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Pharmacovigilance Risk Assessment Committee (PRAC)

Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC minutes of the meeting on 2-5 December 2013

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)

* Kogenate – correction on page 12
** Octocog alfa (Helixate Nexgen/Kogenate Bayer) – correction on page 12
*** PSURs Repository – correction on page 39

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7051
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

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, welcoming all participants to the 2-5 December 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. 24 or more members were present in the room). All decisions, recommendations and advice were agreed unanimously, unless otherwise specified.

The PRAC welcomed at the meeting Jelena Ivanovic as the new alternate for IT and Andri Andreou as alternate for CY. The PRAC noted that Evelyne Falip, will step down as alternate of the PRAC from FR at the end of 2013. The PRAC emphasised her excellent contribution and dedication to the work of the PRAC and wished her all the best for any future appointment.

The Committee also noted the nomination of Alexandra Martinovic as the new alternate for AT and that Daniela Pomponiu stepped down as alternate from RO, the new alternate being Roxana Stefania Stroe.

1.2. Adoption of agenda for the meeting on 2-5 December 2013

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

1.3. Adoption of the minutes of the previous PRAC meeting on 4-7 November 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 4-7 November 2013 EMA/PRAC/729184/2013 were published on the EMA website on 17 December 2013.

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

None

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

3.1. Newly triggered Procedures

3.1.1. **Ponatinib – ICLUSIG** (CAP)

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

Regulatory details:

PRAC Rapporteur: Julia Dunne (UK)
PRAC Co-Rapporteur: Ulla Wändel Liminga (SE)

Background

Following discussion at PRAC and CHMP at their November 2013 meetings on a variation addressing new data on vascular occlusive events associated with ponatinib use, the European Commission sent a notification letter dated 27/11/2013 triggering a referral under Article 20 of Regulation (EC) No 726/2004 for the review of Iclusig (ponatinib) (see PRAC minutes 4-7 November 2013). A further review was necessary since there were a number of outstanding issues which could not be resolved within the variation procedure.

Discussion

The PRAC noted the notification from the European Commission and discussed a list of questions to be addressed during the procedure as well as a timetable for conducting the review. The PRAC also discussed whether provisional measures were needed. The PRAC agreed that since the indication for use of the medicine is restricted to a selected group of patients who have a serious disease for whom there are limited therapeutic alternatives, and that risk minimisation measures have already been put in place with the previously mentioned variation, no provisional measures are warranted at this time. If emerging data gathered in the review or further analyses raise any concern, the need for such measures will be reconsidered.

Summary of recommendation(s) / conclusions

- The MAH should address the agreed list of questions (published on the EMA website EMA/PRAC/746091/2013) in accordance with the adopted timetable (EMA/PRAC/746118/2013).

3.2. Ongoing Procedures

3.2.1. **Domperidone** (NAP)

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

Regulatory details:

PRAC Rapporteur: Isabelle Robine (FR)
PRAC Co-Rapporteur: Jean-Michel Dogné (BE)

Background

A referral procedure under Article 31 is ongoing for domperidone-containing medicines (see PRAC minutes 8-11 July 2013). An assessment of the data submitted to address the outstanding issues, was produced by the Rapporteurs according to the agreed timetable.

Summary of recommendation(s) / conclusions

The PRAC discussed the conclusion reached by the Rapporteurs and discussed that further exploration was needed on the recommended daily dose as well as other aspects. Therefore the PRAC agreed on a second list of outstanding issues to be addressed by the MAHs. The MAHs will be invited to address the outstanding issues in writing and also at an oral explanation, in accordance with an updated timetable for the review (EMA/PRAC/127280/2013 Rev.2).

Post-meeting note: following the conclusion of the meeting, the MAH requested an extension of the deadline for providing a reply to the LoOIs. The PRAC considered that it was important to proceed as per already estabilished timelines and supported maintaining the agreed timetable.

3.2.2. **Zolpidem** (NAP)

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

Regulatory details:
PRAC Rapporteur: Menno van der Elst (NL)
PRAC Co-Rapporteur: Carmela Macchiarulo (IT)

Background

A referral procedure under Article 31 is ongoing for zolpidem-containing medicines (see PRAC minutes 8-11 July 2013) is ongoing. An assessment of the data submitted was produced by the Rapporteurs according to the agreed timetable.

Summary of recommendation(s) / conclusions

The PRAC discussed the conclusions reached by the Rapporteurs and considered that further exploration was needed on the risks of impaired driving and of somnambulism associated with the use of these products and on how this risk could be minimised.

Therefore the PRAC agreed on a second list of outstanding issues to be addressed by the MAHs as well as on a revised timetable for the procedure (EMA/PRAC/418739/2013 Rev1).

3.3. Procedures for finalisation

3.3.1. **Octocog alfa – HELIXATE NEXGEN** (CAP), **KOGENATE BAYER** (CAP)

- Review of the benefit-risk balance following a notification by the European Commission of a referral under Article 20(8) of Regulation (EC) No 726/2004, following procedural steps of Article 31 of Directive 2001/83/EC, based on pharmacovigilance data

Regulatory details:
PRAC Rapporteur: Brigitte Keller-Stanislawski (DE)
PRAC Co-Rapporteur: Ulla Wändel Liminga (SE)

Background

A referral procedure under Article 20(8) of Regulation (EC) No 726/2004 for the octocog alfa – containing medicines Helixate NexGen and Kogenate Bayer (see PRAC minutes 7-10 October 2013 for background) is to be concluded. A final assessment of the data submitted was produced by the Rapporteurs according to the agreed timetable.

Discussion

The PRAC reviewed the available pre-clinical and clinical data on development of factor VIII inhibitors in previously untreated patients with haemophilia A, including results from the RODIN and EUHASS studies, and concluded that the available data did not support that Kogenate Bayer or Helixate NexGen were associated with an increased risk of developing factor VIII inhibitors, compared with other factor VIII products in previously untreated patients. However, some updates of the product information to reflect the newly available data were considered necessary.

Summary of recommendation(s)/conclusions

The PRAC adopted by consensus a recommendation for variation of the marketing authorisations for Helixate NexGen and Kogenate Bayer to be considered by CHMP – see 'PRAC considers benefits of Kogenate Bayer/Helixate NexGen outweigh risks in previously untreated patients' EMA/741427/2013.

Post-meeting note: the press release 'CHMP confirms PRAC recommendations on Kogenate Bayer/Helixate NexGen' representing the opinion provided by the CHMP EMA/781158/2013 was published on the EMA website on 20 December 2013.

3.4. Re-examination procedures

3.4.1. **Diacerein** (NAP)

- Re-examination procedure of the PRAC recommendation following the review of the benefit-risk balance following notification by France of a referral under Article 31 of Directive 2001/83/EC based on pharmacovigilance data

Regulatory details:
PRAC Rapporteur: Margarida Guimarães (PT)
PRAC Co-Rapporteur: Harald Herkner (AT)

Background

A referral procedure under Article 31 of Directive 2001/83/EC for diacerein-containing medicines was concluded at the 4-7 November 2013 PRAC meeting. The MAHs for some of the products concerned submitted a request for re-examination of the PRAC recommendations.

Summary of recommendation(s)/conclusions

The PRAC appointed Margarida Guimarães (PT) to act as Rapporteur and Harald Herkner (AT) to act as Co-rapporteur for the re-examination procedure, to start upon receipt of the scientific grounds for the request. A timetable for the re-examination procedure will also be agreed at that time.

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

None

3.6. Others

3.6.1. **Dihydrocodeine** (NAP)

- Follow-up to PRAC September 2013 discussion

Regulatory details:
PRAC Rapporteur: *not applicable*

Background

For background, see PRAC September 2013 minutes. Following a request of the PRAC, in the light of the concluded referral on codeine toxicity in children (see www.ema.europa.eu – Codeine-containing medicines related pages) a response was received from the Pharmacogenomics Working Party (PGWP) setting out its position on the evidence for dihydrocodeine on risks of opiate toxicity in CYP 2D6 ultra-rapid metabolisers and on the genetic polymorphisms involved in the metabolism of dihydrocodeine as well as other information.

Summary of recommendation(s) / conclusions

The PGWP advised that similarly to codeine, dihydrocodeine is suggested to become pharmacologically active after O-demethylation to dihydromorphine. The polymorphic CYP2D6 is the major enzyme that catalyses dihydrocodeine O-demethylation to dihydromorphine. However, a relevant contribution of the parent drug to the final analgesic effect is expected. This is in contrast to the situation for codeine, where only the O-demethylated active metabolites are responsible for the analgesic effect with hardly any contribution from the parent codeine.

The PRAC discussed that there are some similarities between the metabolism of dihydrocodeine and codeine in the formation of O-demethylated metabolites catalyzed by CYP2D6. However, the clinical importance of this polymorphism had not currently been shown in the few available studies for dihydrocodeine. Overall, there were very limited data on the correlation between dihydrocodeine active metabolites and analgesic effects.

A search in EudraVigilance for case reports of morphine/opioid toxicity related to dihydrocodeine-containing medicines led to the detection of 41 case reports that included terms that could be related to morphine/opioid toxicity, but overall, the cases had limited information. No literature reports of dihydrocodeine related morphine/opioid toxicity, so far, were found in the published literature.

The PRAC concluded that at present, data were insufficient to draw conclusions regarding the risk of opiate toxicity in CYP 2D6 ultra-rapid metabolisers taking dihydrocodeine, or on the clinical importance of the similarities or differences in metabolism between codeine and dihydrocodeine.

The PRAC noted that, in some MSs, companies had submitted variations to provide further information on this issue in the product information. A precautionary general warning on the theoretical concern following these findings could be considered for inclusion in the product information in those member states with a currently marketed product for use in children. Therefore a proposal for a common wording was agreed.

4. Signals assessment and prioritisation

4.1. New signals detected from EU spontaneous reporting systems

4.1.1. **Clindamycin** (NAP)

- Signal of drug interaction with warfarin leading to international normalised ratio (INR) increase

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Background

Clindamycin is an antibiotic used in the treatment of susceptible Gram-positive aerobic organisms.

The exposure for a nationally authorised medicine containing clindamycin for systemic use (originator) is estimated to have been more than 37 million patients worldwide, in the period from 2010 to 2012.

During routine signal detection activities, a signal of drug interaction with warfarin was identified by UK, based on five cases reported in the United Kingdom, some of which leading to increase of the international normalised ratio (INR). UK confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information on the cases of increased INR reported and noted that the product information of warfarin-containing medicines already included information that broad spectrum antibiotics may potentiate the effect of warfarin by reducing the bacterial gut flora which physiologically produces vitamin K.

The PRAC therefore recognised that there was a plausible biological mechanism underlying the interaction and agreed that further information on reported cases of potential interaction between clindamycin and warfarin but also with other vitamin K antagonist anticoagulants (e.g. phenprocoumon and acenocoumarol) should be collected and reviewed.

The PRAC appointed Julie Williams (UK) as Rapporteur for the signal.

Summary of recommendation(s)

- The MAH for the originator clindamycin-containing medicine should submit to the PRAC Rapporteur, within 60 days, further information on the potential interaction of clindamycin with warfarin and with other vitamin K antagonist anticoagulants (e.g. phenprocoumon and acenocoumarol).
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.1.2. **Lamotrigine** (NAP)

- Signal of drug reaction with eosinophilia and systemic symptoms (DRESS)

Regulatory details:
PRAC Rapporteur: *n/a*

Background

Lamotrigine is an antiepileptic used in the treatment of partial seizures and generalised seizures, including tonic-clonic seizures as well as other related clinical conditions including bipolar disorder.

The exposure for nationally authorised medicines containing lamotrigine is estimated to have been more than 7.7 million patient-years worldwide, in the period from 2011 to 2012.

During routine signal detection activities, a signal of DRESS was identified by the NL, based on several reports retrieved from EudraVigilance and supported by eight case review papers published on this

potential association since 2012. NL, as P-RMS for the originator lamotrigine–containing medicine confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information on the suspected cases of DRESS reported and noted that overall other severe skin reactions were already included the product information for lamotrigine containing products with previous updates. Since the latest update the clinical recognition of DRESS has progressed and a large number of cases (namely 567 individual case safety reports) had been progressively reported to EudraVigilance. The PRAC confirmed that based on the information included in the case reports and in the literature, lamotrigine therapy may be associated with the development of DRESS. Therefore it would be appropriate to include DRESS as an adverse drug reaction in the product information.

Summary of recommendation(s)

- The MAH for lamotrigine containing medicines should update the product information (SmPC and package leaflet) as regards to DRESS (the implementation of this update can be carried out in the framework of the currently ongoing PSUR Work Sharing procedure for lamotrigine–containing medicines).

For the full PRAC recommendation see EMA/PRAC/773133/2013 published on the EMA website.

4.1.3. Strontium ranelate - **OSSEOR** (CAP), **PROTELOS** (CAP)

- Signal of eye disorders

Regulatory details:
PRAC Rapporteur: Ulla Wändel Liminga (SE)

Background

Strontium ranelate is used in the treatment of osteoporosis in postmenopausal women and in men.

The exposure for Protelos and Osseor, centrally authorised medicine containing strontium ranelate, is estimated to have been more than 44 million patient-months worldwide, in the period from first authorisation in September 2004 to September 2013.

During routine signal detection activities, a signal of eye disorders was identified by IT, based 10 cases of various eye disorders retrieved from the Italian Pharmacovigilance Database. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information on the cases of eye disorders reported, ranging from reduced visual acuity to eye inflammation. The PRAC noted that in around half of these cases strontium ranelate had been coadministered with other medicines that could provide an alternative explanation for the development of the reaction. In many cases there was scant information to assess causality. However, it was also considered that recently available results of a cohort study, analysing inflammatory eye reactions in patients treated with osteoporosis medications - including strontium ranelate - could provide further insight into the issue. Therefore the PRAC agreed that it would be useful to collect further information on this signal.

Summary of recommendation(s)

- The MAH for Protelos and Osseor should submit a cumulative review of eye disorders/ inflammatory eye reactions, including literature, post-marketing and clinical trials data to the EMA in the framework of the currently on-going PSUR procedure (DLP: 21/09/2013).

4.2. New signals detected from other sources

4.2.1. **Fentanyl**, transdermal patch (NAP)

- Signal of accidental exposure

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Background

Fentanyl is an opioid analgesic used in the treatment of chronic intractable pain, also available as a transdermal patch.

The exposure for fentanyl-containing patches is estimated to have been more than 500 million patient-days worldwide from 2009 to 2012, based on the most recent PSUR received.

A signal of medication errors including accidental exposure following use of the patches, was raised for discussion by the NL based on 19 EU cases retrieved in a search performed following recent communication from US FDA (see FDA Drug Safety Communication: FDA requiring color changes to Duragesic (fentanyl) nationally authorised pain patches to aid safety - emphasizing that accidental exposure to used patches can cause death).

Discussion

The PRAC discussed the information on the cases of accidental exposure reported, which included cases with serious and fatal outcome. The PRAC noted that the reports in the EU, overall, were comparable to those reported in the USA. These cases included accidental exposure in children due to improper handling of patches by patients and caregivers. From preliminary feed-back collected by the MAHs it seemed that in some cases improper handling was involved but it was not clear to what extent a limited visibility of the patch contributed to the accidental exposure. Therefore the PRAC agreed that more information was needed on this signal in order to conclude on appropriate risk minimisation.

The PRAC appointed Sabine Straus (NL) as Rapporteur for the signal.

Summary of recommendation(s)

- The MAH for fentanyl patches should submit to the PRAC Rapporteur, within 60 days, a cumulative review of all cases (EEA/non-EEA and literature) of fentanyl patches and medication error, accidental exposure and improper handling in disposal of patches.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

Post meeting note: following the meeting a request for an extension of the timeline for providing a reply was put forward by the MAH. The PRAC considered that it was important to proceed as per already estabilished timelines and supported maintaining the agreed timetable.

4.3. Signals follow-up and prioritisation

4.3.1. Cabazitaxel - JEVTANA (CAP)

- Signal of medication error potentially leading to inappropriate dose / overdose

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

Background

For background information see PRAC minutes 7-10 October 2013.

The MAH replied to the request of additional information on the cases reported and the responses were assessed by the Rapporteur.

Discussion

The PRAC noted that following discussion at the October 2013 meeting the MAH had issued a Direct Healthcare Professional Communication (DHPC) with a clear recommendation on the correct method of preparation of Jevtana. The PRAC noted that an update of the product information had been submitted for approval as well as a proposal for updating the risk management plan. Regarding the possibility of a change in the presentation of Jevtana, the PRAC welcomed consideration by the MAH of this option and anticipated further discussion in future regulatory procedures. The PRAC concluded on the need to keep this issue under close monitoring.

Summary of recommendation(s)

- The MAHs for Jevtana (cabazitaxel), should be requested to review the cases of medication errors, in particular the reconstitution errors reported and to discuss the effectiveness and impact of the risk minimisation measures implemented and to provide an update on their efforts to explore the possibility of changing the presentation of Jevtana to one-vial in the framework of the next PSUR (DLP: 17/12/2013).

For the full PRAC recommendation see EMA/PRAC/773133/2013 published on the EMA website.

4.3.2. Human papillomavirus vaccine [types 16, 18] (recombinant, adjuvanted, adsorbed) – CERVARIX (CAP)
Human papillomavirus vaccine [types 6, 11, 16, 18] (recombinant, adsorbed) – GARDASIL (CAP), SILGARD (CAP)

- Signal of complex regional pain syndrome (CRPS) linked to the process of vaccination

Regulatory details:
PRAC Rapporteurs: Jean-Michel Dogné (BE), Qun-Ying Yue (SE)

Background

For background information, see PRAC minutes of 8-11 July 2013. The MAH replied to the request for information on the signal of CRPS associated with the process of vaccination and the responses were assessed by the Rapporteur.

Discussion

The PRAC discussed the information received and noted that there were no reports of CRPS from the clinical trial program for Cervarix and Gardasil[1]. There was no consensus in the scientific community concerning the criteria for diagnosing CRPS in children and young people. However, the estimated incidence of the condition in the non-vaccinated population in females between the ages of 10-19 years has been reported to be 14.9 / 100,000 person years (de Mos et al. 2007). Post immunisation CRPS has been previously reported in association with rubella, hepatitis B as well as diphtheria, tetanus and pertussis (DTaP) vaccines; some of the cases reported had confounding factors that could provide an alternative explanation for the development of the suspected cases of CRPS reported. Therefore the PRAC considered that the currently available evidence did not allow confirmation of a causal association between Gardasil and CRPS and that no regulatory action was justified.

However, since some points of the previous request were not fully addressed the PRAC agreed that some final additional clarifications should be provided by the MAHs for completeness.

Summary of recommendation(s)

- The MAHs for Cervarix and Gardasil should provide final clarification to the EMA within 60 days including further details on the cases included in the safety database.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.3.3. Sitagliptin – **JANUVIA** (CAP), **RISTABEN** (CAP), **TESAVEL** (CAP), **XELEVIA** (CAP) **Sitagliptin**, **metformin – EFFICIB** (CAP), **JANUMET** (CAP), **RISTFOR** (CAP), **VELMETIA** (CAP), **Angiotensin-converting enzyme (ACE) inhibitors** (NAP)

- Signal of angioedema due to interaction between sitagliptin and ACE inhibitors

Regulatory details:
PRAC Rapporteur: Menno van der Elst (NL)

Background

For background information, see PRAC minutes 8-11 July 2013. The MAH replied to the request for information on the signal and the responses were assessed by the Rapporteur.

Discussion

The PRAC noted that in response to a previous request the MAH had provided a cumulative review of serious suspected adverse reaction reports of angioedema from clinical trials and post-marketing cases where the DPP-4 inhibitor sitagliptin, was the suspected medicine or where sitagliptin was co-administered with an ACE inhibitor, respectively. Based on the cases presented, the causality of an increased risk posed by the interaction could not be clearly determined although the reaction is listed in the product information for both substances. A review of the published medical literature addressing the risk of angioedema with DDP-4 inhibitors and ACE inhibitors was also provided and showed that among individuals taking an ACE inhibitor, vidagliptin (another member of the DPP-4 inhibitor class) use was associated with an increase of the relative risk of angioedema. However in absolute terms this risk was small and some methodological limitations in the study were pointed out. The PRAC agreed

[1] More than 26,000 patients were recruited in the clinical development for Gardasil

that overall some clarifications were needed on an analysis of the incidence of angioedema and related events within a meta-analysis of safety from 25 sitagliptin clinical trials submitted.

Regarding a plausible biologic explanation, overall the PRAC concluded that while several pharmacodynamic mechanisms were proposed in the literature, none had been clearly demonstrated to play a causal role in the increased incidence of angioedema. In conclusion, a more in depth analysis was considered necessary and the PRAC agreed that some clarifications were needed on specific aspect of pharmacokinetic interaction.

Summary of recommendation(s)

- The MAHs for the above mentioned sitagliptin-containing medicines should submit to the EMA within 60 days some additional information and clarifications on the methodology of the meta-analysis submitted, on the review of the post-marketing spontaneous case reports as well as on the pharmacokinetic mechanism of the suspected interaction.

4.3.4. **Thiopental** (NAP)

- Signal of hypokalaemia and rebound hyperkalamaemia

Regulatory details:
PRAC Rapporteur: Ruchika Sharma (IE)

Background

For background information, see PRAC minutes 8-11 July 2013.The MAH replied to the request for information on the signal of hypokalaemia and rebound hyperkalaemia and the responses were assessed by the Rapporteur.

Discussion

The PRAC discussed the assessment of the cumulative analysis of cases of hypokalaemia and rebound hyperkalaemia reported in relation to thiopental infusion, including case reports in the MAH safety database and a review of literature case reports. Three papers on case series describing serum potassium disturbances in patients with thiopental-induced coma to manage increased intracranial pressure, were identified in the literature. The PRAC agreed that the further information available suggested that a plausible biological mechanism existed and that a causal association could not be ruled out. Therefore the PRAC agreed that the product information for thiopental-containing medicines should be updated as regards hypokalaemia and rebound hyperkalaemia.

Summary of recommendation(s)

- The MAH for the nationally authorised [2] thiopental containing medicines should be requested to submit to the NCAs of the MS within 60 days a variation to update the product information as regards to hypokalaemia and rebound hyperkalaemia.

For the full PRAC recommendation see EMA/PRAC/773133/2013 published on the EMA website.

[2] 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

4.3.5. **Tiotropium bromide** (NAP)

- Signal of increased mortality from cardiovascular disease and all-cause mortality – results of TIOSPIR[3] trial

Regulatory details:

PRAC Rapporteur: Sabine Straus (NL)

Background

For background information, see PRAC minutes of 13-16 May 2013.

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

Discussion

The PRAC discussed the results of the TIOSPIR study (a randomised trial including 17,135 patients with COPD, that directly compared efficacy and safety of tiotropium Respimat (2.5 µg and 5 µg) with tiotropium Handihaler (18 µg)) The PRAC concluded that the data showed comparable efficacy and safety of both tiotropium formulations.

However, a numerical imbalance in the number of fatal myocardial infarctions between the two treatment groups was identified. The PRAC concluded that additional work was needed to further clarify the finding. In particular it was considered important to see if there was a subpopulation for which additional risk minimisation measures might be required.

Summary of recommendation(s)

- The MAHs for tiotropium Respimat should submit, within 60 days, additional clarifications to the PRAC Rapporteur including – among other aspects - a separate analysis for sub-populations with cardiac disorders at baseline to explore if the risk of myocardial infarction could be particularly increased in this sub-population when treated with Spiriva Respimat.

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.

Please refer to the CHMP pages for upcoming information (http://www.ema.europa.eu/ Home>About Us>Committees>CHMP Meetings).

5.1.1. **Acetylsalicylic acid, clopidogrel**

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

5.1.2. **Ataluren**

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

[3] Tiotropium Safety and Performance in Respimat

5.1.3. Bedaquiline

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

5.1.4. Budesonide, formoterol

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

5.1.5. Busulfan

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

5.1.6. Diphteria, tetanus, pertussis and hepatitis B vaccine

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

5.1.7. Empagliflozin

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

5.1.8. Florbetaben (^{18}F)

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

5.1.9. Flutemetamol F-18

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

5.1.10. Laquinimod

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

5.1.11. Misoprostol

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

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

Regulatory details:
PRAC Rapporteur: Ulla Wändel Liminga (SE)

Background

Prolia and Xgeva are two centrally authorised products containing denosumab. Prolia is indicated for the treatment of osteoporosis in postmenopausal women at increased risk of fractures and treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures. Xgeva is indicated for prevention of skeletal related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with bone metastases from solid tumours.

The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMPs for Prolia and Xgeva following assessment of the accompanying PSUR.

Summary of advice

- The updated RMPs version 6 for Xgeva (denosumab) and 7 for Prolia (denosumab) were considered acceptable provided that the MAH submit an RMP update taking in consideration the PRAC recommendations following the PSUR procedure (see below 6.1.4.). The proposed RMP changes related to the new indications under evaluation should be submitted in the respective ongoing variation procedures.

RMP in the context of a variation

5.2.2. Linagliptin, metformin – JENTADUETO (CAP)

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

Regulatory details:
PRAC Rapporteur: Menno van der Elst (NL)

Background

Jentadueto is a centrally authorised medicine containing the association linagliptin and metformin indicated for adult patients with type-2 diabetes mellitus as an adjunct to diet and exercise to improve glycaemic control in patients inadequately controlled on their maximal tolerated dose of metformin alone, or those already being treated with the combination of linagliptin and metformin.

Jentadueto is indicated in combination with a sulphonylurea (i.e. triple combination therapy) as an adjunct to diet and exercise in adult patients inadequately controlled on their maximal tolerated dose of metformin and a sulphonylurea.

The CHMP is evaluating an extension of the therapeutic indication for Jentadueto, to include the treatment as combination therapy with insulin in adult patients with type 2 diabetes when insulin and metformin do not provide adequate glycaemic control. 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 for Jentadueto (linagliptin metformin) submitted in the context of the extension of indication variation under evaluation by the CHMP was considered acceptable.

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

See Bazedoxifene (Conbriza) under 17.1.3. ; Efavirenz (Stocrin, Sustiva) under 17.1.5. ; Liraglutide (Victoza) under **Error! Reference source not found.**; Pneumococcal conjugate vaccine (adsorbed) (Synflorix) under 17.1.11. ; Sevelamer (Renvela) under 17.1.12. , Tacrolimus (Modigraf) under 17.1.13.

RMP in the context of a stand-alone RMP procedure

5.2.3. Capsaicin – QUTENZA (CAP)

- Evaluation of a stand-alone RMP procedure

Regulatory details:
PRAC Rapporteur: Maria Alexandra Pêgo (PT)

Background

Capsaicin is a highly selective agonist for the transient receptor potential vanilloid 1 receptor (TRPV1) used as a topical analgesic (patches) under certain conditions. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP for Qutenza, a centrally authorised product containing capsaicin, following assessment of the PSUSA for capsaicin-containing products.

Summary of advice

The PRAC considered that the updated RMP version 16 for Qutenza (capsaicin) was not acceptable since the proposed pharmacovigilance and risk minimisation activities included were not updated in accordance with the latest PRAC advice provided on version 15 in May 2013. The MAH should submit to EMA within 90 days an updated RMP by means of a variation addressing the unresolved issues raised by the PRAC during the review of the RMP version 15 and in line with the conclusion of the PSUSA for capsaicin-containing products (see also under 6.1.3.).

5.2.4. Fentanyl – EFFENTORA (CAP)

- Evaluation of a stand-alone RMP procedure

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

Background

Effentora is a centrally authorised medicine containing fentanyl available as buccal tablets indicated for the treatment of breakthrough pain (BTP) in adults with cancer who are already receiving maintenance opioid therapy for chronic cancer pain. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP for Effentora following assessment of the PSUSA for fentanyl-containing products.

Summary of advice

The updated RMP version 2 for Effentora (fentanyl) could be acceptable provided an updated risk management plan revised in accordance with a number of minor amendments is submitted within an upcoming procedure or at the latest by 30 July 2014 and in line with the conclusion of the assessment of the PSUSA for fentanyl (see also under 6.1.5.). In particular, identified and potential risks need to be updated and some risks should be accompanied by appropriate definitions.

5.2.5. Fentanyl – INSTANYL (CAP)

- Evaluation of a stand-alone RMP procedure

Regulatory details:
PRAC Rapporteur: Evelyne Falip (FR)

Background

Instanyl is a centrally authorised medicine containing fentanyl available as nasal spray indicated for the management of breakthrough pain in adults already receiving maintenance opioid therapy for chronic cancer pain. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP for Instanyl following assessment of the PSUSA for fentanyl-containing products.

Summary of advice

The updated RMP version 13 for Instanyl (fentanyl) could be acceptable provided an updated risk management plan in accordance with a number of minor amendments is submitted within an upcoming procedure or at the latest by 30 July 2014 and in line with the conclusion of the assessment of the PSUSA for fentanyl (see also under 6.1.5.). Identified and potential risks need to be updated and some risks should be accompanied by appropriate definitions.

The MAH should propose a study to monitor the effectiveness of the updated educational material for patients, pharmacists and physicians, which was approved by the PRAC in July 2013 in order to strengthen risk minimisation measures addressed at ensuring that Instanyl is used in accordance with recommendations for safe and effective use as set out in the product information.

5.2.6. Fentanyl – PECFENT (CAP)

- Evaluation of a stand-alone RMP procedure

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

Background

PecFent is a centrally authorised medicine containing fentanyl available as nasal spray indicated for the management of breakthrough pain in adults already receiving maintenance opioid therapy for chronic cancer pain. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP for PecFent following assessment of the PSUSA for fentanyl-containing products.

Summary of advice

The updated RMP version 6.0 for PecFent (fentanyl) could be acceptable provided an updated risk management plan in accordance with a number of minor amendments is submitted within an upcoming procedure or at the latest by 30 July 2014 and in line with the conclusion of the assessment of the PSUSA for fentanyl (see also under 6.1.5.). Identified and potential risks need to be updated and some risks should be accompanied by appropriate definitions.

6. Periodic Safety Update Reports (PSURs)

6.1. Evaluation of PSUR procedures[4]

6.1.1. Boceprevir – VICTRELIS (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

[4] 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

Background

Boceprevir is an inhibitor of the hepatitis C virus (HCV) NS3 protease and is 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 risk-benefit balance of Victrelis (boceprevir) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to include a contraindication with alfuzosin and silodosin which are known to be highly dependent on CYP3A4/5 for clearance, and for which elevated plasma concentrations are associated with serious and/or life-threatening events. In addition, the risk of pancytopenia should be added as a warning and an undesirable effect with a common frequency. The product information should be also updated to add agranulocytosis and Stevens Johnson syndrome as undesirable effects with common and unknown frequencies respectively. Therefore the current terms of the marketing authorisation should be varied[5].
- In the next PSUR, the MAH should discuss recent publications by Hezode et *al*[6] and Maasoumy et *al (2013)*[7] suggesting poor tolerability of HCV anti-protease drugs including boceprevir in patients with advanced liver disease or cirrhosis, and the need for careful use of these drugs in such patients. The MAH should propose to update the product information as warranted. In addition, the MAH should further review the risk of drug-drug interactions between boceprevir and tamsulosin and doxazosin and should propose to update the product information accordingly. This review should include a discussion on possible therapeutic alternatives to physicians in the management of patients with benign prostatic hyperplasia that do not sufficiently respond to other treatments. Finally, the MAH should present a clear overview of all ongoing clinical trials with boceprevir as previously requested.

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

6.1.2. **Bromfenac – YELLOX** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Line Michan (DK)

[5] Update of SmPC sections 4.3, 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
[6] Hezode et al. Safety and efficacy of telaprevir or boceprevir in combination with peginterferon alfa/ribavirin, in 455 cirrhotic non responders. Week 16 analysis of the French early access program (ANRS CO20-CUPIC) in real-life setting. Hepatology 2012;56(4)
[7] Maasoumy et al. (2013) Eligibility and Safety of Triple Therapy for Hepatitis C: Lessons Learned from the First Experience in a Real World Setting. PLoS ONE 8(2): e55285. doi:10.1371/journal.pone.0055285

Background

Bromfenac is a non-steroidal anti-inflammatory drug (NSAID) indicated for the treatment of postoperative ocular inflammation following cataract extraction in adults.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Yellox (bromfenac) in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation should be maintained.
- In the next PSUR, the MAH should review cases of reported rebound effect including relevant literature and cumulative cases from the post-marketing setting and clinical trials. In addition, the MAH should review cumulative data regarding information not available from clinical trials (RMP missing information). The presentations of usage data, signals and risks should be improved in the next PSUR to ensure full compliance with GVP Module VII guideline. Further regulatory actions could be considered should the MAH fail to provide good quality PSURs in the future.

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

6.1.3. **Capsaicin – QUTENZA** (CAP), NAP

- Evaluation of a PSUSA[8] procedure

Regulatory details:
PRAC Rapporteur: Maria Alexandra Pêgo (PT)

Background

Capsaicin is a highly selective agonist for the transient receptor potential vanilloid 1 receptor (TRPV1) used as a topical analgesic under certain conditions.

Based on the assessment of the individual PSURs part of the PSUR single assessment procedure[9], the PRAC reviewed the benefit-risk balance of capsaicin-containing products and issued a recommendation on their marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of capsaicin-containing products in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation(s) should be maintained.
- Nevertheless, the MAH for Qutenza should submit to EMA within 90 days an updated RMP addressing the concerns stated in the previous PRAC advice on RMP (PRAC Minutes May 2013) for the previous PSUR procedure (see also under 5.2.3.).

[8] PSUR single assessment, referring to CAP, NAP
[9] Abbreviated PSUSA, assessing PSURs for CAPs and NAPs

- In the next PSUR, the MAHs for all capsaicin-containing products should closely monitor several adverse drug reactions, including reactions related to the application site, drug ineffectiveness, procedural aspects of the administration such as accidental exposure to product, drug administered at inappropriate site and occupational exposure. MAHs should also present an analysis of the potential risk of exacerbation of neuro-degeneration in patients with diabetes.

The assessment of safety data for capsaicin-containing products formulated as low-strength creams should be assessed separately from the other pharmaceutical forms, to allow a risk proportionate evaluation. This will be reflected in the updated EURD list. The next PSURs should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC.

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

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Ulla Wändel Liminga (SE)

Background

Denosumab is a human monoclonal antibody (IgG2) indicated for the treatment of osteoporosis in postmenopausal women at increased risk of fractures and for the treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures under certain conditions (Prolia). Denosumab is also indicated for the prevention of skeletal related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with bone metastases from solid tumours (Xgeva).

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Prolia and Xgeva, centrally authorised medicines containing denosumab, and issued a recommendation on their marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Prolia and Xgeva (denosumab) in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation(s) should be maintained.
- Nevertheless, the MAH should submit to EMA within 60 days a variation for Prolia and Xgeva respectively addressing the need for updating the product information to reflect musculoskeletal pain, clinical manifestations of hypocalcaemia such as cardiac arrhythmia, in particular QT interval prolongation, as well as blood parathyroid hormone (PTH) increase in the product information. The need for additional risk minimisation activities should be addressed, and a revised RMP should be submitted as part of these variations in line with the specific safety aspects covered by the applications.
- For Prolia, the MAH should submit to EMA within 60 days a variation addressing the need for updating the product information following further in depth evaluation of the risk of osteonecrosis of the jaw (ONJ). The need for additional risk minimisation activities as well as updates of the RMP should also be addressed.
- For Xgeva, the MAH should submit to EMA within 60 days a variation addressing the need for updating the product information following further in depth evaluation of the risk of ONJ. The

need for additional risk minimisation activities as well as updates of the RMP should also be addressed.

- In the next PSUR, the MAH should provide further data, in particular the number of reported cases of fracture healing complications and a discussion on the risk of new primary malignancy with longer duration of exposure to denosumab.

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

6.1.5. Fentanyl – **EFFENTORA** (CAP), **INSTANYL** (CAP), **PECFENT** (CAP), NAP

- Evaluation of a PSUSA procedure

Regulatory details:
PRAC Rapporteur: Evelyne Falip (FR)

Background

Fentanyl is a μ-opioid receptor agonist indicated for the treatment of analgesia under certain conditions.

Based on the assessment of the PSURs part of the PSUR single assessment procedure[10], the PRAC reviewed the benefit-risk balance of transmucosal fentanyl-containing products and issued a recommendation on their marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of transmucosal fentanyl-containing products in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to add a contraindication in patients without maintenance opioid therapy and treatment of acute pain other than breakthrough pain, inserting a warning for use of fentanyl in patients with current and pre-existing bradyarrhythmia, including the risk of serotonin syndrome, adding adverse reactions (fall, flushing and hot flush, diarrhoea, fatigue, respiratory depression, malaise, peripheral oedema, convulsion, hallucination), and adding preclinical safety data related to carcinogenicity studies and brain lesions in animals. In addition, due to the transfer of fentanyl in breast milk, there should be 48 hours after the last administration of fentanyl before breastfeeding. Moreover, considering the potential interaction between opioids such as fentanyl and selective serotonin re-uptake inhibitors or serotonin-specific reuptake inhibitors (SSRIs)/serotonin–norepinephrine reuptake inhibitors (SNRIs) the risk of serotonin syndrome should be added to the product information. Therefore, the current terms of the marketing authorisation should be varied[11].
- In order to improve consistency of all product information for transmucosal fentanyl-containing products, minimal common elements to be introduced in product information have been determined based on already existing information and available data from the PSURs. This includes amendments of sections on contraindications, special warnings and precautions for use, interactions, pregnancy and lactation, undesirable effects and preclinical safety data.

[10] Abbreviated PSUSA, assessing PSURs for CAPs and NAPs
[11] Update of SmPC sections 4.3, 4.4, 4.5, 4.6, 4.8 and 5.3. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

Therefore, the current terms of these marketing authorisations should be varied as applicable[12].

- In the next PSUR, MAHs for transmucosal fentanyl formulations should provide inter alia cumulative reviews of cases of gastroeosophageal reflux disease, hyperalgesia and ischaemic heart disease as well as on withdrawal syndrome and risk of suicidality. Based on these data, updates of their product information and/or RMP should be proposed as warranted. In addition, MAHs should closely monitor several undesirable effects, in particular, any cases relating to off-label use, medication errors, accidental exposure, abuse, misuse, dependence and overdose, and provide a discussion on possible (further) risk minimisation measures to put in place. Moreover, MAHs should provide an analysis of long-term use focussing on local tolerability and dependence.
- MAHs that have an RMP in place for their medicinal product should submit an updated RMP in the framework of an upcoming procedure and/or no later than 30 July 2014, to reflect several changes, in particular, serotonin syndrome should be added as an important potential risk. In addition MAHs should ensure the correct classification of drug abuse, drug misuse and drug dependence.

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

6.1.6. Linaclotide – **CONSTELLA** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

Background

Linaclotide is a guanylate cyclase-C receptor agonist (GCCA) indicated for the symptomatic treatment of moderate to severe irritable bowel syndrome with constipation (IBS-C) in adults.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Constella (linaclotide) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to add rash as an undesirable effect with a frequency unknown. Therefore the current terms of the marketing authorisation should be varied[13].
- In the next PSUR, the MAH should closely monitor hypersensitivity reactions.

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.

[12] Update of SmPC sections 4.3, 4.4, 4.5, 4.6, 4.8 and 5.3. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion
[13] Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

6.1.7. Pandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) – **ADJUPANRIX** (CAP), **PUMARIX** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Background

Pandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) is indicated for the prophylaxis of influenza caused by A (H1N1)v 2009 virus.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Adjupanrix and Pumarix, centrally authorised pandemic influenza vaccines, and issued a recommendation on their marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Adjupanrix and Pumarix (pandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted)) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to include the risk of fever in children aged less than 6 years as a warning and an undesirable effect. In addition, reactogenicity should be added to the product information as an undesirable effect observed in children aged less than 6 years to reflect the totality of data from additional clinical trials in the paediatric population. Therefore the current terms of the marketing authorisation should be varied[14].

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

6.1.8. Parathyroid hormone (rDNA) – **PREOTACT** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Line Michan (DK)

Background

Preotact is a recombinant human parathyroid hormone and is indicated for the treatment of osteoporosis in postmenopausal women at high risk of fractures.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Preotact (parathyroid hormone (rDNA)) in the approved indication(s) remains favourable.

[14] 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 current terms of the marketing authorisation(s) should be maintained.
- Nevertheless, the MAH should submit to EMA within 90 days a variation to provide a scientific evaluation of allergic reactions and propose an update of the product information.
- In the next PSUR, the MAH should provide an assessment of the effectiveness of risk minimisation activities to reduce the risk of overdose and/or medication errors. In addition, the MAH should characterize the following potential risks: psychiatric disorders, renal disorders, hypertension, off-label, paediatric off-label use, wrist fractures and bone abnormalities.

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

6.1.9. Pramipexole – **MIRAPEXIN** (CAP), **SIFROL** (CAP)

- Evaluation of a PSUSA procedure

Regulatory details:
PRAC Rapporteur: Doris Stenver (DK)

Background

Pramipexole is a dopamine agonist indicated for the treatment of signs and symptoms of idiopathic Parkinson's disease and for the symptomatic treatment of moderate to severe idiopathic restless legs syndrome under certain conditions.

Based on the assessment of the PSURs part of the PSUR single assessment procedure[15], the PRAC reviewed the benefit-risk balance of pramipexole-containing products and issued a recommendation on their marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of pramipexole-containing products in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to reflect mania and delirium as undesirable effects and to add a warning to inform healthcare professionals about the possibility of the occurrence of these events in association with pramipexole treatment, as well as the need for monitoring patients and for dose adjustment. Therefore the current terms of the marketing authorisation should be varied[16].
- In the next PSUR, MAHs should closely monitor several adverse drug reactions, in particular, cases of alcohol use/alcohol abuse/alcoholism/alcohol dependence, visual field defect, rhabdomyolysis, suicide-related behaviour as well as mania, delirium and psychoses in general. In addition, the MAH should comment on the rate and extent of blood lipid measuring in the fasting state in the clinical trials performed to date less in the approved indications.

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

[15] Abbreviated PSUSA, assessing PSURs for CAPs and NAPs
[16] Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

6.1.10. Prepandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) – **PREPANDRIX** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Background

Prepandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) is indicated for the active immunisation against H5N1 subtype of influenza A virus.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Prepandrix, a centrally authorised prepandemic influenza vaccine, and issued a recommendation on its marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Prepandrix (prepandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted)) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to include the risk of fever in children aged less than 6 years as a warning and an undesirable effect. In addition, reactogenicity should be added to the product information as an undesirable effect observed in children aged less than 6 years to reflect the totality of data from additional clinical trials in the paediatric population. Therefore the current terms of the marketing authorisation should be varied[17].

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

6.1.11. Varenicline – **CHAMPIX** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Doris Stenver (DK)

Background

Varenicline binds with affinity and selectivity at α4β2 neuronal nicotinic acetylcholine receptors with both partial agonist and antagonist activities and is indicated for smoking cessation in adults.

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

Summary of recommendation(s) and conclusions

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

[17] 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 current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAH should provide an analysis, including a possible underlying mechanism, of all available data relating to cases of hearing loss, vertigo, epistaxis and other hemorrhagic events. The MAH should also provide a cumulative analysis of all available data regarding memory impairment and interaction with alcohol and consider the need to update the product information as warranted. In addition, the MAH should closely monitor cases of hepatotoxicity, and differences in reporting of some adverse drug reactions such as incorrect dose administration between elderly and non-elderly patients. The MAH was also requested to closely monitor cases of off-label use, particularly in children and adolescents and to discuss any relevant findings.

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

6.2. Follow-up to PSUR procedures[18]

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

- Evaluation of a follow-up to a PSUR procedure

Regulatory details:
PRAC Rapporteur: Ulla Wändel Liminga (SE)

Background

Following the evaluation of the last submitted PSUR-related discussion for the above mentioned medicines, the PRAC requested the MAH to submit further data (see PRAC Minutes June 2013). The responses were assessed by the Rapporteur for further PRAC advice.

Summary of recommendation(s)/conclusions

- The MAH should submit to EMA within 60 days a variation for Prolia and Xgeva respectively to update the product information to include a warning regarding the risk of QT prolongation in context of denosumab-induced hypocalcaemia. In addition, the MAH should update the product information to reflect the risk of secondary hyperparathyroidism in renal impaired patients together with warnings for hypocalcemia.

See also denosumab (Prolia, Xgeva) PSUR procedure under 6.1.4.

7. Post-authorisation Safety Studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)[19]

7.1.1. **Rivaroxaban – XARELTO** (CAP)

- Evaluation of an imposed PASS protocol

Regulatory details:
PRAC Rapporteur: Qun-Ying Yue (SE)

[18] Follow up as per the conclusions of the previous PSUR procedure, assessed outside next PSUR procedure
[19] In accordance with Article 107n of Directive 2001/83/EC

Background

For background, see PRAC minutes 2-5 September 2013. A revised protocol was submitted by the MAH in accordance to the outcome of the latest PRAC discussion which was assessed by the Rapporteur. The PRAC discussed the conclusion of the Rapporteur of the assessment of the protocol and the outcome of a discussion with the MAH with the Rapporteur and EMA representatives.

Endorsement/Refusal of the protocol

The PRAC, having considered the draft protocol version 1.1 in accordance with Article 107n of Directive 2001/83/EC, objected to the draft protocol for the above listed medicinal product, as the Committee considered that the conduct of the study promoted the use of a medicinal product outside the normal prescribing practice and that the design of the study did not fulfil the study objectives. Alternative study designs were considered possible that would reduce the promotional nature of the study and reduce residual sources of bias.

Post-meeting note: a teleconference with the MAH, Rapporteur and EMA representatives was held on 18 December 2013 to facilitate the submission of a revised study protocol addressing the issues identified.

7.1.2. **Trimetazidine** (NAP)

- Evaluation of an imposed PASS protocol

Regulatory details:
PRAC Rapporteur: Dolores Montero Corominas (ES)

Background

For background, see PRAC Minutes December 2012. Following a request from the Member States, the PRAC advised that MSs should encourage MAHs to submit to the PRAC joint study protocols (for a Drug Utilisation Study (DUS) to verify the compliance of prescribers regarding the restricted indication and for a PASS - a nested-case control study within the European Society of Cardiology cohort to investigate the potential association between extrapyramidal symptoms and trimetazidine). More recently IT circulated a Non-Urgent Information (NUI) on the current status of the submission of the protocols in the different MSs and implementation of the PRAC advice. Protocols for the drug utilisation study were now been submitted to the EMA.

Endorsement/Refusal of the protocol

The PRAC appointed Dolores Montero Corominas (ES) as Rapporteur for the assessment of the drug utilisation study protocols submitted and a timetable with PRAC decision at the March 2014 meeting was agreed. The PRAC also advised to provide concerned MAHs with a deadline for submission of the PASS.

7.2. Protocols of PASS non-imposed in the marketing authorisation(s)[20]

See Annex 16.2

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

7.3. Results of PASS imposed in the marketing authorisation(s)[21]

None

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

See Annex 16.4

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

See Annex 16.5

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

8.1.1. Japanese encephalitis vaccine (inactivated, adsorbed) – IXIARO (CAP)

- PRAC consultation on a renewal of the marketing authorisation

Regulatory details:

PRAC Rapporteur: Brigitte Keller-Stanislawski (DE)

Background

Ixiaro (Japanese encephalitis vaccine (inactivated, adsorbed)) is indicated for active immunisation against Japanese encephalitis in adults, adolescents, children and infants aged 2 months and older. Ixiaro, a centrally authorised vaccine, 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 procedure with regard to safety and risk management aspects.

Summary of advice

Based on the review of the available pharmacovigilance data for Ixiaro, and the CHMP Rapporteur's assessment report, the PRAC considered that a second five-year renewal of the marketing authorisation is warranted owing to the limited safety information gathered in the paediatric population.

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

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 PRAC agreed the list of planned pharmacovigilance inspections 2013-1016, first revision, reviewed according to a risk based approach. This list is subsequently due for agreement at CHMP.

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 10-13 June 2013. Following advice of the PRAC further information on this variation was submitted by the MAH. The Rapporteur assessed the information received and PRAC will provide updated advice to CHMP on this variation.

Summary of advice

The PRAC concluded that based on the further information provided a specific test for preformed anti-a3Gal IgE antibodies would not be appropriate. However, the PRAC agreed that a positive test as well as a history of allergy to red meat or tick bites – due to cross reactivity - should be interpreted as a clinical predictor of a major increase in the risk of anaphylactic reactions to cetuximab. Therefore the product information should be updated to reflect this information.

Regarding the use of a test to differentiate suspected anaphylaxis from CRS, the PRAC considered that the potential clinical use was limited given the relatively poor sensitivity of the currently available test.

Regarding a recommendation to stop the infusion when an infusion-related reaction occurs during the first infusion it was considered reasonable to stop the infusion if a reaction occurs within 15 minutes after the infusion start. This advice was included into the product information. Nevertheless, the PRAC considered that further information on this matter could possibly be gained by further data review. The MAH should be requested to provide this information based on additional analyses from patients with preformed antibodies developing infusion reactions. The PRAC agreed on a proposal for updating the product information and further advice will be provided as appropriate.

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

None

10.3. Other requests

10.3.1. Epoetins:
Darbepoetin alfa – ARANESP (CAP);**Epoetin alfa – ABSEAMED** (CAP), **BINOCRIT** (CAP), **EPOETIN ALFA HEXAL** (CAP); **Epoetin beta – NEORECORMON** (CAP); **Epoetin theta – BIOPOIN** (CAP), **EPORATIO** (CAP); **Epoetin zeta – RETACRIT** (CAP), **SILAPO** (CAP)

- PRAC consultation on risk of tumour growth progression and thromboembolic events in cancer patients, upon CHMP's request

Regulatory details:
PRAC Rapporteur (overall): Isabelle Robine (FR)
PRAC Co-Rapporteur (overall): Martin Huber (DE)

Background

For background information, see PRAC minutes 8-11 April 2013. The MAHs responded to the questions of the PRAC concerning pharmacovigilance measures implemented in the RMP to address the potential risk of tumour progression as well as related aspects that were assessed by the Rapporteurs.

Summary of advice

Taking account the review on the available data and the existing recommendations and warnings in the product information, the PRAC agreed that the results of currently ongoing studies were necessary before concluding on the need and feasibility for pharmacovigilance activities for all currently marketed epoetins. In particular the PRAC considered that it was necessary to await the availability of results of the clinical studies EPO-ANE-3010[24] and Amgen 2007082 and of an ongoing non-clinical study on tissue samples conducted by one of the MAH in association with academia. The PRAC agreed further clarity was needed on the timelines for completion of the LungSys Programme[25] from the MAH Roche, performed in collaboration with the German Cancer Research Centre in Heidelberg. Finally, the PRAC considered it important, before recommending any changes to the current risk management plan and related risk minimisation measures, to also await the results of the EPOCAN consortium study[26] (planned for September 2014).

10.3.2. Human papillomavirus vaccine [types 16, 18] (recombinant, adjuvanted, adsorbed) – CERVARIX (CAP)
Human papillomavirus vaccine [types 6, 11, 16, 18] (recombinant, adsorbed) – GARDASIL (CAP), **SILGARD** (CAP)

- PRAC consultation on the need for further investigation and/or communication, further to media attention in France, on EMA's request

[24] A Study of Epoetin Alfa Plus Standard Supportive Care Versus Standard Supportive Care Only in Anemic Patients With Metastatic Breast Cancer Receiving Standard Chemotherapy - to assess the impact on tumor progression as evaluated by progression-free survival (PFS) of epoetin alfa plus standard supportive care as compared with standard supportive care alone (packed red blood cell (RBC) transfusions), for treating anemia according to label guidance in patients with metastatic breast cancer receiving standard chemotherapy
[25] LungSys Roche pre-clinical study ongoing to re-evaluate the presence of EPO-R protein in extended sets of clinical tissue samples using a novel immunohistochemical assay
[26] EpoCan consortium coordinated by Tel Aviv University had been chosen to conduct a study on epoetins and the risk of thromboembolic events and tumour growth progression in cancer patients, and cardiovascular and cancer risk in chronic kidney disease

Regulatory details:
PRAC Rapporteurs: Jean-Michel Dogné (BE), Qun-Ying Yue (SE)

Background

EMA secretariat brought to the attention of the Committee to increased media attention in France in relation to an individual case – already reported in 2011 – of multiple sclerosis diagnosed some time after vaccination with human papillomavirus vaccine. The EMA conducted a review of the data available in the EudraVigilance database on reports of suspected multiple sclerosis following vaccination with human papillomavirus (HPV) vaccines Gardasil and Cervarix, and requested the PRAC to discuss whether the information available warranted further evaluation.

Summary of advice

The PRAC noted the report of the case that had led to media attention in France as well as the review of EudraVigilance data. PRAC confirmed that the case had been included in cumulative analyses in previous PSURs and noted that given the demographics of onset of multiple sclerosis and of the population receiving the vaccines, it was inevitable that a diagnoses of multiple sclerosis would be made, by chance, in temporal relation to vaccination. PRAC concluded that the available evidence does not suggest that either of the HPV vaccines Gardasil or Cervarix are causally associated with multiple sclerosis.

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

None

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 Inspections

12.2.1.1. Union Procedure on Follow-up to Pharmacovigilance Inspections

- Union procedure on the management of pharmacovigilance inspection findings with potential significant impact on the benefit-risk profile of the concerned medicinal products

EMA secretariat outlined a draft paper which is planned to be an appendix to the (GVP) Module III – Pharmacovigilance inspections - proposing procedures to be followed in case of pharmacovigilance inspections revealing significant findings having the potential to impact on the assessment of the current benefit-risk profile of a medicine or creating important gaps in its knowledge. The PRAC made some preliminary comments on the scope and objective of the paper aiming at clarifying processes and principles to involve PRAC in these matters based on previous experiences. A revised version will be discussed at the January 2014 meeting.

12.2.2. Pharmacovigilance Audits

12.2.2.1. One-year report to the European Commission on EMA Human Medicines Pharmacovigilance tasks

Article 29 of Regulation (EU) No 1235/2010 of December 2010 amending Regulation No 726/2004 states that *"The Commission shall make public a report on the performance of pharmacovigilance tasks by the Agency on 2 January, 2014 at the latest and subsequently every 3 years thereafter"*. In order to comply with this requirement, EMA prepared a report on the Agency's pharmacovigilance tasks to support the Commission's information gathering for the report. The EMA secretariat presented a draft report to be transmitted to the EC to present the first year's experience with the EMA's pharmacovigilance tasks - including the PRAC work - subsequent to the entry into force of the 2010 pharmacovigilance legislation. The report aims to summarize the initial measurement of structural and process performance indicators; PRAC Members were invited to comment before the end of 2013.

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

12.3.1. PSURs Repository

12.3.1.1. Repository specifications and confirmation of full functionality

Following initial discussion at the November 2013 PRAC meeting, the EMA secretariat presented the draft PSUR repository functionalities to be audited. Further to the already planned functionalities, it was agreed that the repository should allow for the storage and retrieval of PSUR-related documents to assist assessment and should include a notification system to Member States of any new submissions.

Post-meeting note: the EMA Management Board agreed on the functionalities on 12/12/2013.

12.3.2. Union Reference Date List

12.3.2.1. Consultation on the draft List, version December 2013

The PRAC endorsed the updated EURD list, version December 2013.

Post-meeting note: following the PRAC meeting in December 2013, the updated EURD list was adopted by the CHMP at its December 2013 meeting and was published on the EMA website on 8 January 2014 (see: Home>Regulatory>Human medicines>Pharmacovigilance>EU reference date and PSUR submission).

12.4. Signal Management

12.4.1. Signal Management Review Technical (SMART) Working Group

- Feedback from the SMART Working Group

EMA secretariat informed the PRAC that minutes of the SMART group will now be produced and circulated widely to all PRAC members. The PRAC noted current discussions regarding suggested timelines for submission of variations arising following signal evaluation by the PRAC. The initial date (day 0) will be set as the day of publication of 'PRAC signal recommendations on the EMA website' which happens before the publication of the adopted PRAC minutes (see PRAC recommendations on safety signals on the EMA website. A deadline in days/months for submission will be provided to MAH(s) through the signal publication on the website, calculated from the day of publication on the EMA website.

12.5. Adverse Drug Reactions reporting and Additional Reporting

12.5.1. Management and Reporting of Adverse Reactions to Medicinal Products

12.5.1.1. Guideline on good pharmacovigilance practices (GVP) Module VI – Management and reporting of adverse reactions to medicinal products: Reports from patient support programmes and market research programmes

The Company Roche at their request provided feedback to the PRAC on Roche's experience with data submitted to the MAH as part of Patient Support Programmes (PSPs), where the documentation, including information on medical events, has been submitted in support of a claim for administrative services provided by Roche (for instance to give assistance to patients or their carers with product reimbursement or insurance coverage). The EMA will consider the feedback received from Roche together with feedback from other stakeholders with all other relevant information and perspectives on this issue and in consideration of current legislative requirements and guidelines.

12.5.2. Additional Monitoring

12.5.2.1. List of Products under Additional Monitoring

- Consultation on the draft List, version December 2013

The PRAC was informed of the products newly added to the additional monitoring list. The updated list is due for publication in December 2013.

Post-meeting note: The updated additional monitoring list was published on the EMA website on 19 December 2013 (see: Home>Regulatory>Human medicines>Pharmacovigilance>Signal management>List of medicines under additional monitoring).

12.6. EudraVigilance Database

12.6.1. Activities related to the confirmation of full functionality

- EudraVigilance (EV) functionalities to be audited

Following discussion at the November 2013 meeting EMA secretariat presented the final list of functionalities to be audited following the consultation process of the governance structure for the implementation of the pharmacovigilance legislation and of the European Commission. The EMA Management Board will confirm and announce when full functionality of the EudraVigilance database has been achieved and the system meets the defined functional specifications in accordance with PRAC recommendation. Therefore PRAC will be regularly updated on the project milestones and progress against the plan and its recommendation will be sought for the audit on whether the functionalities have been delivered.

Post-meeting note: the EMA Management Board agreed on the functionalities on 12/12/2013.

12.7. Risk Management Plans and Effectiveness of risk Minimisations

None

12.8. Post-authorisation Safety Studies

None

12.9. Community Procedures

None

12.10. Risk communication and Transparency

None

12.11. Continuous pharmacovigilance

None

12.12. Interaction with EMA Committees and Working Parties

12.12.1. Blood Products Working Party (BPWP)

12.12.1.1. Intravenous immunoglobulins and haemolysis – draft strategy

The topic was deferred to the January 2014 PRAC meeting.

12.13. Interaction within the EU regulatory network

None

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

12.14.1. Guidelines of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)

None

12.14.2. Data Collection on Adverse events of Anti-HIV Drugs (D:A:D) study

- Follow up on MAH's responses to the PRAC letter adopted in March 2013

The EMA secretariat provided an update on the interaction with HAART oversight committee (OC) and presented a summary of the MAH's responses to EMA letter that were sent to investigate their intention in continuing HAART OC membership (including funding until 2017 of the study). It was agreed that PRAC will continue to assess the role of the D:A:D study within the future RMP submissions of each individual antiretroviral product. The relevant MAHs will be informed of this decision. EMA informed the PRAC that a community letter was received from EATG European AIDS Treatment Group and from AIDS Treatment Activists Coalition (ATAC). A reply to this letter will be discussed at the January 2014 meeting.

13. Any other business

None

ANNEX I – List of other advice and recommendations adopted at the meeting

14. ANNEX I Risk Management Plans

14.1. Medicines in the pre-authorisation phase

As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of the RMP for the below mentioned medicines under evaluation for initial marketing authorisation application. Information on the medicines containing the below listed active substance will be made available following the CHMP opinion on their marketing authorisation.

14.1.1. Cabozantinib

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

14.1.2. Canagliflozin, metformin

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

14.1.3. Elosulfase alfa

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

14.1.4. Lurasidone

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

14.1.5. Masitinib

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

14.1.6. Oseltamivir

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

14.1.7. Propranolol

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

14.1.8. Serelaxin

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

14.1.9. Travoprost

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

14.1.10. Vedolizumab

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

14.2. Medicines already authorised

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

RMP in the context of a PSUR procedure

See also related PSUR under 6 or 15 as applicable.

14.2.1. Azacitidine – VIDAZA (CAP)

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

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

14.2.2. Boceprevir – VICTRELIS (CAP)

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

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

14.2.3. Cetrorelix – CETROTIDE (CAP)

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

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

14.2.4. Linaclotide – CONSTELLA (CAP)

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

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

14.2.5. Pandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) – ADJUPANRIX (CAP), **PUMARIX** (CAP)

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

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

14.2.6. Pixantrone dimaleate – PIXUVRI (CAP)

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

Regulatory details:
PRAC Rapporteur: Julia Dunne (UK)

14.2.7. Prepandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) – PREPANDRIX (CAP)

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

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

14.2.8. Tafamidis – VYNDAQEL (CAP)

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

Regulatory details:
PRAC Rapporteur: Evelyne Falip (FR)

14.2.9. Tolvaptan – SAMSCA (CAP)

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

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

14.2.10. Varenicline – CHAMPIX (CAP)

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

Regulatory details:
PRAC Rapporteur: Doris Stenver (DK)

RMP in the context of a variation

14.2.11. Bazedoxifene – CONBRIZA (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

14.2.12. Bevacizumab – AVASTIN (CAP)

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

Regulatory details:
PRAC Rapporteur: Doris Stenver (DK)

14.2.13. Catridecacog – NOVOTHIRTEEN (CAP)

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

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

14.2.14. Human normal immunoglobulin – HIZENTRA (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Brigitte Keller-Stanislawski (DE)

14.2.15. Nitisinone – ORFADIN (CAP)

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

Regulatory details:
PRAC Rapporteur: Carmela Macchiarulo (IT)

14.2.16. Posaconazole – NOXAFIL (CAP)

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

Regulatory details:
PRAC Rapporteur: Julia Dunne (UK)

14.2.17. Raltegravir – ISENTRESS (CAP)

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

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

14.2.18. Regorafenib – STIVARGA (CAP)

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

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

14.2.19. Saquinavir – INVIRASE (CAP)

- Evaluation of an RMP in the context of a variation

Status: *for discussion and agreement of PRAC Assessment Report to CHMP*

Regulatory details:
PRAC Rapporteur: Harald Herkner (AT)

14.2.20. Tocilizumab – ROACTEMRA (CAP)

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

Regulatory details:
PRAC Rapporteur: Brigitte Keller-Stanislawski (DE)

14.2.21. Trabectedin – YONDELIS (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Line Michan (DK)

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

Not applicable

RMP in the context of a stand-alone RMP procedure

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

- Evaluation of a stand-alone RMP procedure

Regulatory details:
PRAC Rapporteur: Jean-Michel Dogné (BE)

14.2.23. Pramipexole – **MIRAPEXIN** (CAP), **SIFROL** (CAP)

- Evaluation of a stand-alone RMP procedure

Regulatory details:
PRAC Rapporteur: Doris Stenver (DK)

15. ANNEX I Periodic Safety Update Reports (PSURs)

Based on the assessment of the following PSURs, the PRAC concluded that the benefit-risk balance of the below mentioned medicines, remained favourable in the approved indication(s) and adopted a recommendation to maintain the current terms of the marketing authorisation(s) together with the assessment report. As per agreed criteria, the procedures listed below were finalised at the PRAC level without further plenary discussion.

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

15.1. Evaluation of PSUR procedures[27]

15.1.1. Anakinra – **KINERET** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Doris Stenver (DK)

15.1.2. Apixaban – **ELIQUIS** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

15.1.3. Azacitidine – **VIDAZA** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

15.1.4. Brinzolamide, timolol – **AZARGA** (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

Regulatory details:
PRAC Rapporteur: Line Michan (DK)

15.1.5. Cetrorelix – CETROTIDE (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

15.1.6. Conestat alfa – RUCONEST (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Julia Dunne (UK)

15.1.7. Eribulin – HALAVEN (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Ulla Wändel Liminga (SE)

15.1.8. Hydrocortisone – PLENADREN (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Qun-Ying Yue (SE)

15.1.9. Influenza vaccine (split virion, inactivated) – IDFLU (CAP), **INTANZA** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Miguel-Angel Macia (ES)

15.1.10. Laronidase – ALDURAZYME (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Julia Dunne (UK)

15.1.11. Linagliptin – TRAJENTA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Menno van der Elst (NL)

15.1.12. Methylthioninium – METHYLTHIONINIUM CHLORIDE PROVEBLUE (CAP)

- Evaluation of a PSUSA procedure

Regulatory details:
PRAC Rapporteur: Qun-Ying Yue (SE)

15.1.13. Piperaquine tetraphosphate, dihydroartemisinin – **EURARTESIM** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

15.1.14. Pixantrone dimaleate – **PIXUVRI** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Julia Dunne (UK)

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

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

15.1.16. Saxagliptin, metformin – **KOMBOGLYZE** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Menno van der Elst (NL)

15.1.17. Sevelamer – **RENAGEL** (CAP), **RENVELA** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Jean-Michel Dogné (BE)

15.1.18. Shingles (herpes zoster) vaccine (live) – **ZOSTAVAX** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Brigitte Keller-Stanislawski (DE)

15.1.19. Stiripentol – **DIACOMIT** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

15.1.20. Tafamidis – **VYNDAQEL** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Evelyne Falip (FR)

15.1.21. Tolvaptan – SAMSCA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

15.1.22. Ulipristal – ELLAONE (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Menno van der Elst (NL)

15.2. Follow-up to PSUR procedures[28]

15.2.1. Capecitabine – XELODA (CAP)

- Evaluation of a follow-up to a PSUR procedure

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

15.2.2. Clofarabine – EVOLTRA (CAP)

- Evaluation of a follow-up to a PSUR procedure

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

16. ANNEX I Post-authorisation Safety Studies (PASS)

Since all comments received on the assessment of these measures were addressed before the plenary meeting, the PRAC endorsed the conclusion of the Rapporteurs on the assessment of the relevant protocols or study reports for the medicines listed below.

16.1. Protocols of PASS imposed in the marketing authorisation(s)[29]

16.1.1. Pomalidomide – IMNOVID (CAP)

- Evaluation of an imposed PASS protocol

Regulatory details:
PRAC Rapporteur: Julia Dunne (UK)

16.2. Protocols of PASS non-imposed in the marketing authorisation(s)[30]

16.2.1. Aflibercept – ZALTRAP (CAP)

- Evaluation of a PASS protocol

[28] Follow up as per the conclusions of the previous PSUR procedure, assessed outside next PSUR procedure
[29] In accordance with Article 107n of Directive 2001/83/EC
[30] In accordance with Article 107m of Directive 2001/83/EC, supervised by PRAC in accordance with Article 61a (6) of Regulation (EC) No 726/2004

Regulatory details:
PRAC Rapporteur: Ulla Wändel Liminga (SE)

16.2.2. Aripiprazole – ABILIFY (CAP)

- Evaluation of a PASS protocol

Regulatory details:
PRAC Rapporteur: Margarida Guimarães (PT)

16.2.3. Ceftaroline fosamil – ZINFORO (CAP)

- Evaluation of a PASS protocol

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

16.2.4. Dextromethorphan, quinidine – NUEDEXTA (CAP)

- Evaluation of a PASS protocol

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

16.2.5. Florbetapir (^{18}F) – AMYVID (CAP)

- Evaluation of a PASS protocol

Regulatory details:
PRAC Rapporteur: Valerie Strassmann (DE)

16.2.6. Human coagulation factor VIII, human von Willebrand factor – VONCENTO (CAP)

- Evaluation of a PASS protocol

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

16.2.7. Pertuzumab – PERJETA (CAP)

- Evaluation of a PASS protocol

Regulatory details:
PRAC Rapporteur: Doris Stenver (DK)

16.2.8. Ulipristal – ESMYA (CAP)

- Evaluation of a PASS protocol

Regulatory details:
PRAC Rapporteur: Ulla Wändel Liminga (SE)

16.3. Results of PASS imposed in the marketing authorisation(s)[31]

None

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

16.4. Results of PASS non-imposed in the marketing authorisation(s)[32]

16.4.1. Retigabine – **TROBALT** (CAP)

- Evaluation of PASS results

Regulatory details:
PRAC Rapporteur: Line Michan (DK)

16.5. Interim results of imposed and non-imposed PASS and results of non-imposed PASS submitted before the entry into force of the revised variations regulation[33]

16.5.1. Etanercept – **ENBREL** (CAP)

- Evaluation of interim PASS results

Regulatory details:
PRAC Rapporteur: Julia Dunne (UK)

16.5.2. Fentanyl – **EFFENTORA** (CAP)

- Evaluation of interim PASS results

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

16.5.3. Rotigotine – **LEGANTO** (CAP), **NEUPRO** (CAP)

- Evaluation of interim PASS results

Regulatory details:
PRAC Rapporteur: Maria Alexandra Pêgo (PT)

16.5.4. Rotigotine – **LEGANTO** (CAP), **NEUPRO** (CAP)

- Evaluation of interim PASS results

Regulatory details:
PRAC Rapporteur: Maria Alexandra Pêgo (PT)

16.5.5. Somatropin – **OMNITROPE** (CAP)

- Evaluation of interim PASS results

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

16.5.6. Tigecycline – **TYGACIL** (CAP)

- Evaluation of interim PASS results

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

Regulatory details:

PRAC Rapporteur: Miguel-Angel Macia (ES)

16.5.7. Ulipristal – ESMYA (CAP)

- Evaluation of interim PASS results

Regulatory details:

PRAC Rapporteur: Ulla Wändel Liminga (SE)

17. ANNEX I Renewals of the Marketing Authorisation, Conditional Renewals and Annual Reassessments

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

17.1.1. Agalsidase alfa – REPLAGAL (CAP)

- PRAC consultation on an annual reassessment of the marketing authorisation

Regulatory details:

PRAC Rapporteur: Sabine Straus (NL)

17.1.2. Alipogene tiparvovec – GLYBERA (CAP)

- PRAC consultation on an annual reassessment of the marketing authorisation

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)

17.1.3. Bazedoxifene – CONBRIZA (CAP)

- PRAC consultation on a renewal of the marketing authorisation

Regulatory details:

PRAC Rapporteur: Martin Huber (DE)

17.1.4. Caffeine – PEYONA (CAP)

- PRAC consultation on a renewal of the marketing authorisation

Regulatory details:

PRAC Rapporteur: Harald Herkner (AT)

17.1.5. Efavirenz – STOCRIN (CAP), SUSTIVA (CAP)

- PRAC consultation on a renewal of the marketing authorisation

Regulatory details:

PRAC Rapporteur: Margarida Guimarães (PT)

17.1.6. Follitropin beta – FERTAVID (CAP)

- PRAC consultation on a renewal of the marketing authorisation

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)

17.1.7. Gefitinib – IRESSA (CAP)

- PRAC consultation on a renewal of the marketing authorisation

Regulatory details:

PRAC Rapporteur: Ulla Wändel Liminga (SE)

17.1.8. Liraglutide – VICTOZA (CAP)

- PRAC consultation on a renewal of the marketing authorisation

Regulatory details:

PRAC Rapporteur: Menno van der Elst (NL)

17.1.9. Panitumumab – VECTIBIX (CAP)

- PRAC consultation on a conditional renewal of the marketing authorisation

Regulatory details:

PRAC Rapporteur: Julia Dunne (UK)

17.1.10. Pantoprazole – CONTROLOC CONTROL (CAP), PANTECTA CONTROL (CAP), PANTOLOC CONTROL (CAP), PANTOZOL CONTROL (CAP), SOMAC CONTROL (CAP)

- PRAC consultation on a renewal of the marketing authorisation

Regulatory details:

PRAC Rapporteur: Julia Dunne (UK)

17.1.11. Pneumococcal polysaccharide conjugate vaccine (adsorbed) – SYNFLORIX (CAP)

- PRAC consultation on a renewal of the marketing authorisation

Regulatory details:

PRAC Rapporteur: Qun-Ying Yue (SE)

17.1.12. Sevelamer – RENVELA (CAP)

- PRAC consultation on a renewal of the marketing authorisation

Regulatory details:

PRAC Rapporteur: Jean-Michel Dogné (BE)

17.1.13. Tacrolimus – MODIGRAF (CAP)

- PRAC consultation on a renewal of the marketing authorisation

Regulatory details:

PRAC Rapporteur: Ulla Wändel Liminga (SE)

17.1.14. **Tocofersolan – VEDROP** (CAP)

- PRAC consultation on an annual reassessment of the marketing authorisation

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)

ANNEX II – List of participants:

Including any restrictions with respect to involvement of members / alternates / experts following evaluation of declared interests for the 2-5 December 2013 meeting.

PRAC member *PRAC alternate*	*Country*	Outcome restriction following evaluation of e-DoI for the meeting	Product / Topics on the current Committee Agenda for which restriction applies substance
Jean-Michel Dogné	Belgium	Cannot act as Rapporteur or Peer-reviewer for:	Octocog alfa, regorafenib, rivaroxaban
Veerle Verlinden	Belgium	Full involvement	
Maria Popova-Kiradjieva	Bulgaria	Full involvement	
Marin Banovac	Croatia	Full involvement	
Viola Macolic Sarinic	Croatia	Full involvement	
Andri Andreou	Cyprus	Full involvement	
Jana Mlada	Czech Republic	Full involvement	
Line Michan	Denmark	Full involvement	
Doris Stenver	Denmark	Full involvement	
Maia Uusküla	Estonia	Full involvement	
Kirsti Villikka	Finland	Full involvement	
Evelyne Falip	France	Full involvement	
Isabelle Robine	France	Full involvement	
Martin Huber	Germany	Full involvement	
Valerie Strassmann	Germany	Full involvement	
Leonidas Klironomos	Greece	Cannot act as Rapporteur or Peer-reviewer for:	clindamycin, tafamidis, varenicline, bazedoxifene, apixaban, etanercept, tigecycline, bazedoxifene
Julia Pallos	Hungary	Full involvement	
Guðrún Kristín Steingrímsdóttir	Iceland	Full involvement	
Almath Spooner	Ireland	Full involvement	
Ruchika Sharma	Ireland	Full involvement	
Jelena Ivanovic	Italy	Full involvement	
Carmela Macchiarulo	Italy	Full involvement	
Andis Lacis	Latvia	Full involvement	
Jolanta Gulbinovic	Lithuania	Full involvement	
Jacqueline Genoux-Hames	Luxembourg	Full involvement	
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	
Adam Przybylkowski	Poland	Full involvement	
Margarida Guimaraes	Portugal	Full involvement	
Milena Radoha-Bergoč	Slovenia	Full involvement	
Miguel-Angel Maciá	Spain	Full involvement	
Dolores Montero	Spain	Full involvement	
Ulla Wändel Liminga	Sweden	Full involvement	

PRAC member *PRAC alternate*	*Country*	Outcome restriction following evaluation of e-DoI for the meeting	Product / Topics on the current Committee Agenda for which restriction applies substance
Qun-Ying Yue	Sweden	Full involvement	
June Munro Raine	United Kingdom	Full involvement	
Julie Williams	United Kingdom	Full involvement	
Julia Dunne	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	
Birgitte Keller-Stanislawski		Full involvement	
Stephen J. W. Evans		Cannot act as Rapporteur or Peer-reviewer for:	Lamotrigine, human papillomavirus vaccine, diphteria, tetanus, pertussis and hepatitis b vaccine, pandemic influenza vaccine, prepandemic influenza vaccine, retigabine, pneumococcal polysaccharide conjugate vaccine
Hervé Le Louet		Full involvement	
Lennart Waldenlind		Full involvement	

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*
Filip Babylon		Full involvement	
Marco Greco		Full involvement	
Albert van der Zeijden		Cannot act as Rapporteur or Peer Reviewer in relation to any medicinal product from the relevant companies for which his institution receives grants as listed in the published Declaration of Interest (2013-05-30) http://www.ema.europa.eu/docs/en_GB/document_l	

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***
		ibrary/contacts/avanderzeijden_DI.pdf	

Additional European experts participating at the meeting for specific Agenda items	**Country**	
Stefan Bonné	Belgium	No restrictions were identified for the participation of European experts attending the PRAC meeting for discussion on specific agenda items
Cécile Lescrainier	Belgium	
Sonja Beken	Belgium	
Jamila Hamdani	Belgium	
Gedske Thomsen	Denmark	
Nathalie Dumarcet	France	
Gaelle Guyader	France	
Violaine Vermillard	France	
Béatrice Saint-Salvi	France	
Sara Khosrovani	Netherlands	
Martin Olling	Netherlands	
Jan Willem van der Laan	Netherlands	
Hanneke van der Woude	Netherlands	
Maria Vanenburg	Netherlands	
Charlotte Backman	Sweden	
Rolf Gedeborg	Sweden	
Elina Rönnemaa	Sweden	
Shahin Kauser	United Kingdom	
Jonathan Rowell	United Kingdom	
Catherine Tregunno	United Kingdom	

Observer from the European Commission
Helen Lee – DG Health and Consumers
European Medicines Agency
Peter Arlett - Head of Sector for Pharmacovigilance and Risk Management
Maria Boulos – Scientific Administrator, Regulatory Affairs
Christelle Bouygues – Scientific Administrator, Regulatory Affairs
Roberto De Lisa – Scientific Administrator, PRAC Secretariat
Corinne De Vries – Head of Service, Risk Management Review
Georgy Genov – Section Head, Signal Detection and Data Analysis
Sheila Kennedy – Section Head, Scientific Committee Support
Kasia Kmiecik – Assistant, PRAC Secretariat
Geraldine Portier - Scientific Administrator, PRAC Secretariat
Tanya Sepehr – Assistant, PRAC Secretariat

Observer from the European Commission

Tania Teixeira – Head of Service, Referral Procedures

ANNEX III – List of abbreviations

For a List of the acronyms and abbreviations used in the PRAC (Pharmacovigilance Risk Assessment Committee) Minutes used in the PRAC minutes, see:

www.ema.europa.eu

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