for the drug utilisation study (DUS) of eliglustat for the treatment of Gaucher disease in Europe using electronic healthcare records] to address the PRAC's request for supplementary information (RSI) adopted in September 2015

16.2.5. Eliglustat – CERDELGA (CAP) - EMEA/H/C/003724/MEA/006.1

Applicant: Genzyme Europe BV

PRAC Rapporteur: Dolores Montero Corominas

Scope: MAH's revised protocol and responses to MEA 006 [PASS protocol for the drug utilisation study (DUS) of eliglustat for the treatment of Gaucher disease in the US population using MarketScan database] to address the PRAC's request for supplementary information (RSI) adopted in September 2015

16.2.6. Fenofibrate, simvastatin – CHOLIB (CAP) - EMEA/H/C/002559/MEA/002.2

Applicant: BGP Products Ltd

PRAC Rapporteur: Julie Williams

Scope: MAH's responses to MEA 002.1 [revised PASS protocol 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) as adopted in October 2014

16.2.7. Human normal immunoglobulin – HYQVIA (CAP) - EMEA/H/C/002491/MEA/004.2

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: MAH's responses to MEA 004 [Pregnancy registry PASS protocol (study 161301)] as per the request for supplementary information (RSI) as adopted in September 2013

16.2.8. Hydrocortisone – PLENADREN (CAP) - EMEA/H/C/002185/MEA/005.2

Applicant: Shire Services BVBA

PRAC Rapporteur: Qun-Ying Yue

Scope: MAH's responses to MEA 005.1 [PASS protocol for study SWE-DUS, study no.: 10918 -404 (SHP617-404): a Swedish, retrospective, study progress reports to be provided on a yearly basis evaluating the pattern of Plenadren use from as part of the PSURs Swedish quality registries], as per the request for supplementary information (RSI) as adopted in September 2015

16.2.9. Liraglutide – SAXENDA (CAP) - EMEA/H/C/003780/MEA/014.1

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Menno van der Elst

Scope: MAH's responses to MEA 014 [Drug utilisation study (DUS) protocol (study NN8022-4241): in-market utilisation of liraglutide used for weight management in Europe: a retrospective medical record review study], as per the request for supplementary information (RSI) as adopted in September 2015

16.2.10. Liraglutide – SAXENDA (CAP) - EMEA/H/C/003780/MEA/015.1

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Menno van der Elst

Scope: MAH's responses to MEA 015 [Drug utilisation study (DUS) protocol (study NN8022-4246): in-market utilisation of liraglutide used for weight management in the UK: a study in the CPRD primary care database], as per the request for supplementary information (RSI) as adopted in September 2015

16.2.11. Olaparib – LYNPARZA (CAP) - EMEA/H/C/003726/MEA/011.2

Applicant: AstraZeneca AB

PRAC Rapporteur: Carmela Macchiarulo

Scope: Revised protocol for a PASS to collect and/or retrieve prospective data from sizeable patient cohorts with ovarian cancer] following MAH's responses to MEA 011.1 request for supplementary information (RSI) as adopted in November 2015

16.2.12. Sonidegib – ODOMZO (CAP) - EMEA/H/C/002839/MEA/021

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Julie Williams

Scope: Protocol for study CLDE225A2404: a non-interventional, multi-national, multi-centre PASS to assess the long-term safety and tolerability of Odomzo (sonidegib) administered in patients with locally advanced basal cell carcinoma (laBCC)

16.2.13. Tenofovir disoproxil– VIREAD (CAP) - EMEA/H/C/000419/MEA/273.1

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Isabelle Robine

Scope: MAH's responses to MEA 0273 [draft protocol for PASS study GS-EU-174-1846: a multicentre, non-interventional, retrospective cohort study of patients with chronic hepatitis B and with moderate or severe renal impairment treated with Viread], as per the request for supplementary information (RSI) as adopted in December 2015

16.3. Results of PASS imposed in the marketing authorisation(s)[34]

None

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

16.4. Results of PASS non-imposed in the marketing authorisation(s)[35]

16.4.1. Agomelatine – THYMANAX (CAP) - EMEA/H/C/000916/II/0028

Applicant: Servier (Ireland) Industries Ltd.

PRAC Rapporteur: Kristin Thorseng Kvande

Scope: Submission of the final report of PASS study CLE-20098- 068: an 'observational cohort study to evaluate the safety of agomelatine in standard medical practice in depressed patients: a prospective, observational (non-interventional), international, multicentre cohort study' to fulfil a post-authorisation measure (MEA 06)

16.4.2. Agomelatine – VALDOXAN (CAP) - EMEA/H/C/000915/II/0030

Applicant: Les Laboratoires Servier

PRAC Rapporteur: Kristin Thorseng Kvande

Scope: Submission of results from an observational cohort study to evaluate the safety of agomelatine in standard medical practice in depressed patients, to fulfil a post-authorisation measure agreed in the RMP (MEA 006)

16.4.3. Anidulafungin – ECALTA (CAP) - EMEA/H/C/000788/II/0030

Applicant: Pfizer Limited

PRAC Rapporteur: Sabine Straus

Scope: Submission of final results of study A8851030: a retrospective cohort study of the risk of severe hepatic injury in hospitalised patients treated with echinocandins for candida infections, to fulfil a post-authorisation measure (MEA 023.10)

16.4.4. Dabigatran etexilate – PRADAXA (CAP) - EMEA/H/C/000829/II/0091/G

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Torbjorn Callreus

Scope: Submission of a group of variations containing 1) the final clinical study report (CSR) for 1160.118: an 'observational cohort study to evaluate the safety and efficacy of switching from Lovenox (enoxaparin) 40 mg to Pradaxa (dabigatran etexilate) 220 mg in patients undergoing elective total hip or knee replacement surgery' and consequent update of the RMP and 2) update of the timeline for availability of study 1160.144 report

16.4.5. Memantine – AXURA (CAP) - EMEA/H/C/000378/WS/0804; EBIXA (CAP) - EMEA/H/C/000463/WS/0804; MEMANTINE MERZ (CAP) - EMEA/H/C/002711/WS/0804

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

PRAC Rapporteur: Dolores Montero Corominas

Scope: Submission of the final results of a non-interventional PASS to examine the use of memantine and risk of prostate cancer (nationwide case-control studies in Denmark and Sweden) in order to fulfil MEA 031.5. The RMP (version 8.0) has been updated to: 1) delete

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

the important potential risk 'prostate cancer' based on the results of case control studies, 2) delete the important identified risk 'overdose with pump device' based on the PSUR#16 PRAC outcome and 3) update clinical trial exposure and post-authorisation experience

16.4.6. Temozolomide – TEMODAL (CAP) - EMEA/H/C/000229/II/0075

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Martin Huber

Scope: Submission of the final results from study MK 7365-295: an observational PASS regarding Temodal and severe acute liver injury in brain cancer patient

16.4.7. Ticagrelor – BRILIQUE (CAP) - EMEA/H/C/001241/II/0031

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Submission of a final study report for a drug utilisation study (DUS) to fulfil a post-authorisation measure (MEA 008): detailed description of patients who are prescribed ticagrelor for the first time and comparison with patients who are prescribed clopidogrel and prasugrel for the first time, with an estimation of the potential off-label use of ticagrelor. The study also aims to ascertain incident cases and estimate the crude incidence rate of selected safety outcomes among new users in the three cohorts of ticagrelor, clopidogrel and prasugrel

16.5. Interim results of imposed and non-imposed PASS submitted before the entry into force of the revised variation regulation[36]

16.5.1. Aflibercept – ZALTRAP (CAP) - EMEA/H/C/002532/MEA/003.3

Applicant: Sanofi-Aventis Groupe

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Second status report of PASS study AFLIBC06660: a drug utilisation study (DUS) to address potential for off-label use and particularly intravitreal off-label use using European databases

16.5.2. Apixaban – ELIQUIS (CAP) - EMEA/H/C/002148/MEA/012.4

Applicant: Bristol-Myers Squibb / Pfizer EEIG

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to MEA 012.3 [second interim report on a drug utilisation study (DUS) to monitor the potential off label use with apixaban: study of the utilisation patterns in Sweden (study B066017) and in the Netherlands (study B066018)] as per the request for supplementary information (RSI) as adopted at CHMP in September 2015

16.5.3. Canagliflozin – INVOKANA (CAP) - EMEA/H/C/002649/MEA/005.4

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Valerie Strassmann

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

Scope: MAH's responses to MEA 005.2 [canagliflozin independent data monitoring committee (IDMC) status reports for the DIA3008 CANVAS study], as per the request for supplementary information (RSI) as adopted in September 2015

16.5.4. Canagliflozin – INVOKANA (CAP) - EMEA/H/C/002649/MEA/005.5

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Valerie Strassmann

Scope: MAH's responses to MEA 005.3 [six-monthly status report of the canagliflozin independent data monitoring committee (IDMC) for the DIA3008 CANVAS study as requested in the RMP additional pharmacovigilance activity], as per the request for supplementary information (RSI) adopted in September 2015

16.5.5. Canagliflozin – INVOKANA (CAP) - EMEA/H/C/002649/MEA/006.1

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Valerie Strassmann

Scope: MAH's responses to MEA 006 [first status report of the canagliflozin independent data monitoring committee (IDMC) for the NE-3001 CREDENCE study as requested in the RMP additional pharmacovigilance activity], as per the request for supplementary information (RSI) adopted in September 2015

16.5.6. Canagliflozin, metformin – VOKANAMET (CAP) - EMEA/H/C/002656/MEA/004.4

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Menno van der Elst

Scope: MAH's responses to MEA 004.2 [canagliflozin independent data monitoring committee (IDMC) status reports for the DIA3008 CANVAS study], as per the request for supplementary information (RSI) adopted in September 2015

16.5.7. Canagliflozin, metformin – VOKANAMET (CAP) - EMEA/H/C/002656/MEA/004.5

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Menno van der Elst

Scope: MAH's responses to MEA 004.3 [Six-monthly status report of the canagliflozin independent data monitoring committee (IDMC) for the DIA3008 CANVAS study as requested in the RMP additional pharmacovigilance activity], as per the request for supplementary information (RSI) adopted in September 2015

16.5.8. Canagliflozin, metformin – VOKANAMET (CAP) - EMEA/H/C/002656/MEA/005.1

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Menno van der Elst

Scope: MAH's responses to MEA 005 [first status report of the canagliflozin independent data monitoring committee (IDMC) for the NE-3001 CREDENCE study as requested in the RMP additional pharmacovigilance activity], as per request for supplementary information (RSI) as adopted in September 2015

16.5.9. Efavirenz – SUSTIVA (CAP) - EMEA/H/C/000249/MEA/079.3

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Margarida Guimarães

Scope: MAH's responses to MEA 079.2 [second annual report for malignant events associated with efavirenz: diagnostic consulting network (DCN) report dated June 2015] as per the request for supplementary information (RSI) as adopted in September 2015

16.5.10. Efavirenz, emtricitabine, tenofovir disoproxil – ATRIPLA (CAP) - EMEA/H/C/000797/MEA/039.3

Applicant: Bristol-Myers Squibb and Gilead Sciences Ltd.

PRAC Rapporteur: Martin Huber

Scope: MAH's responses to MEA 039.2 [second annual report for malignant events associated with efavirenz: diagnostic consulting network (DCN) report dated June 2015] as per the request for supplementary information (RSI) as adopted in September 2015

16.5.11. Etanercept – ENBREL (CAP) - EMEA/H/C/000262/MEA/166

Applicant: Pfizer Limited

PRAC Rapporteur: Rafe Suvarna

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

16.5.12. Filgrastim – FILGRASTIM HEXAL (CAP) - EMEA/H/C/000918/MEA/007.1; ZARZIO (CAP) - EMEA/H/C/000917/MEA/007.1

Applicant: Sandoz GmbH

PRAC Rapporteur: Julie Williams

Scope: MAH's responses to MEA 007 [Submission of fourth interim report of 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], as per the request for supplementary information (RSI) as adopted in September 2015

16.5.13. Filgrastim – RATIOGRASTIM (CAP) - EMEA/H/C/000825/MEA/019.2

Applicant: Ratiopharm GmbH

PRAC Rapporteur: Kirsti Villikka

Scope: Third annual report on safety data concerning suspected cases of immunogenicity including adverse drug reaction data from all sources including spontaneous reports and reports from the severe chronic neutropenia international registry (SCNIR)

16.5.14. Filgrastim – TEVAGRASTIM (CAP) - EMEA/H/C/000827/MEA/019.2

Applicant: Teva GmbH

PRAC Rapporteur: Kirsti Villikka

Scope: Third annual report on safety data concerning suspected cases of immunogenicity including adverse drug reaction data from all sources including spontaneous reports and reports from the severe chronic neutropenia international registry (SCNIR)

16.5.15. Somatropin – OMNITROPE (CAP) - EMEA/H/C/000607/MEA/012.1

Applicant: Sandoz GmbH

PRAC Rapporteur: Sabine Straus

Scope: Interim report for study EP00-502 – PATRO Adults: a non-interventional post-marketing surveillance in adult patients with growth hormone deficiency treated with Omnitrope within routine clinical practice in Europe

16.6. Others

16.6.1. Vernakalant – BRINAVESS (CAP) - EMEA/H/C/001215/LEG 025.1

Applicant: Cardiome UK Limited

PRAC Rapporteur: Menno van der Elst

Scope: MAH's responses to LEG 025 [From II/09: requirement to promptly inform the CHMP of any future serious cases of hypotension, with or without fatal outcome. Such case reports will be accompanied by a causality assessment. With this LEG the MAH provides the details including the causality assessment of a hypotension case related to Brinavess], request for supplementary information (RSI) as adopted in July 2015

16.7. New Scientific Advice

None

16.8. Ongoing Scientific Advice

None

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

None

17. 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.

17.1. Annual reassessments of the marketing authorisation

17.1.1. Anagrelide – XAGRID (CAP) - EMEA/H/C/000480/S/0072 (without RMP)

Applicant: Shire Pharmaceutical Contracts Ltd

PRAC Rapporteur: Corinne Fechant

Scope: Annual reassessment of the marketing authorisation

17.1.2. Histamine dihydrochloride – CEPLENE (CAP) - EMEA/H/C/000796/S/0026 (without RMP)

Applicant: Meda AB

PRAC Rapporteur: Almath Spooner

Scope: Annual reassessment of the marketing authorisation

17.2. Conditional renewals of the marketing authorisation

None

17.3. Renewals of the marketing authorisation

17.3.1. Deferasirox – EXJADE (CAP) - EMEA/H/C/000670/R/0047 (without RMP)

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Corinne Fechant

Scope: 5-year renewal of the marketing authorisation

17.3.2. Entacapone – ENTACAPONE ORION (CAP) - EMEA/H/C/002440/R/00011 (without RMP)

Applicant: Orion Corporation

PRAC Rapporteur: Kirsti Villikka

Scope: 5-year renewal of the marketing authorisation

17.3.3. Ibandronic acid – IBANDRONIC ACID SANDOZ (CAP) - EMEA/H/C/002367/R/0017 (with RMP)

Applicant: Sandoz GmbH

PRAC Rapporteur: Doris Stenver

Scope: 5-year renewal of the marketing authorisation

17.3.4. Ipilimumab – YERVOY (CAP) - EMEA/H/C/002213/R/0035 (with RMP)

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Sabine Straus

Scope: 5-year renewal of the marketing authorisation

17.3.5. Levetiracetam – LEVETIRACETAM RATIOPHARM (CAP) - EMEA/H/C/002244/R/0014 (without RMP)

Applicant: Ratiopharm GmbH

PRAC Rapporteur: Veerle Verlinden

Scope: 5-year renewal of the marketing authorisation

17.3.6. Natalizumab – TYSABRI (CAP) - EMEA/H/C/000603/R/0091 (with RMP)

Applicant: Biogen Idec Ltd

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: 5-year renewal of the marketing authorisation

17.3.7. Pioglitazone, metformin – COMPETACT (CAP) - EMEA/H/C/000655/R/0057 (without RMP)

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Almath Spooner

Scope: 5-year renewal of the marketing authorisation

17.3.8. Temozolomide – TEMOZOLOMIDE SUN (CAP) - EMEA/H/C/002198/R/0019 (without RMP)

Applicant: Sun Pharmaceutical Industries Europe B.V.

PRAC Rapporteur: Martin Huber

Scope: 5-year renewal of the marketing authorisation

18. Annex II – List of participants

including any restrictions with respect to involvement of members / alternates / experts following evaluation of declared interests for the 8-11 February 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
Marianne Lunzer	Alternate	Austria	No interests declared	Full involvement
Jean-Michel Dogné	Member	Belgium	No restrictions applicable to	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			this meeting	
Veerle Verlinden	Alternate	Belgium	No interests declared	Full involvement
Maria Popova-Kiradjieva	Member	Bulgaria	No interests declared	Full involvement
Marina Dimov Di Giusti	Member	Croatia	No interests declared	Full involvement
Nectaroula Cooper	Member	Cyprus	No interests declared	Full involvement
Jana Mladá	Member	Czech Republic	No interests declared	Full involvement
Eva Jirsovà	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
Kimmo Jaakkola	Alternate	Finland	No interests declared	Full involvement
Isabelle Robine	Member	France	No interests declared	Full involvement
Corinne Fechant	Alternate	France	No restrictions applicable to this meeting	Full involvement
Martin Huber	Member	Germany	No interests declared	Full involvement
Valerie Strassmann	Alternate	Germany	No interests declared	Full involvement
Agni Kapou	Alternate	Greece	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	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			declared	
Amelia Cupelli	Alternate	Italy	No interests declared	Full involvement
Zane Neikena	Member	Latvia	No interests declared	Full involvement
Jolanta Gulbinovic	Member	Lithuania	No interests declared	Full involvement
Marcel Bruch	Member	Luxembourg	No interests declared	Full involvement
Amy Tanti	Member	Malta	No interests declared	Full involvement
Sabine Straus	Member	Netherlands	No interests declared	Full involvement
Menno van der Elst	Alternate	Netherlands	No interests declared	Full involvement
Ingebjørg Buajordet	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
Tatiana Magálová	Member	Slovakia	No interests declared	Full involvement
Miroslava Matíková	Alternate	Slovakia	No restrictions applicable to this meeting	Full involvement
Milena Radoha-Bergoč	Member	Slovenia	No restrictions applicable to this meeting	Full involvement
Dolores Montero Corominas	Member	Spain	No interests declared	Full involvement
Ulla Wändel Liminga	Member	Sweden	No interests declared	Full involvement
Qun-Ying Yue	Alternate	Sweden	No interests declared	Full involvement
Julie Williams	Member	United Kingdom	No interests declared	Full involvement
Rafe Suvarna	Alternate	United Kingdom	No interests	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			declared	
Jane Ahlqvist Rastad	Member	Independent scientific expert	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
Lennart Waldenlind	Member	Independent scientific expert	No interests declared	Full involvement
Kirsten Myhr	Alternate	Healthcare Professionals' Representative	No interests declared	Full involvement
Albert van der Zeijden	Member	Patients' Organisation Representative	No restrictions applicable to this meeting	Full involvement
Marco Greco	Alternate	Patients' Organisation Representative	No interests declared	Full involvement
Veronika Deščíková	Expert - via telephone*	Czech Republic	No interests declared	Full involvement
Radim Tobolka	Expert - via telephone*	Czech Republic	No interests declared	Full involvement
Martin Erik Nyeland	Expert - in person*	Denmark	No restrictions applicable to this meeting	Full involvement
Kim Bouillon	Expert - via telephone*	France	No interests declared	Full involvement
Muriel Echemann	Expert - in person*	France	No interests declared	Full involvement
Eleanor Carey	Expert - via telephone*	Ireland	No interests declared	Full involvement
Rhea Fitzgerald	Expert - in person*	Ireland	No restrictions applicable to this meeting	Full involvement
Joan Deckers	Expert - in person*	Netherlands	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
André Elferink	Expert - in person*	Netherlands	No interests declared	Full involvement
Frederika Adriana van Nimwegen	Expert - via telephone*	Netherlands	No interests declared	Full involvement
Sophia Venzke	Expert - via telephone*	Netherlands	No interests declared	Full involvement
Daniel Nogueras Zondag	Expert - in person*	Netherlands	No interests declared	Full involvement
Joanna Plichta	Expert - in person*	Poland	No interests declared	Full involvement
Emilia Cercenado Mansilla	Expert - via telephone*	Spain	No interests declared	Full involvement
Fernando de Andres Trelles	Expert - in person*	Spain	No interests declared	Full involvement
Eva Segovia	Expert - in person*	Spain	No interests declared	Full involvement
Charlotte Backman	Expert - in person*	Sweden	No interests declared	Full involvement
Annika Ekbom Schnell	Expert - via telephone*	Sweden	No restrictions applicable to this meeting	Full involvement
Rolf Gedeborg	Expert - in person*	Sweden	No interests declared	Full involvement
Filip Josephson	Expert - in person*	Sweden	No interests declared	Full involvement
Karl-Mikael Kälkner	Expert - via telephone*	Sweden	No interests declared	Full involvement
Miriam Taekema	Expert - via telephone*	Sweden	No interests declared	Full involvement
Anna Vikerfors	Expert - via telephone*	Sweden	No interests declared	Full involvement
Nourieh Hoveyda	Expert - in person*	United Kingdom	No interests declared	Full involvement
Jennifer Matthissen	Expert - in person*	United Kingdom	No interests declared	Full involvement
Andrew Ruddick	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.

19. 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

20. Explanatory notes

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

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

(Items 2 and 3 of the PRAC minutes)

A referral is a procedure used to resolve issues such as concerns over the safety or benefit-risk balance of a medicine or a class of medicines. In a referral, the EMA is requested to conduct a scientific assessment of a particular medicine or class of medicines on behalf of the European Union (EU). For further detailed information on safety related referrals please see:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000150.jsp&mid=WC0b01ac05800240d0

Signals assessment and prioritisation

(Item 4 of the PRAC minutes)

A safety signal is information on a new or incompletely documented adverse event that is potentially caused by a medicine and that warrants further investigation. Signals are generated from several sources such as spontaneous reports, clinical studies and the scientific literature. The evaluation of safety signals is a routine part of pharmacovigilance and is essential to ensuring that regulatory authorities have a comprehensive knowledge of a medicine's benefits and risks.
The presence of a safety signal does not mean that a medicine has caused the reported adverse event. The adverse event could be a symptom of another illness or caused by another medicine taken by the patient. The evaluation of safety signals is required to establish whether or not there is a causal relationship between the medicine and the reported adverse event.
The evaluation of safety signals may not necessarily conclude that the medicine caused the adverse event in question. In cases where a causal relationship is confirmed or considered likely, regulatory action may be necessary and this usually takes the form of an update of the summary of product characteristics and the package leaflet.

Risk Management Plans (RMPs)

(Item 5 of the PRAC minutes)

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

Assessment of Periodic Safety Update Reports (PSURs)

(Item 6 of the PRAC minutes)

A PSUR is a report providing an evaluation of the benefit-risk balance of a medicine, which is submitted by marketing authorisation holders at defined time points following a medicine's authorisation. PSURs summarises data on the benefits and risks of a medicine and includes the results of all studies carried out with this medicine (in the authorised and unauthorised indications).

Post-authorisation Safety Studies (PASS)

(Item 7 of the PRAC minutes)

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

Product related pharmacovigilance inspections

(Item 9 of the PRAC minutes)

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

More detailed information on the above terms can be found on the EMA website: www.ema.europa.eu/