9 June 2016
EMA/PRAC/457201/2016
Procedure Management and Committees Support Division

Pharmacovigilance Risk Assessment Committee (PRAC)

Minutes of PRAC meeting on 10-13 May 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 10-13 May 2016 meeting by welcoming all participants.

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

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

The PRAC Chair announced that Isabelle Robine and Miguel-Angel Macia were to step down as PRAC member for France and PRAC alternate for Spain respectively after the current PRAC plenary meeting. The PRAC thanked them for their important contribution to the work of the PRAC since the committee's establishment.

1.2. Agenda of the meeting of 10-13 May 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 April 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 April 2016 were published on the EMA website on 2 May 2016 (EMA/PRAC/319149/2016).

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

2.1. Newly triggered procedures

None

2.2. Ongoing procedures

None

2.3. Procedures for finalisation

None

2.4. Planned public hearings

None

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

3.1. Newly triggered procedures

None

3.2. Ongoing procedures

3.2.1. Idelalisib – ZYDELIG (CAP) - EMEA/H/A-20/1439

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Rafe Suvarna; PRAC Co-rapporteur: Ulla Wändel Liminga

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

Background

A referral procedure under Article 20 of Regulation (EC) No 726/2004 is ongoing for Zydelig (idelalisib) to review findings from clinical trials and all available safety data related to idelalisib following an increased rate of death and serious adverse events (SAE) amongst subjects receiving idelalisib compared to control groups, observed in the interim results of three clinical trials[1] and to assess the potential impact on the benefit-risk balance of Zydelig in the approved indications and relevant ongoing variations. For background information, see PRAC minutes March 2016.

Summary of recommendation(s)/conclusions

The PRAC endorsed the list of experts for the Scientific Advisory Group in oncology (SAG-O) scheduled on 12 May 2016. The PRAC had also adopted a list of questions (LoQ) for the SAG-O on 22 April 2016 by written procedure.

3.3. Procedures for finalisation

None

[1] GS-US-312-0123: Phase 3, randomised, double-blind, placebo-controlled study evaluating the efficacy and safety of idelalisib in combination with bendamustine and rituximab for previously untreated chronic lymphocytic leukaemia
GS-US-313-0124: Phase 3, randomised, double-blind, placebo-controlled study evaluating the efficacy and safety of idelalisib (GS-1101) in combination with rituximab for previously treated indolent non-Hodgkin lymphomas
GS-US-313-0125: Phase 3, randomised, double-blind, placebo-controlled study evaluating the efficacy and safety of idelalisib (GS 1101) in combination with bendamustine and rituximab for previously treated indolent non-Hodgkin lymphomas

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. Anakinra – KINERET (CAP); canakinumab – ILARIS (CAP)

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

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Signal of weight increase

EPITT 18641 – New signal
Lead Member States: DE, DK

Background

Anakinra is an interleukin-1α (IL-1α) and interleukin-1β (IL-1β) inhibitor indicated in adults for the treatment of the signs and symptoms of rheumatoid arthritis (RA) in combination with methotrexate, with an inadequate response to methotrexate alone, in adults, adolescents, children and infants aged 8 months and older with a body weight of 10 kg or above for the treatment of cryopyrin-associated periodic syndromes (CAPS) under certain conditions.

Canakinumab is a fully human monoclonal anti-human interleukin-1 beta (IL-1 beta) antibody of the IgG1/κ isotype indicated for the treatment of CAPS in adults, adolescents and children aged 2 years and older with body weight of 7.5 kg or above under certain conditions, for the treatment of active systemic juvenile idiopathic arthritis (SJIA) in patients aged 2 years and older who have responded inadequately to previous therapy with non-steroidal anti-inflammatory drugs (NSAIDs) and systemic corticosteroids, and for the symptomatic treatment of adult patients with frequent gouty arthritis attacks (at least 3 attacks in the previous 12 months) in whom NSAIDs and colchicine are contraindicated, are not tolerated, or do not provide an adequate response, and in whom repeated courses of corticosteroids are not appropriate.

The post-marketing exposure for Kineret, a centrally authorised medicine containing anakinra, is estimated to have been more than 63,758 patient-years worldwide, in the period from first authorisation in 2002 until May 2013.

[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

The post-marketing exposure for Ilaris, a centrally authorised medicine containing canakinumab, is estimated to have been more than 8,366 patient-years worldwide, in the period from first authorisation in 2009 until December 2015.

During routine signal detection activities, a signal of weight increase was identified by the EMA, based on 9 supportive cases for canakinumab and 2 supportive cases for anakinra retrieved from EudraVigilance. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the evidence from case reports in EudraVigilance and the scientific literature. Taking into account that weight gain might give rise to lipid and cholesterol disturbances with increased risk of cardio-vascular complications, the PRAC considered that the MAHs for Kineret and Ilaris should provide a cumulative review of weight increase and associated terms in relation to the use of the products in the different underlying diseases.

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

Summary of recommendation(s)

- The MAH for Kineret (anakinra) and for Ilaris (canakinumab) should submit to the EMA, within 90 days, a cumulative review of weight increase and associated terms (e.g. obesity, increased appetite) in relation to the use of the products in the different underlying diseases. The review should cover studies including registries, spontaneous reports and literature data. In addition, the MAHs should discuss a potential patho-physiological mechanism for weight gain associated with Kineret/Ilaris treatment, as well as risk factors for this observation with a special focus on the paediatric population. The MAHs should also evaluate if any risk minimisation measures are needed. Depending on the outcome, the need for updating the product information should be considered.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.1.2. Metronidazole (NAP)

Applicant: various

PRAC Rapporteur: Martin Huber

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

EPITT 18663 – New signal

Background

Metronidazole is an antibiotic and antiprotozoal medication indicated for the treatment of bacterial vaginosis, pelvic inflammatory disease, pseudomembranous colitis, aspiration pneumonia, rosacea (topical), fungating wounds (topical), intra-abdominal infections, lung abscess, periodontitis, amoebiasis, oral infections, giardiasis, trichomoniasis, and infections caused by susceptible anaerobic organisms such as *Bacteroides, Fusobacterium, Clostridium, Peptostreptococcus,* and *Prevotella* species.

During routine signal detection activities, a signal of severe hepatic and neurologic toxicity in patients with Cockayne syndrome was identified by Poland based on information provided

by the MAH Dr. August Wolff referring to 8 cases reported in the scientific literature[3]. Germany confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the evidence form case reports in the scientific literature. Taking into account the severity and seriousness of such adverse reaction, the PRAC considered that the MAHs should provide a cumulative review of cases of hepatotoxicity in patients suffering from Cockayne syndrome and treated with metronidazole.

The PRAC appointed Martin Huber as Rapporteur for the signal.

Summary of recommendation(s)

- The MAHs Sanofi-Aventis and Dr. August Wolff should submit to the EMA, within 90 days, a cumulative review of cases of hepatotoxicity in patients suffering from Cockayne syndrome and treated with metronidazole. The MAHs should include data from all sources including clinical trials, relevant literature, and post-marketing experience. The MAHs should also discuss the need for any potential amendment to the product information and make a proposal for amendments as appropriate.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.1.3. Regorafenib – STIVARGA (CAP)

Applicant: Bayer Pharma AG

PRAC Rapporteur: Sabine Straus

Scope: Signal of angioedema

EPITT 18656 – New signal
Lead Member State: NL

Background

Regorafenib is a protein kinase inhibitor indicated for the treatment of adult patients with metastatic colorectal cancer (CRC) under certain conditions and for the treatment of unresectable or metastatic gastrointestinal stromal tumours (GIST) under certain conditions.

The exposure for Stivarga, a centrally authorised medicine containing regorafenib, is estimated to have been more than 45,000 patients worldwide, in the period from first authorisation in 2013 until March 2015.

During routine signal detection activities, a signal of angioedema was identified by the EMA, based on 9 supportive cases retrieved from EudraVigilance. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the evidence from case reports in EudraVigilance. Taking into account the short time to onset, that 5 cases reported a positive de-challenge, that angioedema is a

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

known event for other tyrosine kinase inhibitors and that the symptoms in the reported cases are consistent with a diagnosis of angioedema, the PRAC considered that the MAH for Stivarga should provide a cumulative review of all cases of angioedema associated with regorafenib, both from clinical trials and spontaneous sources.

Summary of recommendation(s)

- The MAH for Stivarga (regorafenib) should submit to the EMA, within 90 days, a cumulative review of all cases of angioedema associated with regorafenib, both from clinical trials and spontaneous sources, identified by the narrow search of the standardised MedDRA[4] queries (SMQ) 'angioedema', supplemented with the preferred terms 'anaphylactic reaction', 'anaphylactic shock', 'anaphylactic transfusion reaction', 'anaphylactoid reaction' and 'anaphylactoid shock'. Regarding data from clinical trials, the frequency of the event in treated and comparator group should be provided (if available). Based on the cumulative review, the MAH should discuss the need for an update of the product information and/or the RMP (including any additional pharmacovigilance activities) and should include a proposal for amendments as appropriate.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.1.4. Vedolizumab - ENTYVIO (CAP)

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Adam Przybylkowski

Scope: Signal of hepatotoxicity

EPITT 18646 – New signal
Lead Member State: PL

Background

Vedolizumab is a humanized monoclonal antibody that binds specifically to the $\alpha_4\beta_7$ integrin, which is preferentially expressed on gut homing T helper lymphocytes and is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a tumour necrosis factor-alpha (TNFα) antagonist, and for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a tumour necrosis factor-alpha (TNFα) antagonist.

The exposure for Entyvio, a centrally authorised medicine containing vedolizumab, is estimated to have been more than 25,831 patient-years worldwide, in the period from first authorisation in 2014 until November 2015.

During routine signal detection activities, a signal of hepatotoxicity was identified by the EMA, based on 12 cases retrieved from EudraVigilance. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

[4] Medical Dictionary for Regulatory Activities

The PRAC discussed the available evidence from case reports in EudraVigilance. Taking into account that in 5 cases the time to onset was compatible with an association with vedolizumab and that in 3 cases evidence of liver injury was confirmed by liver biopsy, the PRAC agreed to request the MAH for Entyvio to provide a cumulative and detailed analysis of all the cases of hepato-biliary disorders associated with the use of vedolizumab taking into consideration the available data from studies, spontaneous reports and from the literature.

Summary of recommendation(s)

- The MAH for Entyvio (vedolizumab) should submit to the EMA, within the ongoing PSUR (DLP: 19/11/2015) (PSUSA/00010186/201511), a cumulative and detailed analysis of all the cases of hepato-biliary disorders associated with the use of vedolizumab taking into consideration the available data from studies, spontaneous reports and from the literature. In addition, the MAH should evaluate the possible pathophysiological mechanisms of vedolizumab in the development of liver injuries and consider the need to update of the product information and the RMP as appropriate.

4.2. New signals detected from other sources

4.2.1. Dexlansoprazole (NAP); lansoprazole (NAP)

Applicant: various

PRAC Rapporteur: Kirsti Villikka

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

EPITT 18645 – New signal
Lead Member State: FI

Background

Lansoprazole and dexlansoprazole (an R-enantiomer of lansoprazole) are proton pump inhibitors which suppress gastric acid secretion by inhibition of the H^+/K^+ adenosine triphosphatase enzyme system of the gastric parietal cells, which are indicated for the treatment of peptic ulcers, symptomatic gastroesophageal reflux disease and Zollinger-Ellison syndrome, the treatment and prophylaxis of reflux oesophagitis and nonsteroidal anti-inflammatory drugs (NSAID)-induced ulcers and eradication of *Helicobacter pylori* in combination with antibiotics.

A signal of unexpected histopathological findings from a juvenile rat toxicity study with lansoprazole was identified by Italy, based on the results of a new non-clinical study. Takeda, MAH for lansoprazole/dexlansoprazole containing medicinal products, provided Italy with a preliminary summary of the results of this juvenile rat toxicity study with lansoprazole. Finland confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the preliminary results of the juvenile rat toxicity study provided by the MAH. Considering that at present only preliminary results are available, the relevance of histopathological findings in the specified organs cannot be assessed based on the currently available data. The PRAC also discussed cases reported in EudraVigilance (EV) associated

with the intake of lansoprazole and/or dexlanzoprazole in children aged up to 3 years old. There were no reported cases in EV in infants and toddlers that could be related to abnormal histopathological findings observed in the juvenile rat toxicity study. As the available data is currently scarce, more information is needed on the safety of lansoprazole/dexlansoprazole in young children. Taking into account the available evidence from the preliminary results of the juvenile rat study for lansoprazole and from case reports in EV, and considering that lansoprazole/dexlansoprazole is not authorised to treat children including infants below one year, the PRAC considered that the MAH of lansoprazole/dexlansoprazole (Takeda) should provide the full report of juvenile rat toxicity study, along with a cumulative review of all relevant data available concerning the use of lansoprazole/dexlansoprazole in children.

The PRAC appointed Kirsti Villikka as Rapporteur for the signal.

Summary of recommendation(s)

- The MAH for lansoprazole (Takeda) should submit to the EMA, within 90 days, the full report of the concerned non-clinical data, cumulative review of all relevant data available concerning the use of lansoprazole/dexlansoprazole in children, including case reports and literature findings, as well as any information on the possible off-label use. The review should cover the epidemiologic and clinical trial data in paediatric patients. The MAH should provide an overview of the non-clinical repeat toxicity data with lansoprazole/dexlansoprazole in juvenile and adult animals, and a summary of other non-clinical studies which can be of relevance for the current signal. In addition, the MAH should discuss the potential mechanisms leading to the observed effects in the juvenile rat study. This discussion should include an in depth review of the function as well as tissue location of the H^+/K^+ATPase enzyme system during development of juvenile rats and young children, in comparison with adults. The MAH should also address whether interaction with testosterone metabolism may be involved in the occurrence of the testicular effects. Furthermore, the MAH should discuss, based on the development of the affected organs in the juvenile rat (i.e. heart, lung, testis, and epididymis) and of same organs in the human, the age ranges of concern in children. Based on the histopathological findings in the juvenile rat toxicity study, the MAH should discuss the need for amending the product information and/or the RMP.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.2.2. Fluconazole (NAP)

Applicant: various

PRAC Rapporteur: Doris Stenver

Scope: Signal of spontaneous abortion and stillbirth

EPITT 18666 – New signal
Lead Member State: DK

Background

Fluconazole is an antifungal indicated for the treatment of a variety of fungal infections, especially Candida infections of the vagina, mouth, throat, and bloodstream and as

prophylaxis to prevent infections in immunocompromised patients, including those with neutropenia due to cancer chemotherapy, transplant patients, and premature babies.

Following the publication in JAMA[5] by *Mølgaard-Nielsen D et al.*[6], a signal of spontaneous abortion and stillbirth associated with oral fluconazole during pregnancy was identified by Denmark. Denmark confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the evidence from the published study by *Mølgaard-Nielsen D et al.* Taking into account the findings from this study, the PRAC considered that the originator MAH for fluconazole (Pfizer) should provide a review and an assessment of the study by *Mølgaard-Nielsen D et al.* along with a cumulative review of all available data from clinical trials, post-marketing data and literature publications concerning the risk following exposure to oral fluconazole during pregnancy.

The PRAC appointed Doris Stenver as Rapporteur for the signal.

Summary of recommendation(s)

- The MAH for fluconazole (Pfizer) should submit to the EMA, within 90 days, a review and assessment of the register-based cohort study by *Mølgaard-Nielsen D et al.* as well as a cumulative review of all available data from clinical trials, post-marketing data and literature publications concerning the risk following exposure to oral fluconazole usage during pregnancy. The MAH should discuss the risk according to the cumulative dose received during pregnancy (150-300 mg or higher doses) and/or according to the indication. The review of the post-marketing data should be provided in accordance with the 'Guideline on the exposure to medicinal products during pregnancy: need for post-authorisation data' (EMEA/CHMP/313666/2005). Based on this review, the MAH should discuss the need for any potential amendment to the product information and/or risk management plan as applicable.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.2.3. Fluoroquinolones: Ciprofloxacin (NAP); enoxacin (NAP); flumequine (NAP); levofloxacin (NAP); lomefloxacin (NAP); moxifloxacin (NAP); norfloxacin (NAP); ofloxacin (NAP); pefloxacin (NAP); prulifloxacin (NAP); rufloxacin (NAP)

Applicant: Bayer, Sanofi, various

PRAC Rapporteur: Valerie Strassmann

Scope: Signal of aortic aneurysm and dissection

EPITT 18651 – New signal
Lead Member States: DE, DK, ES, FR, IT, NO, UK

Background

[5] Journal of the American Medical Association
[6] Ditte Mølgaard-Nielsen, Henrik Svanström, Mads Melbye, Anders Hviid and Björn Pasternak et al. Association between use of oral fluconazole during pregnancy and risk of spontaneous abortion and stillbirth. JAMA. 2016;315:58-67

Fluoroquinolones are broad-spectrum antibiotics indicated for a variety of infections including serious bacterial infections, especially hospital-acquired infections and others caused by susceptible microorganisms. Some fluoroquinolones have restricted indications limited to situations where other commonly recommended antibacterials are not appropriate.

Following the publication in JAMA[7] by *Lee C. et al.*[8] and in the BMJ by *Daneman N et al.*[9], a signal of aortic aneurysm and dissection was identified by the United Kingdom. Germany confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed in detail the results from the two published studies by *Lee C. et al.* and *Daneman N. et al.* Taking into account the available evidence, the PRAC considered that the originators/market lead MAHs for fluoroquinolone-containing medicinal products for systemic use (Angelini, Bayer, Delta, Gerda, Mediolanum, MSD, Pierre Fabre, Rottapharm and Sanofi-Aventis) should provide a discussion on the potential association between fluoroquinolone intake and aortic aneurysm and dissection observed within the two published studies by *Lee C. et al.* and *Daneman N. et al.*

The PRAC appointed Valerie Strassmann as Rapporteur for the signal.

Summary of recommendation(s)

- The MAHs of fluoroquinolone-containing medicinal products for systemic use (Angelini, Bayer, Delta, Gerda, Mediolanum, MSD[10], Pierre Fabre, Rottapharm and Sanofi-Aventis) should submit to the EMA and NCAs, by 27 July 2016, a discussion on the potential association between fluoroquinolone intake and aortic aneurysm and dissection observed within the observational studies performed by *Lee C. et al.* and *Daneman N. et al.* taking into account their strengths and limitations. The MAHs should discuss whether there is evidence to support any update of the product information with regard to the events of aortic aneurysm and dissection. The MAHs should also discuss risk factors such as increasing age and other factors that might be of relevance to identify possible populations at increased risk for aortic aneurysm and dissection. Based on the discussion on risk factors, the MAHs should also discuss whether any particular information in the product information is necessary for special populations at risk. The MAHs should provide any other available data that might inform about the possible risk of aortic aneurysm and dissection associated with fluoroquinolone use.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

[7] Journal of the American Medical Association
[8] Lee C, Lee M, Chen Y, et al. Risk of Aortic Dissection and Aortic Aneurysm in Patients Taking Oral Fluoroquinolone. JAMA Intern Med. 2015;175(11):1839-1847
[9] Daneman N, Lu H, Redelmeier DA. Fluoroquinolones and collagen associated severe adverse events: a longitudinal cohort study. *BMJ Open*. 2015 Nov 18; 5(11):e010077
[10] Post-meeting note: MSD informed the EMA that they will not be able to provide the requested responses due to the registration status of their norfloxacin-containing medicinal product. Teofarma, Bialfa, Vianex and Sandoz (MAHs of norfloxacin-containing products authorised according to article 8(3) of Directive No 2001/83/EC) have therefore been requested to provide responses to the list of questions

4.3. Signals follow-up and prioritisation

4.3.1. Adalimumab – HUMIRA (CAP) - EMEA/H/C/000481/SDA/090

Applicant: AbbVie Ltd.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of glomerulonephritis (GN)

EPITT 18528 – Follow-up to December 2015

Background

For background information, see PRAC minutes December 2015. The MAH replied to the request for information on the signal of glomerulonephritis (GN) and the responses were assessed by the Rapporteur.

Discussion

The PRAC discussed the MAH's responses. Taking into account the available data from post-marketing reports, clinical trials and the literature included in the cumulative review provided by the MAH for Humira, the PRAC concluded that that there is insufficient evidence of a causal relation between adalimumab and glomerulonephritis to warrant an update of the product information or any additional risk minimisation measure. Therefore, no further action is deemed necessary at this time.

Summary of recommendation(s)

- No further action is deemed necessary at this time.

4.3.2. Clozapine (NAP)

Applicant: Novartis, various

PRAC Rapporteur: Julie Williams

Scope: Signal of myocarditis

EPITT 18414 – Follow-up to September 2015

Background

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

Discussion

The PRAC discussed the MAH's responses. Having considered the available evidence, the PRAC agreed with the MAH's conclusions that the available clinical data do not provide sufficient evidence to warrant an update of the product information of clozapine-containing medicinal products regarding the incidence of clozapine-induced myocarditis.

Summary of recommendation(s)

- The MAHs for clozapine-containing medicinal should continue to monitor events of myocarditis as part of routine safety surveillance.

4.3.3. Cytarabine – DEPOCYTE (CAP) - EMEA/H/C/000317/SDA/019

Applicant: Pacira Ltd

PRAC Rapporteur: Rafe Suvarna

Scope: Signal of benign intracranial hypertension

EPITT 18533 – Follow-up to January 2016

Background

For background information, see PRAC minutes January 2016. The MAH replied to the request for information on the signal of benign intracranial hypertension and the responses were assessed by the Rapporteur.

Discussion

The PRAC discussed the MAH's responses. Having considered the available evidence from the cumulative review submitted by the MAH, the PRAC agreed that the evidence of a causal association between intrathecal liposomal cytarabine and the development of benign intracranial hypertension is not sufficiently robust at this stage. Taking into account that the adverse reactions related to benign intracranial hypertension are already included in the product information, the PRAC concluded that no further action is warranted.

Summary of recommendation(s)

- The MAH for Depocyte (cytarabine) should continue to monitor events of benign intracranial hypertension and increased intracranial pressure for intrathecal liposomal cytarabine and intrathecal cytarabine as part of routine pharmacovigilance activities.

4.3.4. Dapagliflozin – FORXIGA (CAP)- EMEA/H/C/002322/SDA/017, EDISTRIDE (CAP); dapagliflozin, metformin - XIGDUO (CAP) - EMEA/H/C/002672/SDA/003, EBYMECT (CAP)

Applicant: AstraZeneca AB

PRAC Rapporteur: Qun-Ying Yue

Scope: Signal of pancreatitis

EPITT 18558 – Follow-up to January 2016

Background

For background information, see PRAC minutes January 2016. The MAH replied to the request for information on the signal of pancreatitis and the responses were assessed by the Rapporteur.

Discussion

The PRAC discussed the MAH's responses. Having considered the available data from the cumulative review provided by the MAH, the PRAC agreed that the evidence for a causal relationship between treatment with dapagliflozin-containing medicinal products and the occurrence of pancreatitis is not sufficient to warrant changes to the product information at this stage.

Summary of recommendation(s)

- The MAH for MAH for Forxigo/Edistride (dapagliflozin) and Xigduo/Ebymect (dapagliflozin/metformin) should continue to monitor pancreatitis events as part of routine safety surveillance, and discuss any new cases of pancreatitis in future PSURs, as well as present cases of pancreatitis in the DECLARE[11] study when data become available.

4.3.5. Fluoroquinolones: Ciprofloxacin (NAP); enoxacin (NAP); flumequine (NAP); levofloxacin (NAP); lomefloxacin (NAP); moxifloxacin (NAP); norfloxacin (NAP); ofloxacin (NAP); pefloxacin (NAP); prulifloxacin (NAP); rufloxacin (NAP)

Applicant: Bayer, Sanofi, various

PRAC Rapporteur: Valerie Strassmann

Scope: Signal of retinal detachment

EPITT 15914 – Follow-up to October 2015

Background

For background information, see PRAC minutes November 2012, PRAC minutes March 2013, PRAC minutes April 2013, PRAC minutes June 2014, PRAC minutes June 2015 and PRAC minutes October 2015. The authors of the recent French Agency (ANSM) study submitted answers to an additional list of questions adopted by the PRAC in October 2015 which were assessed by the Rapporteur.

Discussion

The PRAC discussed the answers submitted by the authors of the ANSM study. Having considered the limitations of the epidemiological studies published to date, the inconsistent findings, and taking into account the existing warning on vision disorders in the product information based on a prior PRAC recommendation, the PRAC agreed that the available evidence does not warrant further changes to the product information of fluoroquinolone-containing medicinal products for systemic use.

Summary of recommendation(s)

- The MAHs of fluoroquinolone-containing medicinal products for systemic use should continue to monitor retinal detachment as part of routine safety surveillance.

4.3.6. Gefitinib – IRESSA (CAP) - EMEA/H/C/001016/SDA/020

Applicant: AstraZeneca AB

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of pneumatosis intestinalis

EPITT 18575 – Follow-up to January 2016

Background

[11] Dapagliflozin effect on cardiovascular events: a multicentre, randomized, double-blind, placebo-controlled trial to evaluate the effect of dapagliflozin 10 mg once daily on the incidence of cardiovascular death, myocardial infarction or ischemic stroke in patients with type 2 diabetes

For background information, see PRAC minutes January 2016. The MAH replied to the request for information on the signal of pneumatosis intestinalis and the responses were assessed by the Rapporteur.

Discussion

The PRAC discussed the MAH's responses. Having considered the available evidence from the cumulative review provided by the MAH for Iressa, the PRAC agreed that the number of possible related cases of pneumatosis intestinalis is considered low and that the evidence of a causal relationship between treatment with Iressa and pneumatosis intestinalis is not sufficiently robust. The PRAC considered that the current wording in the product information on gastrointestinal perforation and gastrointestinal symptoms remains adequate and that no changes are warranted at this stage.

Summary of recommendation(s)

- The MAH for Iressa (gefitinib) should continue to monitor events of pneumatosis intestinalis as part of routine safety surveillance.

4.3.7. Infliximab – INFLECTRA (CAP), REMICADE (CAP) - EMEA/H/C/000240/SDA/154, REMSIMA (CAP)

Applicant: Hospira UK Limited (Inflectra), Janssen Biologics B.V. (Remicade), Celltrion Healthcare Hungary Kft. (Remsima)

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of thyroid gland disorders

EPITT 18530 – Follow-up to December 2015

Background

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

Discussion

The PRAC discussed the MAH's responses. Having considered the data from post-marketing reports, clinical trials and the literature provided by the MAH for Remicade in its cumulative review, the PRAC concluded that there is currently insufficient evidence for a causal relationship between infliximab and thyroid gland disorders to warrant an update of the product information or any additional risk minimisation measure. Therefore no further action is deemed necessary at this time.

Summary of recommendation(s)

- No further action is deemed necessary at this time.

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

Applicant: UCB Pharma SA, various

PRAC Rapporteur: Veerle Verlinden

Scope: Signal of medication errors associated with accidental overdose

EPITT 10519 – Follow-up January 2016

Background

For background information, see PRAC minutes January 2016. The MAH replied to the request for information on the signal of medication errors associated with accidental overdose and the responses were assessed by the Rapporteur.

Discussion

The PRAC discussed the MAH's responses. Having considered the available evidence, including the information submitted by the MAH, the PRAC agreed that the MAH for Keppra should submit responses to a further list of questions addressing the readability of the package leaflet (readability test), the need to update the mock-ups taking into consideration the PRAC's suggestions and the need to consider adding the age-range on the syringe. The PRAC also concluded that the MAH should continue to monitor all events of medication error associated with accidental overdose in future PSURs.

Summary of recommendation(s)

- The MAH for Keppra (levetiracetam) should submit to the EMA, within 120 days, responses to a further list of questions on readability testing of the Package Leaflet, the need to update the mock-ups taking into consideration the PRAC's suggestions and the need to consider adding the age-range on the syringe.
- A 30-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.3.9. Methotrexate NAP

Applicant: various

PRAC Rapporteur: Doris Stenver

Scope: Signal of congenital cardiovascular anomaly

EPITT 18481 – Follow-up to November 2015

Background

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

Discussion

The PRAC discussed the MAH's responses to the list of questions regarding the risk of cardiovascular anomalies in children exposed in utero to methotrexate. The PRAC agreed that the data provided, based on a literature review and a cumulative analysis of the innovator MAH's pre- and post-marketing information, did not support the need to update the product information regarding the increased risk of congenital cardiovascular anomalies. The PRAC considered that the level of information in the product information for methotrexate-containing medicinal products is currently sufficient regarding the teratogenic risk and no revision or additional risk minimisation is necessary. Nevertheless, the PRAC

noted that there are inconsistencies throughout the product information in the EU in terms of wording currently in place regarding the teratogenic risk.

Summary of recommendation(s)

- The MAHs of methotrexate-containing medicinal products should continue to monitor the risk of teratogenicity as part of routine pharmacovigilance surveillance.

4.3.10. Natalizumab – TYSABRI (CAP) – EMEA/H/C/000603/SDA/063

Applicant: Biogen Idec Ltd

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Signal of necrotising retinitis

EPITT 18605 – Follow-up to January 2016

Background

For background information, see PRAC minutes January 2016. The MAH replied to the request for information on the signal of necrotising retinitis and the responses were assessed by the Rapporteur.

Discussion

The PRAC discussed the MAH's responses. Having considered the available evidence from case reports in EudraVigilance, published cases reports and the data submitted by the MAH, the PRAC agreed that the product information of Tysabri should be updated to include the risk of rare acute retinal necrosis.

Summary of recommendation(s)

- The MAH for Tysabri (natalizumab) should submit to the EMA, within 60 days, a variation to add a warning on the risk of acute retinal necrosis and to reflect that rare cases of acute retinal necrosis have been observed post-marketing. The MAH should also update the relevant sections of the RMP to include acute retinal necrosis under herpes infections. Communication of the product information update should be agreed at national level.

For the full PRAC recommendations, see EMA/PRAC/313187/2016 published on 06/06/2016 on the EMA website.

4.3.11. Quinine (NAP)

Applicant: various

PRAC Rapporteur: Almath Spooner

Scope: Signal of an increased mortality risk in heart failure patients with and without concomitant use of beta-blockers

EPITT 18529 – Follow-up to January 2016

Background

For background information, see PRAC minutes January 2016. The innovators MAHs (Sanofi and Takeda Pharma A/S) replied to the request for information on the signal of an increased

mortality risk in heart failure patients with and without concomitant use of beta-blockers and the responses were assessed by the Rapporteur.

Discussion

The PRAC discussed the MAHs' responses. Having considered the available evidence, including the data submitted by the MAHs, the PRAC agreed that all the MAHs of quinine-containing medicinal products should continue to closely monitor the issues regarding the use of quinine and mortality risk in patients with heart failure with and without concomitant use of beta-blockers and address a list of questions in the next PSUR.

Summary of recommendation(s)

- The MAHs for quinine-containing medicinal products (Actavis UK Ltd, Alept, Artecef BV, Athlone Laboratories Ltd, Bristol Laboratories Ltd, Casella-Med GmbH & Co.KG, Dalkeith Laboratories Ltd and Laboratoire Innotech International) should continue to closely monitor the issues regarding the use of quinine and mortality-risk in patients with heart failure with and without concomitant use of beta-blockers.
- The MAHs should also submit to the EMA, within the next PSUR (DLP: 30/11/2018) (PSUSA/00002598/201811), any relevant fatal cases reported for quinine, any relevant cases reporting use of quinine in patients with heart failure, as well as any relevant cases reporting quinine with concomitant beta-blocker use. As part of this cumulative review, the MAHs should conduct a literature review, including a discussion of any publications relevant to the signal as well as any late-breaking information. The MAHs should provide any available drug utilisation data on the use of quinine including use per indications, off-label use and use in sub-populations and in special populations, focussing on any trends in use. The MAHs should discuss information relevant to this signal that becomes available during the PSUR reporting interval regarding the effectiveness and/or limitations of the risk minimisation measures in place in the product information. The MAHs should also comment on whether these risk minimisation measures remain sufficient to minimise the risks of QT prolongation in sensitive patients. As quinine is contained in nationally authorised products (NAP) and there may be differences across national product information with regard to the emphasis placed on the risk of QT prolongation with quinine use, any noteworthy insights into significant differences across product information, and into the effectiveness and/or limitations of risk minimisation in particular countries or regions, are of interest.

4.3.12. Selective serotonin reuptake inhibitors (SSRIs): citalopram (NAP); escitalopram (NAP); fluoxetine (NAP); fluvoxamine (NAP); mirtazapine (NAP); paroxetine (NAP); sertraline (NAP)
Serotonin–noradrenaline reuptake inhibitors (SNRIs): duloxetine - ARICLAIM (CAP), DULOXETINE LILLY (CAP), DULOXETINE MYLAN (CAP), DULOXETINE ZENTIVA (CAP), CYMBALTA (CAP), XERISTAR (CAP), YENTREVE (CAP); sibutramine (NAP); venlafaxine (NAP)

Applicant: Eli Lilly Nederland B.V. (Ariclaim, Duloxetine Lilly, Xeristar, Yentreve), Generics UK Limited (Duloxetine Mylan), Zentiva (Duloxetine Zentiva), various

PRAC Rapporteur: Isabelle Robine

Scope: Signal of risk of autistic spectrum disorders (ASD) after in utero exposure to selective serotonin reuptake inhibitors (SSRI)

EPITT 14082 – Follow-up to November 2015

Background

For background information, see PRAC minutes November 2015. The MAHs of citalopram and escitalopram, duloxetine and fluoxetine, fluvoxamine, paroxetine, mirtazapine, sertraline and venlafaxine replied to the request for information on the signal of risk of autistic spectrum disorders (ASD) after in utero exposure to SSRI/serotonin–noradrenaline reuptake inhibitors (SNRI) and the responses were assessed by the Lead Member States for individual substances and by the overall Rapporteur.

Discussion

The PRAC discussed the MAHs' responses. The PRAC considered the available evidence provided by the MAHs on neurodevelopmental disorders including ASD, reported after SSRI/SNRI exposure during pregnancy. The PRAC noted that the results from available studies are limited by confounding by indication and noted the importance of hereditary factors and environmental influences. Furthermore, studies where attempts have been made to address confounding by indication and other relevant risk factors were not considered to support an association.

Based on these limitations, the PRAC agreed by majority vote[12] that at the moment there is insufficient evidence for a potential association between SSRI/SNRI exposure during pregnancy and neurodevelopmental disorders in children and therefore an update of the product information was not considered warranted.

Summary of recommendation(s)

- The MAHs of all SSRI- and SNRI-containing medicinal products should continue to monitor neurodevelopmental disorders, including autistic spectrum disorders, following in utero exposure, as part of routine safety surveillance.
- The EMA, together with the involved Lead Member States for individual substances and overall Rapporteur, will evaluate whether a further study will contribute to the evaluation of the signal and whether a study will be feasible to investigate the possible association between SSRI/SNRI exposure during pregnancy and neurodevelopmental disorders in children exposed in utero.

4.3.13. Warfarin (NAP)

Applicant: various

PRAC Rapporteur: Torbjorn Callreus

Scope: Signal of calciphylaxis

EPITT 18545 – Follow-up to January 2016

Background

[12] Thirty-one members/alternates, out of 32 eligible to vote voted in favour of not changing the product information in the light of the current available evidence, while one member (Isabelle Robine) had a divergent view. Norway and Iceland supporting the majority

For background information, see PRAC minutes January 2016. The originator/market lead MAHs replied to the request for information on the signal of calciphylaxis and the responses were assessed by the Rapporteur.

Discussion

The PRAC discussed the MAHs' responses. Having considered the available evidence from EudraVigilance, the literature, the analyses submitted the originator/market lead MAHs, as well as the existence of a plausible biological mechanism, the PRAC concluded that there is a reasonable possibility of a causal relationship between calciphylaxis and the use of warfarin. The PRAC agreed that the product information of warfarin-containing medicinal products should be updated to include the risk of calciphylaxis.

Summary of recommendation(s)

- The MAHs for warfarin-containing medicinal products should submit to the national competent authorities of the Member States, within 90 days, a variation to include a new warning on the risk of calciphylaxis and to include calciphylaxis as a new undesirable effect.

For the full PRAC recommendations, see EMA/PRAC/313187/2016 published on 06/06/2016 on the EMA website.

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

Applicant: Insmed Limited

Scope: Treatment of *Pseudomonas aeruginosa* lung infection and colonisation in cystic fibrosis patients

5.1.2. Cabozantinib - EMEA/H/C/004163

Scope (accelerated assessment): Treatment of advanced renal cell carcinoma (RCC)

5.1.3. Darunavir - EMEA/H/C/004068

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

5.1.4. Dinutuximab beta - EMEA/H/C/003918, Orphan

Applicant: Apeiron Biologics AG

Scope: Treatment of neuroblastoma

5.1.5. Eluxadoline - EMEA/H/C/004098

Scope: Treatment of irritable bowel syndrome with diarrhoea

5.1.6. Emtricitabine, tenofovir disoproxil - EMEA/H/C/004050

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

5.1.7. Lenvatinib - EMEA/H/C/004224

Scope (accelerated assessment): Treatment of unresectable advanced or metastatic renal cell carcinoma (RCC) in combination with everolimus

5.1.8. Tenofovir disoproxil - EMEA/H/C/004049

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

5.1.9. Tenofovir disoproxil - EMEA/H/C/004120

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

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

See also Annex I 14.2.

5.2.1. Aliskiren – RASILEZ (CAP) - EMEA/H/C/000780/WS/0771 aliskiren, hydrochlorothiazide – RASILEZ HCT (CAP) - EMEA/H/C/000964/WS/0771

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Carmela Macchiarulo

Scope: Revised RMP with regard to identified risks, missing information, concomitant use of other medicines, drug-drug interactions, removal of safety issues attributed to the withdrawn aliskiren/amlodipine (Rasilamlo) and aliskiren/amlodipine/HCTZ (Rasitrio). The variation is supported by study report SPA100A: antihypertensive effects and long-term safety of aliskiren in elderly patients

Background

Aliskiren is a renin–angiotensin–aldosterone system (RAAS) inhibitor and hydrochlorothiazide, a thiazide diuretic, indicated alone or in combination for the treatment of essential hypertension in adults under certain conditions.

The PRAC is evaluating a type II worksharing variation procedure for Rasilez and Rasilez HCT, centrally authorised medicine containing aliskiren and aliskiren/hydrochlorothiazide, to update the RMP. The proposed changes include the deletion of RMP-related information on Rasilamlo (aliskiren/amlodipine) and Rasilamlo HCT

(aliskiren/amlodipine/hydrochlorothiazide) following deregistration in the EU and deletion of several elements, including all risks previously endorsed by the PRAC to return to routine pharmacovigilance. For further background, see PRAC minutes January 2016. 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 12.0 for Rasilez (aliskiren) and Rasilez HCT (aliskiren/hydrochlorothiazide) in the context of the worksharing 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 agreed with the MAH's proposal to remove 'diarrhoea' as an important identified risk but did not support the deletion of 'acute angle closure glaucoma', and 'pharmacological class effect with non-steroidal anti-inflammatory drugs (NSAIDs)' as important identified risks and 'renovascular hypertension' as missing information. In addition, the concern of 'long-term data on concomitant use of angiotensin receptor blockers (ARBs) and/or angiotensin-converting enzyme (ACE) inhibitors only for non-diabetic patients' should be removed as missing information from the safety specification. In addition, the PRAC agreed to remove study CSPP100A2370 (ASSESS) as supported by study report SPA100A entitled 'antihypertensive effects and long-term safety of aliskiren in elderly patients'.

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

See also Annex I 14.3.

5.3.1. Carfilzomib – KYPROLIS (CAP) - EMEA/H/C/003790/II/0001/G

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Marina Dimov Di Giusti

Scope: Extension of indication to include the treatment in combination with either lenalidomide and dexamethasone or dexamethasone alone, of adult patients with multiple myeloma who have received at least one prior therapy. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated accordingly. In addition, the MAH updated section 6.6 of the SmPC to include the option to administer Kyprolis in a 100 mL intravenous bag containing 5% glucose solution for injection in line with the extension of indication part of this variation

Background

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

The CHMP is evaluating an extension of the therapeutic indication for Kyprolis, a centrally authorised product containing carfilzomib, to include that carfilzomib in combination with either lenalidomide and dexamethasone or dexamethasone alone is indicated for the treatment of adult patients with multiple myeloma who have received at least one prior therapy. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this extension of indication. For further background, see also PRAC minutes April 2016, Kyprolis (variation II/0004/G).

Summary of advice

- The RMP version 5.1 for Kyprolis (carfilzomib), in the context of the variation 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 update the RMP to include the possibility of administering a higher dose of carfilzomib during a shorter infusion time (over 10 minutes instead of 30 minutes) in the 'potential for medication error(s)' section as well as to closely monitor adverse drug reactions (ADRs) associated with the possibility of administering a higher dose of carfilzomib during a shorter infusion time, and should present all available data in future PSURs. Furthermore, in view of the reproductive toxicity of carfilzomib and the potential for foetal harm, the MAH should further elaborate on whether any additional measure in terms of a pregnancy prevention programme is needed for patients receiving carfilzomib as monotherapy treatment.

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

Applicant: ThromboGenics NV

PRAC Rapporteur: Julie Williams

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

Background

Ocriplasmin is a recombinant protease indicated in adults for the treatment of vitreomacular traction (VMT), including when associated with macular hole of diameter less than or equal to 400 microns.

The CHMP is evaluating a type II variation procedure for Jetrea, a centrally authorised product containing ocriplasmin, to reflect new long-term safety and efficacy data based on the final clinical study report (CSR) for study TG-MV-014[13]. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this type II variation.

Summary of advice

- The RMP version 7 for Jetrea (ocriplasmin) in the context of the variation 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 MAH should provide further information regarding the proposal to remove 'development of macular hole' and 'increased vitreomacular traction' from the important identified risks of the safety specification. In addition, given that acute vision loss and dyschromatopsia can be clinical manifestations of photoreceptor disruption events, and these remain to be fully characterised, the MAH should comment on

[13] Ocriplasmin for treatment for symptomatic vitreomacular adhesion including macular hole (OASIS): randomised, sham-controlled, double-masked, multicentre study evaluating long-term safety and efficacy for up to 24 months

whether continuing the use of the targeted questionnaire for follow-up of these cases might yield useful information on these adverse events.

5.3.3. Ponatinib – ICLUSIG (CAP) - EMEA/H/C/002695/II/0029/G

Applicant: Ariad Pharma Ltd

PRAC Rapporteur: Rafe Suvarna

Scope: Update of section 5.3 of the SmPC in order to add pre-clinical information on fertility and early embryonic development to implantation (study 2424-001) and on carcinogenity (study 805826). In addition, the MAH has submitted final study results for pre-clinical studies ARP590, ARP591, ARP592, ARP593, ARP593 on the vascular occlusion mechanism and study ARP598 on effects of ponatinib and its metabolites on in vitro kinase activity and cellular viability following commitments taken during the Article 20 referral procedure (EMEA/H/C/002695/A-20/0003, EC decision on 15 January 2015). No impact for the Product information is proposed for these 6 studies. The RMP has been updated accordingly

Background

Ponatinib is a protein kinase inhibitor indicated in adult patients for the treatment of chronic phase, accelerated phase, or blast phase chronic myeloid leukaemia (CML) who are resistant to dasatinib or nilotinib; who are intolerant to dasatinib or nilotinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation. It is also indicated for the treatment of Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ALL) in adults who are resistant to dasatinib; who are intolerant to dasatinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation.

The CHMP is evaluating a grouping of type II variations procedure for Iclusig, a centrally authorised product containing ponatinib, to add pre-clinical information on fertility and early embryonic development to implantation (study 2424-001[14]) and on carcinogenicity (study 805826[15]). Final results of several preclinical studies on the vascular occlusion mechanism and on the effects of ponatinib and its metabolites on in vitro kinase activity and cellular viability are also implemented following the completion of the referral procedure under Article 20 of Regulation (EC) No 726/2004 (EMEA/H/C/002695/A-20) (EC Decision dated 15 January 2015). The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this type II variation. For further background, see PRAC minutes March 2016.

Summary of advice

- The RMP version 14.2 for Iclusig (ponatinib) in the context of the variation 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's proposed non-clinical study to 'evaluate the effects of ponatinib on arterial remodelling and wall thickening in a murine model of stenosis' intended to further explore the mechanism of vascular occlusion should be a category 3 study in line with previous non-clinical studies intended to explore the same mechanism.

[14] Rat fertility and early embryonic development study with ponatinib
[15] 2-year rat carcinogenicity study with ponatinib

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

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Ulla Wändel Liminga

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

Background

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

The CHMP is evaluating an extension of the therapeutic indication for Lucentis, a centrally authorised product containing ranibizumab, to include the treatment of visual impairment due to choroidal neovascularisation (CNV) based on 6-month data from the pivotal study CRFB002G2301[16] (MINERVA). The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this extension of indication.

Summary of advice

- The RMP version 16.0 for Lucentis (ranibizumab) in the context of the variation 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 further explore ways to collect detailed information in relation to use in children. For spontaneously reported adverse events in children, the MAH should implement targeted questionnaires in order to gain as much information as possible on adverse events as well as on patients, including age of child, condition being treated, dose regimen used, and any efficacy data if available. Furthermore, the MAH should provide a detailed review of off-label use in children. Finally, the MAH should discuss the possibility to conduct a drug utilisation study to gain further knowledge on the use of ranibizumab in children and adolescents, including condition treated, age groups, and dose regimens used.

6. Periodic safety update reports (PSURs)

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

See also Annex I 15.1.

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

6.1.1. Bazedoxifene – CONBRIZA (CAP) - PSUSA/00000302/201510

Applicant: Pfizer Limited

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Bazedoxifene is a selective estrogen receptor modulator (SERM) which acts as both an oestrogen-receptor agonist and/or antagonist, depending upon the cell and tissue type and target genes, indicated for the treatment of postmenopausal osteoporosis in women at increased risk of fracture.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Conbriza, a centrally authorised medicine containing bazedoxifene, 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 Conbriza (bazedoxifene) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to move the undesirable effects 'visual acuity reduced', 'blurred vision', 'photopsia', 'visual field defect', 'visual impairment', 'dry eye', 'eyelid oedema', 'blepharospasm', 'eye pain' and 'eye swelling' to the tabulated list of adverse drug reactions under 'vision disorders/ocular events' with an unknown frequency. Therefore the current terms of the marketing authorisation(s) should be varied[17].
- In the next PSUR, the MAH should discuss whether any additional risk minimisation measures regarding off-label use in male patients are deemed necessary. It has been noted in the package leaflet that patients are advised to stop taking bazedoxifene for serious undesirable effects whilst the SmPC does not include such a recommendation. Therefore, the MAH should consider updating the SmPC to include such advice or should provide a justification for not doing so.

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. Deferasirox – EXJADE (CAP) - PSUSA/00000939/201510 (with RMP)

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Isabelle Robine

Scope: Evaluation of a PSUSA procedure

Background

[17] 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

Deferasirox is an iron chelating agent indicated for the treatment of chronic iron overload due to frequent blood transfusions in patients with beta thalassaemia major, for the treatment of chronic iron overload due to blood transfusions when deferoxamine therapy is contraindicated or inadequate in some specific sub-populations, as well as for the treatment of chronic iron overload requiring chelation therapy when deferoxamine therapy is contraindicated or inadequate in patients with non-transfusion-dependent thalassaemia syndromes under certain conditions.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Exjade (deferasirox) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to revise the current wording on toxic epidermal necrolysis (TEN), to add 'acute pancreatitis' and 'toxic epidermal necrolysis' as new undesirable effects with an unknown frequency. In addition, the product information should be updated to include that acute pancreatitis has been reported particularly in children and adolescents, and to update the list of undesirable effects in accordance with the current MedDRA[18] preferred terms. Therefore the current terms of the marketing authorisation(s) should be varied[19].
- In the next PSUR, the MAH should provide a detailed review of cases of cerebral haemorrhage occurring in sickle cell disease patients. In addition, the MAH should clarify the total number of thalassemic patients having experienced ischaemic cerebral vascular attack (CVA) cumulatively and should clarify whether the analysis of ischaemic/haemorrhagic CVA cases in patients without risk factors (as thalassemic patients) is adequate. The MAH should also clarify why gastritis and deep vein thrombosis are considered as risk factors for colitis. The MAH should provide detailed reviews of cases of medication errors, of spontaneous abortions, both cases of fetal abnormalities and fetal death and of therapeutic abortions as well as a detailed review of autoimmune haemolytic anaemia.
- The MAH should be requested to submit a type II variation to remove the current contraindication in combination with other iron chelator therapies.
- The MAH should be requested to await the outcome of the ongoing variation assessing the final clinical study report for study CICL670A2411 before removing the missing information 'long term safety in paediatric patients aged 2 to 6 years old' from the 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.

[18] Medical Dictionary for Regulatory Activities
[19] 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

6.1.3. Empagliflozin – JARDIANCE (CAP); empagliflozin, metformin – SYNJARDY (CAP) - PSUSA/00010388/201510

Applicant: Boehringer Ingelheim International GmbH, Boehringer Ingelheim GmbH

PRAC Rapporteur: Miguel-Angel Macia

Scope: Evaluation of a PSUSA procedure

Background

Empagliflozin is a reversible, highly potent and selective competitive inhibitor of sodium-glucose co-transporter 2 (SGLT2) indicated alone or in combination with metformin, a biguanide, for the treatment of type 2 diabetes in adults aged 18 years old and older under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Jardiance, a centrally authorised medicine containing empagliflozin and of Synjardy, a centrally authorised medicine containing empagliflozin and metformin, 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 Jardiance (empagliflozin) and Synjardy (empagliflozin, metformin) in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include blood creatinine increased/glomerular filtration rate decreased as a new undesirable effect with an uncommon frequency. Therefore the current terms of the marketing authorisation(s) should be varied[20].
- In the next PSUR, the MAH should provide a detailed review of cases of 'hypersensitivity' and 'embolic and thrombotic events'. In addition, the MAH should continue to provide information regarding adverse drug reactions reported in off-label indications.

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. Ledipasvir, sofosbuvir – HARVONI (CAP) - PSUSA/00010306/201510

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Margarida Guimarães

Scope: Evaluation of a PSUSA procedure

Background

[20] 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

Ledipasvir is a hepatitis C virus (HCV) inhibitor targeting the HCV NS5A protein, in combination with sofosbuvir, a pan-genotypic inhibitor of the HCV NS5B RNA-dependent RNA polymerase, is indicated 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 Harvoni, a centrally authorised medicine containing ledipasvir and sofosbuvir, and issued a recommendation on its marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Harvoni (ledipasvir, sofosbuvir) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include rash as a new undesirable effect with a common frequency. Therefore the current terms of the marketing authorisation(s) should be varied[21].
- In the next PSUR, the MAH should provide a cumulative review and analysis of the signals 'severe cutaneous events', 'renal events with tenofovir (TDF) and sofosbuvir (SOF)/ledispavir (LDV) coadministration' and 'hypertension'. As already requested for sofosbuvir-containing medicinal products, the MAH should provide a cumulative review and analysis of the signals of 'worsening of hepatic disease', 'hepatitis B virus (HBV) reactivation in HCV/HBV co-infected patients', 'international normalized ratio (INR) decreases in patients receiving anticoagulants', 'severe transaminitis', 'pulmonary artery hypertension' and 'cardiotoxicity (cardiac arrhythmia without amiodarone, cardiac failure and cardiomyopathy)'. In addition, the MAH should provide a detailed review of post-marketing data regarding convulsion/epilepsy events, including a summary of case reports, along with a review of clinical trial and non-clinical data.
- The MAH should be requested to submit to the EMA, by 30/09/2016, data from study GS-US-337-0124 (SOLAR-2)[22], an ongoing clinical trial in patients with advanced liver disease pre/post-transplant and propose updates to the product information, as appropriate.

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

6.1.5. Lopinavir, ritonavir – ALUVIA (Art 58[23]); KALETRA (CAP) - PSUSA/00001905/201509

Applicant: AbbVie Ltd

PRAC Rapporteur: Isabelle Robine

Scope: Evaluation of a PSUSA procedure

[21] 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

[22] Phase 2, multicentre, open-label study to investigate the safety and efficacy of sofosbuvir/ledipasvir fixed-dose combination + ribavirin administered in subjects infected with chronic HCV who have advanced liver disease or are post-liver transplant

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

Background

Lopinavir and ritonavir are two inhibitors of the human immunodeficiency virus (HIV)-1 and HIV-2 proteases. In combination, ritonavir is used as a pharmacokinetic enhancer of other protease inhibitors. Lopinavir in combination with ritonavir is indicated in combination with other antiretroviral medicinal products for the treatment of human immunodeficiency virus (HIV-1) infected adults, adolescents and children above the age of 2 years.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Aluvia and Kaletra, a medicine to be used outside the EU and a centrally authorised medicine respectively containing lopinavir/ritonavir, and issued a recommendation on their scientific opinion/marketing authorisation.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Aluvia and Kaletra (lopinavir/ritonavir) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation and scientific opinion should be maintained.
- The MAH/Scientific Opinion Holder (SOH) should be requested to submit to the EMA, within 60 days, a variation to update the production information to include the potential drug-drug interaction with afatinib, riociguat, cetirinib and vorapaxar to mirror the information included in the SmPC of these medicinal products on potential drug-drug interactions with lopinavir/ritonavir.

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. Nintedanib – OFEV (CAP) - PSUSA/00010319/201510

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Marina Dimov Di Giusti

Scope: Evaluation of a PSUSA procedure

Background

Nintedanib is a tyrosine kinase inhibitor indicated in adults for the treatment of idiopathic pulmonary fibrosis (IPF).

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Ofev (nintedanib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to replace ‘epistaxis’ with ‘bleeding’ as an undesirable effect with a common frequency and to include

'pancreatitis' as a new undesirable effect with an uncommon frequency. Therefore the current terms of the marketing authorisation(s) should be varied[24].

- In the next PSUR, the MAH should provide the list of countries where the protocol for study 1199.229[25] was submitted and state the reason for changing the protocol at the request of the EC. The MAH should also provide a cumulative review of cases of eye disorders, of cases of renal failure and should review cases related to suicide, suicidal ideation and depression and consider if any further action is needed. The MAH should also evaluate a signal of 'dehydration' and consider whether information currently present in section 4.4 of the SmPC, which describes management of adverse reactions of diarrhoea and vomiting, is sufficient to prevent cases of dehydration. Furthermore, the MAH should provide the cumulative incidence of bleeding cases (including serious and non-serious) from the pooled database of all clinical trials, stratified by concomitant use of medications that can alter haemostasis. Moreover, the MAH should provide an updated cumulative review of post marketing cases of bleeding stratified by concomitant use of medications that can alter haemostasis. Depending on the results, additional risk minimisation measures related to bleeding should be proposed by the MAH.
- The MAH should be requested to upgrade the safety concern 'bleeding' from a potential to an identified risk within the next update of the 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.

6.1.7. Para-aminosalicylic acid – GRANUPAS (CAP) - PSUSA/00010171/201510

Applicant: Lucane Pharma

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

Background

Para-aminoslicylic acid is bacteriostatic against *Mycobacterium tuberculosis* inhibiting onset of bacterial resistance to streptomycin and isoniazid and is indicated for use as part of an appropriate combination regimen for multi-drug resistant tuberculosis in adults and paediatric patients from 28 days of age and older when an effective treatment regimen cannot otherwise be achieved for reasons of resistance or tolerability.

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

[24] 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

[25] Investigation of drug-drug interaction between nintedanib and pirfenidone in patients with IPF (open label, multiple-dose, two group study followed by nintedanib open label treatment)

- Nevertheless, the product information should be updated to include a warning on an increased risk of hypothyroidism in human immunodeficiency virus (HIV) co-infected patients and to include hypothyroidism in HIV co-infected patients as an undesirable effect with a very common frequency. Therefore the current terms of the marketing authorisation(s) should be varied[26].
- In the next PSUR, the MAH should provide a detailed review of cases of hypothyroidism, including an explanation of how the distinction between serious and non-serious adverse events was made and how the treatment regimen was administered. Further details of the paediatric case of increased levels of thyroid-stimulating hormone (TSH) should also be provided.

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

6.1.8. Thalidomide – THALIDOMIDE CELGENE (CAP) - PSUSA/00002919/201510

Applicant: Celgene Europe Limited

PRAC Rapporteur: Isabelle Robine

Scope: Evaluation of a PSUSA procedure

Background

Thalidomide is an immunosuppressant with anti-inflammatory and potential anti-neoplastic activities indicated in combination with melphalan and prednisone as first line treatment of patients with untreated multiple myeloma, aged ≥ 65 years or ineligible for high dose chemotherapy.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Thalidomide Celgene (thalidomide) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include the risk of pulmonary hypertension and the risk of viral reactivation including serious cases of herpes zoster and hepatitis B virus (HBV) reactivation associated with thalidomide treatment as new warnings, also reflected in the undesirable effects section. Therefore the current terms of the marketing authorisation(s) should be varied[27].
- Furthermore, the PRAC considered that a direct healthcare professional communication (DHPC) should be distributed to relevant healthcare professionals to inform them about the risk of pulmonary hypertension and viral reactivation, in line with an agreed communication plan.

[26] 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
[27] 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 MAH should update the relevant sections of the healthcare professional's educational material in order to reflect the new recommendation.
- In the next PSUR, the MAH should provide a detailed analysis on any new cases of increased intracranial pressure, leukocytoclastic vasculitis, Sweet's Syndrome, pulmonary fibrosis, progressive multifocal leukoencephalopathy and all fatal cases and paediatric cases. Finally, the MAH should provide a detailed analysis of cases of off-label use.
- The MAH should be requested to include the safety concern 'pulmonary hypertension' as a new important identified risk and 'viral reactivation of hepatitis B virus (HBV)' under the current important identified risk 'severe infections' within the next update of the RMP to be submitted no later than 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.

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

See also Annex I 15.2.

6.2.1. Somatropin – NUTROPINAQ (CAP); OMNITROPE (CAP); SOMATROPIN BIOPARTNERS (CAP); NAP - PSUSA/00002772/201509

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

PRAC Rapporteur: Torbjorn Callreus

Scope: Evaluation of a PSUSA procedure

Background

Somatropin is a polypeptide hormone of recombinant DNA origin whose amino acid sequence is identical to that of human growth hormone (hGH) of pituitary origin. Somatropin is indicated for the replacement therapy of endogenous growth hormone in childhood- or adult-onset growth hormone deficiency (GHD) under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Nutropinaq, Omnitrope, Somatropin Biopartners, centrally authorised medicines containing somatropin, and nationally authorised medicines containing somatropin, and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of somatropin-containing medicinal products in the approved indications remains unchanged.
- With regard to Saizen, the product information should be updated to include localised and generalised hypersensitivity reactions as a new undesirable effect with an unknown

frequency. Therefore the current terms of the marketing authorisation(s) should be varied[28].

- With regard to Humatrope, the product information should be updated to include hypersensitivity to the active substance as a new contraindication and to amend the current undesirable effect on hypersensitivity to include 'to the active substance'. Therefore the current terms of the marketing authorisation(s) should be varied[29].
- With regard to all the other somatropin-containing medicinal products, the current terms of the marketing authorisations should be maintained.
- In the next PSUR, the MAHs should present their evaluation of the results from the study on Safety and Appropriateness of Growth Hormone Treatment in Europe (SAGhE). The MAHs should also review the evidence relating to acute adrenal insufficiency and make proposals for updating the product information as appropriate. Finally, the MAHs should provide a review of off-label use of somatropin for precocious puberty.

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

6.2.2. Tadalafil – ADCIRCA (CAP); CIALIS (CAP); NAP - PSUSA/00002841/201510

Applicant: Eli Lilly Nederland B.V.(Adcirca, Cialis), various

PRAC Rapporteur: Miguel-Angel Macia

Scope: Evaluation of a PSUSA procedure

Background

Tadalafil is a selective, reversible inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5) indicated for the treatment of erectile dysfunction in adult males and in adults for the treatment of pulmonary arterial hypertension (PAH) classified as WHO functional class II and III, to improve exercise capacity.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Adcirca and Cialis, centrally authorised medicines containing tadalafil, and nationally authorised medicines containing tadalafil, 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 tadalafil-containing medicinal products in the approved indications remains unchanged.
- With regard to tadalafil-containing medicinal products indicated for the treatment of erectile dysfunction, the product information should be amended following updated number of patients taking tadalafil and placebo in the clinical trials safety database. Thus, 'Undesirable effects' section, should be updated to include 'nausea', 'vomiting',

[28] Update of SmPC sections 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion
[29] Update of SmPC sections 4.3 and 4.8. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

'peripheral oedema' and 'fatigue' as new undesirable effects with an uncommon frequency, to update the frequency of the undesirable effects 'gastro-oesophageal reflux' to uncommon, 'hyperhydrosis', 'penile haemorrhage' and 'haematopsermia' to rare and 'prolonged erections' to uncommon, to add a footnote that no cases of seizure were reported in clinical trials for the undesirable effect 'seizure' and to delete the footnote on priapism as a case has now been reported in clinical trials. Therefore the current terms of the marketing authorisations should be varied[30].

- With regard to tadalafil-containing medicinal products indicated for the treatment of pulmonary arterial hypertension, the current terms of the marketing authorisations should be maintained.
- In the next PSUR, the MAH should explain the reason for the increase in the number of patients from 0-17 years old exposed to Cialis and Adcirca. The MAHs should discuss data regarding off-label use. The MAH should also provide the results of study H6D-MC-LVJE[31] and of three non-interventional ongoing studies expected to be finalised during the reporting period of the next PSUR, if available. The MAHs should also provide information on the ongoing studies FREEDOM-EV[32] and ATPAHSS[33] as available. Finally, the MAHs should provide detailed reviews of cases of increased uterine bleeding, including menorrhagia, metrorrhagia, menometrorrhagia and vaginal haemorrhage.
- The MAHs should be requested to submit to the EMA, within 60 days, a cumulative analysis with detailed information on cases of sudden hearing loss, both from clinical trials and post-marketing sources, including the narratives, seriousness, time to onset, and reversibility.

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. Diclofenac (systemic formulations) (NAP) - PSUSA/00001048/201509

Applicant: various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

Background

[30] Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion
[31] Phase 3, randomized, double-blind, placebo controlled, parallel-design, multicentre study to evaluate the efficacy and safety of tadalafil once-daily dosing in men with signs and symptoms of benign prostatic hyperplasia and erectile dysfunction
[32] Phase 3, international, multicentre, randomized, double- blind, placebo-controlled, clinical worsening study of UT-15C (treprostinil) in subjects with pulmonary arterial hypertension receiving background oral monotherapy
[33] Clinical trial of ambrisentan and tadalafil in pulmonary arterial hypertension associated with systemic sclerosis

Diclofenac is a non-steroidal anti-inflammatory substance, an inhibitor of both 1 (COX-1) and cyclooxygenase 2 (COX-2) indicated for the treatment of pain, the relief of inflammation and swelling in various conditions and for the reduction of fever.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing diclofenac (systemic formulations), 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 diclofenac-containing medicinal products (systemic formulations) in the approved indications remains unchanged.
- With regard to diclofenac-containing medicinal products (oromucosal solutions, sprays and mouthwash formulations), the current terms of the marketing authorisations should be maintained.
- With regard to other diclofenac-containing medicinal products (systemic formulations excluding oromucosal solutions, sprays and mouthwash formulation), the product information should be updated to amend the current information on interaction with anticoagulants, to include ischaemic colitis as a new undesirable effect with an unknown frequency. In addition, the product information of intramuscular formulations should be updated to include a warning on the risk of injection site adverse events and injection site necrosis as an undesirable effect with an unknown frequency. Therefore the current terms of the marketing authorisations should be varied[34].
- In the next PSUR, the MAHs should provide a cumulative review of cases of bronchospasm, asthma (including dyspnoea), pneumonitis, rhabdomyolysis, atrial fibrillation (special focus on patients with prior cardiac disorders), bradycardia, Kounis syndrome, tachycardia, deafness, metabolic acidosis, use in patients with renal insufficiency and drug reaction with eosinophilia and systemic symptoms (DRESS), and discuss the need to update the product information as appropriate. In addition, the MAHs should discuss the possible underlying mechanism for Kounis syndrome and DRESS. The MAHs should also monitor interaction with metformin and lactic acidosis, ischaemic colitis, interaction with tenofovir and acute kidney injury as well as agranulocytosis, haemolytic anaemia and aplastic anaemia.
- In the next PSUR, the MAH Crescent Pharma should comment on the two reported cases under the preferred term 'bradycardia' and the reported case under the preferred term 'Kounis syndrome'.

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

6.3.2. Glycopyrronium (all indications except for chronic obstructive pulmonary disease) (NAP) - PSUSA/00001556/201509

Applicant: various

[34] Update of SmPC sections 4.5 and 4.8 for systemic formulations excluding oromucosal solutions, sprays and mouthwash formulation. In addition, update of SmPC section 4.4 for intramuscular formulations. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

PRAC Lead: Almath Spooner

Scope: Evaluation of a PSUSA procedure

Background

Glycopyrronium bromide (hereafter referred to as glycopyrronium) is a synthetic quaternary ammonium, antimuscarinic agent that exerts its mode of action by competitive antagonism of acetylcholine at postganglionic cholinergic nerves. As solution for injection, it is indicated as a preoperative anticholinergic medication to reduce salivary, tracheobronchial and pharyngeal secretions, either as a preoperative or intraoperative antimuscarinic agent to suppress or prevent bradycardia and to prevent the peripheral muscarinic effects of cholinergic agents such as neostigmine and pyridostigmine.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing glycopyrronium (all indications except for chronic obstructive pulmonary disease), 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 glycopyrronium-containing medicinal products (all indications except for chronic obstructive pulmonary disease) in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include 'hypersensitivity' and 'angioedema' as new undesirable effects with an unknown frequency. Therefore the current terms of the marketing authorisation(s) should be varied[35].

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

6.3.3. Glycopyrronium, neostigmine (NAP) - PSUSA/00001557/201509

Applicant: various

PRAC Lead: Almath Spooner

Scope: Evaluation of a PSUSA procedure

Background

Neostigmine, belonging to the quaternary ammonium compounds, is a parasympathomimetic compound that acts as a reversible acetylcholinesterase inhibitor. Glycopyrronium bromide is an anticholinergic agent that inhibits the effects of acetylcholine at muscarinic cholinergic neurons (postganglionic) and is used to prevent the muscarinic effects of neostigmine. The combination of glycopyrronium and neostigmine is indicated for the reversal of residual non-depolarising neuromuscular block.

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

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing glycopyrronium and neostigmine, 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 glycopyrronium and neostigmine in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include 'hypersensitivity', 'angioedema' and 'anaphylactic reaction' as new undesirable effects with a not known frequency. Therefore the current terms of the marketing authorisation(s) should be varied[36].

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

6.4. Follow-up to PSUR/PSUSA procedures

See also Annex I 15.4.

6.4.1. Pemetrexed – ALIMTA (CAP) - EMEA/H/C/000564/LEG 025

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Isabelle Robine

Scope: Evaluation of a cumulative review and detailed analysis of all cases pertaining to local and systemic scleroderma submitted by the MAH following the recommendation of the PSUSA/00002330/201502 procedure adopted in September 2015

Background

Pemetrexed is a folic acid analogue indicated in combination for the treatment of chemotherapy naïve patients with unresectable malignant pleural mesothelioma. It is also indicated in combination for the first line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) other than predominantly squamous cell histology, and as monotherapy for the maintenance treatment of patients with locally advanced or metastatic NSCLC other than predominantly squamous cell histology. Finally, it is indicated as monotherapy for the second line treatment of patients with locally advanced or metastatic NSCLC other than predominantly squamous cell histology.

Following the evaluation of the most recently submitted PSUR for the above mentioned medicine(s), the PRAC requested the MAH to submit further data (for background, see PRAC minutes September 2015). The responses were assessed by the Rapporteur for further PRAC advice.

Summary of advice/conclusion(s)

[36] 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

- Taking into account the cumulative review and detailed analysis of all cases of local and systemic scleroderma and related terms, including data from studies, spontaneous reports and from the literature submitted by the MAH, the PRAC considered that there is insufficient information to assess definitively the diagnosis of scleroderma in the majority of cases and therefore concluded that there is currently insufficient evidence to include 'scleroderma' to the product information. Nevertheless, the data reviewed showed that erythematous painful oedema of the lower limb resembling erysipelas or scleroderma-like changes could be associated with pemetrexed treatment. Therefore, the PRAC concluded that the product information should be updated to include erythematous oedema as an undesirable effect to avoid any error or delay in the patient's management if such a side effect occurs, even though pain, oedema and infection are listed in the current product information.
- The MAH should submit to EMA, within 60 days, a variation to include in the product information that erythematous oedema mainly of the lower limb has been reported from post-marketing experience with an unknown frequency.

6.4.2. Pemetrexed – ALIMTA (CAP) - EMEA/H/C/000564/LEG 026

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Isabelle Robine

Scope: Evaluation of a cumulative analysis of cases of acute myeloid leukaemia and rhabdomyolysis, cumulative review of cases of atrial fibrillation, cumulative review of cases of posterior reversible encephalopathy syndrome (PRES) and leukoencephalopathy and a cumulative review of cases of palmar-plantar erythrodysaesthesia submitted by the MAH following the recommendation of the PSUSA/00002330/201502 procedure adopted in September 2015

Background

Pemetrexed is a folic acid analogue indicated in combination for the treatment of chemotherapy naïve patients with unresectable malignant pleural mesothelioma. It is also indicated in combination for the first line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) other than predominantly squamous cell histology, and as monotherapy for the maintenance treatment of patients with locally advanced or metastatic NSCLC other than predominantly squamous cell histology. Finally, it is indicated as monotherapy for the second line treatment of patients with locally advanced or metastatic NSCLC other than predominantly squamous cell histology.

Following the evaluation of the most recently submitted PSUR for the above mentioned medicine(s), the PRAC requested the MAH to submit further data (fur background, see PRAC minutes September 2015). The responses were assessed by the Rapporteur for further PRAC advice.

Summary of advice/conclusion(s)

- Taking into account the cumulative reviews of atrial fibrillation, rhabdomyolysis, posterior reversible encephalopathy syndrome/leukoencephalopathy and acute myeloid leukaemia cases provided by the MAH, the PRAC concluded that no new safety issue had emerged from the data provided by the MAH, and the PRAC endorsed the MAH's proposal to continue to monitor these events through routine pharmacovigilance.

- Taking into account the new cumulative review of palmar-plantar erythrodysaesthesia cases provided by the MAH, the PRAC concluded that no new safety issue had emerged from the data provided by the MAH but nevertheless did not support the MAH's disproportionality analyses and recommendation to monitor this topic through routine pharmacovigilance. The PRAC also concluded that the MAH should continue to closely monitor palmar-plantar erythrodysaesthesia cases and should discuss new information in the next PSUR. In addition, for all serious cases the MAH should provide the CIOMS[37] forms and case narratives.

7. Post-authorisation safety studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)[38]

See also Annex I 16.1.

7.1.1. Imatinib – GLIVEC (CAP) - EMEA/H/C/PSP/0042.A.1

Applicant: Novartis Europharm Ltd.

PRAC Rapporteur: Dolores Montero Corominas

Scope: Revised PASS protocol for study CSTI571I2201: a European observational registry collecting efficacy and safety data in newly diagnosed paediatric Philadelphia positive (Ph+) acute lymphoblastic leukaemia (ALL) patients treated with chemotherapy + imatinib ± hematopoietic stem cell treatment (±HSCT)

Background

Glivec is a centrally authorised medicine containing imatinib. It is indicated for the treatment of adult and paediatric patients with newly diagnosed Philadelphia chromosome (bcr-abl) positive (Ph+) chronic myeloid leukaemia (CML) for whom bone marrow transplantation is not considered as the first line of treatment, with Ph+ CML in the chronic phase after failure of interferon-alpha therapy, or in accelerated phase or blast crisis, with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) integrated with chemotherapy, with relapsed or refractory Ph+ ALL as monotherapy, with myelodysplastic/myeloproliferative diseases (MDS/MPD) associated with platelet-derived growth factor receptor (PDGFR) gene re-arrangements, with advanced hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukaemia (CEL) with FIP1L1-PDGFRα rearrangement. Imatinib is also indicated for the treatment of adult patients with Kit (CD 117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumours (GIST), as adjuvant treatment of adult patients who are at significant risk of relapse following resection of Kit (CD117)-positive GIST and for the treatment of adult patients with unresectable dermatofibrosarcoma protuberans (DFSP) and adult patients with recurrent and/or metastatic DFSP who are not eligible for surgery.

The PRAC adopted in January 2014 the draft protocol for PASS study CSTI571I2201: a European observational registry collecting efficacy and safety data in newly diagnosed paediatric Philadelphia positive (Ph+) acute lymphoblastic leukaemia (ALL) patients treated with chemotherapy + imatinib ± hematopoietic stem cell treatment (±HSCT). The MAH

[37] Council for International Organizations of Medical Sciences
[38] In accordance with Article 107n of Directive 2001/83/EC

submitted a substantial protocol amendment for this study to the PRAC to reduce the number of patients to be enrolled in this registry from 100 to a minimum of 50.

Endorsement/Refusal of the protocol

- The PRAC, having considered the amended protocol in accordance with Article 107o of Directive 2001/83/EC, endorsed by consensus the substantial amendments to the PASS protocol for the above listed medicinal product.
- In addition the MAH should amend the due date of the corresponding Annex II condition to June 2022 via the appropriate variation procedure within 60 days.

7.2. Protocols of PASS non-imposed in the marketing authorisation(s)[39]

See also Annex I 16.2.

7.2.1. Rituximab – MABTHERA (CAP) - EMEA/H/C/000165/MEA/093.2

Applicant: Roche Registration Limited

PRAC Rapporteur: Doris Stenver

Scope: MAH's responses to MEA 093.1 [revised PASS registry protocol for a long-term surveillance study of rituximab (Mabthera)-treated patients with granulomatosis, with polyangiitis (GPA) or microscopic polyangiitis (MPA)] as per request for supplementary information adopted in February 2016

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 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 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. For background information, see PRAC minutes September 2015 and PRAC minutes February 2016. 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. All the issues raised in the previous round of assessment are now considered resolved provided that the statistical analysis plan (SAP) is submitted

[39] 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

before the first analysis point and that it includes a specification of the predefined risk windows to which the MAH committed.

- The PRAC, having considered the draft protocol version 1.2, endorsed the protocol for the PASS study for the above listed medicinal product.

7.3. Results of PASS imposed in the marketing authorisation(s)[40]

None

7.4. Results of PASS non-imposed in the marketing authorisation(s)[41]

See Annex I 16.4.

7.5. Interim results of imposed and non-imposed PASS submitted before the entry into force of the revised variation regulation[42]

See Annex I 16.5.

7.6. Others

None

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

8.1.1. Afamelanotide – SCENESSE (CAP) - EMEA/H/C/002548/S/0007 (without RMP)

Applicant: Clinuvel (UK) Limited

[40] In accordance with Article 107p-q of Directive 2001/83/EC
[41] 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
[42] In line with the revised variations regulation for any submission before 4 August 2013

PRAC Rapporteur: Valerie Strassmann

Scope: Annual reassessment of the marketing authorisation

Background

Afamelanotide is a melanocortin receptor agonist indicated for the prevention of phototoxicity in adult patients with erythropoietic protoporphyria (EPP).

Scenesse, a centrally authorised product containing afamelanotide was authorised in 2014 under exceptional circumstances. The benefit-risk of Scenesse is reviewed on a yearly basis by the CHMP 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 annual re-assessment procedure for Scenesse (afamelanotide) could be finalised taking into account that already existing conditions and obligations will be maintained by the MAH (RMP, educational material, controlled distribution system, retrospective chart review, and disease registry).

8.1.2. Antithrombin alfa – ATRYN (CAP) - EMEA/H/C/000587/S/0026 (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 in 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. For further background, see PRAC minutes February 2016.

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 annual re-assessment procedure for ATryn (antithrombin alfa) could be finalised provided that the MAH undertakes to fulfil the conditions and obligations.
- The MAH should submit to EMA, within 30 days, an updated RMP.

8.2. Conditional renewals of the marketing authorisation

See Annex I 17.2.

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 in 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. For further background, see PRAC minutes February 2016.

Summary of advice

- Based on the review of the available pharmacovigilance data for ATryn (antithrombin alfa) and the CHMP Rapporteur's assessment report, the PRAC considered that the renewal of the marketing authorisation could be granted with unlimited validity.
- The MAH should submit to EMA, within 30 days, an updated RMP.

8.3.2. Piperaquine tetraphosphate, dihydroartemisinin – EURARTESIM (CAP) - EMEA/H/C/001199/R/0023 (without RMP)

Applicant: Sigma-Tau Industrie Farmaceutiche Riunite S.p.A.

PRAC Rapporteur: Julie Williams

Scope: 5-year renewal of the marketing authorisation

Background

Piperaquine is a bisquinoline and dihydroartemisinin (DHA), a semi-synthetic derivative of artemisinin. In combination, these substances are indicated for the treatment of uncomplicated *Plasmodium falciparum* malaria in adults, children and infants 6 months and over and weighing 5 kg or more.

Eurartesim, a centrally authorised medicine containing piperaquine tetraphosphate/dihydroartemisinin, was authorised in 2011.

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

Summary of advice

- Based on the review of the available pharmacovigilance data relating to Eurartesim (piperaquine tetraphosphate/dihydroartemisinin), the PRAC considered that the MAH should submit satisfactory responses to a request for supplementary information (RSI) before this procedure can be concluded.
- The MAH should make proposals for addressing the issue of compliance with advice on avoiding food before and after administration in view of the potential for impaired efficacy and the risk of QT interval prolongation.

9. Product related pharmacovigilance inspections

9.1. List of planned pharmacovigilance inspections

None

9.2. Ongoing or concluded pharmacovigilance inspections

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

9.3. Others

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

10.4. 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.

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

11.1. Safety related variations of the marketing authorisation

None

11.2. Other requests

None

12. Organisational, regulatory and methodological matters

12.1. Mandate and organisation of the PRAC

12.1.1. PRAC working group - Recommendations on efficiency of plenary meetings – best practice guide

PRAC lead: Martin Huber, Rafe Suvarna, Ulla Wändel Liminga

Following the PRAC 'Strategic Review & Learning Meeting' in Luxemburg and the discussion at the organisational matters teleconference on 19 November 2015 (see PRAC minutes November 2015), as part of the agreed action plan, a PRAC working group on using PRAC plenary time efficiently and effectively was set up and developed a best practice guidance aimed at providing hands-on guidance to PRAC members/alternates. The draft of the best practice guidance was presented and discussed during the May 2016 PRAC and adopted during the organisational matters teleconference held on 26 May 2016. A follow-up discussion is planned at the June 2016 PRAC meeting on the implementation plan.

12.2. Coordination with EMA Scientific Committees or CMDh

12.2.1. Advancing the Development of Paediatric Therapeutics (ADEPT): successes and challenges of performing long-term paediatric safety studies – report from the FDA public workshop held in April 2016

Dirk Mentzer, Chair of the Paediatric Committee (PDCO), presented to PRAC on the EMA experience with long-term safety studies in children following the report from the FDA public workshop: Advancing the Development of Pediatric Therapeutics (ADEPT) held in April 2016. The PRAC welcomed this update and asked to be kept informed of developments in this important area.

12.2.2. Joint Paediatric Committee (PDCO)-PRAC Working Group - guideline on conduct of pharmacovigilance for medicines used by the paediatric population - proposal for creation of new GVP chapter for special populations

Following previous PRAC discussions on the proposed revision of the guideline on conduct of pharmacovigilance for medicines used by the paediatric population (see PRAC minutes December 2015 and PRAC minutes January 2016), the EMA secretariat proposed to develop a new GVP chapter for special populations with a special focus on the paediatric population. The EMA secretariat launched a call for interests in providing input in developing sections on

adverse drug reactions and signals management, RMP as well as PASS. Julie Williams, Ulla Wändel Liminga and Sabine Straus expressed interest in participating in order to present a draft GVP chapter to PRAC in September 2016 before initiating a public consultation.

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

12.3.1. Advisory Group on Summary of Product Characteristics (SmPC) - 2010-2015 activity report

The PRAC was updated on the five-year activity report of the 'Summary of Product Characteristics Advisory Group' (SmPC AG) since its creation in 2010 following the second revision of the SmPC guideline. The SmPC AG was established to promote and facilitate the application of the SmPC guideline. Its main activities consist of training, answers to SmPC queries raised by the regulatory network, and preparation of its annual activity report, considering the impact of the SmPC implementation plan on product information and related regulatory guidance and processes.

12.3.2. Vaccines Working Party (VWP) / PRAC: Stakeholders proposal for the implementation of the principles of passive enhanced safety surveillance (ESS) for the upcoming pilot seasons

The PRAC discussed the Vaccines Europe's proposal for the implementation of the principles of passive enhanced safety surveillance (ESS) systems for seasonal influenza vaccines for the season 2016-2017, together with the recommendations made by the PRAC Vaccines ESS Guidance drafting group and the Vaccines Working Party (VWP). The PRAC supported the findings of the review of the implementation of the guidance so far, and acknowledged the challenges encountered but also the public health benefits of the manufacturers' efforts in moving towards a sustainable infrastructure. The PRAC supported the continuation of the surveillance plans in the next season and endorsed the paper drafted by the VWP and the PRAC drafting group. The adopted document, supplementing the existing interim guidance, is expected to facilitate the planning of passive enhanced surveillance in the coming seasons by the MAHs of seasonal influenza vaccines.

12.4. Cooperation within the EU regulatory network

None

12.5. Cooperation with International Regulators

None

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

None

12.7. PRAC work plan

None

12.8. Planning and reporting

None

12.9. Pharmacovigilance audits and inspections

12.9.1. Pharmacovigilance systems and their quality systems

None

12.9.2. Pharmacovigilance inspections

None

12.9.3. Pharmacovigilance audits

None

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

12.10.1. 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.

12.10.2. Periodic safety update reports

None

12.10.3. PSUR action group – roadmap for PSUR issues: Joint PRAC/CMDh recommendation paper on common understanding - finalisation

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

At the organisation matters teleconference held on 26 May 2016, following the February, March and April 2016 PRAC discussions (see PRAC minutes February 2016 and PRAC minutes March 2016, PRAC minutes March 2016 and PRAC minutes April 2016), the EMA Secretariat presented a revised calendar detailing the planned steps for the proposed implementation activities and a revised version of the draft joint PRAC/CMDh recommendation paper on a common understanding on the EU PSUR single assessment for nationally authorised products taking into account the discussion held in April 2016 and the comments raised. The PRAC adopted the paper and endorsed the plan for implementation activities, including preparing assessors guidance.

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

The PRAC endorsed the draft revised EURD list version May 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 May 2016, the updated EURD list was adopted by the CHMP and CMDh at their May 2016 meetings and published on the EMA website on 03/06/2016, see:

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

12.11. Signal management

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

PRAC lead: Sabine Straus

The topic was deferred to the June 2016 PRAC meeting.

12.12. Adverse drug reactions reporting and additional reporting

12.12.1. Good Pharmacovigilance Practice (GVP) module VI on Management and reporting of adverse reactions to medicinal products - revision 2

At the organisational matters teleconference held on 26 May 2016, following consolidation by Project Maintenance groups 1 and the EudraVigilance Expert Working Group (EV-EWG), the PRAC discussed the GVP module VI on Management and reporting of adverse reactions to medicinal products. The draft GVP module has been circulated for comments to the PRAC, CHMP, CMDh, CAT and the Pharmacovigilance Inspectors Working Group (PhV IWG) for comments. PRAC delegates were invited to provide their comments by 17 June 2016.

12.12.2. Management and reporting of adverse reactions to medicinal products

None

12.12.3. Additional monitoring

None

12.12.4. 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 25/05/2016 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

None

12.14. Risk management plans and effectiveness of risk minimisations

12.14.1. Risk management systems

None

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

None

12.15. Post-authorisation safety studies (PASS)

12.15.1. Post-authorisation Safety Studies – imposed PASS

None

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

None

12.16. Community procedures

12.16.1. Referral procedures for safety reasons

None

12.17. Renewals, conditional renewals, annual reassessments

None

12.18. Risk communication and transparency

12.18.1. Public hearings - Plan for a 'mock-up' public hearing

Following previous discussion at PRAC on the organisation of a mock-up (or dry-run) public hearing in July 2016 (see PRAC minutes April 2016) the EMA secretariat presented to the PRAC further information and practical details on the set-up of the planned 'dry-run' public hearing. In addition, the PRAC discussed a fictitious procedure based on a previously completed PRAC-safety referral procedure selected to be used as a mock-procedure for the dry-run public hearing in July 2016.

12.18.2. Safety communication

None

12.19. Continuous pharmacovigilance

12.19.1. Incident management

None

12.20. Others

12.20.1. Strategy on measuring the impact of pharmacovigilance - update

PRAC lead: Marieke De Bruin

Following the adoption of the strategy on measuring the impact of pharmacovigilance activities in January 2016 (see PRAC minutes January 2016) and the adoption of the PRAC interest group mandate in February 2016 (see PRAC minutes February 2016), the EMA Secretariat presented to the PRAC an update on progress made with the work plan deliverables.

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. Allogeneic T cells genetically modified to express suicide gene - EMEA/H/C/002801, Orphan

Applicant: MolMed SpA, ATMP[43]

Scope: Treatment in haploidentical haematopoietic stem cell transplantation

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. Albiglutide – EPERZAN (CAP) - EMEA/H/C/002735/II/0023/G

Applicant: GlaxoSmithKline Trading Services

[43] Advanced-therapy medicinal product

PRAC Rapporteur: Julie Williams

Scope: Revised RMP (version 5) in order to add a new phase IV study to evaluate the effect of albiglutide on cholecystokinin-induced gallbladder emptying in fasting healthy subjects as an additional pharmacovigilance activity, to add 'medication error' as an important potential risk, to add 'serious hypersensitivity reaction' as important identified risk and to update the description and due dates for seven studies in the RMP

14.2.2. Characterised viable autologous cartilage cells expanded ex vivo expressing specific marker proteins – CHONDROCELECT (CAP) - EMEA/H/C/000878/II/0018/G

Applicant: TiGenix NV

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Revised RMP (version 10) in order to add information resulting from the assessment of MEA 016 and MEA 018 in relation to the confirmatory randomized controlled trial in small lesions. Two new important potential risks 'transmission of infective agents' and 'allergic/hypersensitivity reaction' (from PSUSA/00000273/201504) are also added together with other updated information in the RMP

14.2.3. 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)'

14.2.4. 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

14.2.5. Sonidegib – ODOMZO (CAP) - EMEA/H/C/002839/II/0004/G

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Julie Williams

Scope: Submission of the final clinical study reports for exploratory studies X2114 and X2203, whereby the MAH committed to collect cardiac events, second primary malignancies and fractures. In addition, the MAH updated the RMP (version 3.2) to reflect the completion of studies X2114 and X2203 and changes to the due dates for provision of the final study reports for the category 3 studies LDE225C2301 and LDE225X2104

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. Abiraterone – ZYTIGA (CAP) - EMEA/H/C/002321/X/0039

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Dolores Montero Corominas

Scope: Extension application to introduce a new pharmaceutical form associated with a new strength (500 mg film-coated tablets)

14.3.2. 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 template (version 9.1) and to implement minor changes within age-related macular degeneration (AMD) and DME posology sections

14.3.3. Ataluren – TRANSLARNA (CAP) - EMEA/H/C/002720/II/0012

Applicant: PTC Therapeutics International Limited

PRAC Rapporteur: Sabine Straus

Scope: Extension of indication to include the treatment of cystic fibrosis resulting from a nonsense mutation in at least one allele of the cystic fibrosis transmembrane conductance regulator (CFTR) gene. Consequently, sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet and RMP are updated accordingly

14.3.4. Ataluren – TRANSLARNA (CAP) - EMEA/H/C/002720/II/0019

Applicant: PTC Therapeutics International Limited

PRAC Rapporteur: Sabine Straus

Scope: Submission of the final results from the non-clinical study PTC124-15055: assessment of uncoupling protein 1 (UCP1) protein levels in brown adipose tissue (BAT) in weanling rats administered ataluren via oral gavage for two weeks, in order to address MEA 007. Part II: module SII of RMP (version 4.4) was updated to reflect in tumor findings that in-vivo exposure to ataluren and the M4 metabolite does not activate BAT. Other sections of the RMP were updated to reflect completion of the study

14.3.5. Capecitabine – XELODA (CAP) - EMEA/H/C/000316/II/0070

Applicant: Roche Registration Limited

PRAC Rapporteur: Martin Huber

Scope: Update of sections 4.4 and 4.8 of the SmPC in order to include a warning on fingerprint loss. The Package Leaflet and the RMP are updated accordingly. In addition, the MAH took the opportunity to bring the product information in line with the latest QRD template (version 9.1)

14.3.6. Ceritinib – ZYKADIA (CAP) - EMEA/H/C/003819/II/0006/G

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of section 4.5 of the SmPC based on the final results of the clinical pharmacology study CLDK378A2113 and results of a sub-group evaluating the impact of gastric pH-elevating agents on the steady-state pharmacokinetic (PK), efficacy, and safety of ceritinib in anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC) patients. The final clinical study report for study CLDK378A2113 is submitted to fulfill MEA 003. In addition, the MAH is proposing a change to the due date for the provision of the final study report for study CLDK378A2110 (MEA 001). The RMP is updated (version 3.0) accordingly

14.3.7. Cobimetinib – COTELLIC (CAP) - EMEA/H/C/003960/II/0004/G

Applicant: Roche Registration Limited

PRAC Rapporteur: Sabine Straus

Scope: Update of section 5.1 of the SmPC in order to update the safety and efficacy results of studies GO28141 and NO25395. The RMP has been updated accordingly. In addition, the MAH took the opportunity to make minor amendments in sections 4.6, 5.1 and 5.3 of the SmPC

14.3.8. Crizotinib – XALKORI (CAP) - EMEA/H/C/002489/II/0039

Applicant: Pfizer Limited

PRAC Rapporteur: Isabelle Robine

Scope: Extension of indication to include the treatment of adults with ROS1-positive advanced non-small cell lung cancer (NSCLC) based on the results of study A8081001 (a multinational, multicentre, open-label, single-arm study of the safety, pharmacokinetics, pharmacodynamics, and antitumor activity of crizotinib in patients with advanced cancer). Consequential changes are proposed to SmPC sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 and the Package Leaflet and RMP (version 7.0) are updated accordingly

14.3.9. Dolutegravir – TIVICAY (CAP) - EMEA/H/C/002753/X/0018/G

Applicant: ViiV Healthcare UK Limited

PRAC Rapporteur: Julie Williams

Scope: Extension application to add two new strengths (10 mg and 25 mg tablets) to support the extension of the indication for the treatment of paediatric patients from 6 years of age infected with human immunodeficiency virus (HIV). Data from cohort I and II A of the clinical trial ING112578 are presented in support of the new therapeutic indication

14.3.10. Eltrombopag, eltrombopag olamine – REVOLADE (CAP) - EMEA/H/C/001110/II/0029/G

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Dolores Montero Corominas

Scope: Update of sections 4.4 and 4.8 of the SmPC with reference to bone marrow reticulin formation and risk of bone marrow fibrosis and section 5.1 of the SmPC with updated exposure data, based on the final study reports for study TRA112940 (a longitudinal 2-year bone marrow study of eltrombopag olamine (SB-497115-GR) in previously treated adults, with chronic immune (idiopathic) thrombocytopenic purpura (ITP)) and study TRA105325 (EXTEND (Eltrombopag eXTENded Dosing study) an extension study of eltrombopag olamine (SB-497115-GR) in adults with chronic immune (idiopathic) thrombocytopenic purpura (ITP) previously enrolled in an eltrombopag study). As a consequence, Annex II is updated in order to delete 'increased bone marrow reticulin fibres' from the key elements to be included in the educational material. In addition, the MAH took the opportunity to propose an update of the due date in the RMP for the provision of the final clinical study report (CSR) for MEA 022.1 (effectiveness of educational materials for hepatitis C associated thrombocytopenia). The RMP (version 36) is updated accordingly

14.3.11. Empagliflozin, metformin – SYNJARDY (CAP) - EMEA/H/C/003770/II/0015

Applicant: Boehringer Ingelheim GmbH

PRAC Rapporteur: Miguel-Angel Macia

Scope: Extension of indication to include the treatment with Synjardy as adjunct to standard care therapy in adult patients with type 2 diabetes mellitus and high cardiovascular risk when the treatment with empagliflozin and metformin is appropriate and empagliflozin is needed to reduce the risk of all-cause mortality by reducing cardiovascular death and cardiovascular death or hospitalization for heart failure. As a consequence, sections 4.1, 4.4, 4.8 and 5.1 of the SmPC are updated based on the final clinical study report of study EMPA-REG OUTCOME. The Package Leaflet and RMP (version 5.0) is updated accordingly

14.3.12. Erlotinib – TARCEVA (CAP) - EMEA/H/C/000618/II/0045

Applicant: Roche Registration Limited

PRAC Rapporteur: Doris Stenver

Scope: Submission of the clinical study report for study BO25460 (IUNO) 'a randomized, double-blind, placebo controlled, phase III study of first-line maintenance Tarceva *versus* Tarceva at the time of disease progression in patients with advanced non-small cell lung cancer(NSCLC) who have not progressed following 4 cycles of platinum-based chemotherapy' requested as part of variation II/0043. The RMP is updated accordingly

14.3.13. 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

14.3.14. Golimumab – SIMPONI (CAP) - EMEA/H/C/000992/II/0063

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of sections 4.2 and 5.1 of the SmPC in order to reflect the data from a multicentre, placebo-controlled, double-blind, randomised-withdrawal, parallel group study (GO KIDS) in children (2 to 17 years of age) with active polyarticular juvenile idiopathic arthritis (pJIA). The Package Leaflet and the RMP are updated accordingly

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

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of sections 4.8 and 5.1 of the SmPC in order to update the safety and efficacy information with the data from the final clinical study reports of studies C0524T18 and P07642 in fulfilment of MEA 031 and MEA 032. In addition, the MAH took the opportunity to combine the SmPC for the pre-filled pen and pre-filled syringe for 50 mg strength and for the pre-filled pen and pre-filled syringe for 100 mg strength respectively, in line with the latest QRD template (version 9.1). Moreover, the RMP (version 15) is updated accordingly

14.3.16. Imiquimod – ALDARA (CAP) - EMEA/H/C/000179/II/0067

Applicant: Meda AB

PRAC Rapporteur: Rafe Suvarna

Scope: Update of sections 4.2 and 5.1 of the SmPC in order to add data on the results of study X-03016-3284 (LEIDA 2, a phase IV randomised active controlled study) and of a meta-analysis of studies X-03016-3271 (LEIDA, a phase IV randomized active controlled study) and X-03016-3284. The RMP is updated (version 3) accordingly

14.3.17. Linagliptin – TRAJENTA (CAP) - EMEA/H/C/002110/WS/0915 linagliptin, metformin – JENTADUETO (CAP) - EMEA/H/C/002279/WS/0915

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to include the use of Trajenta as a combination therapy with metformin and a sodium-glucose co-transporter-2 (SGLT-2) inhibitor as well as the use of Jentadueto with a SGLT-2 inhibitor. As a consequence, sections 4.1, 4.8 and 5.1 of the SmPC are updated based on studies 1245.30, 1275.10 and 1275.1. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to introduce minor editorial changes in the SmPC for Jentadueto only. Moreover, the RMPs for Trajenta (version 10) and for Jentadueto (version 12) are updated accordingly

14.3.18. Lipegfilgrastim – LONQUEX (CAP) - EMEA/H/C/002556/II/0023

Applicant: Sicor Biotech UAB

PRAC Rapporteur: Julie Williams

Scope: Update of sections 4.4 and 4.8 of the SmPC in order to update the safety information in relation to splenomegaly. The Package Leaflet and Labelling as well as the RMP (version 9) are updated accordingly. In addition, the MAH took the opportunity to bring

the product information in line with the latest QRD template (versions 9.1 and 10). Furthermore, minor editorial changes are introduced in the Package Leaflet

14.3.19. Meningococcal group a, c, w135 and y conjugate vaccine – MENVEO (CAP) - EMEA/H/C/001095/II/0056

Applicant: GSK Vaccines S.r.l

PRAC Rapporteur: Menno van der Elst

Scope: Update of section 4.8 of the SmPC in order to add facial paresis as a new adverse drug reaction and to provide further safety information based on the final clinical study report for study V59_34OB in order to fulfil MEA 023. The Package Leaflet and the RMP (version 8.2) are updated accordingly

14.3.20. Nintedanib – OFEV (CAP) - EMEA/H/C/003821/II/0006

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Marina Dimov Di Giusti

Scope: Update of sections 4.2 and 4.4 of the SmPC in order to revise the dose recommendations for patients with mild hepatic impairment, based on PK/PD modelling data. In addition, the MAH took the opportunity to bring the Annex II in line with the latest QRD template (version 10)

14.3.21. Perampanel – FYCOMPA (CAP) - EMEA/H/C/002434/X/0025

Applicant: Eisai Europe Ltd.

PRAC Rapporteur: Julie Williams

Scope: Line extension to add a new strength of 0.5 mg/ml and to add a new pharmaceutical form, oral solution

14.3.22. Rivaroxaban – XARELTO (CAP) - EMEA/H/C/000944/II/0042/G

Applicant: Bayer Pharma AG

PRAC Rapporteur: Qun-Ying Yue

Scope: Update of section 5.1 of the SmPC following the submission of a prospective, single-arm, non-interventional, open-label cohort study conducted to investigate the safety and effectiveness in a real-world setting, study XANTUS (SN 15914) in order to fulfill MEA 025. In addition, update of section 5.1 of the SmPC following the submission of a prospective, non-interventional, open-label cohort study that was conducted in patient with acute deep vein thrombosis (DVT) to investigate the safety and effectiveness in a real-world setting, study XALIA (SN 15915) in order to fulfill MEA 027. The RMP (version 9.0) is updated accordingly. Additionally the final clinical study reports for studies X-TRA (SN 16320, phase IIIb) and VENTURE-AF (SN 15694, phase IIIb) were also included in the RMP. Finally, the MAH took the opportunity to introduce a minor editorial change in the list of representatives in the package leaflets of all strengths

14.3.23. Tedizolid phosphate – SIVEXTRO (CAP) - EMEA/H/C/002846/II/0009

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Miguel-Angel Macia

Scope: Update of sections 4.4, 4.5 and 5.2 of the SmPC based on the completed drug-drug interaction study MK-1986-004. The Package Leaflet is updated accordingly. In addition the MAH took the opportunity to implement editorial changes in the annexes and to update the annexes in line with the latest QRD template (version 10). The RMP (version 2.0) is updated by removing the missing information for potential risks for drug-drug interactions mediated by CYP3A4, as well as addressing the identified risk for drug-drug interactions mediated via inhibition of breast cancer resistance protein (BCRP), adding updates made to timelines for ongoing and planned studies for long term safety and Asian population experience

14.3.24. Teduglutide – REVESTIVE (CAP) - EMEA/H/C/002345/II/0020

Applicant: NPS Pharma Holdings Limited

PRAC Rapporteur: Torbjorn Callreus

Scope: Extension of indication to include the treatment of the paediatric population. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated in order to update the safety information. The Package Leaflet is updated accordingly

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. Adefovir – HEPSERA (CAP) - PSUSA/00000060/201509 (with RMP)

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Isabelle Robine

Scope: Evaluation of a PSUSA procedure

15.1.2. Alipogene tiparvovec – GLYBERA (CAP) - PSUSA/00010056/201510

Applicant: UniQure biopharma B.V.

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

15.1.3. Budesonide, formoterol – BIRESP SPIROMAX (CAP); BUDESONIDE/FORMOTEROL TEVA (CAP); BUDESONIDE/FORMOTEROL TEVA PHARMA B.V. (CAP); DUORESP SPIROMAX (CAP); VYLAER SPIROMAX (CAP) - PSUSA/00010202/201510

Applicant: Teva Pharma B.V.

PRAC Rapporteur: Torbjorn Callreus

Scope: Evaluation of a PSUSA procedure

15.1.4. Carbidopa, entacapone, levodopa – CORBILTA (CAP); LEVODOPA/CARBIDOPA/ENTACAPONE ORION (CAP); STALEVO (CAP) - PSUSA/00000547/201510

Applicant: Orion Corporation

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

15.1.5. Ceftaroline fosamil – ZINFORO (CAP) - PSUSA/00010013/201510

Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

15.1.6. Ceritinib – ZYKADIA (CAP) - PSUSA/00010372/201510

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

15.1.7. Defibrotide – DEFITELIO (CAP) - PSUSA/00010086/201510

Applicant: Gentium S.r.l.

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

15.1.8. Delamanid – DELTYBA (CAP) - PSUSA/00010213/201510 (with RMP)

Applicant: Otsuka Novel Products GmbH

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of a PSUSA procedure

15.1.9. Eptotermin alfa – OPGENRA (CAP); OSIGRAFT (CAP) - PSUSA/00001247/201509

Applicant: Olympus Biotech International Limited

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

15.1.10. Eslicarbazepine acetate – ZEBINIX (CAP) - PSUSA/00001267/201510

Applicant: Bial - Portela & Cª, S.A.

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

15.1.11. Flutemetamol (^{18}F) – VIZAMYL (CAP) - PSUSA/00010293/201510

Applicant: GE Healthcare Ltd

PRAC Rapporteur: Julie Williams

Scope of procedure: Evaluation of a PSUSA procedure

15.1.12. Granisetron – SANCUSO (CAP) - PSUSA/00010101/201510

Applicant: ProStrakan Limited

PRAC Rapporteur: Jolanta Gulbinovic

Scope: Evaluation of a PSUSA procedure

15.1.13. Hydrocortisone – PLENADREN (CAP) - PSUSA/00009176/201511

Applicant: Shire Services BVBA

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

15.1.14. Insulin detemir – LEVEMIR (CAP) - PSUSA/00001750/201510

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Doris Stenver

Scope: Evaluation of a PSUSA procedure

15.1.15. Levofloxacin – QUINSAIR (CAP) - PSUSA/00010429/201509

Applicant: Raptor Pharmaceuticals Europe BV

PRAC Rapporteur: Miguel-Angel Macia

Scope: Evaluation of a PSUSA procedure

15.1.16. Lurasidone – LATUDA (CAP) - PSUSA/00010114/201510 (with RMP)

Applicant: Sunovion Pharmaceuticals Europe Ltd

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

15.1.17. Macitentan – OPSUMIT (CAP) - PSUSA/00010115/201510

Applicant: Actelion Registration Ltd.

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

15.1.18. Meningococcal group a, c, w135 and y conjugate vaccine – NIMENRIX (CAP) - PSUSA/00010044/201510

Applicant: Pfizer Limited

PRAC Rapporteur: Rafe Suvarna
Scope: Evaluation of a PSUSA procedure

15.1.19. Micafungin – MYCAMINE (CAP) - PSUSA/00002051/201510

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

15.1.20. Miglustat – ZAVESCA (CAP) - PSUSA/00002062/201510

Applicant: Actelion Registration Ltd.

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

15.1.21. Netupitant, palonosetron – AKYNZEO (CAP) - PSUSA/00010393/201510

Applicant: Helsinn Birex Pharmaceuticals Ltd

PRAC Rapporteur: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure

15.1.22. Obinutuzumab – GAZYVARO (CAP) - PSUSA/00010279/201510

Applicant: Roche Registration Limited

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

15.1.23. Ocriplasmin – JETREA (CAP) - PSUSA/00010122/201510

Applicant: ThromboGenics NV

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

15.1.24. Ofatumumab – ARZERRA (CAP) - PSUSA/00002202/201510

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Doris Stenver

Scope: Evaluation of a PSUSA procedure

15.1.25. Oseltamivir – TAMIFLU (CAP) - PSUSA/00002225/201509

Applicant: Roche Registration Limited

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

15.1.26. Pandemic influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) – FOCLIVIA (CAP) - Prepandemic influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) - AFLUNOV (CAP) - PSUSA/00010008/201510

Applicant: Novartis Vaccines Influenza Srl

PRAC Rapporteur: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure

15.1.27. Pasireotide – SIGNIFOR (CAP) - PSUSA/00009253/201510

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

15.1.28. Pazopanib – VOTRIENT (CAP) - PSUSA/00002321/201510

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Doris Stenver

Scope: Evaluation of a PSUSA procedure

15.1.29. Posaconazole – NOXAFIL (CAP) - PSUSA/00002480/201510

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of a PSUSA procedure

15.1.30. Propranolol – HEMANGIOL (CAP) - PSUSA/00010250/201510

Applicant: Pierre Fabre Dermatologie

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

15.1.31. Prucalopride – RESOLOR (CAP) - PSUSA/00002568/201510 (with RMP)

Applicant: Shire Pharmaceuticals Ireland Ltd.

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of a PSUSA procedure

15.1.32. Ramucirumab – CYRAMZA (CAP) - PSUSA/00010323/201510 (with RMP)

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

15.1.33. Siltuximab – SYLVANT (CAP) - PSUSA/00010254/201510

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

15.1.34. Tocilizumab – ROACTEMRA (CAP) - PSUSA/00002980/201510

Applicant: Roche Registration Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

15.1.35. Turoctocog alfa – NOVOEIGHT (CAP) - PSUSA/00010138/201510

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

15.1.36. Umeclidinium bromide – INCRUSE (CAP) - PSUSA/00010263/201510

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure

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

15.2.1. Filgrastim – ACCOFIL (CAP); FILGRASTIM HEXAL (CAP); GRASTOFIL (CAP); NIVESTIM (CAP); RATIOGRASTIM (CAP) ; TEVAGRASTIM (CAP); ZARZIO (CAP), NAP - PSUSA/00001391/201509

Applicant: Accord Healthcare Ltd (Accofil), Hexal AG (Filgrastim Hexal), Apotex Europe BV (Gastrofil), Hospira UK Limited (Nivestim), Ratiopharm GmbH (Ratiograstim), Teva GmbH (Tevagrastim), Sandoz GmbH (Zarzio), various

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

15.2.2. Influenza vaccine (H1N1)v (whole virion, vero cell derived, inactivated) – CELVAPAN (CAP), NAP - PSUSA/00002280/201510

Applicant: Nanotherapeutics Bohumil Sro, various

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

15.2.3. Sodium oxybate – XYREM (CAP); NAP - PSUSA/00002757/201510

Applicant: UCB Pharma Ltd., various

PRAC Rapporteur: Leonor Chambel

Scope: Evaluation of a PSUSA procedure

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

15.3.1. Acetylcysteine (NAP) - PSUSA/00000034/201509

Applicant: various

PRAC Lead: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

15.3.2. Alfentanil (NAP) - PSUSA/00000082/201509

Applicant: various

PRAC Lead: Almath Spooner

Scope: Evaluation of a PSUSA procedure

15.3.3. Beractant (NAP) - PSUSA/00000384/201510

Applicant: various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

15.3.4. Bisoprolol (NAP) - PSUSA/00000419/201509

Applicant: various

PRAC Lead: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

15.3.5. Carmustine (implant) (NAP) - PSUSA/00010348/201509

Applicant: various

PRAC Lead: Isabelle Robine

Scope: Evaluation of a PSUSA procedure

15.3.6. Chlorquinaldol (vaginal tablet), promestriene (NAP) - PSUSA/00009272/201509

Applicant: various

PRAC Lead: Roxana Stefania Stroe

Scope: Evaluation of a PSUSA procedure

15.3.7. Desogestrel, ethinylestradiol (NAP) - PSUSA/00000967/201509

Applicant: various

PRAC Lead: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

15.3.8. Diclofenac (topical formulations) (NAP) - PSUSA/00010342/201509

Applicant: various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CMDh

15.3.9. Fenoterol (obstetric indications) (NAP) - PSUSA/00010001/201509

Applicant: various

PRAC Lead: Marina Dimov Di Giusti

Scope: Evaluation of a PSUSA procedure

15.3.10. Ketoprofen (topical use only) (NAP) - PSUSA/00009205/201509

Applicant: various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

15.3.11. Lactitol (NAP) - PSUSA/00001819/201509

Applicant: various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

15.3.12. Latanoprost (paediatric indication only) (NAP) - PSUSA/00001834/201510

Applicant: various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

15.3.13. Levofloxacin (NAP) - PSUSA/00001854/201510

Applicant: various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

15.3.14. Lisinopril (NAP) - PSUSA/00001894/201509

Applicant: various

PRAC Lead: Margarida Guimarães

Scope: Evaluation of a PSUSA procedure

15.3.15. Phloroglucinol, trimethylphloroglucinol (NAP) - PSUSA/00010355/201509

Applicant: various

PRAC Lead: Isabelle Robine

Scope: Evaluation of a PSUSA procedure

15.4. Follow-up to PSUR procedures

15.4.1. Omalizumab – XOLAIR (CAP) - EMEA/H/C/000606/LEG 050.1

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Qun-Ying Yue

Scope: MAH's response to LEG 050 [venous thromboembolism cumulative review as requested in the conclusions of EMEA/H/C/PSUSA/00002214/201412 adopted by the PRAC in July 2015] as per the request for supplementary information adopted in January 2016

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)[44]

16.1.1. Asfotase alfa – STRENSIQ (CAP) - EMEA/H/C/PSP/0032.1

Applicant: Alexion Europe SAS

PRAC Rapporteur: Almath Spooner

Scope: Revised PASS protocol for study ALX-HPP-501: an observational, longitudinal, prospective, long-term registry of patients with hypophosphatasia to collect information on

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

the epidemiology of the disease, including clinical outcomes and quality of life, and to evaluate safety and effectiveness data in patients treated with Strensiq

16.1.2. Ivabradine – PROCORALAN (CAP); CORLENTOR (CAP); IVABRADINE ANPHARM (CAP) - EMEA/H/C/PSP/j/0019.1.A.1

Applicant: Les Laboratoires Servier (Corlentor, Procorolan), Anpharm Przedsiębiorstwo Farmaceutyczne S.A. (Ivabradine Anpharm)

PRAC Rapporteur: Menno van der Elst

Scope: Revised protocol for a drug utilisation study (DUS) for a multinational, retrospective, observational study to assess the effectiveness of risk-minimisation measures

16.1.3. Sebelipase alfa – KANUMA (CAP) - EMEA/H/C/PSP/0036.1

Applicant: Alexion Europe SAS

PRAC Rapporteur: Qun-Ying Yue

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

16.2. Protocols of PASS non-imposed in the marketing authorisation(s)[45]

16.2.1. Alemtuzumab – LEMTRADA (CAP) - EMEA/H/C/003718/MEA/007

Applicant: Genzyme Therapeutics Ltd

PRAC Rapporteur: Torbjorn Callreus

Scope: PASS protocol for study No. OBS13434: a prospective, multicentre, observational, post-authorisation safety study (PASS) to evaluate the long term safety profile of alemtuzumab treatment in patients with relapsing forms of multiple sclerosis (RMS)

16.2.2. Bromelain enriched proteolytic enzyme preparation from ananas comosus – NEXOBRID (CAP) - EMEA/H/C/002246/MEA/003.4

Applicant: MediWound Germany GmbH

PRAC Rapporteur: Valerie Strassmann

Scope: MAH's responses to MEA 003.3 [revised PASS protocol for study MW2013-06-01: drug utilisation study (DUS) to further evaluate the effectiveness of the risk minimisation activities (including evaluation of educational and training materials)] as per request for supplementary information adopted in January 2016

16.2.3. Collagenase clostridium histolyticum – XIAPEX (CAP) - EMEA/H/C/002048/MEA/027.2

Applicant: Swedish Orphan Biovitrum AB (publ)

[45] 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

PRAC Rapporteur: Martin Huber

Scope: MAH's responses to MEA 027.1 [PASS protocol for a non-interventional survey to evaluate the effectiveness of Xiapex educational material for healthcare professionals in the treatment of Peyronie's disease] as per request for supplementary information adopted in January 2016

16.2.4. Desloratadine – AERIUS (CAP) - EMEA/H/C/000313/MEA/065.1; AZOMYR (CAP) - EMEA/H/C/000310/MEA/065.1; NEOCLARITYN (CAP) - EMEA/H/C/000314/MEA/065.1

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Jean-Michel Dogné

Scope: MAH's responses to MEA 065 [PASS investigating the association between the use of desloratadine and the risk of seizures, supraventricular tachycardia, and atrial fibrillation or flutter: a nordic register-based study] as per request for supplementary information adopted in October 2015

16.2.5. Empagliflozin – JARDIANCE (CAP) - EMEA/H/C/002677/MEA/004.1

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Miguel-Angel Macia

Scope: MAH's responses to MEA 004 [PASS study1245.97 to assess the risk of urinary tract malignancies in relation to empagliflozin exposure in patients with type 2 mellitus diabetes: a multi-database European study, preceded by feasibility assessment] as per request for supplementary information adopted in December 2015

16.2.6. Estrogens conjugated, bazedoxifene – DUAVIVE (CAP) - EMEA/H/C/002314/MEA/003.2

Applicant: Pfizer Limited

PRAC Rapporteur: Martin Huber

Scope: MAH's responses to MEA 003.1 [revised protocol for drug utilisation study (DUS) No. B2311061] as per request for supplementary information adopted in October 2015

16.2.7. Human normal immunoglobulin – PRIVIGEN (CAP) - EMEA/H/C/000831/MEA/022.4

Applicant: CSL Behring GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: MAH's responses to MEA 022.3 [revised protocol for study IgPro10_5003: an observational hospital-based cohort study in the US: Privigen use and haemolytic anaemia in adults and children and the Privigen safety profile in children with chronic inflammatory demyelinating polyneuropathy (CIDP)] as per request for supplementary information adopted in January 2016

16.2.8. Lumacaftor, ivacaftor – ORKAMBI (CAP) - EMEA/H/C/003954/MEA/003

Applicant: Vertex Pharmaceuticals (Europe) Ltd.

PRAC Rapporteur: Almath Spooner

Scope: PASS protocol for study VX14 809 108: an observational study to evaluate the utilisation patterns and long-term effects of lumacaftor and ivacaftor combination therapy in patients with cystic fibrosis

16.2.9. Panobinostat – FARYDAK (CAP) - EMEA/H/C/003725/MEA/002.1

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Julie Williams

Scope: MAH's responses to MEA 002 [PASS study LBH589D2408 of panobinostat use in relapsed or relapsed/refractory multiple myeloma patients who have received at least two prior regimens including bortezomib and an immunomodulatory agent in a real-world setting according to the current EU prescribing information and document adherence to dosing regimen (including the dosing card, blister pack) by describing clinical characteristics, frequency and severity of the medication error events] as per request for supplementary information adopted in December 2015

16.2.10. Sacubitril, valsartan – ENTRESTO (CAP) - EMEA/H/C/004062/MEA/002

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Rafe Suvarna

Scope: PASS protocol for study No. CLCZ696B2014: a non-interventional post-authorisation European database safety study (category3) to characterize the risk of angioedema and other specific safety events of interest in association with use of Entresto (sacubitril/valsartan) in adult patients with heart failure

16.2.11. Sacubitril, valsartan – ENTRESTO (CAP) - EMEA/H/C/004062/MEA/004

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Rafe Suvarna

Scope: PASS protocol for study No. CLCZ696B2015: a non-interventional post-authorisation European database safety study (category 3) to assess the risk of myotoxicity, hepatotoxicity and acute pancreatitis in statin-exposed heart failure patients with or without concomitant use of sacubitril/valsartan

16.3. Results of PASS imposed in the marketing authorisation(s)[46]

None

16.4. Results of PASS non-imposed in the marketing authorisation(s)[47]

16.4.1. Dabigatran etexilate – PRADAXA (CAP) - EMEA/H/C/000829/II/0093

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Torbjorn Callreus

Scope: Submission of the final clinical trial report of study 1160.149: a post-authorisation safety study to evaluate the effectiveness of the risk minimisation activities in the treatment

[46] In accordance with Article 107p-q of Directive 2001/83/EC
[47] 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

of stroke prevention in atrial fibrillation in order to address part of follow-up measure MEA 026. The RMP (version 31.6) is updated with results from clinical study 1160.149

16.4.2. Eptacog alfa (activated) – NOVOSEVEN (CAP) - EMEA/H/C/000074/II/0089

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Sabine Straus

Scope: Submission of the final study teport for study NN7025-3601 : a prospective observational study on NovoSeven room temperature (VII25) in patients with haemophilia A and B. The submission of this study report addresses MEA 046.4. The RMP (version 6.1) is updated accordingly

16.4.3. Golimumab – SIMPONI (CAP) - EMEA/H/C/000992/II/0068/G

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of the final results of a non-interventional, prospective registry study CNTO148ART4003 in order to fulfill the post-authorisation commitment MEA 006: a registry study Swedish database initiative for exposure to golimumab: a review and analysis of adverse events from the Swedish national registry system. The RMP is updated accordingly to update the due date of the completion and final report of studies: - P04480 (MEA 005.4) 'long-term observation of treatment with biologics in rheumatoid arthritis' from December 2017 to December 2021 and December 2018 to December 2022 respectively. - CNTO148ART4001 (MEA 007.1) 'exposure to golimumab during pregnancy in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis: a review and analysis of birth outcomes from the Swedish, Danish, and Finnish medical birth registers' from February 2016 to December 2021 and February 2017 to December 2022 respectively. -MK-8259-042 (MEA0027.3) 'safety study of golimumab in ulcerative colitis using the Spanish ENEIDA registry' from July 2015 to March 2022 and December 2018 to December 2022 respectively and to introduce the date of provision of the final report (March 2023). In addition, the need to submit interim report for study CNTO148ART4002 was removed following the completion of MEA 008.2

16.4.4. Imatinib – GLIVEC (CAP) - EMEA/H/C/000406/II/0100

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Dolores Montero Corominas

Scope: Submission of the final clinical study report for study CSTI571A2403: 'a global Gleevec/Glivec and Tasigna pregnancy exposure registry' (category 3 study)

16.4.5. Nilotinib – TASIGNA (CAP) - EMEA/H/C/000798/II/0080

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Doris Stenver

Scope: Submission of the final clinical study report for study CSTI571A2403: 'a global Gleevec/Glivec and Tasigna pregnancy exposure registry' (category 3) in fulfilment of MEA 038

16.4.6. Voriconazole – VFEND (CAP) - EMEA/H/C/000387/II/0115

Applicant: Pfizer Limited

PRAC Rapporteur: Sabine Straus

Scope: Submission of the final study report for a non-interventional post authorisation safety study A1501097: evaluation of the potential association between voriconazole use and squamous cell carcinoma (SCC) of the skin among patients with lung or lung/heart transplants in order to fulfil MEA 071.11. The RMP (version 4.0) is updated accordingly

16.5. Interim results of imposed and non-imposed PASS submitted before the entry into force of the revised variation regulation[48]

16.5.1. Abatacept – ORENCIA (CAP) - EMEA/H/C/000701/MEA/046.3

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Kirsti Villikka

Scope: Annual update for study IM101240: observational registry of abatacept in patients with juvenile idiopathic arthritis (JIA registry)

16.5.2. Abatacept – ORENCIA (CAP) - EMEA/H/C/000701/MEA/048.4

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Kirsti Villikka

Scope: Annual report on the juvenile idiopathic arthritis (JIA) registry, an observational registry of abatacept in patients with juvenile idiopathic arthritis

16.5.3. Dolutegravir – TIVICAY (CAP) - EMEA/H/C/002753/MEA/001

Applicant: ViiV Healthcare UK Limited

PRAC Rapporteur: Julie Williams

Scope: Interim annual report from EuroSIDA PASS study No. 201177: a prospective observational cohort study in patients receiving dolutegravir (category 3) to investigate the risk of hypersensitivity reactions, hepatotoxicity and serious rash (division of acquired immune deficiency syndrome (AIDS) (category 3 or 4)

16.5.4. Dolutegravir, abacavir, lamivudine – TRIUMEQ (CAP) - EMEA/H/C/002754/MEA/007

Applicant: ViiV Healthcare UK Limited

PRAC Rapporteur: Julie Williams

Scope: Interim annual report form a prospective observational cohort study to monitor occurrence of hypersensitivity reactions and hepatotoxicity in patients receiving dolutegravir (category 3)

16.5.5. Infliximab – INFLECTRA (CAP) – EMEA/H/C/002778/MEA 008.2, REMSIMA (CAP) - EMEA/H/C/002576/MEA/008.2

Applicant: Celltrion Healthcare Hungary Kft.

PRAC Rapporteur: Rafe Suvarna

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

Scope: Evaluation of the MAH's responses to MEA 008.1 [Fifth periodic report for post marketing surveillance of Remsima 100 mg to evaluate safety and efficacy in Korea] as per the request for supplementary information adopted in December 2015

16.6. Others

None

16.7. 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.

16.8. 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.

16.9. 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.

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

None

17.2. Conditional renewals of the marketing authorisation

17.2.1. Crizotinib – XALKORI (CAP) - EMEA/H/C/0002489/R/0041 (without RMP)

Applicant: Pfizer Limited

PRAC Rapporteur: Isabelle Robine

Scope: Conditional renewal of the marketing authorisation

17.3. Renewals of the marketing authorisation

17.3.1. Dasatinib – SPRYCEL (CAP) - EMEA/H/C/000709/R/0050 (without RMP)

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Doris Stenver

Scope: 5-year renewal of the marketing authorisation

17.3.2. Emtricitabine, rilpivirine, tenofovir disoproxil – EVIPLERA (CAP) - EMEA/H/C/002312/R/0074 (without RMP)

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Menno van der Elst

Scope: 5-year renewal of the marketing authorisation

17.3.3. Exenatide – BYETTA (CAP) - EMEA/H/C/000698/R/0053 (with RMP)

Applicant: AstraZeneca AB

PRAC Rapporteur: Qun-Ying Yue

Scope: 5-year renewal of the marketing authorisation

17.3.4. Fidaxomicin – DIFICLIR (CAP) - EMEA/H/C/002087/R/0026 (with RMP)

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Qun-Ying Yue

Scope: 5-year renewal of the marketing authorisation

17.3.5. Hydrocortisone – PLENADREN (CAP) - EMEA/H/C/002185/R/0020 (without RMP)

Applicant: Shire Services BVBA

PRAC Rapporteur: Qun-Ying Yue

Scope: 5-year renewal of the marketing authorisation

17.3.6. Levetiracetam – LEVETIRACETAM ACCORD (CAP) - EMEA/H/C/002290/R/0012 (with RMP)

Applicant: Accord Healthcare Ltd

PRAC Rapporteur: Veerle Verlinden

Scope: 5-year renewal of the marketing authorisation

17.3.7. Levetiracetam – LEVETIRACETAM ACTAVIS (CAP) - EMEA/H/C/002355/R/0013 (without RMP)

Applicant: Actavis Group PTC ehf

PRAC Rapporteur: Veerle Verlinden

Scope: 5-year renewal of the marketing authorisation

17.3.8. Levetiracetam – LEVETIRACETAM TEVA (CAP) - EMEA/H/C/002316/R/0021 (without RMP)

Applicant: Teva B.V.

PRAC Rapporteur: Veerle Verlinden

Scope: 5-year renewal of the marketing authorisation

17.3.9. Perflutren – LUMINITY (CAP) - EMEA/H/C/000654/R/0021 (without RMP)

Applicant: Lantheus MI UK Ltd

PRAC Rapporteur: Almath Spooner

Scope: 5-year renewal of the marketing authorisation

17.3.10. Pramipexole – PRAMIPEXOLE ACCORD (CAP) - EMEA/H/C/002291/R/0010 (without RMP)

Applicant: Accord Healthcare Ltd

PRAC Rapporteur: Doris Stenver

Scope: 5-year renewal of the marketing authorisation

17.3.11. Rilpivirine – EDURANT (CAP) - EMEA/H/C/002264/R/0022 (with RMP)

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Sabine Straus

Scope: 5-year renewal of the marketing authorisation

17.3.12. Saxagliptin, metformin hydrochloride – KOMBOGLYZE (CAP) - EMEA/H/C/002059/R/0032 (without RMP)

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: 5-year renewal of the marketing authorisation

17.3.13. Tafamidis – VYNDAQEL (CAP) - EMEA/H/C/0002294/R/0032 (without RMP)

Applicant: Pfizer Limited

PRAC Rapporteur: Isabelle Robine

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 10-13 May 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
Jean-Michel Dogné	Member	Belgium	No restrictions applicable to this meeting	Full involvement
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
Željana Margan Koletić	Alternate	Croatia	No interests declared	Full involvement
Nectaroula Cooper	Member	Cyprus	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
Isabelle Robine	Member	France	No interests declared	Full involvement
Martin Huber	Member	Germany	No interests declared	Full involvement
Valerie Strassmann	Alternate	Germany	No interests declared	Full involvement
Leonidas Klironomos	Member	Greece	No restrictions applicable to this meeting	Full involvement
Julia Pallos	Member	Hungary	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
Guðrún Kristín Steingrímsdóttir	Member	Iceland	No interests declared	Full involvement
Carmela Macchiarulo	Member	Italy	No interests declared	Full involvement
Amelia Cupelli	Alternate	Italy	No interests declared	Full involvement
Zane Neikena	Member	Latvia	No interests declared	Full involvement
Zane Stade	Alternate	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
Adam Przybylkowski	Member	Poland	No interests declared	Full involvement
Margarida Guimarães	Member	Portugal	No interests declared	Full involvement
Leonor Chambel	Alternate	Portugal	No interests declared	Full involvement
Roxana Stefania Stroe	Member	Romania	No interests declared	Full involvement
Tatiana Magálová	Member	Slovakia	No interests declared	Full involvement
Miroslava Matíková	Alternate	Slovakia	No restrictions applicable to this meeting	Full involvement
Gabriela Jazbec	Alternate	Slovenia	No interests declared	Full involvement
Dolores Montero Corominas	Member	Spain	No interests declared	Full involvement
Miguel-Angel Macia	Alternate	Spain	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Ulla Wändel Liminga	Member	Sweden	No interests declared	Full involvement
Qun-Ying Yue	Alternate	Sweden	No interests declared	Full involvement
Julie Williams	Member	United Kingdom	No interests declared	Full involvement
Rafe Suvarna	Alternate	United Kingdom	No interests declared	Full involvement
Marie Louise (Marieke) De Bruin	Member	Independent scientific expert	No interests declared	Full involvement
Stephen J. W. Evans	Member	Independent scientific expert	No interests declared	Full involvement
Brigitte Keller-Stanislawski	Member	Independent scientific expert	No interests declared	Full involvement
Thierry Trenque	Member	Independent scientific expert	No interests declared	Full involvement
Lennart Waldenlind	Member	Independent scientific expert	No interests declared	Full involvement
Raymond Anderson	Member	Healthcare Professionals' Representative	No interests declared	Full involvement
Kirsten Myhr	Alternate	Healthcare Professionals' Representative	No interests declared	Full involvement
Marco Greco	Member	Patients' Organisation Representative	No interests declared	Full involvement
Albert van der Zeijden	Alternate	Patients' Organisation Representative	No restrictions applicable to this meeting	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
Arnaud Batz	Expert - via telephone*	France	No interests declared	Full involvement
Claire Ferard	Expert - in person*	France	No interests declared	Full involvement
Fanny Raguideau	Expert - via	France	No	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
	telephone*		restrictions applicable to this meeting	
Simone Bergner	Expert - via telephone*	Germany	No interests declared	Full involvement
Thomas Grüger	Expert - via telephone*	Germany	No interests declared	Full involvement
Dirk Mentzer	Expert - via telephone*	Germany	No interests declared	Full involvement
Wiebke Seemann	Expert - via telephone*	Germany	No interests declared	Full involvement
Eleanor Carey	Expert - in person*	Ireland	No interests declared	Full involvement
Rhea Fitzgerald	Expert - in person*	Ireland	No restrictions applicable to this meeting	Full involvement
Maarten Lagendijk	Expert - in person*	Netherlands	No interests declared	Full involvement
Eirik Hagtvet	Expert - via telephone*	Norway	No interests declared	Full involvement
Joanna Plichta	Expert - in person*	Poland	No interests declared	Full involvement
Charlotte Backman	Expert - in person*	Sweden	No interests declared	Full involvement
Rolf Gedeborg	Expert - in person*	Sweden	No interests declared	Full involvement
Filip Josephson	Expert - in person*	Sweden	No interests declared	Full involvement
Philip Bryan	Expert - via telephone*	United Kingdom	No interests declared	Full involvement
John Clements	Expert - via telephone*	United Kingdom	No restrictions applicable to this meeting	Full involvement
Katherine Donegan	Expert - via telephone*	United Kingdom	No interests declared	Full involvement
Julia Double	Expert - via telephone*	United Kingdom	No interests declared	Full involvement
Ana Fernandez Duenas	Expert - in person*	United Kingdom	No interests declared	Full involvement
Sarah Jane Mee	Expert - via telephone*	United Kingdom	No restrictions	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			applicable to this meeting	
Andrew Ruddick	Expert - via telephone*	United Kingdom	No restrictions applicable to this meeting	Full involvement
Catherine Tregunno	Expert - via telephone*	United Kingdom	No interests declared	Full involvement
A representative from the European Commission attended the meeting				
Meeting run with support from relevant EMA staff				

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

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/