EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

11 July 2013
EMA/PRAC/430682/2013
Pharmacovigilance Risk Assessment Committee (PRAC)

Pharmacovigilance Risk Assessment Committee (PRAC)

Minutes of the 10-13 June 2013 meeting

Chair: June Raine – Vice-Chair: Almath Spooner

Explanatory notes

The notes give a brief explanation of relevant minutes 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 agenda)

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 reports of adverse events from healthcare professionals or patients (so called 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.
After evaluation of a safety signal the conclusion could be that the medicine caused the adverse reaction, that a causal relationship with the adverse event was considered unlikely, or that no clear answer could be given and the signal therefore is to be further investigated. 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 product information (the summary of product characteristics and the package leaflet).
For completeness the information on signals is complemented, when available, by information on worldwide population exposure.

Risk Management Plans (RMPs)
(Item 5 of the PRAC Minutes)

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The RMP describes what is known and not known about the safety of a medicine and states how the side effects 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 summarise data on the benefits and risks of a medicine and include 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 minimisation activities that have been introduced. The results of a PASS help regulatory agencies to further evaluate the safety and benefit-risk profile of a medicine already in use.

Product-related pharmacovigilance inspections
(Item 9 of the PRAC Minutes)
These are inspections carried out by regulatory agencies to ensure that marketing authorisation holders have systems in place that enable them to comply with their obligations to closely follow the safety of a medicine after authorisation.

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

The use and indications of some of the medicines mentioned as background information in the minutes is described in abbreviated form. We recommend the readers to refer to the EMA website: 'Search for medicines' to find the full product information (Summary of the Product Characteristics and Package Leaflet) of all centrally authorised medicines included.

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1. Introduction

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

The Chairperson opened the meeting and welcomed all participants to the 10-13 June 2013 meeting of the PRAC.

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 for the 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 the already declared interests on the matters for discussion (see Annex II). 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. 23 or more members were present in the room). All decisions, recommendations and advice were agreed unanimously, unless otherwise specified.

1.2. Adoption of the agenda of the PRAC meeting on 10-13 June 2013

The agenda was adopted with the addition of the following topics upon request from the members of the Committee and the EMA secretariat: solutions for parenteral nutrition 2.1.1.

1.3. Adoption of the minutes of the previous PRAC meeting on 13-16 May 2013

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 on 13-16 May 2013 were published on 13 June 2013 (EMA/PRAC/336080/2013).

2. EU Referral Procedures for Safety Reasons: Urgent EU Procedures

2.1. Newly triggered procedures

2.1.1. Solutions for parenteral nutrition, combination - NUMETA G13%E and NUMETA G16%E EMULSION FOR INFUSION and associated names (NAP)

- Review of the benefit-risk following notification by Sweden of a referral under Article 107i of Directive 2001/83/EC

Regulatory details:

PRAC Rapporteur: Almath Spooner (IE)
PRAC Co-Rapporteur: Ulla Wändel Liminga (SE)

Background

Numeta G13% E is a parenteral nutrition indicated for preterm neonates, for whom oral or enteral nutrition is not possible, insufficient or contraindicated. Numeta G16% E is indicated for parenteral nutrition in term newborn infants and children up to 2 years when oral or enteral nutrition is not possible, insufficient or contraindicated.

The Swedish Medicines Agency (MPA) sent a letter of notification on 13 June 2013 along with a rationale for triggering a referral under Article 107i of Directive 2001/83/EC for Numeta G13%E (glucose, lipids, amino-acids and electrolytes), an industrially manufactured, heat sterilized parenteral nutrition solution designed for preterm neonates, for whom oral or enteral nutrition is not possible, insufficient or contraindicated.

Discussion

Sweden, as Reference Member State for Numeta G13%E, had been informed by the marketing authorisation holder (MAH) that Numeta G13%E batches had been put on hold at the warehouse level and a decision had been taken to recall the product from the market following concerns over the level of magnesium that is suspected to have resulted in hypermagnesemia in preterm neonates.

The PRAC was informed that post-marketing cases of hypermagnesemia had been reported in preterm neonates who have been receiving Numeta G13%E. Cases of hypermagnesemia were also reported from a small investigator-initiated clinical trial.

Although no reports were received for Numeta G16%E, the Pharmacovigilance Risk Assessment Committee (PRAC) decided that this product should also be included in the EMA review because of its magnesium content and its use in newborn infants/toddlers up to the age of 2 years, who may also be at risk of developing hypermagnesemia.

The PRAC appointed Almath Spooner (IE) as Rapporteur and Ulla Wändel Liminga (SE) as Co-Rapporteur for the procedure.

The PRAC discussed a list of questions to be addressed by the MAH during the procedure as well as a timetable for conducting the review and a list of questions to stakeholders. The PRAC also discussed a Direct Healthcare Professional Communication (DHPC) to be circulated to inform healthcare professionals of the case reports of hypermagnesemia in preterm neonates and to inform of voluntary the recall of Numeta G13%E from the market by the MAH.

Summary of recommendation(s) /conclusions

- A list of questions should be addressed by the MAHs (published on the EMA website EMA/PRAC/365946/2012) and data will be gathered from the stakeholders (healthcare professionals, patients' organisations and the general public) by means of responses to a list of questions (EMA/PRAC/366917/2013). The procedure will follow the adopted timetable (EMA/PRAC/364380/2013).
- A Direct Healthcare Professional Communication was also endorsed.

2.2. Ongoing Procedures

None

2.3. Procedures for finalisation

2.3.1. **Flupirtine** (NAP)

- Review of the benefit-risk balance of flupirtine-containing medicines following notification by Germany of a referral under Article 107i of Directive 2001/83/EC

Regulatory details:

PRAC Rapporteur: Margarida Guimarães (PT)
PRAC Co-Rapporteur: Martin Huber (DE)

Background

A final assessment of the data submitted was produced by the Rapporteurs, according to the agreed timetable, for the conclusion of a referral procedure under Article 107i of Directive 2001/83/EC for flupirtine-containing medicines (see minutes of the PRAC 13-16 May 2013 for background).

Discussion

The PRAC discussed the conclusion reached by the Rapporteurs. The PRAC discussed the evidence on the risk of hepatic reactions in the context of the therapeutic effect of flupirtine; two oral explanations took place during the meeting.

The PRAC considered that the benefit-risk balance for flupirtine-containing medicines in the management of acute pain is favourable with a restricted duration and further risk minimisation measures. The PRAC recommended that oral flupirtine medicines and suppositories are indicated for the treatment of acute pain in adults and must only be used if treatment with other analgesics (e.g. non-steroidal anti-inflammatory drugs, weak opioids) is contraindicated. The PRAC further recommended that the duration of treatment with oral flupirtine medicines and suppositories must not exceed 2 weeks. Furthermore liver function tests must be performed at weekly intervals during treatment. The PRAC discussed a DHPC to be circulated to inform healthcare professionals of these changes.

Summary of recommendation(s)/conclusions

The PRAC recommended, by majority, the variation of the marketing authorisations for flupirtine-containing medicines and adopted a recommendation to be considered by the CMDh – see EMA/362055/2013 published on the EMA website on 4 June 2013. A Direct Healthcare Professional Communication (DHPC) and communication plan were also endorsed.

Twenty-one members/alternates, out of 32 eligible to vote present in the room, voted in favour of the variation together with Iceland and Norway, while 11 members[1] had divergent views (see EMA/PRAC/430682/2013 Assessment report for flupirtine containing medicinal products).

Post-meeting note: the press release 'Restrictions in the use of flupirtine-containing medicines - CMDh endorses PRAC recommendation' representing the position provided by the CMDh EMA/384191/2013 was published on the EMA website on 28 June 2013.

[1] Jean-Michel Dogné (BE); Kamila Czajkowska (PL); Isabelle Robine (FR); Julie Williams (UK); Dolores Montero Corominas (ES); Sabine Straus (NL); Almath Spooner (IE); Stephen Evans, Hervé Le Louet, Lennart Waldenlind, Marieke De Bruin (independent scientific experts nominated by the European Commission)

3. EU Referral Procedures for Safety Reasons: Other EU Referral Procedures

3.1. Newly triggered Procedures

None

3.2. Ongoing Procedures

3.2.1. Combined hormonal contraceptives:
desogestrel, **gestodene, norgestimate**, **etonogestrel, drospirenone**, **dienogest**, **chlormadinone**, **norgestimate** (NAP), **nomegestrol acetate / estradiol – IOA** (CAP), **ZOELY** (CAP), **norelgestromin / ethinylestradiol** - **EVRA** (CAP)

- Review of the benefit-risk balance of combined hormonal contraceptives following notification by France of a referral under Article 31 of Directive 2001/83/EC based on pharmacovigilance data

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)
PRAC Co-Rapporteur: Evelyne Falip (FR)

Background

Ongoing referral procedure under Article 31 of Directive 2001/83/EC for combined hormonal contraceptives (see PRAC minutes 13-16 May 2013).

An overview of the aspects being considered during the assessment and of the main data submitted was provided by the Rapporteur. The PRAC was provided with the draft list of participants for the ad-hoc expert meeting including experts nominated by the Member States (MSs) and a draft agenda for the meeting.

Summary of recommendation(s) / conclusions

The PRAC welcomed the summary provided on the ongoing review in preparation for the discussion at the July 2013 meeting. The PRAC also adopted the list of participants to be invited for the 2 July 2013 ad-hoc expert group meeting and endorsed the agenda for the meeting.

Post-meeting note: further to receipt of additional nominations for experts for the ad-hoc experts meeting, the PRAC adopted a revised list of experts by written procedure on Friday 21 June 2013.

3.3. Procedures for finalisation

3.3.1. Codeine (NAP)

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

Regulatory details:

PRAC Rapporteur: Dolores Montero Corominas (ES)
PRAC Co-Rapporteur: Julie Williams (UK)

Background

A final assessment of the responses submitted to the list of outstanding issues was produced by the Rapporteurs according to the agreed timetable for the conclusion of a referral procedure under Article 31 of Directive 2001/83/EC for codeine-containing medicines used in pain relief in the paediatric population (see PRAC minutes 13-16 May).

Discussion

The PRAC discussed the conclusion reached by the Rapporteurs, including the comments received on the proposed wording for the product information. The PRAC discussed the evidence on the risks of opioid toxicity in the context of the therapeutic effect of codeine-containing medicines in pain relief in children.

The PRAC agreed that codeine should not be used in children below the age of 12 years because of the risk of opioid toxicity due to the variable and unpredictable metabolism of codeine to morphine. Codeine should be contraindicated in all paediatric patients (0-18 years of age) who undergo tonsillectomy and/or adenoidectomy for obstructive sleep apnoea syndrome due to an increased risk of developing serious and life-threatening adverse reactions and in patients known to be CYP2D6 ultra-rapid metabolisers as well as in women during breastfeeding.

The PRAC also discussed that further information on dihydrocodeine-containing medicines should be gathered to assess the need for a full benefit-risk review of dihydrocodeine for the same safety concern. Furthermore the PRAC agreed that it should be further investigated whether the same safety concern should be considered when codeine is used in other indications outside pain relief. Follow-up on these aspects will be scheduled for the September 2013 PRAC meeting.

The PRAC discussed key messages to be circulated at national level to inform healthcare professionals of these changes.

Summary of recommendation(s) / conclusions

The PRAC recommended, by majority, a variation of the marketing authorisations for codeine-containing medicines and adopted a recommendation to be considered by CMDh restricting the use of codeine when used for pain relief in children – see EMA/350259/2013 published on 14 June 2013. The key messages for communication were endorsed.

Thirty-three members/alternates, out of 34 eligible to vote present in the room, voted in favour of the variation together with Iceland and Norway, while one member[2] had divergent views (see PRAC Assessment report for codeine-containing medicinal products [3]).

Post-meeting note: the press release 'Restrictions on use of codeine for pain relief in children – CMDh endorses PRAC recommendation' representing the position provided by the CMDh EMA/385716/2013 was published on the EMA website on 28 June 2013.

3.3.2. **Diclofenac** (NAP)

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

[2] Eva Jirsovà (CZ)
[3] Publication of the assessment report pending at 17 July 1013 (see Codeine-containing medicines: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Codeine-containing_medicines/human_referral_prac_000008.jsp&mid=WC0b01ac05805c516f)

Regulatory details:

PRAC Rapporteur: Doris Stenver (DK)
PRAC Co-Rapporteur: Julie Williams (UK)

Background

A final assessment of the data submitted was produced by the Rapporteurs according to the agreed timetable, for the conclusion of a referral procedure under Article 31 of Directive 2001/83/EC for diclofenac-containing medicines (systemic formulations) (see PRAC minutes 13-16 May).

Discussion

The PRAC discussed the conclusions reached by the Rapporteurs and the available evidence on cardiovascular risk (myocardial infarction and stroke) for diclofenac-containing medicines and considered it to be similar to that of selective Cox-2 (cyclo-oxygenase-2 inhibitors). One oral explanation took place during the meeting.

The PRAC agreed that the benefit-risk balance for diclofenac-containing medicinal products remains favourable subject to some restrictions, warnings, and other changes to the product information and additional risk minimisation measures in line with existing contraindications and cardiovascular precautions for selective Cox-2 inhibitors.

The PRAC also discussed whether the evidence reviewed suggested that a safety concern existed for other products belonging to the same therapeutic class, such as aceclofenac. The PRAC agreed that, in principle, aceclofenac should be subject to the same review given the similar pharmacokinetic and pharmacodynamic profile. A follow-up on this aspect will be discussed in more details at the September 2013 PRAC meeting.

Summary of recommendations/conclusions

The PRAC recommended, by majority, the variation of the marketing authorisations for diclofenac-containing medicines and adopted a recommendation to be considered by CMDh for a position – see EMA/353084/2013. The key elements for a Direct Healthcare Professional Communication (DHPC) and a communication plan were also endorsed.

Twenty-nine members/alternates, out of 33 eligible to vote present in the room, voted in favour of the variation together with Iceland and Norway, while four members[4] had divergent views (see PRAC Assessment report for diclofenac containing medicinal products[5]).

Post-meeting note: the press release 'New safety advice for diclofenac – CMDh endorses PRAC recommendation' representing the position provided by the CMDh EMA/380947/2013 was published on the EMA website on 28 June 2013.

3.3.3. **Hydroxyethyl starch** (**HES**), **solutions for infusion** (NAP)

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

[4] Jolanta Gulbinovic(LT); Stephen Evans, Hervé Le Louet, Marieke De Bruin (independent scientific experts nominated by the European Commission).
[5] Publication of the assessment report pending at 17 July 1013 (See Diclofenac-containing medicines: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Diclofenac-containing_medicines/human_referral_prac_000009.jsp&mid=WC0b01ac05805c516f)

Regulatory details:

PRAC Rapporteur: Qun-Ying Yue (SE)
PRAC Co-Rapporteur: Martin Huber (DE)

Background

A final assessment of the data submitted was produced by the Rapporteurs according to the agreed timetable for the conclusion of a referral procedure under 31 of Directive 2001/83/EC for solutions for infusion containing hydroxyethyl starch (see PRAC minutes 13-16 May).

Discussion

The PRAC discussed the conclusion reached by the Rapporteurs.

Two oral explanations took place during the meeting. In addition, the preliminary results of the BaSES Trial (Basel Starch Evaluation in Sepsis, designed to determine whether initial infusion therapy with Hydroxyethylstarch and Ringer's lactate reduces Intensive Care Unit and hospital length of stay in septic patients without impairment of renal function) were presented by the principal investigator[6] of the study.

The PRAC discussed the available evidence on the risks of renal injury and increased mortality in patients treated with HES in the context of the current clinical indications in the treatment of hypovolaemia or hypovolaemic shock conditions. The PRAC considered that the results of large randomised clinical trials indicate a consistent pattern of harm in terms of increased mortality and adverse renal effects in the populations and settings studied. The PRAC also noted that the lack of robust evidence that HES provides any substantive clinical benefit over crystalloids in any indication or population.

The PRAC was of the opinion that the available evidence indicates, when compared with those given crystalloid solutions, that the patients treated with HES were at a greater risk of kidney injury requiring dialysis and had a greater risk of mortality. Therefore, the PRAC concluded that the benefit-risk balance of hydroxyethyl starch solutions for infusion was no longer favourable.

Summary of recommendation(s)/conclusions

The PRAC recommended, by majority, the suspension of the marketing authorisations for infusion solutions containing hydroxyethyl-starch, with conditions for lifting the suspension, and adopted a recommendation to be considered by CMDh for a position – see EMA/349341/2013.

A Direct Healthcare Professional Communication (DHPC) and communication plan were also endorsed.

Twenty-one members/alternates, out of 30 eligible to vote present in the room, voted in favour of the suspension together with Iceland and Norway, while nine members[7] had divergent views [8].

Post-meeting note: the EMA was notified by the MAHs on their intention to request a re-examination of the PRAC recommendation. Follow up discussion on this request will take place at the July 2013 PRAC meeting.

[6] Dr Martin Siegemund. Declared interest: the infusion bags and payment for the blinding at the pharmacy of the University Hospital Basel were provided by Fresenius Kabi; Dr Siegemund received speakers fees and refund of travel expenses from Fresenius-Kabi, B. Braun, Baxter and CSL Behring
[7] Eva Jirsova (CZ); Christos Petrou (CY) ,Jolanta Gulbinovic (LT); Andis Lacis (LV), Sabine Straus (NL), Qun-Ying Yue (SE), Tatiana Magalova (SK); Jane Ahlqvist Rastad (independent scientific expert nominated by the European Commission); Filip Babylon (representative of the healthcare professionals nominated by the European Commission)
[8] The PRAC assessment report including divergent views will be published once the re-examination procedure is fully concluded; see post-meeting note.

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

3.4.1. **GLP-1 based therapy products** (**glucagon-like-peptide-1** (**GLP-1**) **agonists and dipeptidylpeptidase-4** (**DPP-4**) **inhibitors**) (CAP)

- Review of findings on pancreatic risks following notification by the European Medicines Agency (EMA) under Article 5(3) of Regulation (EC) 726/2004

Regulatory details:

PRAC Rapporteur: Qun-Ying Yue (SE)
PRAC Co-Rapporteur: Menno van der Elst (NL)

Background

An Article 5(3) is ongoing for GLP-1 based therapy products (see PRAC minutes 8-11 April 2013). The PRAC was informed of the publication of an editorial[9] and some articles[10] in the British Medical Journal on pancreatic damage from glucagon-suppressing diabetes drugs and on related media coverage of the subject.

Discussion and summary of recommendation(s)/conclusions

The PRAC noted that an expert meeting in the context of the current procedure is planned for 10 July 2013. The Rapporteurs continue to assess all information that is becoming available (including the study by Butler et al. published on 22 March 2013, which triggered the procedure), in order to determine whether there are any changes to the balance of benefits and risks of these medicines that require regulatory action. A CHMP opinion is expected in July 2013.

4. Signal assessment and prioritisation[11]

4.1. New signals detected from EU spontaneous reporting systems

4.1.1. **Adalimumab – HUMIRA** (CAP)

- Signal of immune reconstitution inflammatory syndrome (IRIS)

Regulatory details:

PRAC Rapporteur: Ulla Wändel Liminga (SE)

[9] Gale E. Incretin therapy: should adverse consequences have been anticipated? BMJ. 2013 Jun 10;346:f3617. doi: 10.1136/bmj.f3617. BMJ. 2013 Jun 10;346:f3617. doi: 10.1136/bmj.f3617.
[10] Halfdanarson TR, Pannala R. Incretins and risk of neoplasia. BMJ. 2013 Jun 10;346:f3750. doi: 10.1136/bmj.f3750 Cohen D. Has pancreatic damage from glucagon suppressing diabetes drugs been underplayed? BMJ. 2013 Jun 7;346:f3680. doi: 10.1136/bmj.f3680, Montori V. Helping patients make sense of the risks of taking GLP-1 agonists. BMJ. 2013 Jun 10;346:f3692 doi: 10.1136/bmj.f3692

[11] 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.

Background

Adalimumab is a monoclonal antibody used in the treatment of ankylosing spondylitis, rheumatoid arthritis, Crohn's disease, psoriatic arthritis, psoriasis, axial spondyloarthritis, polyarticular juvenile idiopathic arthritis and ulcerative colitis.

The patient exposure for Humira, a centrally authorised medicine containing adalimumab, is estimated to have been more than 1.4 million patient-years worldwide in the period from 2003 until 2010.

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

Discussion

The PRAC discussed the information on the cases available and agreed that an overwhelming inflammatory response by an immune system reconstituting from suppression, when TNF-inhibitors are withdrawn, could provide a plausible biological mechanism for the development of IRIS (see also infliximab 4.1.3). Moreover, four of the 9 cases provided relatively strong evidence of a possible causal relationship between adalimumab and IRIS.

The PRAC agreed that it would be important to gather further information on the time elapsed between withdrawal of adalimumab and onset of IRIS, and to discuss causality based on available pharmacokinetic knowledge. Therefore the PRAC agreed that the signal needed further investigation.

Summary of recommendation(s)

- The MAH for Humira (adalimumab) should submit to the EMA, within the next PSUR (DLP 31 December 2013), a cumulative review of the signal of IRIS.

4.1.2. Capecitabine – XELODA (CAP)

- Signal of acute renal failure

Regulatory details:

PRAC Rapporteur: Martin Huber (DE)

Background

Capecitabine is an antineoplastic agent used in the treatment of colorectal, colon, stomach and breast cancer.

The exposure for Xeloda and other centrally authorised medicines containing capecitabine is estimated to have been more than 3,700,000 patients worldwide, in the period from first authorisation until 2012.

During routine signal detection activities, a signal of acute renal failure was identified by the EMA, based on 4 cases retrieved from EudraVigilance, in which capecitabine was the only reported drug and which did not include concomitant conditions often associated with renal failure such as diarrhoea, dehydration, multi-organ-failure or sepsis, or a history of renal disorder or dihydropyrimidine dehydrogenase deficiency. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information on the cases reported and agreed that the signal warranted further investigation.

Summary of recommendation(s)

- The MAH for Xeloda (capecitabine) should submit to the EMA, within 60 days, a cumulative review of the signal acute renal failure.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.1.3. Infliximab – REMICADE (CAP)

- Signal of immune reconstitution inflammatory syndrome (IRIS)

Regulatory details:

PRAC Rapporteur: Ulla Wändel Liminga (SE)

Background

Infliximab is a monoclonal antibody used in the treatment of rheumatoid arthritis; adult and paediatric Crohn's disease; adult and paediatric ulcerative colitis; ankylosing spondylitis; psoriatic arthritis and psoriasis.

The exposure for Remicade, a centrally authorised medicine containing infliximab, is estimated to have been more than 1,300,000 patients worldwide, in the period from first authorisation in 1998 to 2010.

During routine signal detection activities, a signal of immune reconstitution inflammatory syndrome (IRIS) was identified by the EMA, based on 19 cases retrieved from EudraVigilance. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information on the cases of IRIS reported. The majority of the cases were also described in the literature. Seven of them provided relatively strong evidence of a possible causal relationship between infliximab and IRIS. The PRAC agreed that an overwhelming inflammatory response by an immune system reconstituting from suppression, when TNF-inhibitors are withdrawn, could provide a plausible biological mechanism for the development of IRIS (see also adalimumab 4.1.1.). Therefore the PRAC agreed that the signal needed further investigation.

Summary of recommendation(s)

- The MAH for Remicade (infliximab) should submit to the EMA, within the next PSUR (DLP 23 August 2013), a cumulative review of the signal.

4.1.4. Lenograstim (NAP)

- Signal of (systemic) capillary leak syndrome (CLS)

Regulatory details:

PRAC Rapporteur: *To be appointed*

Background

Lenograstim is a recombinant human granulocyte colony-stimulating factor (G-CSF) used to stimulate the proliferation and differentiation of granulocytes, especially polymorphonuclear granulocytes (PMNG), in various forms of neutropenia.

Following the conclusion of the PRAC on two medicines of the same class reached at the March 2013 PRAC meeting, a signal of systemic capillary leak syndrome (CLS) was identified by the EMA for lenograstim, based on 2 cases retrieved from EudraVigilance. France, as reference Member State for Granocyte (lenograstim), confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information on the cases of reported CLS and considered that the available data and the similarities between lenograstim and filgrastim, as regards their pharmacodynamic properties and uses, might suggest a possible class effect. However, the PRAC agreed that more information was considered necessary for a further evaluation of the signal, including information on time to onset, exposure status at the time of event (naïve vs multiple exposures), action taken to manage the reaction, treatment given and outcome. Moreover information on similar reactions reported should also be gathered, including cytokine release syndrome (CRS).

The PRAC appointed Isabelle Robine (FR) as Rapporteur for follow-up of this signal.

Summary of recommendation(s)

- The MAH for Granocyte (lenograstim) should submit to the Rapporteur, within 60 days, a cumulative review of the signal of CLS.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.2. New signals detected from other sources

4.2.1. **Orlistat - ALLI** (CAP), **XENICAL** (CAP)

- Signal of inhibition of carboxylesterase-2 from an in vitro study

Regulatory details:

PRAC Rapporteur: *To be appointed*

Background

Orlistat is an inhibitor of gastrointestinal lipases used in the treatment of obesity in adults who are overweight (body mass index, BMI, ≥28 kg/m2) and which should be taken in conjunction with a mildly hypocaloric, low-fat diet.

The exposure for centrally authorised medicines containing orlistat is estimated to have been more than 50 million patients/consumers worldwide, in the period from first authorisation in 1998 to 2012.

A signal of inhibition of carboxylesterase-2 by orlistat, which may have implications for the activation of anticancer prodrugs, was identified by the UK, based on an article published in the literature

describing the results of an in-vitro study[12]. UK confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the results of the study and considered that at present there is insufficient data to translate these in vitro findings to potential clinical drug reactions and/or make changes to the product information. However, a proposal to collect relevant data regarding this potential safety concern should be explored.

Summary of recommendation(s)

- The MAHs for Xenical (orlistat) should provide comments on the signal as part of the latest Xenical RMP, as well as a proposal for collection of further relevant data. The MAH for Alli (orlistat) should also be equally asked to address this issue in the next Alli RMP, currently being updated.

4.3. Signals follow-up and prioritisation

4.3.1. **Etanercept – ENBREL** (CAP)

- Signal of dermatomyositis

Regulatory details:

PRAC Rapporteurs: Julie Williams (UK)

Background

For background information, see PRAC minutes 7-10 January 2013. The MAH replied to the request for information on the signal of dermatomyositis and the responses were assessed by the Rapporteur.

Discussion

The PRAC discussed the findings of the cumulative review submitted. Data from clinical trials provided limited information, as expected given the low frequency of dermatomyositis reports. However, reports identified in the literature and from the safety database of the MAH were supportive of an association between etanercept and dermatomyositis. The cases of worsening of dermatomyositis with positive dechallenge were the ones most supportive of a causal association. The PRAC agreed that the evidence supported an update of the product information with regards to worsening of dermatomyositis in line with what was previously discussed for adalimumab - see minutes of the PRAC 10-13 May 2013. Moreover, 'de novo' dermatomyositis should be kept under close review and proposals on how this will be achieved should be discussed by the MAH.

Summary of recommendation(s)

- The MAHs for Enbrel (etanercept) should be requested to submit a variation to the EMA to update the product information as regards as 'worsening of symptoms of dermatomyositis', within 60 days.

[12] Xiao D, et al. Carboxylesterase-2 is a highly sensitive target of the antiobesity agent orlistat with profound implications in the activation of anticancer prodrugs. Biochem Pharmacol (2012), http://dx.doi. org/10.1016/ j.bcp.2012.11.026

4.3.2. Exenatide – **BYDUREON** (CAP), **BYETTA** (CAP); **liraglutide – VICTOZA** (CAP)

- Signal of gastrointestinal stenosis and obstruction

Regulatory details:

PRAC Rapporteurs: Qun-Ying Yue (SE); Menno van der Elst (NL)

Background

For background, see PRAC minutes 7-10 January 2013. The MAHs for the centrally authorised medicines containing exenatide and liraglutide replied to the request for information on the signal and the responses were assessed by the Rapporteurs.

Discussion

The PRAC discussed the assessment of the evidence available on the signal. The totality of the available data, including published data, indicated a plausible biological rationale for the effect of GLP-1 on intestinal motility. Moreover, gastrointestinal side effects for exenatide are well known. Therefore the PRAC concluded that a causal relationship between exenatide and intestinal obstruction cannot be excluded. Regarding liraglutide, the PRAC also agreed that gastrointestinal side effects are known and occur commonly. Considering the totality of the available data, including the unconfounded cases with compatible time to onset and the cases with positive dechallenge and rechallenge, the information available was sufficient to conclude that liraglutide can be associated with intestinal obstruction and that the product information should be updated with regards to this.

Summary of recommendation(s)

- The MAHs for the centrally authorised exenatide (Bydureon, Byetta) and liraglutide (Victoza) containing medicines[13] should be requested to submit to the EMA within 60 days a variation to update the product information to include "intestinal obstruction"[14] as an undesirable effect.

4.3.3. Leflunomide – **ARAVA** (CAP)

- Signal of myositis

Regulatory details:

PRAC Rapporteur: Sabine Straus (NL)

Background

For background information, see PRAC minutes of 26-29 November 2013. The MAH replied to the request for information on the signal of myositis and the responses were assessed by the Rapporteur.

[13] In line with Article 16(3) of Regulation No (EU) 726/2004 and Article 23(3) of Directive 2001/83/EC, the marketing authorisation holder shall ensure that the product information is kept up to date with the current scientific knowledge including the conclusions of the assessment and recommendations made public by means of the European medicines web-portal established in accordance with Article 26 of Regulation (EC) No 726/2004 (EMA website). For nationally authorised medicines, it is the responsibility of the National Competent Authorities of the Member States to oversee that these recommendations are adhered to

[14] Section 4.8 of the Summary of Product Characteristics

Discussion

The PRAC discussed the assessment of the data provided. The majority of the cases involved myositis but cases of polymyositis and dermatomyositis were also reported. The PRAC agreed that, overall, epidemiological data suggests that myositis is associated with systemic autoimmune or connective tissue disease and polymyositis can occur in association with a systemic autoimmune or connective tissue disease, or with a known viral or bacterial infection. Several drugs may also trigger an inflammatory myopathy similar to polymyositis.

A search was performed by the EMA in The Health Improvement Network (THIN) database to assess the feasibility to further investigate this signal. The assessment led to the conclusion that, in view of the limited exposure and limited number of cases, further investigation in the THIN data base of this possible signal was not feasible.

The PRAC, given that the number of cases reported was limited in consideration of the population exposure to leflunomide, and that in the majority of cases confounding factors were present or alternative explanations could be found, concluded that no further regulatory action would be justified at this time.

Summary of recommendation(s)

- No regulatory action was considered necessary at this time. However, the MAH for Arava (leflunomide) should continue to closely monitor the occurrence of myositis in the next PSURs.

4.3.4. Pandemic influenza vaccine (H1N1)v (split virion, inactivated, adjuvanted) – PANDEMRIX (CAP)

- Signal of narcolepsy: further information following conclusion of the data review of Pandemrix and narcolepsy under Article 20 of Regulation (EC) No 726/2004

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)

Background

The risk of narcolepsy has been discussed in the past by the PRAC, see PRAC minutes 8-11 April 2013. Follow-up discussion on new information arising on this risk had been planned following publication and assessment of the results of a comparative registry cohort study carried out in Sweden, investigating the association of narcolepsy with Pandemrix as well as a range of other neurological and immune related/ autoimmune diseases. In addition to an increased risk for narcolepsy in subjects below the age of 20 years, this study had shown a signal of an increased risk of narcolepsy in certain age groups above 20 years. Furthermore, a Finnish retrospective nationwide registry based cohort study by THL (National Institute for Health and Welfare) and the Finnish Narcolepsy Task Force was published on 22 May 2013, reporting a higher incidence of narcolepsy in the adult population (link).

Discussion

The PRAC discussed an overview of the findings of the Finnish study, presented by Dr Hanna Nohynek from the THL research group. The adult narcolepsy cases were independently verified by sleep experts and the results showed a 3-5 fold, depending on the criteria used for narcolepsy onset, increased risk of narcolepsy in the Pandemrix-vaccinated adults aged over 20 years. The results corresponded to one additional case per 100,000 doses of Pandemrix. It was noted that 23 of the 25 cases were aged less

than 40 years, and the THL concluded that the Finnish data indicated an increased risk of narcolepsy after Pandemrix vaccination in young adults.

The PRAC also discussed the assessment of the study conducted in Sweden, which investigated the associations between Pandemrix vaccination and a large number of outcomes, including narcolepsy, by linking data from vaccination registries with various healthcare databases. The lack of association between Pandemrix and the neurological (excluding narcolepsy) and autoimmune events included in this study raised no further signals on the safety of this vaccine.

Regarding narcolepsy, the study showed an increased incidence in young adults (aged 21-30 years HR 2.2, 95%CI 1.00-4.8), as well as in those aged 20 years or less. The PRAC pointed out the strengths (e.g. its large size and ability to comprehensively link data from various databases using the national identification number) and limitations of the study, including uncertainty over expert validation of diagnoses and onset information (in relation to vaccination), despite a previous validation of the cases in previous Swedish studies.

However, based on these new findings, which were consistent with a previously published French case-control study titled 'Increased risk of narcolepsy in children and adults after pandemic H1N1 vaccination in France' suggesting a relative risk of 3.88 (95% CI 1.37-10.95) for narcolepsy in the >20 year age group, the PRAC agreed that an update of the Pandemrix product information was now warranted. Since the product information currently reported that the increase in risk of narcolepsy has not been found in adults (older than 20 years), the PRAC considered this statement is no longer appropriate and should be removed.

Summary of recommendation(s)

- The MAH for Pandemrix, should be requested to submit to the EMA within 60 days a variation to update the product information to reflect these new findings, including a review of the current totality of evidence on the risk of narcolepsy with Pandemrix in children, adolescents and older age groups, in the context of the benefits of the vaccine in these respective age groups.

4.3.5. Somatropin – **NUTROPINAQ** (CAP), **OMNITROPE** (CAP) and NAPs

- Signal of convulsions

Regulatory details:

PRAC Rapporteur: Sabine Straus (NL)

Background

For background information, see PRAC minutes of 3-5 September 2012. The MAHs replied to the request for information on the signal of convulsions and the responses were assessed by the Rapporteur.

Discussion

The PRAC discussed the assessment of the evidence provided. It was discussed that somatotropin has been reported to cross the blood brain barrier and therefore could potentially affect the central nervous system.

Somatropin has been associated with benign intracranial hypertension which may be a risk factor for convulsions. However there has been no indication that somatotropin could influence neuronal activity.

Furthermore any causality assessment was complicated by the fact that existing underlying conditions (e.g. trauma, cranial tumours, fever) may contribute to the risk on convulsions. Moreover, seizures are most commonly symptoms of various underlying disorders such as congenital Prader Willi syndrome, Turner syndrome or metabolic diseases.

The PRAC agreed that, in 6 of the 1,117 unique cases reporting a convulsion as per defined criteria, the causality could be considered 'possible', given positive dechallenge and/or rechallenge information in these cases. The background incidence varies to a large extent depending on age, population and literature reviewed. The PRAC confirmed that causality assessment was hampered by underlying conditions and confounding by indication (e.g. cranial tumour) in the cases reported.

The incidence of convulsions in GH-treated groups in registries ranged from 0.06% to 1.23%. Patient populations in the registries may differ from the general population with regards to contributing risk factors. However, in the registries analysed (KIGS[15]/KIMS[16], GeNeSIS[17] and NCGS[18]), no untreated group was included.

Given such limitations, the current information in the product information regarding benign intracranial pressure and possible drug interactions with anticonvulsants was considered still adequate at this moment, and more specific wording regarding convulsions was not considered justified.

Summary of recommendation(s)

- No regulatory action was considered necessary at this time. However, the MAH for somatropin containing medicines should keep under close monitoring the potential association between somatropin and convulsions and this issue should be discussed in the next PSUR (DLP 31 March 2014)
- The PRAC Rapporteur should be notified immediately in case of unexpected findings or trends that would warrant updates to the product information or RMP.

4.3.6. **Tiotropium bromide** (NAP)

- Signal of anaphylactic reaction

Regulatory details:

PRAC Rapporteur: Sabine Straus (NL)

Background

For background information, see PRAC minutes 17-10 January 2013. The MAH replied to the request for information on the signal of anaphylactic reaction and the responses were assessed by the Rapporteur.

Discussion

The PRAC discussed the assessment of the additional information submitted and agreed that the number of reported cases of anaphylactic reactions was very low considering the large number of patients exposed (68 post marketing reports over more than 30 million patient-years since first authorisation). Nevertheless, there were some cases of anaphylactic reaction with a positive re-

[15] Pfizer International Growth Database
[16] Pfizer International Metabolic Database
[17] Genetics and NeuroEndocrinology of Short Stature International Study
[18] Genentech's National Cooperative Growth Study

challenge that appeared shortly after the first dose of tiotropium. The PRAC noted that some information on hypersensitivity is already contained in the product information, however, adding anaphylactic reactions would provide more detailed information to the prescriber/patient with regard to the nature of the hypersensitivity reactions that have been described.

Summary of recommendation(s)

- The MAHs for tiotropium [19] should be requested to submit to the NCAs of the MSs within 60 days a variation to update the product information to include "anaphylactic reaction"[20] as an undesirable effect.

4.3.7. **Tramadol** (NAP)

- Signal of hypoglycaemia

Regulatory details:

PRAC Rapporteur: Evelyne Falip (FR)

Background

For background, see PRAC minutes of 4-7 February 2013. The MAH replied to the request for information on the signal of hypoglycaemia and the responses were assessed by the Rapporteur.

Discussion

The PRAC discussed the assessment of the new information available and pointed out that, based on qualitative analysis, there were highly relevant cases supporting an association between tramadol and hypoglycaemia. Cases with positive re-challenge and de-challenge were relevant. Moreover a highly plausible temporal relationship with a short time to onset (from 1 hour to few days) was apparent, sometimes in well-controlled diabetic patients who then required dose insulin adjustment but also in non-diabetic patients. Published analysis of spontaneous reports[21,22] showed that tramadol is associated with the occurrence of hypoglycaemia especially in 'predisposed' patients (elderly patients, diabetic patients under treatment, patients with renal failure). Available data show that tramadol has a glucose-lowering effect in two experimental models of diabetes mellitus[23,24]. Therefore, the PRAC agreed on the need to update the product information regarding occurrence of hypoglycaemia.

[19] In line with Article 16(3) of Regulation No (EU) 726/2004 and Article 23(3) of Directive 2001/83/EC, the marketing authorisation holder shall ensure that the product information is kept up to date with the current scientific knowledge including the conclusions of the assessment and recommendations made public by means of the European medicines web-portal established in accordance with Article 26 of Regulation (EC) No 726/2004 (EMA website). For nationally authorised medicines, it is the responsibility of the National Competent Authorities of the Member States to oversee that these recommendations are adhered to

[20] Section 4.8 of the Summary of Product Characteristics

[21] Tramadol and hypoglycaemia: comparison with other step 2 analgesic drugs. Bourne C, Gouraud A, Daveluy A, Grandvuillemin A, Auriche P, Descotes J, Vial T; French Association of Regional Pharmacovigilance Centres. Br J Clin Pharmacol. 2013 Apr;75(4):1063-7. doi: 10.1111/j.1365-2125.2012.04451.x.

[22] Tavassoli N, Lapeyre-Mestre M, Sommet A, Montastruc JL; French Association of Regional Pharmacovigilance Centres. Reporting rate of adverse drug reactions to the French pharmacovigilance system with three step 2 analgesic drugs: dextropropoxyphene, tramadol and codeine (in combination with paracetamol). Br J Clin Pharmacol. 2009 Sep;68(3):422-6. doi: 10.1111/j.1365-2125.2009.03472.x.

[23] Cheng JT, Liu IM, Chi TC, Tzeng TF, Lu FH, Chang CJ. Plasma glucose-lowering effect of tramadol in streptozotocin-induced diabetic rats. Diabetes. 2001 Dec;50(12):2815-21.

[24] Choi SB, Jang JS, Park S. Tramadol enhances hepatic insulin sensitivity via enhancing insulin signaling cascade in the cerebral cortex and hypothalamus of 90% pancreatectomized rats. Brain Res Bull. 2005 Sep 30;67(1-2):77-86.

Summary of recommendation(s)

- The MAHs for the reference, nationally authorised tramadol containing medicines[25] should be requested to submit to the NCA of the MSs within 60 days a variation to update the product information to include "hypoglycaemia"[26] as an undesirable effect.
- The MAHs of generic products should then be requested to submit to the national competent authorities of the MSs, as applicable, a variation to align their product information to that of the originator.

4.3.8. **Zolpidem** (NAP)

- Signal of next-morning impaired mental alertness, including impaired driving ability

Regulatory details:

PRAC Rapporteur: Carmela Macchiarulo (IT)

Background

For background information, see PRAC minutes 4-7 February 2013. The MAH replied to the request for information on the signal, and the responses were assessed by the Rapporteur.

Discussion

Zolpidem is a hypnotic agent which is indicated for the short-term treatment of insomnia in situations where the insomnia is debilitating or is causing severe distress for the patient.

The PRAC discussed the outcome of the review performed on spontaneous cases, clinical studies and published literature of 'impaired driving ability', 'road traffic accident' and 'somnambulism' associated with zolpidem. The PRAC noted that factors with an impact on pharmacokinetic variables (liver impairment, elderly patients) were underrepresented in the case reports (2.2% liver impairment, 7% elderly) and therefore did not significantly influence the onset of the adverse drug reaction. Overdose and/or high blood levels of zolpidem were reported in 21% of adult cases (22% in female and 20% in male). The concomitant intake of other central nervous system depressants, alcohol consumption or illicit drug use were identified as being among the most frequently reported risk factors for impaired driving in adults.

The PRAC discussed whether lower doses of zolpidem could reduce the probability for next-morning impaired mental alertness including impaired driving ability and whether a dose reduction should be considered in certain patients. The PRAC concluded that further data and review could be useful to clarify this aspect and noted that Italy is considering the need for a full benefit-risk review to optimise risk minimisation.

Summary of recommendation(s)

- No regulatory action is considered necessary at this time pending further consideration of a benefit-risk review.

[25] In line with Article 16(3) of Regulation No (EU) 726/2004 and Article 23(3) of Directive 2001/83/EC, the marketing authorisation holder shall ensure that the product information is kept up to date with the current scientific knowledge including the conclusions of the assessment and recommendations made public by means of the European medicines web-portal established in accordance with Article 26 of Regulation (EC) No 726/2004 (EMA website). For nationally authorised medicines, it is the responsibility of the National Competent Authorities of the Member States to oversee that these recommendations are adhered to

[26] Section 4.8 of the Summary of Product Characteristics

5. Risk Management Plans

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.

5.1.1. Alemtuzumab

5.1.2. Alogliptin

5.1.3. Alogliptin, metformin

5.1.4. Alogliptin, pioglitazone

5.1.5. Bedaquiline

5.1.6. Canagliflozin

5.1.7. Cholic acid

5.1.8. Dabrafenib

5.1.9. Elvitegravir

5.1.10. Esomeprazole

5.1.11. Fenofibrate, simvastatin

5.1.12. Indacaterol, glycopyrronium bromide

5.1.13. Infliximab

5.1.14. Levodopa, carbidopa, entacapone

5.1.15. Lidocaine, prilocaine

5.1.16. Mercaptine

5.1.17. Regorafenib

5.1.18. Riociguat

5.1.19. Trametinib

5.1.20. Trastuzumab emtasine

5.1.21. Vortioxetine

- Evaluation of an RMP in the context of an initial marketing authorisation application procedure

5.2. Medicines already authorised

RMP in the context of a PSUR procedure

5.2.1. Bosentan – TRACLEER (CAP)

- Evaluation of an RMP in the context of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Evelyne Falip (FR)

As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of this updated version 4 of the RMP for the above mentioned medicine.

See also 6.1.4.

5.2.2. Denosumab – PROLIA (CAP), **XGEVA** (CAP)

- Evaluation of an RMP in the context of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Ulla Wändel Liminga (SE)

As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of this updated version 4 of the RMP for the above mentioned medicine.

See also 6.1.6.

5.2.3. Erlotinib – TARCEVA (CAP)

- Evaluation of an RMP in the context of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Doris Stenver (DK)

As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of this updated version 3.3 of the RMP for the above mentioned medicine.

See also 6.1.8.

5.2.4. Indacaterol – HIROBRIZ BREEZHALER (CAP), **ONBREZ BREEZHALER** (CAP), **OSLIF BREEZHALER** (CAP)

- Evaluation of an RMP in the context of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Line Michan (DK)

As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of this updated version 7 of the RMP for the above mentioned medicine.

See also 6.1.10.

5.2.5. Ivabradine – **CORLENTOR** (CAP), **PROCORALAN** (CAP)

- Evaluation of an RMP in the context of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Menno van der Elst (NL)

As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of this updated version 3 of the RMP for the above mentioned medicine.

See also 6.1.11.

5.2.6. Rilpivirine – **EDURANT** (CAP)

- Evaluation of an RMP in the context of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Sabine Straus (NL)

As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of this updated version 3 of the RMP for the above mentioned medicine.

See also 6.1.20.

5.2.7. Tafamidis – **VYNDAQEL** (CAP)

- Evaluation of an RMP in the context of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Evelyne Falip (FR)

As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of this updated version 5 of the RMP for the above mentioned medicine.

See also 6.1.27.

RMP in the context of a variation

5.2.8. Aflibercept – **EYLEA** (CAP)

- Evaluation of an RMP in the context of a variation, extension of indication

Regulatory details:

PRAC Rapporteur: Evelyne Falip (FR)

Background

Eylea is a centrally authorised medicine containing aflibercept, an antineovascularisation agent indicated for adults for the treatment of neovascular (wet) age-related macular degeneration (AMD).

The CHMP is evaluating an extension of the therapeutic indication for Eylea (aflibercept), to include treatment of macular oedema following central retinal vein occlusion (CRVO). 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 9 for Eylea (aflibercept) submitted in the context of the extension of indication variation under evaluation by the CHMP was considered acceptable provided that an updated RMP is submitted addressing some revisions recommended by the PRAC regarding the alignment with the current product information and the description of the study to 'Evaluate Physician and Patient Knowledge of Safety and Safe Use Information for Eylea (aflibercept) in Europe'.

5.2.9. Bevacizumab – AVASTIN (CAP)

- Evaluation of an RMP in the context of a variation, extension of indication

Regulatory details:

PRAC Rapporteur: Doris Stenver (DK)

As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of this updated version 13 of the RMP for the above mentioned medicine provided in support of a variation for an extension of indication in combination with radiotherapy and temozolomide for the treatment of adult patients with newly diagnosed glioblastoma.

5.2.10. Bortezomib – VELCADE (CAP)

- Evaluation of an RMP in the context of a variation, extension of indication

Regulatory details:

PRAC Rapporteur: Carmela Macchiarulo (IT)

As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of MAH's responses to the PRAC requests on the RMP for the above mentioned medicine provided in support of a variation for an extension of indication in combination with pegylated liposomal doxorubicin or in combination with dexamethasone in patients with relapsed and/or progressive multiple myeloma who have received at least 1 prior therapy.

5.2.11. Dexamethasone – OZURDEX (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)

Ozurdex is a centrally authorised medicine containing dexamethasone for intravitreal use, indicated for the treatment of adult patients with macular oedema following either branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO), as well as for the treatment of adult patients with inflammation of the posterior segment of the eye presenting as non-infectious uveitis.

The CHMP is evaluating a type II variation procedure for Ozurdex (dexamethasone), to make some updates to the educational material package. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this variation.

Summary of advice

- The RMP version 2 for Ozurdex (dexamathasone) in the context of the variation under evaluation by the CHMP was considered acceptable.
- The next update of the RMP should include some revisions requested by the PRAC regarding the description of the eight ongoing safety studies and other minor points.

5.2.12. Golimumab – SIMPONI (CAP)

- Evaluation of an RMP in the context of a variation, extension of indication

Regulatory details:

PRAC Rapporteur: Ulla Wändel Liminga (SE)

Background

Simponi is a centrally authorised medicine containing golimumab, a monoclonal antibody indicated in the treatment rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis.

The CHMP is evaluating an extension of the therapeutic indication for Simponi (golimumab) to include treatment of moderately to severely active ulcerative colitis in adult patients. 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 8.1 for Simponi (golimumab) submitted in the context of the extension of indication variation under evaluation by the CHMP was considered acceptable provided that the MAH submits to the EMA, within 6 months of the CHMP Opinion, the protocol for the study called 'Ulcerative Colitis Registry within the Nordic National Registries Database' for review.
- Before the procedure is finalised at CHMP level, the MAH is also requested to provide an updated version of the RMP specifying the timelines for the feasibility assessment for utilising the ENEIDA Inflammatory Bowel Disease Registry in Spain as an additional source of information for collection of long-term safety data in patients with ulcerative colitis.

5.2.13. Golimumab – SIMPONI (CAP)

- Evaluation of an RMP in the context of a variation, line extension

Regulatory details:

PRAC Rapporteur: Ulla Wändel Liminga (SE)

Background

Simponi is a centrally authorised medicine containing golimumab, a monoclonal antibody indicated in the treatment rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis.

The CHMP is evaluating a line extension of the therapeutic indication for Simponi (golimumab), to introduce a new strength (100 mg), for subcutaneous use. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this line extension.

Summary of advice

- The updated RMP version 8.2 for Simponi (golimumab) in the context of the extension of indication under evaluation by the CHMP was considered acceptable provided that an update is submitted in response to a request for supplementary information to be adopted by CHMP.
- The update should take into account some additions proposed by the PRAC, such as measures to accurately reflect and emphasize the correct use of the new strength in patients with rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis, and measures to maximise the difference between the various strengths and reduce any risk of medication errors.

5.2.14. Paliperidone – INVEGA (CAP)

- Evaluation of an RMP in the context of a variation, extension of indication

Regulatory details:

PRAC Rapporteur: Qun-Ying Yue (SE)

As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of this updated version 3 of the RMP for the above mentioned medicine provided in support of a variation for an extension of indication to add the treatment of schizophrenia in adolescents 12 years and older.

5.2.15. Panitumumab – VECTIBIX (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:

PRAC Rapporteur: Julia Dunne (UK)

As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of this updated version 10 of the RMP for the above mentioned medicine provided in support of a variation to further restrict the colorectal cancer indications.

5.2.16. Voriconazole – VFEND (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:

PRAC Rapporteur: Sabine Straus (NL)

The PRAC endorsed via written procedure on 24 June 2013 the conclusions of the Rapporteur on the assessment of this updated version 1.3 of the RMP for the above mentioned medicine provided in support of a variation to recommend regular dermatologic evaluation regarding the risk of risk of squamous-cell carcinoma (SCC).

5.2.17. Ulipristal – ESMYA (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:

PRAC Rapporteur: Ulla Wändel Liminga (SE)

As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of this updated version 11 of the RMP for the above mentioned medicine provided in support of a variation to include some updates to the product information regarding new results from studies identified as post-authorisation measures.

RMP in the context of a renewal of the marketing authorisation, conditional renewal or annual reassessment

See Filgrastim Hexal, Zarzio under 8.1.5. ; Evicel under 8.1.7.

RMP in the context of a stand-alone RMP procedure

5.2.18. Boceprevir – VICTRELIS (CAP)

- Evaluation of an RMP in the context of a stand-alone RMP procedure

Regulatory details:

PRAC Rapporteur: Isabelle Robine (FR)

As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of this updated version 6 of the RMP for the above mentioned medicine.

5.2.19. Deferasirox – EXJADE (CAP)

- Evaluation of an RMP in the context of a stand-alone RMP procedure

Regulatory details:

PRAC Rapporteur: Isabelle Robine (FR)

Background

Exjade is a centrally authorised medicine containing desferasirox, an iron chelator, indicated in the treatment of chronic iron overload due to frequent blood transfusions in patients with beta thalassaemia and for the treatment of chronic iron overload due to blood transfusions when deferoxamine therapy is contraindicated or inadequate in the some patient groups.

An updated version of the RMP was submitted by the MAH as a stand-alone procedure to comply with the new template according to current requirements. The PRAC is responsible for providing advice to the CHMP on this updated version.

Summary of advice

- The updated RMP version 8 for Exjade (desferasirox) was considered acceptable provided that an update is submitted to the EMA within one month including provision of a complete protocol and case report form for a survey to be conducted in various EU countries to gather information on physician clinical knowledge gained from, and prescribers awareness of, current educational material, together with the final report of a previously conducted survey.
- Some other points should be addressed in the RMP accompanying the next PSUR, including the addition of long-term safety in paediatric use as important missing information and severe cutaneous reactions as an important potential risk; the interaction or potential interaction with busulfan should be added as identified in accordance with the conclusions of the review requested; clarification on the educational material and its distribution should be provided (including amendment of Annex II of the marketing authorisation in order to ensure continuous distribution of educational material).

5.2.20. Human normal immunoglobulin – PRIVIGEN (CAP)

- Evaluation of an RMP in the context of a stand-alone RMP procedure

Regulatory details:

PRAC Rapporteur: Brigitte Keller-Stanislawski (DE)

As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of this updated version 2.5 of the RMP for the above mentioned medicine.

5.2.21. Ibandronic acid – IASIBON (CAP)

- Evaluation of an RMP in the context of a stand-alone RMP procedure

Regulatory details:

PRAC Rapporteur: Doris Stenver (DK)

As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of this updated version 3 of the RMP for the above mentioned medicine.

5.2.22. Ibandronic acid – IBANDRONIC ACID SANDOZ (CAP),

- Evaluation of an RMP in the context of a stand-alone RMP procedure

Regulatory details:

PRAC Rapporteur: Doris Stenver (DK)

As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of this updated version 2 of the RMP for the above mentioned medicine.

5.2.23. Interferon alfa-2b – INTRONA (CAP)

- Evaluation of an RMP in the context of a stand-alone RMP procedure

Regulatory details:

PRAC Rapporteur: Jean-Michel Dogné (BE)

As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of this updated version 2 of the RMP for the above mentioned medicine.

5.2.24. Raltegravir – ISENTRESS (CAP)

- Evaluation of an RMP in the context of a stand-alone RMP procedure

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)

As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of this updated version 9.3 of the RMP for the above mentioned medicine.

6. Assessment of Periodic Safety Update Reports (PSURs)

6.1. Evaluation of PSUR procedures[27]

6.1.1. Antithrombin alfa – ATRYN (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Isabelle Robine (FR)

Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Atryn, a centrally authorised medicine containing antithrombin alfa, remained favourable in the approved indication(s) and adopted a recommendation to maintain the current terms of the marketing authorisation together with the assessment report. As per agreed criteria, this procedure was finalised at the PRAC level without further plenary discussion.

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 and published on the European medicines web-portal.

6.1.2. Apixaban – ELIQUIS (CAP)

- Evaluation of a PSUR procedure

[27] Where a regulatory action is recommended (variation, suspension or revocation of the terms of Marketing Authorisation(s)), the assessment report and PRAC recommendation are transmitted to the CHMP for adoption of an opinion. Where PRAC recommends the maintenance of the terms of the marketing authorisation(s), the procedure finishes at the PRAC level.
For each PRAC recommendation, in cases where other medicinal products containing the same substance are currently authorised in the EU, or subject to future authorisation procedures in the EU, the PRAC recommends that the concerned Member States and MAHs take due consideration of it.

Regulatory details:

PRAC Rapporteur: Sabine Straus (NL)

Background

Apixaban is a factor Xa inhibitor indicated for the prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective hip or knee replacement surgery and for the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF) under certain conditions.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Eliquis (apixaban) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to refine the contraindication relating to the use of Eliquis in patients with a lesion or condition considered to be a significant risk factor for major bleeding. In addition, the product information should be updated to consider the consultation of a coagulation expert in case of a major bleeding episode. The current terms of the marketing authorisation(s) should therefore be varied[28].

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

6.1.3. Boceprevir – VICTRELIS (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Isabelle Robine (FR)

Background

Boceprevir is a protease inhibitor indicated for the treatment of chronic hepatitis C (CHC) genotype 1 infection, in combination with peginterferon alfa and ribavirin, in adult patients with compensated liver disease who are previously untreated or who have failed previous therapy.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Victrelis (boceprevir) in the approved indication(s) remains favourable.

[28] Update of SmPC sections 4.3 and 4.9. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion.

- Nevertheless, the product information should be updated to include a warning relating to a drug-drug interaction between boceprevir and calcium channel antagonists. Therefore the current terms of the marketing authorisation should be varied[29].
- In the next PSUR, the MAH should address some issues, including the provision of a comprehensive safety analysis of all cases of infection- and sepsis-related events in boceprevir-treated patients. In addition, the MAH should provide a comprehensive safety analysis of all cases of pancytopenia agranulocytosis and consider an update of the product information if warranted.

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 and published on the European medicines web-portal.

6.1.4. Bosentan – TRACLEER (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Evelyne Falip (FR)

Background

Bosentan is a dual endothelin receptor antagonist (ERA) indicated for the treatment of pulmonary arterial hypertension (PAH) to improve exercise capacity and symptoms in patients with WHO functional class III under certain conditions. Bosentan is also indicated to reduce the number of new digital ulcers in patients with systemic sclerosis and ongoing digital ulcer disease.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Tracleer (bosentan) in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation should be maintained. Nevertheless, the MAH should submit to EMA within 60 days a safety review including all available data, in particular, BUILD-1[30] and BUILD-3[31] final study reports, published references, and pharmacovigilance data relating to the use of bosentan in patients with idiopathic pulmonary fibrosis. The MAH should consider an update of the product information and submit a variation accordingly if warranted.
- In the next PSUR, the MAH should closely monitor several undesirable effects and provide reviews on cases of cardiac disorders, blurred vision, arthralgia, myalgia and pain as well as menstrual disorders and vaginal haemorrhage. In addition, the MAH should provide a review of

[29] Update of SmPC section 4.5. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion.
[30] BUILD-1 (Bosentan Use in Interstitial Lung Disease): double-blind, randomised, placebo-controlled, multicenter study to assess the efficacy and safety of bosentan in improving the exercise capacity of patients suffering from idiopathic pulmonary fibrosis (IPF)
[31] BUILD-3: multicenter, double-blind, randomised, placebo-controlled, parallel group, event-driven morbidity/mortality study evaluating the safety and efficacy of bosentan in IPF patients

transplant rejection due to interaction with tacrolimus and sirolimus and should discuss the necessity to identify this as a potential important risk in the next 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 and published on the European medicines web-portal.

See also 5.2.1.

6.1.5. **Bromfenac – YELLOX** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Line Michan (DK)

Based on the assessment of the PSUR(s), the PRAC concluded that the benefit-risk balance of Yellox, a centrally authorised medicine containing bromfenac, 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, this procedure was finalised at the PRAC level without further plenary discussion.

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 and published on the European medicines web-portal.

6.1.6. **Denosumab – PROLIA** (CAP), **XGEVA** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Ulla Wändel Liminga (SE)

Based on the assessment of the PSUR(s), the PRAC concluded that the benefit-risk balance of Prolia and Xgeva, centrally authorised medicines containing denosumab, 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, this procedure was finalised at the PRAC level without further plenary discussion.

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 and published on the European medicines web-portal.

See also 5.2.2.

6.1.7. **Doxorubicin – MYOCET** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Ulla Wändel Liminga (SE)

Background

Myocet is an antineoplastic agent indicated in combination with cyclophosphamide for the first line treatment of metastatic breast cancer in adult women.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Myocet (doxorubicin) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to add palmar–plantar erythrodysaesthesia syndrome with a frequency category 'not known'. Therefore the current terms of the marketing authorisation should be varied[32].
- The MAH should submit to EMA within 60 days a review of all available data related to potential pharmacokinetic interactions for liposomal doxorubicin and to update the product information[33] in line with the product information for other conventional doxorubicin-containing products unless this is not supported by the review for this specific pharmaceutical form.

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 and published on the European medicines web-portal.

6.1.8. Erlotinib – TARCEVA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Doris Stenver (DK)

Background

Erlotinib is an antineoplastic agent protein kinase inhibitor indicated in combination with gemcitabine for the treatment of patients with metastatic pancreatic cancer. Erlotinib is also indicated for the treatment of patients with non-small cell lung cancer (NSCLC) under certain conditions.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Tarceva (erlotinib) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to add a warning to ensure that patients with bullous and exfoliative skin disorders are tested for skin infection and treated

[32] 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.
[33] SmPC section 4.5 and package leaflet accordingly.

according to local management guidelines, and to add a warning to underline the higher incidence of interstitial lung disease (ILD) amongst patients of Japanese origin and to amend the frequency of this undesirable effect from uncommon to common. In addition, the warning on nephrotoxicity should be slightly amended to better reflect the potential risk factors and nephrotoxicity should also be added as an undesirable effect. Moreover, the product information should be updated to include a risk of interaction with proteasome inhibitors such as bortezomib. Therefore the current terms of the marketing authorisation should be varied[34].

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 and published on the European medicines web-portal.

See also 5.2.3.

6.1.9. Filgrastim – NIVESTIM (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Kirsti Villikka (FI)

Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Nivestim, a centrally authorised medicine containing filgrastim, 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, this procedure was finalised at the PRAC level without further plenary discussion.

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 and published on the European medicines web-portal.

6.1.10. Indacaterol – HIROBRIZ BREEZHALER (CAP), ONBREZ BREEZHALER (CAP), OSLIF BREEZHALER (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Line Michan (DK)

Background

Indacaterol is a long-acting $beta_2$-adrenergic agonist indicated for maintenance bronchodilator treatment of airflow obstruction in adult patients with chronic obstructive pulmonary disease (COPD).

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Hirobriz Beezhaler, Onbrez Breezhaler and Oslif Breezhaler, centrally authorised medicines containing indacaterol, and issued a recommendation on their marketing authorisation(s).

[34] Update of SmPC sections 4.4, 4.5 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Hirobriz Beezhaler, Onbrez Breezhaler and Oslif Breezhaler (indacaterol) in the approved indication(s) remains favourable.
- The product information should be updated in line with other long-acting beta-adrenoceptor agonists (LABAs) to include a warning highlighting the risk of serious asthma-related adverse events when used to treat asthma. In addition the wording of the warning relating to the risk of QT-prolongation for indacaterol should be revised in line with other LABAs. Therefore the current terms of the marketing authorisations should be varied[35].
- In the next PSUR, the MAH should conduct a review of cases relating to lack of efficacy. Complications and possible confounders are acknowledged and should be considered in the MAH's data analysis.

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 and published on the European medicines web-portal.

See also 5.2.4.

6.1.11. Ivabradine – **CORLENTOR** (CAP), **PROCORALAN** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Menno van der Elst (NL)

Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Corlentor and Procoralan, centrally authorised medicines containing ivabradine, 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, this procedure was finalised at the PRAC level without further plenary discussion.

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 and published on the European medicines web-portal.

See also 5.2.5.

6.1.12. Levetiracetam – **KEPPRA** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Jean-Michel Dogné (BE)

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

Background

Levetiracetam is an antiepileptic indicated as monotherapy in the treatment of partial onset seizures with or without secondary generalisation in adults and adolescents from 16 years of age with newly diagnosed epilepsy and as adjunctive therapy in the treatment of partial onset seizures, myoclonic seizures and primary generalised tonic-clonic seizures under certain conditions.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Keppra (levetiracetam) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to include information on the interaction between levetiracetam and macrogol-containing laxatives, to add agranulocytosis as a rare undesirable effect, to add information on the cumulative experience in women exposed to levetiracetam during pregnancy as well as the increased risk of congenital malformations with antiepileptic polytherapy including levetiracetam compared to levetiracetam monotherapy. Therefore the current terms of the marketing authorisation should be varied[36].
- The MAH should submit to EMA within 60 days cumulative reviews of cases of drug reaction with eosinophilia and systemic symptoms (DRESS) and hypereosinophilia as well as cases of rhabdomyolysis and increased blood creatine phosphokinase (CPK). The MAH should submit a variation if warranted by the conclusions.
- In the next PSUR, the MAH should closely monitor several adverse events and provide an update on the FDA investigations in relation to the signal of abuse of levetiracetam.
- In addition, the MAH should submit an updated RMP within 6 months in order to address risks associated with the use of levetiracetam in the population of patients of 4 years of age and older.

The frequency of submission of PSURs should be changed from yearly to 3-yearly with a data lock point set at 30 November 2015 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.

6.1.13. Mercaptamine bitartrate – CYSTAGON (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Dolores Montero Corominas (ES)

Background

Mercaptamine bitartrate is indicated for the treatment of proven nephropathic cystinosis.

[36] Update of SmPC sections 4.5, 4.6 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.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Cystagon (mercaptamine bitartrate) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to better reflect and characterize the skin reactions reported in children treated with high doses and by including other vascular elbow lesions as a warning. In addition, the product information should be updated to remove the exact figures related to the reported cases of nephrotic syndrome. Therefore the current terms of the marketing authorisation should be varied[37].
- In the next PSUR, the MAH should include a safety review of all case reports of potential systemic lupus erythematosus.

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 and published on the European medicines web-portal.

6.1.14. Mercaptopurine – XALUPRINE (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Ulla Wändel Liminga (SE)

Background

Mercaptopurine is an antineoplastic agent indicated for the treatment of acute lymphoblastic leukaemia (ALL) in adults, adolescents and children.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Xaluprine (mercaptopurine) in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation should be maintained.
- The PRAC noted that the MAH did not submit a comprehensive review of hepatosplenic T-cell lymphoma and lymphoproliferative disorders as requested during the assessment of this PSUR procedure. The MAH should submit to EMA no later than 10 July 2013 the requested review to ensure this is assessed together with the latest submitted 6-monthly PSUR currently under assessment and due for PRAC recommendation in October 2013.

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

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

6.1.15. Natalizumab – TYSABRI (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Brigitte Keller-Stanislawski (DE)

Background

Natalizumab is a selective immunosuppressive agent indicated as single disease modifying therapy in highly active relapsing remitting multiple sclerosis under certain conditions.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Tysabri (natalizumab) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to include a warning statement that anti-John Cunningham virus (JCV) antibody negative patients may still be at risk of progressive multifocal leukoencephalopathy (PML), due to a possible new JCV infection, fluctuating antibody status or a false negative test result. Therefore the current terms of the marketing authorisation should be varied[38].
- In the next PSUR, the MAH should provide additional information, including a more detailed and meaningful review of pregnancy data taking into account gestational age and treatment duration to determine the risk of abortions, elective terminations, malformations, stillbirths or prematurity in pregnant women as well as a reconsideration of the risk algorithm used to describe the risk of developing PML, including the treatment duration, history of prior immunosuppressant therapy and JCV serostatus. Finally, with regard to the PML scientific consortium and research agenda, the MAH should comment on whether some sections of the research project should be included in 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 and published on the European medicines web-portal.

6.1.16. Nepafenac – NEVANAC (CAP)

- Evaluation of a PSUR procedure

[38] Update of SmPC section 4.4.The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion.

Regulatory details:

PRAC Rapporteur: Dolores Montero Corominas (ES)

Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Nevanac, a centrally authorised medicine containing nepafenac, 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, this procedure was finalised at the PRAC level without further plenary discussion.

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 and published on the European medicines web-portal.

6.1.17. Ofatumumab – ARZERRA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Doris Stenver (DK)

Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Arzerra, a centrally authorised medicine containing ofatumumab, 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, this procedure was finalised at the PRAC level without further plenary discussion.

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 and published on the European medicines web-portal.

6.1.18. Pegvisomant – SOMAVERT (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Evelyne Falip (FR)

Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Somavert, a centrally authorised medicine containing pegvisomant, 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, this procedure was finalised at the PRAC level without further plenary discussion.

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 and published on the European medicines web-portal.

6.1.19. Piperaquine tetraphosphate / dihydroartemisinin – EURARTESIM (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)

Based on the assessment of the PSUR(s), the PRAC concluded that the benefit-risk balance of Eurartesim, a centrally authorised medicine containing piperaquine tetraphosphate/dihydroartemisinin 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, this procedure was finalised at the PRAC level without further plenary discussion.

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 and published on the European medicines web-portal.

6.1.20. Rilpivirine – EDURANT (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Sabine Straus (NL)

Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Edurant, a centrally authorised medicine containing rilpivirine, 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, this procedure was finalised at the PRAC level without further plenary discussion.

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 and published on the European medicines web-portal.

See also 5.2.6.

6.1.21. Rituximab – MABTHERA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Doris Stenver (DK)

Background

Rituximab is a monoclonal antibody indicated for the treatment of Non-Hodgkin's lymphoma (NHL) under certain conditions as well as in combination with chemotherapy for the treatment of patients with previously untreated and relapsed/refractory chronic lymphocytic leukaemia (CLL) and for rheumatoid arthritis.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of MabThera (rituximab) in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation should be maintained.
- In the next PSUR, the MAH should include a review of malignancies in the autoimmune indication and consider an update of the product information as warranted. In addition, the MAH should continue to collect data as part of the ongoing long-term follow-up for other autoimmune indications and long-term clinical data. Moreover, the MAH should comment on the frequency of long term B-Cell depletion after rituximab treatment, and whether this subgroup displays other characteristics that may help define it.
- The MAH should also update the RMP to reflect all types of off-label use settings.

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 and published on the European medicines web-portal.

6.1.22. **Rotavirus vaccine**, **live**, **oral – ROTATEQ** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Julia Dunne (UK)

Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of RotaTeq, a centrally authorised rotavirus vaccine (live, oral), 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, this procedure was finalised at the PRAC level without further plenary discussion.

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 and published on the European medicines web-portal.

6.1.23. **Sapropterin – KUVAN** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Almath Spooner (IE)

Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Kuvan, a centrally authorised medicine containing sapropterin, 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, this procedure was finalised at the PRAC level without further plenary discussion.

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 and published on the European medicines web-portal.

6.1.24. Saquinavir – INVIRASE (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Harald Herkner (AT)

Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Invirase, a centrally authorised medicine containing saquinavir, 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, this procedure was finalised at the PRAC level without further plenary discussion.

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 and published on the European medicines web-portal.

6.1.25. Saxagliptin, metformin – KOMBOGLYZE (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Menno van der Elst (NL)

Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Komboglyze, a centrally authorised medicine containing saxagliptin/metformin, 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, this procedure was finalised at the PRAC level without further plenary discussion. The PRAC recommendation is without prejudice to the future outcome of the ongoing Article 5(3) procedure (see EMA review on GLP-1-based therapies).

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 and published on the European medicines web-portal.

6.1.26. Stiripentol – DIACOMIT (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)

Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Diacomit, a centrally authorised medicine containing stiripentol, 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, this procedure was finalised at the PRAC level without further plenary discussion.

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 and published on the European medicines web-portal.

6.1.27. Tafamidis – VYNDAQEL (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Evelyne Falip (FR)

Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Vyndaqel, a centrally authorised medicine containing tafamidis, 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, this procedure was finalised at the PRAC level without further plenary discussion.

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 and published on the European medicines web-portal.

See also 5.2.7.

6.1.28. Temoporfin – FOSCAN (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Sabine Straus (NL)

Background

Temoporfin is an antineoplastic photosensitising agent indicated for the palliative treatment of patients with advanced head and neck squamous cell carcinoma failing prior therapies and if unsuitable for radiotherapy, surgery or systemic chemotherapy.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Foscan (temoporfin) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated:
  - to include a warning on the risk of fistula related to photodynamic therapy (PDT), and) as well as sepsis. These should also be included as undesirable effects with a frequency unknown;
  - to include the risk of vascular rupture as an undesirable effect with a frequency unknown and a contraindication;
  - to include a warning that off-label use in malignant biliary strictures and oesophageal perforation after treatment of mesothelioma has been associated with cases of cholangitis/cholecystitis and liver abscess,. In addition a warning should be added

highlighting that off-label use outside the head and neck region in squamous cell carcinoma patients can lead to substantial and clinically relevant damage of surrounding tissues;

- based on the publication by *Nyst et al*[39], to add headache as an undesirable effect with a frequency very common;
- based on the publication by *Durbec et al* [40], to refine the wording of the warning relating to the risk of pain following photodynamic therapy, to reflect the time to onset and duration;
- to add more detailed information on the risk of oedema as an undesirable effect following reported cases of life-threatening or fatal oedema and tongue oedema;
- to include that use of headlamps instead of surgical lamps is recommended in case of (emergency) surgery.

Therefore the current terms of the marketing authorisation should be varied[41].

- In the next PSUR, the MAH should closely monitor the risk of off label use in children.
- The MAH should be requested to implement an RMP to further characterise the safety profile of temoporfin and implement possible risk minimisation measures. In particular, the MAH should consider the important risk of photosensitivity and discuss additional risk minimisation activities.

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 and published on the European medicines web-portal.

6.2. Follow-up to PSUR procedures[42]

6.2.1. **Agalsidase alfa – REPLAGAL** (CAP)

- Evaluation of a follow-up to a PSUR procedure

Regulatory details:

PRAC Rapporteur: Sabine Straus (NL)

Background

During the evaluation of the most recently submitted PSUR for the above mentioned medicine(s), the PRAC requested the MAH to submit further data (see PRAC Minutes February 2013). The responses were assessed by the Rapporteur for further PRAC advice.

As per agreed criteria, the Committee endorsed the conclusions of the Rapporteur without further plenary discussion.

[39] Durbec et al, Eur Arch Otorhinolaryngol. 2013 Mar;270(4):1433-9
[40] Nyst et al, Photodiagnosis Photodyn Ther. 2012 Sep;9(3):274-81
[41] Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion
[42] Follow up procedures as per the conclusions of PSUR procedures, assessed outside next PSUR procedures.

Summary of recommendation(s)/conclusions

- In the next PSUR, the MAH for Replagal (agalsidase alfa) should continue to closely monitor several adverse drug reactions, and discuss the risk infusion related reactions (IRR) and the relationship with the possibility of administration errors.

6.2.2. Azilsartan medoxomil – EDARBI (CAP), IPREZIV (CAP)

- Evaluation of a follow-up to a PSUR procedure

Regulatory details:

PRAC Rapporteur: Menno van der Elst (NL)

Background

During the evaluation of the most recently submitted PSUR for the above mentioned medicine(s), the PRAC requested the MAH to submit further data (see PRAC Minutes March 2013). The responses were assessed by the Rapporteur for further PRAC advice.

As per agreed criteria, the Committee endorsed the conclusions of the Rapporteur without further plenary discussion.

Summary of recommendation(s) and conclusions

- Since the MAH for Edarbi/Ipreziv (azilsartan medoxomil) already submitted to the EMA a variation to update the product information to reflect relevant contraindications and warnings regarding concomitant use of azilsartan and aliskiren (see EPAR Rasilez (aliskiren)), the PRAC considered that no further request is warranted in the light of the current knowledge.

6.2.3. Pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed) – PREVENAR 13 (CAP)

- Evaluation of a follow-up to a PSUR procedure

Regulatory details:

PRAC Rapporteur: Qun-Ying Yue (SE)

Background

During the evaluation of the most recently submitted PSUR for the above mentioned medicine(s), the PRAC requested the MAH to submit further data (see PRAC Minutes January 2013). The responses were assessed by the Rapporteur for further PRAC advice.

Summary of recommendation(s) and conclusions

- The MAH for Prevenar 13 (pneumococcal polysaccharide conjugate vaccine) should an update of the product information to reflect the increased risk of neurological reactions when Prevenar 13 is co-administered with Infanrix Hexa (diphtheria (D), tetanus (T), pertussis (acellular, component) (Pa), hepatitis B (rDNA) (HBV) vaccine) upon finalisation of the next PSUR evaluation to be concluded in September 2013.
- In addition, the MAH should submit to EMA an updated RMP to include the potential increased risk of neurological events with co-administration of Prevenar 13 and Infanrix Hexa. The MAH

is requested to include these updates to the RMP after finalisation of the next PSUR evaluation to be concluded in September 2013.

7. Post-authorisation Safety Studies (PASS)

7.1. Protocols of post-authorisation safety studies

7.1.1. **Adalimumab – HUMIRA** (CAP)

- PRAC consultation on a PASS protocol included in the pharmacovigilance plan of the RMP in accordance to Article 107m Directive 2001/83/EC

Regulatory details:

PRAC Rapporteur: Ulla Wändel Liminga (SE)

Since all comments were addressed during the consultation phase, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of a protocol for a study (as part of the RMP but outside the scope of Article 107n of Directive 2001/83/EC) for a long-Term Non-Interventional Registry to Assess Safety and Effectiveness of Humira (adalimumab) in Paediatric Patients with Moderately to Severely Active Crohn's Disease (CD).

7.1.2. **Aflibercept – EYLEA** (CAP)

- PRAC consultation on a PASS protocol included in the pharmacovigilance plan of the RMP in accordance to Article 107m Directive 2001/83/EC

Regulatory details:

PRAC Rapporteur: Evelyne Falip (FR)

Background

Eylea is a centrally authorised medicine containing aflibercept, an inhibitor of vascular endothelial growth factor indicated for adults for the treatment of neovascular (wet) age-related macular degeneration (AMD).

As part of the RMP for Eylea, the MAH for was required to conduct a PASS. The MAH submitted a protocol for a non-interventional study (as part of the RMP but outside the scope of Article 107n of Directive 2001/83/EC) to assess the safety and real-life treatment practice with aflibercept in patients with wet age-related macular degeneration (AMD), and a protocol for a post-authorisation safety study to evaluate physician and patient knowledge of information on safety and safe use of Eylea in Europe, which were assessed by the Rapporteur. The PRAC is to provide advice to CHMP on the protocols submitted by the MAH.

Summary of advice

- The study protocols discussed could be appropriate to investigate the study objectives provided updated protocols addressing some points raised by the PRAC on the study design, study participation and statistical analysis are submitted to the EMA prior to study initiation.

7.1.3. Aflibercept – ZALTRAP (CAP)

- PRAC consultation on a PASS protocol included in the pharmacovigilance plan of the RMP in accordance to Article 107m Directive 2001/83/EC

Regulatory details:

PRAC Rapporteur: Ulla Wändel Liminga (SE)

Background

Zaltrap is a centrally authorised medicine containing aflibercept, an antineoplastic used in combination with the Folfiri chemotherapy regimen in the treatment of adults with metastatic colorectal cancer resistant to or having progressed after oxaliplatin regimen.

As part of the RMP for Zaltrap, the MAH was required to conduct a PASS in order to study the long term safety and effectiveness of Zaltrap (and Folfiri) in daily clinical practice. The MAH submitted a protocol for an observational cohort study (as part of the RMP but outside the scope of Article 107n of Directive 2001/83/EC) to provide further safety information on important identified and potential risks and in subpopulations such as elderly patients, patients with hepatic or renal impairment and non-Caucasian patients (OBS13957), which was assessed by the Rapporteur. The PRAC is to provide advice to CHMP on the protocol submitted by the MAH.

Summary of advice

- The study protocol discussed could be appropriate to investigate the study objectives provided an updated protocol addressing some points raised by the PRAC on patient participation, clarifications about procedures to monitor and avoid selection bias and clarification on the statistical analysis, is submitted to the EMA prior to study initiation.

7.1.4. Asenapine – SYCREST (CAP)

- PRAC consultation on a PASS protocol included in the pharmacovigilance plan of the RMP in accordance to Article 107m Directive 2001/83/EC

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)

Since all comments were addressed during the consultation phase the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of an amendment of the study for an observational PASS study of asenapine among patients aged 18 and older diagnosed with bipolar disorder.

7.1.5. Florbetapir (18F) – AMYVID (CAP)

- PRAC consultation on a PASS protocol included in the pharmacovigilance plan of the RMP in accordance to Article 107m Directive 2001/83/EC

Regulatory details:

PRAC Rapporteur: Martin Huber (DE)

Since all comments were addressed during the consultation phase the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of a study protocol of a PASS to assess a) the effectiveness of the reader training programme including different training methods; b) understanding of and compliance of readers with the approved indication and c) the frequency of reading errors in routine clinical practice following implementation of the reading training.

7.1.6. Florbetapir (18F) – AMYVID (CAP)

- PRAC consultation on a PASS protocol included in the pharmacovigilance plan of the RMP in accordance to Article 107m Directive 2001/83/EC

Regulatory details:

PRAC Rapporteur: Martin Huber (DE)
Since all comments were addressed during the consultation phase the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of a study protocol of a PASS for the evaluation of usage patterns of Amyvid including off-label use.

7.1.7. Human normal immunoglobulin – PRIVIGEN (CAP)

- PRAC consultation on a PASS protocol included in the pharmacovigilance plan of the RMP in accordance to Article 107m Directive 2001/83/EC

Regulatory details:

PRAC Rapporteur: Brigitte Keller-Stanislawski (DE)

Background

Privigen is a centrally authorised medicine containing human normal immunoglobulin, used as a replacement therapy in various conditions of immunoglobulin deficiencies and in immunomodulation.

As part of the RMP for Privigen, the MAH for was required to conduct a PASS in order to mitigate the risk of haemolysis. The MAH submitted a protocol for a study (as part of the RMP but outside the scope of Article 107n of Directive 2001/83/EC) to compare the rate of haemolysis after implementation of risk minimisation measures with the data submitted from a 5-year report, which was assessed by the Rapporteur. The PRAC was requested to provide advice to CHMP on the protocol submitted by the MAH.

Summary of advice

- The study protocol discussed could be appropriate to investigate the study objectives provided an updated protocol addressing some clarifications requested by the PRAC is submitted to the EMA prior to study initiation. The PRAC requests include information on how the use of anonymised data will be ensured, clarification on the statistical analysis, and presentation of a first analysis of the reactions to be studied in order to define the basis of calculation.

7.1.8. Human papillomavirus vaccine [types 16, 18] (recombinant, adjuvanted, adsorbed) – CERVARIX (CAP)

- PRAC consultation on a PASS protocol included in the pharmacovigilance plan of the RMP in accordance to Article 107m Directive 2001/83/EC

Regulatory details:

PRAC Rapporteur: Jean-Michel Dogné (BE)

Since all comments received were addressed during the consultation phase, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on a study protocol of a PASS for the evaluation of the risk of autoimmune diseases in adolescent and young adult women aged 9 to 25 years exposed to Cervarix in the United Kingdom (EPI-HPV-040).

7.1.9. Ivacaftor – KALYDECO (CAP)

- PRAC consultation on PASS protocol conducted pursuant an obligation imposed in accordance with Article 21a and 22a of Directive 2001/83/EC

Regulatory details:

PRAC Rapporteur: Miguel-Angel Macia (ES)

Background

For background, see PRAC minutes 4-7 March 2013.

Following receipt of the previously agreed letter of objection from the PRAC, the MAH submitted a revised protocol (third re-submission), as recommended, which was assessed by the Rapporteur.

Endorsement/Refusal of the protocol

The PRAC, having considered the draft protocol version 2.2, submitted in accordance with Article 107n of Directive 2001/83/EC, endorsed the protocol for the PASS for the above listed medicinal product, as the Committee considered that the design of the study fulfils the requirements, and since all the points from the PRAC in March 2013 had been adequately addressed by the MAH.

7.1.10. Loxapine – ADASUVE (CAP)

- PRAC consultation on a PASS protocol included in the pharmacovigilance plan of the RMP in accordance to Article 107m Directive 2001/83/EC

Regulatory details:

PRAC Rapporteur: Sabine Straus (NL)

Background

Adasuve is a centrally authorised medicine containing loxapine, an antipsychotic, as an inhalation powder, pre-dispensed, intended for the rapid control of mild-to-moderate agitation in adult patients with schizophrenia or bipolar disorder.

As part of the RMP for Adasuve, the MAH for was required to conduct further studies on drug safety and drug utilisation. Therefore, the MAH submitted a protocol for a post-authorisation observational study to evaluate the safety of Adasuve in agitated persons in routine clinical care and a protocol (204-403, a drug utilisation study DUS) for a multinational retrospective medical record review study to evaluate utilisation patterns of Adasuve in agitated persons in routine clinical care. These study protocols were assessed by the Rapporteur. The PRAC was requested to provide advice to CHMP on the protocols submitted by the MAH.

Summary of advice

- The study protocol for the assessment of the effectiveness of the education programme for Adasuve (loxapine) could be appropriate to investigate the study objectives provided an updated protocol and satisfactory responses to a list of questions agreed by the PRAC is submitted to the EMA prior to study initiation.
- In particular, the PRAC requested the MAH to consider a pilot to test data collection methods for this study and requested measures to guarantee that there is no interference between the prospective PASS and the retrospective DUS. Moreover the MAH should translate the overall goals of the PASS and DUS into more specific measurable objectives that will also be the focus of more detailed planned statistical analyses.

7.1.11. Mirabegron – BETMIGA (CAP)

- PRAC consultation on a PASS protocol included in the pharmacovigilance plan of the RMP in accordance to Article 107m Directive 2001/83/EC

Regulatory details:

PRAC Rapporteur: Miguel-Angel Macia (ES)

Since all comments were addressed during the consultation phase the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of a protocol for a PASS (as part of the RMP but outside the scope of Article 107n of Directive 2001/83/EC) to address the issue of cardiovascular safety, especially in elderly patients.

7.1.12. Nalmefene – SELINCRO (CAP)

- PRAC consultation on a PASS protocol included in the pharmacovigilance plan of the RMP in accordance to Article 107m Directive 2001/83/EC

Regulatory details:

PRAC Rapporteur: Martin Huber (DE)

Since all comments were addressed during the consultation phase the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of a protocol for 3 PASSs (as part of the RMP but outside the scope of Article 107n of Directive 2001/83/EC) to investigate patterns of use of Selincro and the frequency of adverse drug reactions in routine clinical practice; to describe use of Selincro in the European database, particularly in defined sub-populations, and further describe the frequency and duration of Selincro intake over time; and to investigate the pharmacokinetic properties of Selincro in subjects with renal impairment (mild, moderate, or severe) and in healthy subjects.

7.1.13. Romiplostim – NPLATE (CAP)

- PRAC consultation on a PASS protocol included in the pharmacovigilance plan of the RMP in accordance to Article 107m Directive 2001/83/EC

Regulatory details:

PRAC Rapporteur: Dolores Montero Corominas (ES)

Background

Nplate is a centrally authorised medicine containing romiplostin, an antihaemorragic agent, used in the treatment of adult chronic immune (idiopathic) thrombocytopenic purpura (ITP) in splenectomised patients who are refractory to other treatments (e.g. corticosteroids, immunoglobulins).

As part of the RMP for Nplate, the MAH for was required to conduct a PASS in order to assess risk minimisation. The MAH submitted a protocol for a cross-sectional study in patients with chronic immune thrombocytopenic purpura and their caregivers to estimate the proportion who administer romiplostim correctly after receipt of home administration training materials (20120269), and this protocol was assessed by the Rapporteur. The PRAC was requested to provide advice to CHMP on the protocol submitted by the MAH.

Summary of advice

- The study protocol for the assessment of the effectiveness of the education programme for Nplate (romiplostin) could be appropriate to address the study objectives provided an updated protocol is submitted to the EMA prior to study initiation, addressing some points raised by the PRAC on patient enrolment, the approach to minimise selection bias and providing a clarification that the approach being used would be able to select a representative sample of the eligible patient population.

7.2. Results of post-authorisation safety studies

None

See Finasteride under 11.3.1.

8. Renewals of the Marketing Authorisation, Conditional Renewals and Annual Reassessments

8.1.1. **Aliskiren**, **hydrochlorothiazide – RASILEZ HCT** (CAP)

- PRAC consultation on a renewal of the marketing authorisation

Regulatory details:

PRAC Rapporteur: Carmela Macchiarulo (IT)

Background

The combination aliskiren and hydrochlorothiazide is used for the treatment of essential hypertension in adults under certain conditions.

Rasilez HCT, a centrally authorised medicine containing aliskiren/hydrochlorothiazide, was authorised in 2009.

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

Summary of advice

Based on the review of the available pharmacovigilance data for Rasilez HCT (aliskiren/hydrochlorothiazide), and the CHMP/PRAC Rapporteur's assessment reports, the PRAC considered that this first five year renewal procedure for Rasilez HCT (aliskiren/hydrochlorothiazide) could be concluded with one additional five-year renewal provided the MAH addresses satisfactorily several pending issues. Further PRAC advice will be provided as applicable.

8.1.2. **Brentuximab vedotin – ADCETRIS** (CAP)

- PRAC consultation on a conditional renewal of the marketing authorisation

Regulatory details:

PRAC Rapporteur: Sabine Straus (NL)

Based on the review of the available information on the status of fulfilment of specific obligations and the safety data submitted, the PRAC considered that this annual re-assessment procedure for Adcetris (brentuximab vedotin) could be concluded. As per agreed criteria, the procedure was finalised at the PRAC level without further plenary discussion.

8.1.3. **Crizotinib – XALKORI** (CAP)

- PRAC consultation on a conditional renewal of the marketing authorisation

Regulatory details:

PRAC Rapporteur: Isabelle Robine (FR)

Based on the review of the available information on the status of fulfilment of specific obligations and the safety data submitted, the PRAC considered that this annual re-assessment procedure for Xalkori (crizotinib) could be concluded. As per agreed criteria, the procedure was finalised at the PRAC level without further plenary discussion.

8.1.4. **Darunavir – PREZISTA** (CAP)

- PRAC consultation on a renewal of the marketing authorisation

Regulatory details:

PRAC Rapporteur: Sabine Straus (NL)

Based on the review of the available pharmacovigilance data for Prezista (darunavir) and the CHMP Rapporteur's assessment report, the PRAC considered that this first five year renewal procedure could be concluded. As per agreed criteria, the procedure was finalised at the PRAC level without further plenary discussion.

8.1.5. **Filgrastim – FILGRASTIM HEXAL** (CAP), **ZARZIO** (CAP)

- PRAC consultation on a renewal of the marketing authorisation

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)

Based on the review of the available pharmacovigilance data for Filgrastim Hexal and Zarzio (filgrastim) and the CHMP Rapporteur's assessment reports, the PRAC considered that these first renewal procedures could be concluded. As per agreed criteria, the procedure was finalised at the PRAC level without further plenary discussion.

8.1.6. Histamine dihydrochloride – CEPLENE (CAP)

- PRAC consultation on a renewal of the marketing authorisation

Regulatory details:

PRAC Rapporteur: Almath Spooner (IE)

Based on the review of the available pharmacovigilance data for Ceplene (histamine dihydrochloride) and the CHMP Rapporteur's assessment reports, the PRAC considered that this first five year renewal procedure could be concluded. As per agreed criteria, the procedure was finalised at the PRAC level without further plenary discussion.

8.1.7. Human fibrinogen, human thrombin – EVICEL (CAP)

- PRAC consultation on a renewal of the marketing authorisation

Regulatory details:

PRAC Rapporteur: Brigitte Keller-Stanislawski (DE)

Based on the review of the available pharmacovigilance data for Evicel (human fibrinogen/human thrombin) and the CHMP Rapporteur's assessment reports, the PRAC considered that this first five year renewal procedure could be concluded. As per agreed criteria, the procedure was finalised at the PRAC level without further plenary discussion.

8.1.8. Idursulfase – ELAPRASE (CAP)

- PRAC consultation on an annual reassessment procedure

Regulatory details:

PRAC Rapporteur: Julia Dunne (UK)

Based on the review of the available information on the status of fulfilment of specific obligations and the safety data submitted, the PRAC considered that this annual re-assessment procedure for Elaprase (idursulfase) could be concluded. As per agreed criteria, the procedure was finalised at the PRAC level without further plenary discussion.

8.1.9. Irbesartan – IFIRMASTA (CAP)

- PRAC consultation on a renewal of the marketing authorisation

Regulatory details:

PRAC Rapporteur: Dolores Montero Corominas (ES)

Based on the review of the available pharmacovigilance data for Ifirmasta (irbesartan) and the CHMP Rapporteur's assessment reports, the PRAC considered that this first five year renewal procedure could be concluded. As per agreed criteria, the procedure was finalised at the PRAC level without further plenary discussion.

8.1.10. Olanzapine – ZYPADHERA (CAP)

- PRAC consultation on a renewal of the marketing authorisation

Regulatory details:

PRAC Rapporteur: Terhi Lehtinen (FI)

Background

Olanzapine pamoate (suspension for injection) is an antipsychotic, antimanic and mood stabilising agent indicated for the maintenance treatment of adult patients with schizophrenia sufficiently stabilised during acute treatment with oral olanzapine.

Zypadhera, a centrally authorised medicine containing olanzapine, was authorised in 2008.

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 (see PRAC Minutes May 2013).

Summary of advice

Based on the review of the additional late breaking information concerning the important identified risk of post-injection syndrome, the PRAC considered that this safety issue should be further evaluated in the context of the ongoing PSUR procedure due for PRAC recommendation in October 2013.

8.1.11. Pramipexole – PRAMIPEXOLE TEVA (CAP)

- PRAC consultation on a renewal of the marketing authorisation

Regulatory details:

PRAC Rapporteur: Qun-Ying Yue (SE)

Based on the review of the available pharmacovigilance data for Pramipexole Teva (pramipexole) and the CHMP Rapporteur's assessment reports, the PRAC considered that this first five year renewal procedure could be concluded. As per agreed criteria, the procedure was finalised at the PRAC level without further plenary discussion.

8.1.12. Saproterin – KUVAN (CAP)

- PRAC consultation on a renewal of the marketing authorisation

Regulatory details:

PRAC Rapporteur: Almath Spooner (IE)

Based on the review of the available pharmacovigilance data for Kuvan (saproterin) and the CHMP Rapporteur's assessment reports, the PRAC considered that this first five year renewal procedure could be concluded. As per agreed criteria, the procedure was finalised at the PRAC level without further plenary discussion.

8.1.13. Ziconotide – PRIALT (CAP)

- PRAC consultation on an annual reassessment procedure

Regulatory details:

PRAC Rapporteur: Jean-Michel Dogné (BE)

Background

Prialt is a centrally authorised product containing ziconotide indicated for the treatment of severe, chronic pain in adults who require intrathecal (IT) analgesia.

Prialt was authorised under exceptional circumstances in 2005. The benefit-risk is reviewed on a yearly basis by the CHMP based on the additional post-authorisation data (i.e. specific obligations) submitted. 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 fulfilment of specific obligations and the safety data submitted, the PRAC considered that the lifting of the exceptional circumstances could be acceptable provided the MAH provides satisfactory answers to pending issues. Further PRAC advice will be provided as applicable.

9. Product related pharmacovigilance inspections

9.1. List of planned pharmacovigilance inspections

9.1.1. Risk-based programme for routine pharmacovigilance inspections of Marketing Authorisation Holders of Centrally Authorised Products for human use

The list of planned pharmacovigilance inspections is reviewed twice a year according to a risk based approach. The PRAC members were requested to provide any comments on the first revision for 2013 by 17 June 2013. After that date the current revision of the programme will be considered agreed by the PRAC.

9.2. On-going or concluded pharmacovigilance inspection

The PRAC discussed the results of some inspections conducted in the EU. 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 published minutes.

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

10.1. Safety related variations of the marketing authorisation (MA)

10.1.1. Cetuximab – ERBITUX (CAP)

- PRAC consultation on a safety-related variation, upon CHMP request

Regulatory details:

PRAC Rapporteur: Ulla Wändel Liminga (SE)

Background

For background, see PRAC minutes 29-31 October 2013.

Erbitux is a centrally authorised medicine containing cetuximab, a chimeric monoclonal Immunoglobulin G1 (IgG1) antibody directed against the Epidermal Growth Factor Receptor (EGFR).

A signal of cytokine release syndrome (CRS) was previously discussed by the PRAC and a variation was submitted by the MAH to address this signal following PRAC recommendations, and is currently under evaluation by the CHMP.

PRAC advice was requested on the assessment of this variation.

Summary of advice

The PRAC agreed on the need to update the product information with such a variation, with some revisions. The MAH should discuss the published literature (Grandvuillemin A et al, 2012[43]) suggesting anti- α3Gal IgE is found in some patients before exposure to cetuximab. Furthermore, it should discuss cross-reactivity as an explanation for occurrence of anaphylactic reactions at first infusion of cetuximab as well as sensitization occurring through certain foods (pork and beef), some parasites or tick bites. Moreover, the potential clinical use of a test to differentiate suspected anaphylaxis from CRS should be explored.

10.1.2. Ruxolitinib – JAKAVI (CAP)

- PRAC consultation on a safety-related variation, upon CHMP request

Regulatory details:

PRAC Rapporteur: Ulla Wändel Liminga (SE)

Background

Jakavi is a centrally authorised medicine containing ruxolitininb, a Janus kinase (JAK1 and JAK2) inhibitor, indicated for disease related splenomegaly or symptoms in adult patients with primary myelofibrosis (PMF), post polycythaemia vera (PPV-MF) or post essential thrombocythaemia myelofibrosis (PET-MF). Jakavi was approved in EU in August 2012 and exposure has been estimated to be approximately 3,000 patient years up until 2013.

A variation is under evaluation by the CHMP to update the product information, adding that progressive multifocal leukoencephalopathy (PML) has been reported with ruxolitinib treatment for myelofibrosis, following a case of PML reported in 2013.

PRAC advice was requested on the assessment of this variation.

Summary of advice

The PRAC agreed that the well-described case provided sufficient evidence to support such a variation to update the product information, and that patients should be monitored at regular intervals for any new or worsening neurological symptoms or signs. If such symptoms occur, the patient should be

[43] Aurélie Grandvuillemin, Anne Disson-Dautriche, Ghada Miremont-Salamé, Annie Fourrier-Reglat, Catherine Sgro, and The Réseau des Centres Régionaux de Pharmacovigilance Français - Cetuximab infusion reactions: French pharmacovigilance database analysis - J Oncol Pharm Pract June 2013 19: 130-137, first published on November 15, 2012 doi:10.1177/1078155212457965

referred to a neurologist and appropriate diagnostic measures for PML should be considered. If PML is suspected, further dosing must be suspended until PML has been excluded.

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

11.1. Safety related variations of the marketing authorisation

None

11.2. Renewals of the marketing authorisation

None

11.3. Other requests

11.3.1. **Finasteride** (NAP)

- PRAC consultation on PASS results, upon Member State's request

Regulatory details:

Lead member: Ulla Wändel-Liminga (SE)

Background

For background, see PRAC Minutes 4-7 March 2013.

Following previous PRAC advice, the MAH submitted supplementary information to the Swedish Medicines Agency which was assessed by SE in the framework of a follow up measure of the mutual recognition procedure for Propecia (finasteride).

The PRAC was informed that, regarding analyses according to the different posologies, data will be presented this way in countries where finasteride 1 mg usage has been captured reliably.

Regarding the recommendation to provide a justification for excluding data from Norway and Sweden, the PRAC was informed of a change of approach to perform an analysis that includes all four countries and time periods, an analysis that includes the long time series (Denmark-Finland), and an analysis that includes the shorter time series (all four countries 2004-2011: Denmark, Finland, Norway and Sweden).

Summary of advice

The PRAC agreed that, according to the response submitted, the points raised previously have been satisfactorily addressed. Some remaining points on details of the analysis to be performed need to be further addressed once a final protocol for the 'Stage 2' study is submitted.

12. Organisational, regulatory and methodological matters

12.1. Mandate and organisation of the PRAC

None

12.2. Pharmacovigilance audits and inspections

12.2.1. Pharmacovigilance Systems and their Quality Systems

None

12.2.2. Draft Key Performance Indicators for measuring performance of pharmacovigilance activities of the EMA and European Network

At the organisational matters teleconference of the PRAC on 27 June 2013, EMA consulted the Committee the draft Key Performance Indicators (KPIs) for pharmacovigilance activities. The EMA requested the PRAC to nominate several members to review the draft KPIs together with EMA. Almath Spooner (IE) and Julie Williams (UK) agreed to participate in this work. EMA will contact these members to agree on the timelines and next steps.

12.3. Signal Management

Signal Management

- Feedback from Signal Management Review Technical (SMART) Working Group

The PRAC was updated, at the organisational matters teleconference of the PRAC on 27 June 2013, on the progress of the SMART Work Stream 1. The Good Practice Guide on *'Good Practice on Implementation of PRAC signal recommendation for national/MRP/DCP products where a product information change is required'* has been updated by EMA and will be adopted by the SMART at its July 2013 meeting and subsequently circulated to the PRAC. In addition, the PRAC was informed that the *PRAC rapporteur signal assessment report template* is available as one of templates for assessors on the EMA website: PRAC Rapporteur's signal AR Template. The template will be reviewed within 6 months of use as applicable.

12.4. Periodic Safety Update Reports & Union Reference Date (EURD) List

12.4.1. Union Reference Date List

12.4.1.1. Consultation on the draft List, version June 2013

The EURD list version June 2013 was presented to the PRAC at the organisational matters teleconference of the PRAC on 27 June 2013.

Regarding herbal substances in the EURD list, several substances included in the composition of homeopathic products, referred to in Article 14 of Directive 2001/83/EC as amended, have been added to the list. However, it was clarified that PSURs for homeopathic products should not be required through the EURD list in absence of a valid justification.

In terms of the upcoming PSUR single assessments of substances contained in CAPs and NAPs, The PRAC was reminded of the principle of Rapporteurship appointment agreed in April 2013 (see PRAC Minutes April 2013) (appointment of the rapporteur of the first CAP authorised). Any deviations from this principle need to be duly justified and endorsed by the PRAC. The Committee agreed to transfer the PRAC Rapporteurship for fentanyl-containing products from Martin Huber (DE) to Evelyne Falip (FR). The PRAC endorsed the updated version of the EURD list for further adoption at the June 2013 CHMP meeting.

Post-meeting note: following the PRAC meeting in June 2013, the updated EURD list was adopted by the CHMP at its June 2013 meeting and was published on the EMA website on 3 July 2013 (see: Home>Regulatory>Human medicines>Pharmacovigilance>EU reference date and PSUR submission).

12.5. Signal Management

12.5.1. Signal Management

- Feedback from Signal Management Review Technical (SMART) Working Group

The PRAC was updated, at the organisational matters teleconference of the PRAC on 27 June 2013, on the progress of the SMART Work Stream 1. The Good Practice Guide on *'Good Practice on Implementation of PRAC signal recommendation for national/MRP/DCP products where a product information change is required'* has been updated by EMA and will be adopted by the SMART at its July 2013 meeting and subsequently circulated to the PRAC. In addition, the PRAC was informed that the '*PRAC rapporteur signal assessment report template'* is available as one of the assessors' templates on the EMA website: PRAC Rapporteur's signal AR Template. The template will be reviewed within 6 months of use as applicable.

12.6. Adverse Drug Reactions reporting and additional reporting

12.6.1. List of Product under Additional Monitoring

12.6.1.1. Consultation on the draft List, version June 2013

At the organisational matters teleconference of the PRAC on 27 June 2013, the Committee was updated on the changes made to the list of products under Additional Monitoring, version June 2013. Two CAPs which were recently granted a Commission Decision as well as 3 CAPs with Annex II conditions for the conduct of a PASS were added to the list. The PRAC endorsed these changes. The PRAC was informed that the list is due for publication on the EMA website in the week starting 1 July 2013.

Post-meeting note: the list of products under Additional Monitoring, version June 2013 was published on the EMA website on 5 July 2013 (EMA/245297/2013 Rev.2).

12.7. EudraVigilance Database

None

12.8. Risk Management Plans and Effectiveness of Risk Minimisations

12.8.1. Risk Management Plans (RMPs)

12.8.2. RMP procedural timetables

- Proposal for the initial marketing authorisation application timetable (day-180-210)

EMA clarified that the clock-stop timetable when PRAC is assessing the RMP submitted after an oral explanation in the context of an initial marketing authorisation will be applied in order to allow for further PRAC assessment. In these important RMP update cases, the CHMP opinion would be issued in the subsequent month following the oral explanation.

12.9. Post-authorisation Safety Studies

12.9.1. Post-Authorisation Safety Studies

12.9.2. Patient Registries

- Proposal to initiate the process of encouraging and supporting joint disease-based registries

At the organisational matters teleconference of the PRAC on 27 June 2013, EMA and Ulla Wändel-Liminga (SE) presented an overview and proposal for encouraging and supporting joint disease-based registries. Various options to encourage pharmaceutical industries to collaborate were discussed and key deliverables were presented and supported by the PRAC. The EMA launched a call for PRAC volunteers to develop a strategy paper by the end of 2013. Interested members were requested to contact EMA by 5 July 2013.

12.10. Community Procedures

None

12.11. Risk communication and Transparency

None

12.12. Continuous pharmacovigilance

None

12.13. Interaction with EMA Committees and Working Parties

12.13.1. Human Scientific Committees Working Party with Healthcare Professionals' Organisations (HCPWP) and Patients' and Consumers' Working Party (PCWP)

- Nomination of PRAC representative at the HCPWP and PCWP

The PRAC was informed at the organisational matters teleconference on 27 June 2013 that Marco Greco (PRAC patient alternate) agreed to be the PRAC representative at PCWP, Albert van der Zeijden (PRAC patient member) will be his alternate. Kirsten Myhr (PRAC healthcare professional alternate) agreed to be the PRAC representative at HCPWP, Filip Babylon (PRAC healthcare professional member) will be her alternate. The PRAC representatives will participate in the next Joint PCWP-HCPWP meeting organised on 25-26 September 2013 at the EMA.

12.14. Interaction within the EU regulatory network

None

12.15. Contacts of the PRAC with external parties and interaction of the EMA with interested parties

12.15.1. Novel influenza strain (H7N9) in humans

- Preparatory activities

At the organisational matters teleconference of the PRAC on 27 June 2013, EMA and Brigitte Keller-Stanislawski (DE) presented to the Committee a proposal for PRAC preparatory activities in case of a possible H7N9 pandemic. These activities relate to: finalisation of the GVP Module P.I Vaccine pharmacovigilance, exposure data for signal detection, risk management plans, additional monitoring, background incidence rates, signal detection from EudraVigilance, signal management, exchange of information, communication planning and the need for the nomination by the PRAC of an additional representative in the EMA Task Force. EMA will organise a meeting in the margins of the July 2013 PRAC meeting with PRAC members with expertise in vaccines, and well qualified to act as PRAC Rapporteurs for H7N9 vaccines.

12.15.2. Medication errors workshop

- Outcome of workshop and implementation plan

At the organisational matters teleconference of the PRAC on 27 June 2013, the EMA presented to the PRAC a draft implementation plan as per the medication errors workshop's recommendations (see also PRAC Minutes May 2013) to support the implementation of the new legal provisions for medication errors. The EU regulatory network proposing five key deliverables (good practices guides and reflection papers) to be taken further through existing framework on the implementation of the Pharmacovigilance legislation, and working collaboration with other initiatives and groups active in this area.

PRAC welcomed the initiative and commented that it would be appropriate to consider Key performance Indicators (KPIs) to measure how these deliverables impact on medication errors in practice and requested to be get regular progress updates.

As a next step, EMA will send a call for expression of interest to PRAC to volunteer as Rapporteur for each of the deliverables which will be further aligned with the Project Teams implementation checklist and milestones.

12.15.3. Others

None

13. Any other business

13.1.1. Proactive publication of clinical trial data

At the organisational matters teleconference of the PRAC on 27 June 2013, the PRAC was updated on the further EMA development since the announcement in April 2012 on the EMA external website of the proactive publication of clinical trial data and access to full data sets by interested parties.

EMA informed the PRAC that on 24 June 2013, the Agency released for public consultation a draft policy on publication and access to clinical trial data for a three-month public consultation until 30 September 2013 (Policy 70: Publication and access to clinical-trial data). The policy concerns all clinical trials submitted in the future as part of initial Marketing Authorisation or post-authorisation procedure. The policy scope does not cover clinical data not held by the EMA, pre-existing clinical data for marketed products, and pharmacovigilance data based on Individual Case Safety Reports (ICSR). The final EMA policy is due for publication on 30 November 2013 and will come into force on 1 January 2014.

ANNEX I – List of abbreviations

For a List of the abbreviation used in the PRAC minutes, see:

www.ema.europa.eu

Home>About Us>Committees>PRAC Agendas, minutes and highlights

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 June 2013 meeting.

PRAC member PRAC alternate	*Country*	*Outcome restriction following evaluation of e-DoI for the meeting*	*Topics on the current Committee Agenda for which restriction applies*
			Product / substance
Harald Herkner	Austria	Full involvement	
Bettina Schade	Austria	Full involvement	
Jean-Michel Dogne	Belgium	Cannot act as Rapporteur or Peer-reviewer for:	regorafenib, riociguat, aflibercept
Maria Popova-Kiradjieva	Bulgaria	Full involvement	
Christos Petrou	Cyprus	Full involvement	
Eva Jirsova	Czech Republic	Full involvement	
Line Michan	Denmark	Full involvement	
Doris Stenver	Denmark	Full involvement	
Maia Uusküla	Estonia	Full involvement	
Terhi Lehtinen	Finland	Involvement in discussions only with respect to procedures involving the following products i.e. no part in final deliberations and voting as appropriate as regards these medicinal products. - Cannot act as Rapporteur for these products.	Tiotropium, desferasirox, levodopa, carbidopa, entacapone
Kirsti Villikka	Finland	Full involvement	
Evelyne Falip	France	Full involvement	
Isabelle Robine	France	Full involvement	
Martin Huber	Germany	Full involvement	
Leonidas Klironomos	Greece	Cannot act as Rapporteur or Peer-reviewer for:	diclofenac, etanercept, tafamidis, voriconazole, apixaban, pegvisomant, pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed), crizotinib
Julia Pallos	Hungary	Full involvement	
Gudrun Kristin Steingrimsdottir	Iceland	Full involvement	
Almath Spooner	Ireland	Full involvement	
Carmela Macchiarulo	Italy	Full involvement	
Andis Lacis	Latvia	Full involvement	
Jolanta Gulbinovic	Lithuania	Full involvement	
Jacqueline Genoux-Hames	Luxembourg	Full involvement	

PRAC member PRAC alternate	Country	Outcome restriction following evaluation of e-DoI for the meeting	Topics on the current Committee Agenda for which restriction applies Product / substance
Amy Tanti	Malta	Full involvement	
Sabine Straus	Netherlands	Full involvement	
Menno van der Elst	Netherlands	Full involvement	
Ingebjorg Buajordet	Norway	Full involvement	
Pernille Harg	Norway	Full involvement	
Kamila Czajkowska	Poland	Full involvement	
Margarida Guimaraes	Portugal	Full involvement	
Daniela Pomponiu	Romania	Full involvement	
Tatiana Magalova	Slovakia	Full involvement	
Milena Radoha-Bergoc	Slovenia	Full involvement	
Miguel-Angel Macia	Spain	Full involvement	
Dolores Montero	Spain	Full involvement	
Ulla Wandel Liminga	Sweden	Full involvement	
Qun-Ying Yue	Sweden	Full involvement	
Julia Dunne	United Kingdom	Full involvement	
June Munro Raine	United Kingdom	Full involvement	
Julie Williams	United kingdom	Full involvement	

Independent scientific experts nominated by the European Commission	Country	Outcome restriction following evaluation of e-DoI for the meeting:	Topics on the current Committee Agenda for which restriction applies Product / substance
Jane Ahlqvist Rastad	Not applicable	Full involvement	
Marie Louise (Marieke) De Bruin		Full involvement	
Stephen Evans		Cannot act as Rapporteur or Peer-reviewer for:	Pandemrix, dabrafenib, trametinib, human papillomavirus vaccine
Birgitte Keller-Stanislawski		Full involvement	
Herve Le Louet		Cannot act as Rapporteur or Peer-reviewer for:	ivabradine
Lennart Waldenlind		Full involvement	

Additional European experts participating at the meeting for specific Agenda items	Country

Veerle Verlinden	Belgium	No restrictions were identified for the participation of European experts attending the PRAC meeting for discussion on specific agenda items
Rikke Jensen	Denmark	
Per Sindahl	Denmark	
Hanna Nohynek	Finland	
Christine Diesinger	Germany	
Jutta Krappweis	Germany	
Jens Rotthauwe	Germany	
Janet Schriever	Germany	
Anna Marie Coleman	Ireland	
Anna-Marie Coleman	Ireland	
Sophia Venzke	Netherlands	
Charlotte Backman	Sweden	
Nils Feltelius	Sweden	
Rolf Gedeborg	Sweden	
Ingemar Persson	Sweden	
Hans Sjögren	Sweden	
Lars Ståhle	Sweden	
Tomas Salmonson	Sweden	
Patrick Batty	United Kingdom	
Phil Bryan	United Kingdom	
Inga Bellahn	United Kingdom	
Claire Davies	United Kingdom	
Elena Elliot-Smith	United Kingdom	
Alison Shaw	United Kingdom	
Angeliki Siapkari	United Kingdom	
Andrew Thomson	United Kingdom	
Catherine Tregunno	United Kingdom	
Jane Woolley	United Kingdom	

Health care professionals and patients observers	Country	Outcome restriction following evaluation of e-DoI for the meeting:	Topics on the current Committee Agenda for which restriction applies Product/substance
Flip Babylon		Full involvement	
Kirsten Myhr		Full involvement	
Albert van der Zeijden		Cannot act as Rapporteur or Peer-reviewer for:	denosumab, panitumumab, romiplostim, exenatide, florbetapir, olanzapine, diclofenac, etanercept, tafamidis, voriconazole, apixaban, pegvisomant, pneumococcal polysaccharide conjugate vaccine (13-

Health care professionals and patients observers	Country	Outcome restriction following evaluation of e-DoI for the meeting:	Topics on the current Committee Agenda for which restriction applies Product/substance
			valent, adsorbed), crizotinib, pandemrix, dabrafenib, trametinib, Cervarix, indacaterol, glycopyrronium bromide, indacaterol, deferasirox, aliskiren hydrochlorothiazide, ruxolitinib

Observer from the European Commission
Helen Lee - DG Health and Consumers

European Medicines Agency
Peter Arlett – Sector Head, Pharmacovigilance and Risk Management
Roberto De Lisa - Scientific Administrator, PRAC Secretariat
Zaide Frias - Section Head, Regulatory Affairs
Georgy Genov – Section Head, Signal Detection and Data Analysis
Grace Hernandez – Assistant, CHMP/PRAC Secretariat
Ana Hidalgo-Simon – Section Head, Risk Management
Kasia Kmiecik – Assistant, PRAC Secretariat
Sheila Kennedy – Section Head, Scientific Committee Support
Anabela Marcal – Section Head, Community Procedures
Geraldine Portier - Scientific Administrator, PRAC Secretariat
Tanya Sepehr – Assistant, PRAC Secretariat