7 February 2013
EMA/91065/2013
Pharmacovigilance Risk Assessment Committee (PRAC)

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Minutes of the meeting – 7-10 January 2013

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)

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.

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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 8 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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Chair: June Raine – Vice-Chair: Almath Spooner

1. Introduction

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

The Chairperson opened the meeting and welcomed all participants to the 7-10 January 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. 22 or more members were present in the room). All decisions, recommendations and advice were agreed unanimously, unless otherwise specified.

1.2. Adoption of the agenda of the PRAC meeting on 7-10 January 2013

The agenda was adopted with the addition of the following topics upon request from the members of the Committee and the EMA secretariat: tiotropium 4.3.3. ; filgrastim 5.2.28. .

1.3. Adoption of the minutes of the previous PRAC meeting on 26-29 November 2012

The minutes were adopted with some changes and will be published on the EMA website.

Post-meeting note: the minutes were published on 23 January 2013 on the EMA website (EMA/36832/2013).

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

2.1. Newly triggered procedures

2.1.1. **Nicotinic acid** / **laropiprant** – **TREDAPTIVE** (CAP), **TREVACLYN** (CAP), **PELZONT** (CAP)

- Review of the benefit-risk balance - procedure under Article 20 of Regulation (EC) No 726/2004 following procedural steps of Article 107j and 107k of Directive 2001/83/EC

Regulatory details:

PRAC Rapporteur: Martin Huber (DE)
PRAC Co-Rapporteur: Menno van der Elst (NL)

Background

On 20 December 2012, the European Commission initiated a procedure under Article 20 of Regulation (EC) No 726/2004 - following the procedural steps laid out in Article 107j and 107k of Directive 2001/83/EC,see notification published on the EMA website - for the review of Tredaptive, Trevaclyn and Pelzont, identical medicines containing the active substances nicotinic acid and laropiprant.

The procedure was initiated following the preliminary results from the study HPS2-THRIVE, which did not meet its primary endpoint of reduction of major vascular events and showed a statistically significant increase in the incidence of non-fatal serious adverse events in the nicotinic acid/laropiprant group compared to the statin group.

Discussion

The PRAC noted the notification letter from the European Commission and discussed the assessment of the responses to the list of questions addressed by the MAH (published on the EMA website EMA/PRAC/821161/2012) in accordance with the published timetable for the procedure (EMA/PRAC/821171/2012).

The PRAC considered that once the current procedure is finalised, consideration should be given on whether the safety concern observed for the combination products would be relevant to medicinal products containing nicotinic acid or analogues thereof as a mono-component with the same clinical indications. Follow-up discussion will take place at the 4-7 February 2013 PRAC meeting

Summary of recommendation(s) / conclusions

- The PRAC concluded that the benefit-risk balance for Tredaptive, Trevaclyn and Pelzont is not favourable in the approved indication and adopted a set of recommendations to the CHMP for the suspension of the marketing authorisations (EMA/5817/2013). In addition, the PRAC considered that provisional measures were needed and recommended that the marketing authorisation, the marketing and the supply of Tredaptive, Trevaclyn and Pelzont be suspended forthwith, awaiting the adoption of the final measures.

Post meeting note: the CHMP confirmed the recommendation to suspend the marketing authorisations on 18 January 2012.

2.1.2. Tetrazepam (NAPs)

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

Regulatory details:

PRAC Rapporteur: Jean-Michel Dogné (BE)
PRAC Co-Rapporteur: Evelyne Falip (FR)

Background

The French Medicines Agency (ANSM) sent a letter of notification on 20 December 2012 along with a rationale for triggering a referral under Article 107i of Directive 2001/83/EC for a review of tetrazepam-containing medicines, used orally to treat painful muscle spasms mainly in patients with

rheumatological conditions due to serious cutaneous risks including Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiform, DRESS[1] syndrome.

Discussion

The PRAC noted the rationale provided by the ANSM 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 the safety concern was common to all products belonging to the same therapeutic class.
The PRAC appointed Jean-Michel Dogné (BE) as Rapporteur and Evelyne Falip (FR) as Co-Rapporteur for the procedure.

Summary of recommendation(s)/conclusions

- A list of questions should be addressed by the MAHs (published on the EMA website EMA/PRAC/15160/2013) and data will be gathered from the stakeholders (healthcare professionals, patients' organisations and the general public) by means of responses to a list of questions (EMA/PRAC/5086/2013). The procedure will follow the adopted timetable (EMA/PRAC/15074/2013).
- The PRAC noted the concerns that the risk of serious cutaneous reactions with tetrazepam may be greater than that for other products belonging to the same therapeutic class.

2.2. Ongoing Procedures

None

2.3. Procedures for finalisation

See procedure listed at point 2.1.1. (nicotinic acid / laropiprant), initiated on 20 December 2012 and finalised, at PRAC level, during the current meeting.

2.4. Planned public hearings

None

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

None

4. Signals assessment and prioritisation

4.1. New signals detected from EU spontaneous reporting systems

4.1.1. **Exenatide – BYETTA** (CAP), **BYDUREON** (CAP); **Liraglutide – VICTOZA** (CAP)

- Signal of gastrointestinal stenosis and obstruction

[1] Drug Reaction with Eosinophilia and other Systemic Symptoms

Regulatory details:

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

Background

Exenatide and liraglutide are substances belonging to the class of glucagon-like peptide-1 (GLP-1) receptor agonists, used in the treatment of type II diabetes.

The exposure for centrally authorised medicines containing exenatide and liraglutide is estimated to have been more than 2 million and 1.2 million patient-years respectively worldwide, in the period from their first authorisation (2006 and 2009) until 2012.

Following a safety communication from the Japanese medicines agency (Pharmaceuticals and Medical Devices Safety Information No. 291 June 2012) reporting intestinal obstruction in patients treated with exenatide and liraglutide, the EMA performed a search in EudraVigilance for intestinal obstruction and related terms which retrieved 35 cases for exenatide and 24 for liraglutide. The Rapporteurs confirmed the signal needed further analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information on the cases retrieved and noted that the risk of gastrointestinal adverse drug reactions is well known with glucagon-like peptide-1 (GLP-1) receptor agonists and, as such, is already reported in the product information of the medicines of the class. Therefore, the PRAC noted that the signal of gastrointestinal stenosis and obstruction may be considered as new information on a known effect.

Summary of recommendation(s)

- The MAH for the centrally authorised products containing exenatide and liraglutide should be requested to submit to the EMA within 60 days a variation proposing appropriate amendments to the RMP and product information.

4.1.2. Tiotropium (NAP)

- Signal of anaphylactic reaction

Regulatory details:

PRAC Rapporteur: Sabine Straus (NL)

Background

Tiotropium is a widely prescribed inhaled anticholinergic agent used as bronchodilator treatment to relieve symptoms in patients with chronic obstructive pulmonary disease (COPD).

During routine signal detection activities, a signal of anaphylactic reaction was identified by the UK Medicines Agency (MHRA), based on 6 reported cases. NL, as lead Member State for signal detection activities confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information on the cases of anaphylactic reactions and noted that the product information for some tiotropium-containing medicines already reports hypersensitivity (including immediate reactions) and angioedema as rare adverse reactions.

A search in EudraVigilance identified further cases of anaphylactic reactions and 6 cases of anaphylactic shock, some of which had tiotropium-containing medicines as the only reported medication. In several cases, anaphylactic reactions resulted in hospitalisation. Therefore the PRAC agreed that the signal needed further investigation.

The PRAC appointed Sabine Straus as Rapporteur for the assessment of the review.

Summary of recommendation(s)

- The MAH for the innovator product should submit a cumulative review of cases of anaphylactic reactions and related terms within 60 days to the PRAC Rapporteur;
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.1.3. Thalidomide - **THALIDOMIDE CELGENE** (CAP)

- Signal of posterior reversible encephalopathy syndrome

Regulatory details:

PRAC Rapporteur: Isabelle Robine (FR)

Background

Thalidomide is an immunomodulatory agent used in the treatment of multiple myeloma.

The exposure for Thalidomide Celgene, a centrally authorised medicine containing thalidomide, is estimated to have been more than 300 000 patients worldwide, in the period from first authorisation in 2008 until 2012.

Following a safety communication from Health Canada (Canadian Adverse Reaction Newsletter Volume 22 - Issue 4 - October 2012 http://www.hc-sc.gc.ca/dhp-mps/medeff/bulletin/carn-bcei_v22n4-eng.php#a3) reporting a case of posterior reversible encephalopathy syndrome (PRES) [2], the EMA performed a search in EudraVigilance which retrieved 5 cases. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information on the cases of PRES and agreed that a cumulative review of the signal with a view to amending the product information for thalidomide-containing medicines was needed.

Summary of recommendation(s)

- The MAH for Thalidomide Celgene (thalidomide) should submit within 60 days a cumulative review of the reports of posterior reversible encephalopathy syndrome and related ADRs, including those reported spontaneously and those collected from clinical trials and an analysis of the literature to the EMA.
- This review will be assessed in the framework of the next PSUR to be discussed at the 13 -16 May 2013 meeting of the PRAC.

[2] The signs and symptoms of PRES include headaches, visual disturbances, seizures, altered mental function and radiologic findings (symmetrical posterior hemispheric oedema), often associated with abrupt hypertension

4.2. New signals detected from other sources

None

4.3. Signal follow-up and prioritisation

4.3.1. Clopidogrel – **PLAVIX** (CAP) & **generic products**

- Signal of eosinophilic pneumonia

Regulatory details:

PRAC Rapporteur: Maria Alexandra Pego (PT)

Background

For background see the Minutes of PRAC meeting of 3-5 September 2012.

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

Discussion

The PRAC confirmed that the reaction had been very rarely reported taking into account the high worldwide exposure to clopidogrel. However, the data reviewed supported a causal association between clopidogrel and eosinophilic pneumonia. The reaction may not only be life threatening on its own, but almost always triggers hospitalisation, aggressive investigation, antibiotic treatment and corticosteroid therapy in population treated at increased cardiovascular risk. Given that eosinophilic pneumonia is a serious adverse event that warrants prompt treatment and may require discontinuation of the medicine should it occur, the PRAC agreed that it would be useful to update the product information with respect to this.

Summary of recommendation(s)

- The MAHs for the reference, centrally authorisedclopidogrel-containing medicines[3] should be requested to submit to the EMA within 60 days a variation to update the product information to include "eosinophilic pneumonia - very rare"[4] as an undesirable effect.
- The MAHs of generics products should then be requested to submit to the EMA or to the national competent authorities of the MSs, as applicable, a variation to align their product information to that of the originator.

4.3.2. Duloxetine – **ARICLAIM** (CAP), **CYMBALTA** (CAP), **XERISTAR** (CAP), **YENTREVE** (CAP)

- Signal of increased serotonin syndrome due to a potential interaction with aripiprazole

[3] 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] Section 4.8 of the Summary of Product Characteristics

Regulatory details:

PRAC Rapporteur: Dolores Montero (ES)

Background

For background see PRAC minutes 3-5 September 2012.

The MAH replied to the request for information on the signal of potential interaction with aripiprazole and the occurrence of serotonin syndrome and the responses were assessed by the Rapporteur.

Discussion

The PRAC discussed the assessment of the data provided. A total of 9 cases reported serotonin syndrome with the use of duloxetine and concomitant aripiprazole. However, the information provided in the cases reported was limited, making a thorough assessment of the signal difficult.

Additionally, the cases reporting serotonin syndrome in association with use of the combination, were a small percentage of all the reports describing concomitant aripiprazole use and very low in absolute number in the context of the large estimated population exposure.

The PRAC acknowledged that the product information already provides overall advice information regarding duloxetine's potential pharmacokinetic and pharmacodynamic drug interactions, including risk of serotonin syndrome with serotonergic drugs. Therefore the product information was still considered appropriate.

Summary of recommendation(s)

- No regulatory action is considered necessary at this time;
- Routine pharmacovigilance activities should continue assessing the issue.

4.3.3. **Tiotropium** (NAP)

- Signal of increased mortality from cardiovascular disease and all-cause mortality raised by an editorial in the British Medical Journal (BMJ) for tiotropium Respimat mist inhaler

Regulatory details:

PRAC Rapporteur: Sabine Straus

Background

An editorial published in the BMJ[5] reported a signal of increased cardiovascular and all-cause mortality with tiotropium administered by means of the Respimat mist inhaler device. The editorial discussed data from published trials and systematic reviews that had been submitted and assessed by the Reference Member State (NL) in the past and had been previously closely reviewed and discussed by the PhVWP in 2011. NL, as lead Member State for signal detection activities for tiotropium confirmed that this signal needed follow-up analysis and prioritisation by the PRAC.

[5] Beasley R ,Singh S ,Loke YK ,Enright P ,Furberg CD. Call for worldwide withdrawal of tiotropium Respimat mist inhaler. BMJ 2012;345:e7390

Discussion

The PRAC noted that this issue has been under close review and that data concerning mortality and cardiovascular risks were reflected in the wording of the product information for tiotropium Respimat.

The PRAC was aware of two ongoing studies involving tiotropium Respimat (trial 205.452 and trial 205.458) for which the results are expected in the course of 2013. In particular trial 205.452 is a PASS designed to compare the efficacy and safety of the Respimat and HandiHaler devices. Submission is currently planned for early 2014.

However, given the important issues raised in the editorial in the BMJ concerning a possible difference in the risk profile between Respimat and Handihaler, the PRAC agreed that it would be important to explore with the MAH whether there was any new data or analysis on this issue that should be considered by the PRAC for further investigation before the results from the above mentioned studies become available.

The PRAC appointed Sabine Straus as Rapporteur for the assessment of the review.

Summary of recommendation(s)

- The MAH for Tiotropium Respimat (tiotropium) should submit to the PRAC Rapporteur any new data or analyses relevant to the concerns raised by the BMJ publication within 60 days
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.3.4. Hormonal contraceptives: norelgestromin / ethinylestradiol - EVRA (CAP); **etonogestrel**; **etonogestrel and ethinylestradiol**; **drospirenone and ethinylestradiol** (NAPs)

- Signal of arterial thrombotic events - risk of arterial thrombotic events (ATE) thrombotic stroke and myocardial infarction raised by *Lidegaard et al 2012*[6].

Regulatory details:

PRAC Rapporteur: Menno van der Elst (NL)

Background

For background information see PRAC Minutes 26-29 November 2012.

The Rapporteur presented an updated assessment of the study by Lidegaard et al. 2012.

Discussion

The PRAC emphasised that arterial thrombotic events are a known risk of combined hormonal contraceptives. In this respect, the results from the study by Lidegaard et al. confirmed findings from previous studies. The PRAC confirmed that relevant information is reflected in the product information of the hormonal contraceptives included in the study. In addition, as previously highlighted by the PRAC, a vast majority of other combined hormonal contraceptives in the EU already include information on the risk of arterial thrombotic events in their product information.

Summary of recommendation(s)

[6] Lidegaard O, Lokkegaard E, Jensen A, Skovland CW, Keiding N. Thrombotic stroke and myocardial infarction with hormonal contraception. N Engl J Med 2012;366:2257-2266

- The results from the study by Lidegaard et al. show that the risk of ATE is increased with the use of combined hormonal contraceptives, which is in line with findings from previous studies;
- The study findings are consistent with the current regulatory understanding of this risk in the EU;
- Since relevant information is reflected in the product information of the hormonal contraceptives included in the study, an update of the product information for those products is not currently recommended.

Post meeting note: on 7 February 2013, at the request of France, the PRAC started a review of several combined hormonal contraceptives to evaluate the risk of both venous and arterial thromboembolism. The review includes contraceptives containing drospirenone, etonogestrel and norelgestromin.

4.3.5. Etanercept – ENBREL (CAP)

- Signal of dermatomyositis

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)

Background

For background see the PRAC minutes 26-29 November 2012.

Following the signal of dermatomyositis with adalimumab, the PRAC requested the EMA to look into EudraVigilance cases with etanercept. The PRAC Rapporteur for etanercept presented the conclusions of the review of cases of dermatomyositis.

Discussion

The PRAC discussed the information on the cases reported and concluded that in some cases a causal association cannot be excluded. In light of this, and given the previous recommendations that dermatomyositis should be included in the product information for some other Tumour Necrosis Factor (TNF)-alpha inhibitors (adalimumab and infliximab), the PRAC agreed that the signal warranted further investigation.

Summary of recommendation(s)

- The MAH for Enbrel (etanercept) should submit within 60 days a cumulative review of the signal, discussing a plausible biological mechanism and proposing amendment to the product information to the EMA;
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

5. Risk management plans

5.1. Medicines in the pre-authorisation phase

The PRAC provided advice to the CHMP on the proposed RMPs for a number of products (identified by active substance below) that are under evaluation for initial marketing authorisation. Information on

the PRAC advice will be available in the European Public Assessment Reports (EPARs) to be published at the end of the evaluation procedure.

5.1.1. Afatinib (dimaleate)

- Evaluation of the RMP in the context of an initial Marketing Authorisation Application procedure

5.1.2. Atosiban

- Evaluation of the RMP in the context of an initial Marketing Authorisation Application procedure

5.1.3. Avanafil

- Evaluation of the RMP in the context of an initial Marketing Authorisation Application procedure

5.1.4. Bedaquiline

- Evaluation of the RMP in the context of an initial Marketing Authorisation Application procedure

5.1.5. Fenofibrate / simvastatin

- Evaluation of the RMP in the context of an initial Marketing Authorisation Application procedure

5.1.6. Infliximab

- Evaluation of the RMP in the context of an initial Marketing Authorisation Application procedure

5.1.7. Infliximab

- Evaluation of the RMP in the context of an initial Marketing Authorisation Application procedure

5.1.8. Lorcaserin Hydrochloride

- Evaluation of the RMP in the context of an initial Marketing Authorisation Application procedure

5.1.9. Masitinib mesylate

- Evaluation of the RMP in the context of an initial Marketing Authorisation Application procedure

5.1.10. Memantine hydrochloride

- Evaluation of the RMP in the context of an initial Marketing Authorisation Application procedure

5.1.11. Ponatinib

- Evaluation of the RMP in the context of an initial Marketing Authorisation Application procedure

5.1.12. Regorafenib

- Evaluation of the RMP in the context of an initial Marketing Authorisation Application procedure

5.1.13. Somatropin

- Evaluation of the RMP in the context of an initial Marketing Authorisation Application procedure

5.1.14. Telmisartan / hydrochlorothiazide

- Evaluation of a RMP in the context of an initial Marketing Authorisation Application procedure

5.1.15. Trastuzumab emtansine

- Evaluation of the RMP in the context of an initial Marketing Authorisation Application procedure

5.1.16. Votrioxetine

- Evaluation of the 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. 5-aminolevulinic acid hydrochloride – AMELUZ (CAP)

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

Regulatory details:

PRAC Rapporteur: Martin Huber (DE)

Background

5-aminolevulinic acid is an antineoplastic agent used to treat mild to moderate actinic keratosis on the face and scalp. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP following assessment of the accompanying PSUR for Ameluz, a centrally authorised product containing 5-aminolevulinic acid hydrochloride.

Summary of advice

- The updated RMP version 6 for Ameluz (5-Aminolevulinic acid HCl) was considered acceptable.
- The next update of the RMP should address some minor revisions raised by the PRAC.

See also 6.1.1.

5.2.2. Ambrisentan – VOLIBRIS (CAP)

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

Regulatory details:

PRAC Rapporteur: Dolores Montero (ES)

Background

Ambrisentan is an endothelin receptor agonist (ERA) used in the treatment of selected populations of patients with pulmonary arterial hypertension (PAH).The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP following assessment of the accompanying PSUR for Volibris, a centrally authorised product containing ambrisentan.

Summary of advice

- The updated RMP version 5 for Volibris (ambrisentan) was considered acceptable.
- An updated RMP should be submitted to the EMA within 6 months to address a list of questions agreed by the PRAC.

See also 6.1.2.

5.2.3. Amifampridine – FIRDAPSE (CAP)

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

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)

Background

Amifampridine is a voltage-dependent potassium channel blocker used to treat the symptoms of Lambert-Eaton myasthenic syndrome (LEMS) in adults. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP following assessment of the accompanying PSUR for Firdapse, a centrally authorised product containing amifampridine.

Summary of advice

- The updated RMPs version 3 for Firdapse (amifampridine) was considered acceptable.
- The next update of the RMP should address some administrative issues raised by the PRAC.

See also 6.1.3.

5.2.4. Belatacept – NULOJIX (CAP)

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

Regulatory details:

PRAC Rapporteur: Ulla Wändel-Liminga (SE)

Background

Belatacept is an immunosuppressant used in combination with other medicines for the prophylaxis of graft rejection in adults receiving a renal transplant. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP following assessment of the accompanying PSUR for Nulojix, a centrally authorised product containing belatacept.

Summary of advice

- The updated RMP version 8 for Nulojix (belatacept) was considered acceptable.

See also 6.1.4.

5.2.5. Besilesomab – SCINTIMUN (CAP)

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

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)

Background

Besilesomab is a diagnostic radiopharmaceutical used in scintigraphic imaging, in conjunction with other appropriate imaging modalities, for determining the location of inflammation/infection in peripheral bone in adults with suspected osteomyelitis. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP following assessment of the accompanying PSUR for Scintimun, a centrally authorised product containing besilesomab.

Summary of advice

- The updated RMP version 9 for Scintimun (basilesomab) was considered acceptable.
- The next update of the RMP should address some editorial issues raised by the PRAC.

See also: 6.1.5.

5.2.6. Cabazitaxel – JEVTANA (CAP)

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

Regulatory details:

PRAC Rapporteur: Isabelle Robine (FR)

Background

Cabazitaxel is an antineoplastic agent indicated in the treatment of patients with hormone refractory metastatic prostate cancer. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP following assessment of the accompanying PSUR for Jevtana, a centrally authorised product containing cabazitaxel.

Summary of advice

- The updated RMP version 4 for Jevtana (cabazitaxel) was considered acceptable.
- The next update of the RMP (requested to be submitted in connection with the variation requested in the PSUR recommendation at point 6.1.8.) should include some additions as proposed by the PRAC regarding some 'important potential risks'. Pulmonary toxicity should be considered as an 'important potential risk'.

See also 6.1.8.

5.2.7. Caffeine – PEYONA (CAP)

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

Regulatory details:

PRAC Rapporteur: Harald Herkner (AT)

Background

Caffeine is a xanthine derivative. Peyona, a centrally authorised medicine containing caffeine as citrate, is indicated for treatment of primary apnoea of premature newborns. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP following assessment of the accompanying PSUR for Peyona (caffeine citrate).

Summary of advice

- The updated RMP version 11 for Peyona (caffeine citrate) was considered acceptable.
- The next update of the RMP should consider the new timelines for submission of PSURs - and the PSUR itself - as milestones for discussion on effectiveness of risk minimisation measures (RMMs).

See also 6.1.9.

5.2.8. Dasatinib – SPRYCEL (CAP)

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

Regulatory details:

PRAC Rapporteur: Doris Stenver (DK)

Background

Dasatinib is an antineoplastic agent used in the treatment of certain forms of chronic myelogenous leukaemia and acute lymphoblastic leukaemia. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP following assessment of the accompanying PSUR for Sprycel, a centrally authorised product containing dasatinib.

Summary of advice

- The updated RMP version 11 for Sprycel (dasatinib) was considered acceptable.
- The next update of the RMP should take into account some editorial issues raised by the PRAC.

See also 6.1.11.

5.2.9. Efavirenz / emtricitabine / tenofovir disoproxil – ATRIPLA (CAP)

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

Regulatory details:

PRAC Rapporteur: Martin Huber (DE)

Background

Atripla, a centrally authorised medicine containing a combination of efavirenz, emtricitabine and tenofovir disoproxil, is indicated in the treatment of human immunodeficiency virus-1 (HIV-1). The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP following assessment of the accompanying PSUR for Atripla (efavirenz, emtricitabine and tenofovir disoproxil).

Summary of advice

- The updated RMP version 11 for Atripla (efavirenz, emtricitabine and tenofovir disoproxil) was considered acceptable.

See also 6.1.12.

5.2.10. Fidaxomicin – **DIFICLIR** (CAP)

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

Regulatory details:

PRAC Rapporteur: Qun-Ying Yue (SE)

Background

Fidaxomicin is an antibiotic used for the treatment of *Clostridium difficile* infections. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP following assessment of the accompanying PSUR for Dificlir, a centrally authorised product containing fidaxomicin.

Summary of advice

- The updated RMP version 2 for Dificlir (fidaxomicin) was considered acceptable.
- The next update of the RMP should include some additions proposed by the PRAC including a clinical drug-drug interaction study with rosuvastatin to further assess the impact of fidaxomicin on intestinal efflux transporters.

See also 6.1.13.

5.2.11. Galsulfase – **NAGLAZYME** (CAP)

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

Regulatory details:

PRAC Rapporteur: Julia Dunne (UK)

Background

Galsulfase is an enzyme used in long-term enzyme replacement therapy in patients with mucopolysaccharidosis VI. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP following assessment of the accompanying PSUR for Naglazyme, a centrally authorised product containing galsulfase.

Summary of advice

- The updated RMP version 4 for Naglazyme (galsulfase) could be considered approvable.
- The next update of the RMP should address some points raised by the PRAC such as the development of neutralising antibodies to be included as ‘important potential risk’ and the MAH should propose appropriate pharmacovigilance activities and risk minimisation measures.

See also 6.1.14.

5.2.12. Imiglucerase – **CEREZYME** (CAP)

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

Regulatory details:

PRAC Rapporteur: Sabine Straus (NL)

Background

Imiglucerase is an enzyme used as long-term enzyme replacement therapy in patients with a non-neuronopathic (type 1) or chronic neuronopathic (type 3) Gaucher disease. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP following assessment of the accompanying PSUR for Cerezyme, a centrally authorised product containing imiglucerase.

Summary of advice

- The updated RMP version 5 for Cerezyme (imiglucerase) could be considered acceptable provided that an updated RMP addressing some additions and clarifications requested by the PRAC on the educational material is submitted to EMA.

See also 6.1.21.

5.2.13. Liraglutide – VICTOZA (CAP)

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

Regulatory details:

PRAC Rapporteur: Menno van der Elst (NL)

Background

Liraglutide is a glucagon-like peptide-1 (GLP-1) analogue used in the treatment of type 2 diabetes mellitus. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP following assessment of the accompanying PSUR for Victoza, a centrally authorised product containing liraglutide.

Summary of advice

- The updated RMP version 18 for Victoza (liraglutide) was considered acceptable.

See also 6.1.22.

5.2.14. Pneumococcal polysaccharide conjugate vaccine – PREVENAR 13 (CAP)

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

Regulatory details:

PRAC Rapporteur: Qun-Ying Yue (SE)

Background

Prevenar 13 is a centrally authorised pneumococcal polysaccharide conjugate vaccine. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP following assessment of the accompanying PSUR for Prevenar 13.

Summary of advice

- The updated RMP version 5 for Prevenar 13 (Pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed)) was considered acceptable.

See also 6.1.27.

5.2.15. Saxagliptin / metformin hydrochloride – KOMBOGLYZE (CAP)

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

Regulatory details:

PRAC Rapporteur: Menno van der Elst (NL)

Background

The combination saxagliptin / metformin hydrochloride is used in the treatment of type II diabetes mellitus. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP following assessment of the latest PSUR for Komboglyze (see 6.1.30.), a centrally authorised product containing saxagliptin / metformin hydrochloride. The MAH submitted a RMP version 3.0 with this PSUR which also included changes supporting a parallel procedure reported at point 5.2.24. of this agenda.

Summary of advice

Refer to 6.1.30.

5.2.16. Stavudine – ZERIT (CAP)

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

Regulatory details:

PRAC Rapporteur: Qun-Ying Yue (SE)

Background

Stavudine is an antiviral (nucleoside reverse transcriptase inhibitor) used in combination with other antiretroviral medicinal products for the treatment of HIV. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP following assessment of the accompanying PSUR for Zerit, a centrally authorised product containing stavudine.

Summary of advice

- The updated RMP version 2 for Zerit (stavudine) was considered acceptable.

The PRAC noted that results of a Drug Utilisation Study (DUS), performed in order to gather information on the use of stavudine in the EU and to evaluate whether the prescriptions of stavudine are in line with the restricted indication, had been submitted and will be further discussed at PRAC level.

See also 6.1.32.

5.2.17. Tobramycin – TOBI PODHALER (CAP)

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

Regulatory details:

PRAC Rapporteur: Sabine Straus (NL)

Background

Tobi Podhaler is a centrally authorised tobramycin-containing antibiotic that is indicated for the suppressive therapy of chronic pulmonary infection due to *Pseudomonas aeruginosa* in adults and children aged 6 years and older with cystic fibrosis. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP following assessment of the accompanying PSUR for Tobi Podhaler.

Summary of advice

- The updated RMP version 4 for Tobi Podhaler (tobramycin) was considered acceptable.

See also 6.1.34.

5.2.18. Topotecan – HYCAMTIN (CAP)

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

Regulatory details:

PRAC Rapporteur: Ulla Wändel-Liminga (SE)

Background

Topotecan is an antineoplastic used in the treatment of ovarian and small cell lung cancer in selected patient populations. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP following assessment of the accompanying PSUR for Hycamtin, a centrally authorised product containing topotecan.

Summary of advice

- The updated RMP version 4 for Hycamtin (topotecan) could be considered acceptable provided that an updated version addressing some points for clarification requested by the PRAC on 'important missing information' and 'important identified risks' is submitted.

See also 6.1.35.

RMP in the context of a variation procedure

5.2.19. Bimatoprost / timolol – GANFORT (CAP)

- Evaluation of an RMP in the context of a 60 day-Type II variation

Regulatory details:

PRAC Rapporteur: Line Michan (DK)

Background

Ganfort is a centrally authorised product, available as eye drop solution, containing the combination timolol/bimatoprost as active substances. It is indicated for the reduction of intraocular pressure (IOP) in selected patients with open-angle glaucoma or ocular hypertension.

The CHMP is evaluating a type II variation procedure for Ganfort to introduce changes in the composition to create a new presentation. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this variation.

Summary of advice

- The RMP version 2 for Ganfort (timolol/bimatorprost) in the context of the variation under evaluation by the CHMP was considered acceptable
- The next update of the RMP should provide some clarification requested by the PRAC on cases of hypoglycaemia reported post marketing and provide an assessment of causality. Furthermore, details regarding the cases of depression in the clinical trials as well as any post marketing cases should be provided and an assessment of causality should be made.

5.2.20. Bortezomib – VELCADE (CAP)

- Evaluation of an RMP in the context of a 90 day type II variation (extension of indication)

Regulatory details:

PRAC Rapporteur: Carmela Macchiarulo (IT)

Background

Velcade is an antineoplastic used as monotherapy or, in combination with melphalan and prednisone, for the treatment of multiple myeloma in certain patients.

The CHMP is evaluating a type II variation procedure for Velcade, a centrally authorised product containing bortezomib, to extend the indication to include the treatment of multiple myeloma, in certain patients, in combination with pegylated liposomal doxorubicin or dexamethasone.

The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this variation.

Summary of advice

- The RMP version 18 for Velcade (bortezomib) in the context of the variation under evaluation by the CHMP was considered acceptable provided that satisfactory responses to a list of questions are submitted before finalisation of the variation procedure by the CHMP.
- The MAH should provide an updated version to the EMA addressing editorial comments raised by the PRAC (i.e. a single version collating all previously submitted updates).

5.2.21. Natalizumab – TYSABRI (CAP)

- Evaluation of an RMP in the context of a 60-day type II variation

Regulatory details:

PRAC Rapporteur: Brigitte Keller-Stanislawski (DE)

Background

Natalizumab is a monoclonal antibody used in the treatment of multiple sclerosis.

The CHMP is evaluating a type II variation procedure for Tysabri, a centrally authorised product containing natalizumab, to include in the product information further guidance to patients and healthcare professionals on the risk of progressive multifocal leukoencephalopathy (PML) following discontinuation of Tysabri. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this variation.

Summary of advice

- The RMP version 15 for Tysabri (natalizumab) in the context of the variation under evaluation by the CHMP was considered acceptable. However, the MAH should clarify within one month the communication strategy to accompany the changes introduced in the product information and educational materials following the finalisation of current variation.
- The next update of the RMP should take into account an issue raised by the PRAC regarding the fact that the overall population of John Cunningham virus (JCV) antibody positive patients with multiple sclerosis, who have discontinued Tysabri after 24 months, is not currently known. Therefore, the MAH is advised to review data from observational studies and registries to provide a robust risk estimate after discontinuation of Tysabri

5.2.22. Octocog alfa – ADVATE (CAP)

- Evaluation of an RMP in the context of a 60-day type II variation

Regulatory details:

PRAC Rapporteur: Brigitte Keller-Stanislawski (DE)

Background

Octocog alfa is recombinant coagulation factor VIII used in the treatment of Haemophilia A.

The CHMP is evaluating a type II variation procedure for Advate, a centrally authorised product containing octocog alfa, to introduce updated information regarding an individualised pharmacokinetic guided dosing regimen for long term prophylaxis against bleeding. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this variation.

Summary of advice

- The RMP version 13 for Advate (octocog alfa) in the context of the variation under evaluation by the CHMP was considered acceptable.

5.2.23. Raltegravir – ISENTRESS (CAP)

- Evaluation of the updated RMP in the context of a 60-day type II variation

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)
PRAC Co-Rapporteur: Isabelle Robine (FR)

Background

Raltegravir is an integrase inhibitor used in the treatment of HIV infection.

The CHMP is evaluating a type II variation procedure for Isentress, a centrally authorised product containing raltegravir, to include in the product information data from a phase III study (Protocol 021) in treatment naïve patients. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this variation.

Summary of advice

- The RMP version 9 for Isentress (raltegravir) in the context of the variation under evaluation by the CHMP was considered acceptable.
- Additional data in children aged 2 to < 6 years should be collected to provide further information on the adequacy of the recommended posology. A study proposal should be included in a next update of the RMP to be submitted to the EMA in February 2013.

5.2.24. Saxagliptin – ONGLYZA (CAP) , Saxagliptin / metformin - KOMBOGLYZE (CAP)

- Evaluation of the updated RMP in the context of a Type II variation, extension of indication

Regulatory details:

PRAC Rapporteur: Menno van der Elst (NL)

Background

See PRAC Minutes 1-3 October 2012.

Responses of the MAH to the PRAC list of questions were submitted and assessed.

Summary of advice

- The RMP version 3 for Komboglyze (saxagliptin / metformin) and Onglyza (saxagliptin) in the context of the variation under evaluation by the CHMP was considered acceptable.
- The next updated version of the RMP in which the responses to the list of questions raised during the extension of indication procedure are reflected, and addressing some editorial issues raised by the PRAC, should be submitted to the EMA within three months following CHMP opinion.

5.2.25. Tygecycline – TYGACIL (CAP)

- Evaluation of a RMP in the context of a 60-day type II variation

Regulatory details:

PRAC Rapporteur: Miguel-Angel Macia (ES)

Background

Tygecycline is an antibiotic used, under certain circumstances, in the treatment of skin and soft tissue infections and complicated intra-abdominal infections.

The CHMP is evaluating a type II variation procedure for Tygacil, a centrally authorised product containing tygecycline, to include wording on impaired healing in the product information and to update the frequency of thrombocytopenia. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this variation.

Summary of advice

- The RMP version 11 for tigecycline (Tygacil) in the context of the variation under evaluation by the CHMP was considered acceptable.

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

5.2.26. Doripenem – DORIBAX (CAP)

- Evaluation of an RMP in the context of a renewal of the marketing authorisation

Regulatory details:

PRAC Rapporteur: Qun-Ying Yue (SE)

Background

Doripenem is an antibiotic used in the treatment of nosocomial pneumonia (including ventilator–associated pneumonia), complicated intra-abdominal infections and complicated urinary tract infections. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP in the context of the renewal of the MA for Doribax, a centrally authorised product containing doripenem.

Summary of advice

- The updated RMP version 6 for Doribax (doripenem) was considered acceptable.

See also 9.2.1.

5.2.27. Ranolazine – RANEXA (CAP)

- Evaluation of an RMP in the context of a renewal of the marketing authorisation

Regulatory details:

PRAC Rapporteur: Qun-Ying Yue (SE)

Background

Ranolazine is used as add-on therapy for the symptomatic treatment of patients with stable angina pectoris who are inadequately controlled or intolerant to first-line anti-anginal therapies (such as beta-blockers and/or calcium antagonists).

The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP in the context of the renewal of the MA for Ranexa, a centrally authorised product containing ranolazine.

Summary of advice

- The updated RMP version 7.1 for Ranexa (ranolazine) was considered acceptable.
- The next update of the RMP should address some corrections requested by the PRAC on the information included on the ‘identified risk angioedema’ and on the study ‘GS-US-259-0143’.

See also 9.2.9.

RMP in the context of a stand-alone RMP procedure

5.2.28. Filgrastim – NIVESTIM (CAP)

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

Regulatory details:

PRAC Rapporteur: Kirsti Villikka (FI)

Background

Filgrastim is a recombinant granulocyte colony stimulating factor (G-CSF) used in the treatment of neutropenia in specific conditions. The PRAC is responsible for providing advice to the CHMP on an updated version of the RMP for Nivestim, a centrally authorised medicine containing filgrastim, submitted to address some changes resulting from previous post-authorisation commitments.

Summary of advice

- The updated RMP version 7 for Nivestim (filgrastim) was considered acceptable.
- The next update of the RMP should take into account some editorial changes proposed by the PRAC. Moreover 'pregnancy and lactation' should be listed as safety concern in the section 'important missing information' in the RMP.

5.2.29. Granisetron – SANCUSO (CAP)

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

Regulatory details:

PRAC Rapporteur: Jolanta Gulbinovic (LT)

Background

Granisetron is a serotonin ($5HT_3$) antagonist used for the prevention of nausea and vomiting in specific conditions. The PRAC is responsible for providing advice to the CHMP on an update to the RMP for Sancuso, a centrally authorised medicine containing granisetron as a transdermal patch, resulting from previous post-authorisation commitments.

Summary of advice

- The updated RMP version 2 for Sancuso (granisetron) was considered acceptable.
- The next update of the RMP should take into account some editorial changes requested by the PRAC.

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

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

Regulatory details:

PRAC Rapporteur: Brigitte Keller-Stanislawski (DE)

Background

See 5.2.22. .

The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP for Helixate Nexgen and Kogenate Bayer, centrally authorised medicines containing octocog alfa, to include current data from the European Haemophilia Safety Surveillance System (EUHASS) registry regarding new data to be included in the product information on immune tolerance induction (ITI) and to address some points previously raised by the CHMP.

Summary of advice

- The updated RMP version 10 for Helixate Nexgen and Kogenate Bayer (octocog alfa) could be considered acceptable provided an updated risk management plan and satisfactory responses to a list of questions agreed by the PRAC are submitted to the EMA.

In the context of the discussion the PRAC was informed that the project EUHASS is now finalised. In order to continue with some of the objectives of the EUHASS project, a new project, the European Haemophilia Network (EUHANET), started on 1st June 2012 and will continue until 31 May 2015 with the University of Sheffield (UK) as main coordinator. EMA will be regularly interacting with the new consortium.

See also 5.2.22.

5.2.31. Prasugrel – EFIENT (CAP)

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

Regulatory details:

PRAC Rapporteur: Doris Stenver (DK)

Background

Prasugrel is an antiplatelet agent used in the treatment and for the prevention of atherothrombotic events in patients with acute coronary syndrome or ST segment elevation myocardial infarction (STEMI).

The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP for Efient, a centrally authorised medicine containing prasugrel, to include results from a phase 3 study 'A Comparison of Prasugrel and Clopidogrel in Acute Coronary Syndrome Subjects (TRILOGY ACS)' in the product information.

Summary of advice

- The updated RMP version 6 for Efient (prasugrel) was considered acceptable provided that an updated risk management plan and satisfactory responses to a list of questions agreed by the PRAC are submitted.

5.2.32. Pyronaridine / artesunate – PYRAMAX (Art 58)

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

Regulatory details:

PRAC Rapporteur: Isabelle Robine (FR)

Background

Pyronaridine / artesunate is an antimalarial used in the treatment of acute, uncomplicated malaria infection caused by *Plasmodium falciparum* or by *Plasmodium vivax*.

The PRAC is responsible for providing advice to the CHMP on an update to the RMP for Pyramax, a product containing pyronaridine / artesunate that received a CHMP Scientific Opinion under Article 58 of Regulation (EC) No 726/2004.

Summary of advice

- The updated RMP version 3 for Pyramax (pyronaridine / artesunate) was considered acceptable.
- The next update of the RMP should take into account a number of clarifications proposed by the PRAC, including data related to repeated doses of Pyramax as well as all other 'potential' and 'important risks' that could occur when Pyramax is re-administered and to update the next RMP including pregnant and breastfeeding women as 'important missing information'.

PRAC requested that at a future meeting the EMA secretariat presents details on Article 58 of Regulation (EC) No 726/2004 and on the guidelines for pharmacovigilance follow-up.

5.2.33. Topotecan – TOPOTECAN EAGLE (CAP)

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

Regulatory details:

PRAC Rapporteur: Ulla Wändel-Liminga (SE)

Background

Topotecan is an antineoplastic used in the treatment of small cell lung cancer (SCLC) and cancer of the cervix. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP for Topotecan Eagle, a centrally authorised medicine containing topotecan, to include results of a user evaluation study and to remove the obligation to repeat the user testing study given that this had been fulfilled.

Summary of advice

- The updated RMP version 10 for Topotecan Eagle (topotecan) was considered acceptable provided that an updated risk management plan with satisfactory responses to an agreed list of questions by the PRAC are submitted.

5.2.34. Ulipristal – ESMYA (CAP)

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

Regulatory details:

PRAC Rapporteur: Ulla Wändel-Liminga (SE)
PRAC Co-Rapporteur: Menno van der Elst (NL)

Background

Esmya is a centrally authorised medicines containing ulipristal acetate, indicated for pre-operative treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age. The duration of treatment is limited to 3 months.

At the time of the marketing authorisation of Esmya, the MAH was requested to present a finalised protocol on prescription patterns of the medicine in the EU (PGL11-020), in consideration of the recommended duration of treatment, within three months. An update of the RMP was presented to submit a protocol for the study. The PRAC is responsible for providing advice to the CHMP on this update.

Summary of Advice

- The updated RMP version 8 for Esmya (ulipristal) was considered acceptable provided that an updated risk management plan with satisfactory responses to a list of questions agreed by the PRAC, to clarify some aspect of the study design, are submitted to the EMA.

6. Assessment of Periodic Safety Update Reports (PSURs)

6.1.1. 5-aminolevulinic acid hydrochloride – AMELUZ (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Martin Huber (DE)

Background

5-aminolevulinic acid is used in the treatment in photodynamic therapy to treat mild to moderate actinic keratosis on the face and scalp.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Ameluz, a centrally authorised medicine containing 5-aminolevulinic acid, and issued a recommendation on its marketing authorisation.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Ameluz (5-aminolevulinic acid hydrochloride) in the approved indication(s) remains favourable.
- The PRAC recommended the maintenance of the current terms of the marketing authorisation.

The frequency of submission of PSURs should remain 6-monthly and the next PSUR should be submitted to the EMA within 70 days of the data lock point.

6.1.2. Ambrisentan – VOLIBRIS (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Dolores Montero (ES)

Background

Ambrisentan is an endothelin receptor agonist (ERA) used in the treatment of selected populations of patients with pulmonary arterial hypertension (PAH).

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Volibris, a centrally authorised medicine containing ambrisentan, and issued a recommendation on its marketing authorisation.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Volibris (ambrisentan) in the approved indication(s) remains favourable.
- The PRAC recommended the maintenance of the current terms of the marketing authorisation.
- Several adverse drug effects, including hepatic and cardiac adverse effects should be kept under close monitoring and a cumulative review of blurred vision/vision impairment should be provided in the next PSUR.

The frequency of submission of PSURs should be changed from yearly to 6-monthly until the final results of the study 'a Post-Marketing Observational Surveillance Programme for Ambrisentan (VOLT)' (completion expected mid 2013) are assessed and the next PSUR should be submitted to the EMA within 70 days of the data lock point.

6.1.3. Amifampridine – FIRDAPSE (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)

Background

Amifampridine is a voltage-dependent potassium channels blocker used to treat the symptoms of Lambert-Eaton myasthenic syndrome (LEMS) in adults.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Firdapse, a centrally authorised medicine containing amifampridine, and issued a recommendation on its marketing authorisation.

Summary of recommendation(s) and conclusion

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Firdapse (amifampridine) in the approved indication(s) remains favourable.
- The PRAC recommended the maintenance of the current terms of the marketing authorisation.

The frequency of submission of PSURs should remain 6-monthly and the next PSUR should be submitted to the EMA within 70 days of the data lock point.

6.1.4. Belatacept – NULOJIX (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Ulla Wändel-Liminga (SE)

Background

Belatacept is an immunosuppressant used in combination with other medicines, for the prophylaxis of graft rejection in adults receiving a renal transplant.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Nulojix, a centrally authorised medicine containing belatacept, and issued a recommendation on its marketing authorisation.

Summary of recommendation(s) and conclusion

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Nulojix (belatacept) in the approved indication(s) remains favourable.
- The PRAC recommended the maintenance of the current terms of the marketing authorisation.

The frequency of submission of PSURs should remain 6-monthly and the next PSUR should be submitted to the EMA within 70 days of the data lock point.

6.1.5. Besilesomab – SCINTIMUN (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)

Background

Besilesomab is a diagnostic radiopharmaceutical used in scintigraphic imaging, in conjunction with other appropriate imaging modalities, for determining the location of inflammation/infection in peripheral bone in adults with suspected osteomyelitis.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Scintimun, a centrally authorised medicine containing besilesomab, and issued a recommendation on its marketing authorisation.

Summary of recommendation(s) and conclusion

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Scintimun (besilesomab) in the approved indication(s) remains favourable.
- The PRAC recommended the maintenance of the current terms of the marketing authorisation.

The frequency of submission of PSURs should remain 6-monthly and the next PSUR should be submitted to the EMA within 70 days of the data lock point.

6.1.6. Bromfenac – YELLOX (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Doris Stenver (DK)

Background

Bromfenac is a non-steroidal anti-inflammatory drug (NSAID) indicated in 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.

Summary of recommendation(s) and conclusion

- 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 PRAC recommended the maintenance of the current terms of the marketing authorisation.

The frequency of submission of PSURs should remain 6 monthly and the next PSUR should be submitted to the EMA within 70 days of the data lock point.

6.1.7. C1 inhibitor (human) – CINRYZE (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Martin Huber (DE)

Background

C1 inhibitor (human) is a serine protease inhibitor used in prevention of angioedema attacks in selected patients with hereditary angioedema (HAE).

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Cinryze, a centrally authorised medicine containing C1 inhibitor (human), and issued a recommendation on its marketing authorisation.

Summary of recommendation(s) and conclusion

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Cinryze (C1 inhibitor human) in the approved indication(s) remains favourable.
- The PRAC recommended the maintenance of the current terms of the marketing authorisation.

The frequency of submission of PSURs should remain 6-monthly and the next PSUR should be submitted to the EMA within 70 days of the data lock point.

6.1.8. Cabazitaxel – JEVTANA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Isabelle Robine (FR)

Background

Cabazitaxel is an antineoplastic agent indicated in the treatment of patients with hormone refractory metastatic prostate cancer.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Jevtana, a centrally authorised medicine containing cabazitaxel, and issued a recommendation on its marketing authorisation.

Summary of recommendation(s) and conclusion

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Jevtana (cabazitaxel) in the approved indication(s) remains favourable.
- The PRAC recommended the maintenance of the current terms of the marketing authorisation.
- Nevertheless, further assessment of the gastrointestinal disorder reactions is warranted. The MAH should submit a type II variation within 2 months to update the product information. In addition the MAH should be requested to submit an updated RMP with the variation.
- The MAHs should monitor closely cases of severe respiratory disorders and provide a safety review within the next PSUR.

The frequency of submission of PSURs should remain 6-monthly and the next PSUR should be submitted to the EMA within 70 days of the data lock point.

6.1.9. Caffeine – PEYONA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Harald Herkner (AT)

Background

Caffeine is a xanthine derivative and Peyona as caffeine citrate is indicated in the treatment of primary apnoea of premature newborns.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Peyona, a centrally authorised medicine containing caffeine citrate, and issued a recommendation on its marketing authorisation.

Summary of recommendation(s) and conclusion

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Peyona (caffeine) in the approved indication(s) remains favourable.
- The PRAC recommended the maintenance of the current terms of the marketing authorisation.

The frequency of submission of PSUR should remain 6-monthly and the next PSUR should be submitted to the EMA within 70 days of the data lock point.

6.1.10. Canakinumab – ILARIS (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Birgitte Keller-Stanislawski (DE)

Background

Canakinumab is a monoclonal anti-human interleukin-1 beta (IL-1 beta) antibody, used in the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS).

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Ilaris, a centrally authorised medicine containing canakinumab, and issued a recommendation on its marketing authorisation.

Summary of recommendation(s) and conclusion

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Ilaris (canakinumab) in the approved indication(s) remains favourable.
- The PRAC recommended the maintenance of the current terms of the marketing authorisation.

The frequency of submission of PSURs should remain 6-monthly and the next PSUR should be submitted to the EMA within 70 days of the data lock point.

6.1.11. Dasatinib – SPRYCEL (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Doris Stenver (DK)

Background

Dasatinib is an antineoplastic agent used in the treatment of certain forms of chronic myelogenous leukaemia and acute lymphoblastic leukaemia.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Sprycel, a centrally authorised medicine containing dasatinib, and issued a recommendation on its marketing authorisation.

Summary of recommendation(s) and conclusion

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Sprycel (dasatinib) in the approved indication(s) remains favourable.
- The PRAC recommended the maintenance of the current terms of the marketing authorisation.
- The MAH is requested to present a cumulative safety review of reports of pulmonary arterial hypertension in the next PSUR.

The frequency of submission of PSURs should remain once yearly and the next PSUR should be submitted to the EMA within 70 days of the data lock point.

6.1.12. Efavirenz / emtricitabine / tenofovir disoproxil – ATRIPLA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Martin Huber (DE)

Background

Efavirenz, emtricitabine and tenofovir disoproxil in combination are used in the treatment of human immunodeficiency virus-1 (HIV-1).

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Atripla, a centrally authorised medicine containing efavirenz, emtricitabine and tenofovir disoproxil, and issued a recommendation on its marketing authorisation.

Summary of recommendation(s) and conclusion

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Atripla (efavirenz/emtricitabine/tenofovir disoproxil) in the approved indication(s) remains favourable.
- The PRAC recommended the maintenance of the current terms of the marketing authorisation.

The frequency of submission of PSURs should be changed from yearly to 3-yearly and the next PSUR should be submitted to the EMA within 90 days of the data lock point.

6.1.13. Fidaxomicin – **DIFICLIR** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Qun-Ying Yue (SE)

Background

Fidaxomicin is an antibiotic used for the treatment of *Clostridium difficile* infections.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Dificlir, a centrally authorised medicine containing fidaxomicin, and issued a recommendation on its marketing authorisation.

Summary of recommendation(s) and conclusion

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Dificlir (fidaxomicin) in the approved indication(s) remains favourable.
- The PRAC recommended the maintenance of the current terms of the marketing authorisation.
- Nevertheless, further assessment of the risk of hypersensitivity reactions is warranted. The MAH should submit to the EMA a type II variation within 1 month to update the product information.

The frequency of submission of PSURs should remain 6-monthly and the next PSUR should be submitted to the EMA within 70 days of the data lock point.

6.1.14. Galsulfase – **NAGLAZYME** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Julia Dunne (UK)

Background

Galsulfase is an enzyme used as long-term enzyme replacement therapy in patients with mucopolysaccharidosis VI.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Naglazyme, a centrally authorised medicine containing galsulfase, and issued a recommendation on its marketing authorisation.

Summary of recommendation(s) and conclusion

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Naglazyme (galsulfase) in the approved indication(s) remains favourable.
- The PRAC recommended the maintenance of the current terms of the marketing authorisation.
- The MAH should update the RMP (see also 5.2.11.) to include the development of neutralising antibodies as an 'important potential risk' and propose appropriate pharmacovigilance activities and risk minimisation measures.

The frequency of submission of PSURs should remain once yearly and the next PSUR should be submitted to the EMA within 70 days of the data lock point.

6.1.15. Gefitinib – IRESSA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Ulla Wändel-Liminga (SE)

Background

Gefitinib is used in the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating mutations of EGFR-TK (Epidermal Growth Factor Receptor Tyrosine Kinase).

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Iressa, a centrally authorised medicine containing gefitinib, and issued a recommendation on its marketing authorisation.

Summary of recommendation(s) and conclusion

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Iressa (gefitinib) in the approved indication(s) remains favourable.
- The PRAC recommended the maintenance of the current terms of the marketing authorisation.

The frequency of submission of PSURs should remain yearly and the next PSUR should be submitted to the EMA within 70 days of the data lock point.

6.1.16. Human normal immunoglobulin – **FLEBOGAMMA DIF** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Brigitte Keller-Stanislawski (DE)

Background

Human normal immunoglobulin contains mainly immunoglobulin G (IgG) and is used in replacement therapy, in particular, for patients with primary immunodeficiency syndromes with impaired antibody production or hypogammaglobulinaemia.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Flebogamma DIF, a centrally authorised medicine containing human normal immunoglobulin, and issued a recommendation on its marketing authorisation.

Summary of recommendation(s) and conclusion

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Flebogamma DIF (human normal immunoglobulin) in the approved indication(s) remains favourable.
- The PRAC recommended the maintenance of the current terms of the marketing authorisation.

The frequency of submission of PSURs should be changed from 6 monthly to yearly and the next PSUR should be submitted to the EMA within 70 days of the data lock point.

6.1.17. Human papillomavirus vaccine – **GARDASIL** (CAP), **SILGARD** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Qun-Ying Yue (SE)

Background

Gardasil/Silgard is an adjuvanted recombinant quadrivalent vaccine used for the prevention of premalignant genital lesions (cervical, vulvar and vaginal) and cervical cancer causally related to certain oncogenic human papillomavirus (HPV) types and is also used for the prevention of genital warts (condyloma acuminata) causally related to specific HPV types.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Gardasil/Silgard, centrally authorised human papillomavirus vaccines, and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusion

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Gardasil/Silgard (human papillomavirus vaccine) in the approved indication(s) remains favourable.
- The PRAC recommended the maintenance of the current terms of the marketing authorisation.

- The MAH should provide in the next PSUR a cumulative review of the serious cases of asthma (see also PRAC Minutes of the meeting 3-5 October 2012) in patients with and without a medical history/ concurrent condition of asthma.

The frequency of submission of PSURs should remain once yearly and the next PSUR should be submitted to the EMA within 70 days of the data lock point.

6.1.18. Hydroxycarbamide – **SIKLOS** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Jean-Michel Dogné (BE)

Background

Hydroxycarbamide is an antineoplastic agent used for the prevention of recurrent painful vaso-occlusive crises including acute chest syndrome in patients suffering from symptomatic Sickle Cell syndrome.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Siklos, a centrally authorised medicine containing hydroxycarbamide, and issued a recommendation on its marketing authorisation.

Summary of recommendation(s) and conclusion

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Siklos (hydroxycarbamide) in the approved indication(s) remains favourable.
- The PRAC recommended the maintenance of the current terms of the marketing authorisation.
- The MAH should closely monitor cases of dermatomyositis /dermatomyositis-like eruption, palmar-plantar erythrodysaesthesia and interstitial lung disease in the SCD populations and provide a cumulative review in the next PSUR.

The frequency of submission of PSURs should remain once yearly and the next PSUR should be submitted to the EMA within 70 days of the data lock point.

6.1.19. Ibandronic acid – **BONDENZA** (CAP), **BONDRONAT** (CAP), **BONVIVA** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Doris Stenver (UK)

Background

Ibandronic acid is a bisphosphonate belonging to the nitrogen-containing group and is used in treatment of osteoporosis in postmenopausal women at increased risk of fracture.

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

Summary of recommendation(s) and conclusion

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Bondenza, Bondronat and Bonviva (ibandronic acid) in the approved indication(s) remains favourable.
- The PRAC recommended the maintenance of the current terms of the marketing authorisation.
- The MAH should provide a review of the incidence of cases of coagulopathy within the next PSUR.

The frequency of submission of PSURs should be changed from once yearly to 3-yearly and the next PSUR should be submitted to the EMA within 90 days of the data lock point; the EURD list should be updated accordingly.

6.1.20. Influenza vaccine – FLUENZ (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Isabelle Robine (FR)

Background

Fluenz is a centrally authorised intranasal live attenuated influenza vaccine used in the prophylaxis of influenza in individuals from 24 months to less than 18 years of age.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Fluenz and issued a recommendation on its marketing authorisation.

Summary of recommendation(s) and conclusion

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Fluenz (influenza vaccine) in the approved indication(s) remains favourable.
- The PRAC recommended the maintenance of the current terms of the marketing authorisation.
- The MAH should provide further information to the EMA regarding some specific case reports and should continue to closely monitor several unlisted adverse events, including medically significant wheezing in children under 24 months of age, hypersensitivity disorders, Guillain-Barré syndrome and secondary transmission to severely immunocompromised patients.

The frequency of submission of PSURs should remain 6-monthly and the next PSUR should be submitted to the EMA within 70 days of the data lock point.

6.1.21. Imiglucerase – CEREZYME (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Sabine Straus (NL)

Background

Imiglucerase is an enzyme used as long-term enzyme replacement therapy in patients with a non-neuronopathic (type 1) or chronic neuronopathic (type 3) Gaucher disease.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Cerezyme, a centrally authorised medicine containing imiglucerase, and issued a recommendation on its marketing authorisation.

Summary of recommendation(s) and conclusion

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Cerezyme (imiglucerase) in the approved indication(s) remains favourable.
- The PRAC recommended the maintenance of the current terms of the marketing authorisation.
- The MAH should continue to closely monitor cases of pneumonia and provide in the next PSUR a comparison of pneumonia incidence of treated and untreated patients with the general population. In addition, the MAH should discuss the use of the medicinal product via the Cerezyme Emergency Access Program (CEAP).

The frequency of submission of PSURs should remain every 3 years and the next PSUR should be submitted to the EMA within 90 days of the data lock point.

6.1.22. Liraglutide – VICTOZA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Menno van der Elst (NL)

Background

Liraglutide is a glucagon-like peptide-1 (GLP-1) analogue used in the treatment of type 2 diabetes mellitus.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Victoza, a centrally authorised medicine containing liraglutide, and issued a recommendation on its marketing authorisation.

Summary of recommendation(s) and conclusion

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Victoza (liraglutide) in the approved indication(s) remains favourable.
- The PRAC recommended that the product information should be updated to reflect the adverse reactions "increased heart rate" with a frequency "unknown" and "pancreatitis (including necrotising pancreatitis") with a frequency of "very rare"[7]. The current terms of the marketing authorisation should be varied[8].

The frequency of submission of PSURs should remain once yearly and the next PSUR should be submitted to the EMA within 70 days of the data lock point.

6.1.23. Nepafenac – NEVANAC (CAP)

- Evaluation of a PSUR procedure

[7] In SmPC section 4.8. The package leaflet should be updated accordingly as agreed by the PRAC.
[8] The PRAC Assessment Report and PRAC recommendation are transmitted to the CHMP for adoption of an opinion.

Regulatory details:

PRAC Rapporteur: Dolores Montero (ES)

Background

Nepafenac is a non-steroidal anti-inflammatory and analgesic medicinal product used for prevention and treatment of postoperative pain and inflammation associated with cataract surgery and for reducing the risk of postoperative macular oedema associated with cataract surgery in diabetic patients.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Nevanac, a centrally authorised medicine containing nepafenac, and issued a recommendation on its marketing authorisation.

Summary of recommendation(s) and conclusion

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Nevanac (nepafenac) in the approved indication(s) remains favourable.
- The PRAC recommended the maintenance of the current terms of the marketing authorisation.
- The MAH should provide further information on, and should continue to closely monitor, cases of long term and off-label use, corneal epithelium defect, corneal disorders, reduced visual acuity, blurred vision, eye infection, scleritis, endophthalmitis, haemorrhage, ocular bleeding, and anaphylactic reaction and address these in the next PSUR.

The frequency of submission of PSURs should remain 6-monthly and the next PSUR should be submitted to the EMA within 70 days of the data lock point.

6.1.24. Nitric oxide – INOMAX (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)

Background

Inomax, a centrally authorised product containing nitric oxide, is indicated for the treatment of newborn infants with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension, in order to improve oxygenation and to reduce the need for extracorporeal membrane oxygenation. Nitric oxide is also used as part of the treatment of peri- and post-operative pulmonary hypertension in conjunction with heart surgery, in order to selectively decrease pulmonary arterial pressure and improve right ventricular function and oxygenation.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Inomax, a centrally authorised medicine containing nitric oxide, and issued a recommendation on its marketing authorisation.

Summary of recommendation(s) and conclusion

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

- The PRAC recommended the maintenance of the current terms of the marketing authorisation

The frequency of submission of PSURs should remain 6-monthly and the next PSUR should be submitted to the EMA within 70 days of the next data lock point.

6.1.25. Paliperidone – **INVEGA** (CAP), **XEPLION** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Qun-Ying Yue (SE)

Background

Paliperidone is a selective blocking agent of monoamine effects and is used for maintenance treatment of schizophrenia in selected patients.

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

Summary of recommendation(s) and conclusion

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Invega and Xeplion (paliperidone) in the approved indication(s) remains favourable.
- The PRAC recommended the maintenance of the current terms of the marketing authorisation.
- The MAH is requested to implement changes in the RMP with regard to antiemetic effect and neonatal withdrawal syndrome and monitor these ADRs via routine pharmacovigilance.

The frequency of submission of PSURs should remain 6-monthly and the next PSUR should be submitted to the EMA within 70 days of the next data lock point.

6.1.26. Pegaptanib – **MACUGEN** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Jean-Michel Dogné (BE)

Background

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

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Macugen, a centrally authorised medicine containing pegaptanib, and issued a recommendation on its marketing authorisation.

Summary of recommendation(s) and conclusion

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

- The PRAC recommended the maintenance of the current terms of the marketing authorisation.
- The MAH should closely monitor cases of endophthalmitis in future PSURs and should reflect it as an important identified risk in the RMP.
- The MAH should continue to closely monitor cases of raised intraocular pressure (IOP) cases and other ocular events and present in the next PSUR at the latest a cumulative review of raised IOP case reports in case a positive association between elevated IOP and the number of injections received is shown.

The frequency of submission of PSURs should remain once yearly and the next PSUR should be submitted to the EMA within 70 days of the next data lock point.

6.1.27. Pneumococcal polysaccharide conjugate vaccine – PREVENAR 13 (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Qun-Ying Yue (SE)

Background

Prevenar 13 is a centrally authorised pneumococcal polysaccharide conjugate vaccine.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Prevenar 13, a centrally authorised pneumococcal polysaccharide conjugate vaccine, and issued a recommendation on its marketing authorisation.

Summary of recommendation(s) and conclusion

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Prevenar 13 (pneumococcal polysaccharide conjugate vaccine) in the approved indication(s) remains favourable.
- The PRAC recommended the maintenance of the current terms of the marketing authorisation.
- Nevertheless the MAH should provide to the EMA, within 2 months, a literature review of the background incidence of febrile and non-febrile convulsions in infants and a literature review of the incidence of convulsions and hypotonic–hyporesponsive episodes (HHE) associated with other childhood vaccines.
- In addition, the MAH should provide to the EMA in the next PSUR a cumulative review of cases of apnoea and anaphylaxis as well as a review of cases of fever reported in patients with HHE.

The frequency of submission of PSURs should remain 6-monthly and the next PSUR should be submitted to the EMA within 70 days of the next data lock point.

6.1.28. Ranibizumab – LUCENTIS (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Ulla Wändel-Liminga (SE)

Background

Ranibizumab is a humanised recombinant monoclonal antibody fragment used in the treatment of neovascular (wet) age-related macular degeneration (AMD), of visual impairment due to diabetic macular oedema (DME) and treatment of visual impairment due to macular oedema secondary to retinal vein occlusion.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Lucentis, a centrally authorised medicine containing ranibizumab, and issued a recommendation on its marketing authorisation.

Summary of recommendation(s) and conclusion

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Lucentis (ranibizumab) in the approved indication(s) remains favourable.
- The PRAC recommended the maintenance of the current terms of the marketing authorisation.
- The MAH should closely monitor cases of wound healing complications which should be presented by indication and in total in the next PSUR and be discussed in relation to increase in exposure. In addition, the MAH should perform in the next PSUR a cumulative review of cases of hypertensive crisis, angioedema and other hypersensitivity reactions.

The frequency of submission of PSURs should remain once yearly and the next PSUR should be submitted to the EMA within 70 days of the next data lock point.

6.1.29. Roflumilast – DALIRESP (CAP), **DAXAS** (CAP), **LIBERTEK** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Miguel-Angel Macia (ES)

Background

Roflumilast is a PDE4 inhibitor, a non-steroidal anti-inflammatory agent used for maintenance treatment of severe chronic obstructive pulmonary disease (COPD) associated with chronic bronchitis in adult patients with a history of frequent exacerbations as add on to bronchodilator treatment.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Daliresp, Daxas and Libertek, centrally authorised medicines containing roflumilast, and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusion

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Daliresp, Daxas and Libertek (roflumilast) in the approved indication(s) remains favourable.
- Based on the assessment of the safety data and the benefit-risk analysis on the risk of suicide (currently included in the product information), the PRAC recommended that the completion of the post authorisation long-term observational study RO-2455-403 should be a condition of the

marketing authorisation[9]. Therefore the current terms of the marketing authorisation should be varied[10] in line with this change.

- The MAH should perform a risk assessment of a number of adverse reactions including cardiac arrhythmias, pneumonia, hepatic disorders and anaphylactic reactions. In addition, the MAH should address in the RMP the limited evidence of efficacy in current clinical practice of COPD.

The frequency of submission of PSURs should remain 6-monthly and the next PSUR should be submitted to the EMA within 70 days of the next data lock point.

6.1.30. Saxagliptin / metformin hydrochloride – KOMBOGLYZE (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Menno van der Elst (NL)

Background

The combination saxagliptin / metformin hydrochloride is used in the treatment of type II diabetes mellitus.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Komboglyze, a centrally authorised medicine containing saxagliptin / metformin, and issued a recommendation on its marketing authorisation.

Summary of recommendation(s) and conclusion

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Komboglyze (saxagliptin/metformin) in the approved indication(s) remains favourable.
- The PRAC recommended the maintenance of the current terms of the marketing authorisation.
- The MAH should provide in the next PSUR a cumulative review of all case reports of medication residuesin stool, taking into account all available data, including case reports from clinical trials and the formulation of the product and comment on whether the bioavailability of Komboglyze could be affected.

The frequency of submission of the next PSURs should remain 6-monthly and the next PSUR should be submitted to the EMA within 70 days of the next data lock point.

6.1.31. Sildenafil – REVATIO (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Sabine Straus (NL)

[9] Inclusion in Annex II "conditions or restrictions with regard to the safe and effective use of the medicinal product" to the Marketing Authorisation
[10] The PRAC Assessment Report and PRAC recommendation are transmitted to the CHMP for adoption of an opinion.

Background

Sildenafil is a potent and selective inhibitor of cyclic guanosine monophosphate (cGMP) specific phosphodiesterase type 5 (PDE5). Revatio, a centrally authorised medicine containing sildenafil, is used in the treatment of patients with pulmonary arterial hypertension (PAH).

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Revatio, and issued a recommendation on its marketing authorisation.

Summary of recommendation(s) and conclusion

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Revatio (sildenafil) in the approved indication(s) remains favourable.
- The PRAC recommended the maintenance of the current terms of the marketing authorisation
- The MAH should closely monitor cases of non-arteritic anterior ischemic optic neuropathy (NAION), hearing loss, aneurysms, artery dissections and vaso-occlusive crisis in patients with pulmonary arterial hypertension (PAH) secondary to sickle cell disease.

The frequency of submission of PSURs should remain once yearly and the next PSUR should be submitted to the EMA within 70 days of the next data lock point.

6.1.32. Stavudine – **ZERIT** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Qun-Ying Yue (SE)

Background

Stavudine is an antiviral (nucleoside reverse transcriptase inhibitor) used combination with other antiretroviral medicinal products for the treatment of HIV.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Zerit, a centrally authorised medicine containing stavudine, and issued a recommendation on its marketing authorisation.

Summary of recommendation(s) and conclusion

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Zerit (stavudine) in the approved indication(s) remains favourable.
- The PRAC recommended the maintenance of the current terms of the marketing authorisation.

The frequency of submission of PSURs should remain two-yearly and the next PSUR should be submitted to the EMA within 90 days of the next data lock point.

6.1.33. Ticagrelor – **BRILIQUE** (CAP), **POSSIA** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Sabine Straus (NL)

Background

Ticagrelor belongs to the chemical class cyclopentyltriazolopyrimidines (CPTP) and is given with acetylsalicylic acid (aspirin) for the prevention of atherothrombotic events in selected patients with acute coronary syndromes.

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

Summary of recommendation(s) and conclusion

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Brilique, Possia (ticagrelor) in the approved indication(s) remains favourable.
- The PRAC recommended the maintenance of the current terms of the marketing authorisation.
- Nevertheless, in view of the post marketing reports of drug interactions with acetylsalicylic acid, enoxaparin and heparin, the MAH should submit within 2 months to the EMA a variation to update the product information[11] to ensure that it adequately reflects all the available data.
- The MAH should also provide a cumulative review to the EMA of the balance between the bradyarrhythmia cases with positive and negative (de-)rechallenge in the next PSUR.

The frequency of submission of PSURs should remain 6-monthly and the next PSUR should be submitted to the EMA within 70 days of the next data lock point.

6.1.34. Tobramycin – TOBI PODHALER (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Sabine Straus (NL)

Background

Tobramycin is an aminoglycoside antibiotic used for the suppressive therapy of chronic pulmonary infection due to *Pseudomonas aeruginosa* in adults and children aged 6 years and older with cystic fibrosis.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Tobi Podhaler, a centrally authorised medicine containing tobramycin, and issued a recommendation on its marketing authorisation.

Summary of recommendation(s) and conclusion

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Tobi Podhaler (tobramycin) in the approved indication(s) remains favourable.
- The PRAC recommended the maintenance of the current terms of the marketing authorisation.
- The MAH should provide to the EMA a cumulative analysis of cases reporting dizziness irrespective of with and without ototoxicity in the next PSUR.

[11] SmPC sections 4.4 and 4.5

The frequency of submission of PSURs should remain 6-monthly and the next PSUR should be submitted to the EMA within 70 days of the next data lock point.

6.1.35. Topotecan – **HYCAMTIN** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Ulla Wändel-Liminga (SE)

Background

Topotecan is an antineoplastic used in the treatment of ovarian, cervix and small cell lung cancer in selected patient populations.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Hycamtin, a centrally authorised medicine containing topotecan, and issued a recommendation on its marketing authorisation.

Summary of recommendation(s) and conclusion

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Hycamtin (topotecan) in the approved indication(s) remains favourable.
- The PRAC recommended the maintenance of the current terms of the marketing authorisation.

The frequency of submission of PSURs should remain three-yearly and the next PSUR should be submitted to the EMA within 90 days of the next data lock point.

7. Post-authorisation safety studies (PASS)

7.1. Protocols of post-authorisation safety studies

See also 5.2.34. Ulipristal

7.2. Results of post-authorisation safety studies

7.2.1. Insulin glargine – **LANTUS** (CAP), **OPTISULIN** (CAP)

- PRAC consultation on PASS study results, upon CHMP request

Regulatory details:

PRAC Rapporteur: Menno van der Elst (NL)

Background

Insulin glargine is a human insulin analogue used for the treatment of diabetes.

In 2009 the CHMP concluded that the available data did not provide a cause for concern over evidence to substantiate a possible relationship between insulin glargine and cancer (see European Medicines Agency update on safety of insulin glargine), in particular breast cancer. However, because of the limitations of the existing evidence, the Committee requested the MAH for Lantus, a centrally authorised insulin, to develop a strategy for generation of further research in this area.

The MAH recently submitted the final study report for the International Study of Insulin and Cancer (ISICA) Breast Cancer study, together with the requested literature review of all studies investigating a possible association between insulin glargine and breast cancer. Furthermore, the MAH also provided as requested a discussion on how the benefit-risk of Lantus is affected by all information that has become available since the publications of some studies in Diabetologia in 2009.

The CHMP requested advice from the PRAC on assessment of the results of the ISICA study and the literature review of all studies investigating a possible association between insulin glargine and breast cancer. The PRAC discussed the literature review of publications investigating the association between insulin glargine and breast cancer.

Summary of advice

- Based on the reviewed studies, overall, the available data do not indicate a causal association of use of insulin glargine with an increased risk of breast cancer. However, there are some inconclusive results regarding a possible increased risk of breast cancer in new users of insulin glargine which need to be taken into consideration.
- Since the results of the currently available studies do not provide fully conclusive answers, and considering the limitation of the studies previously discussed (e.g. confounding by indication, selection bias, diagnostic bias, presence of risk factors that have not been addressed sufficiently) the issue should continue to be closely monitored, bearing in mind that further research is ongoing.

7.2.2. **Pioglitazone – ACTOS** (CAP), **GLUSTIN** (CAP), **pioglitazone / metformin - COMPETACT** (CAP), **GLUBRAVA** (CAP), **pioglitazone / glimepiride - TANDEMACT** (CAP)

- PRAC consultation on the assessment of interim (and final) data from a Drug Utilisation Study (DUS), upon CHMP request

Regulatory details:

PRAC Rapporteur: Almath Spooner (IE)

Background

Pioglitazone hydrochloride is a member of the thiazolidinedione class, used in the treatment of type II diabetes.

Centrally authorised medicines containing pioglitazone were subject to a referral procedure under Article 20 of Regulation (EC) No 726/2004.

Arising from previous PSUR and RMP assessments for pioglitazone containing products, the MAH was requested in 2010 to perform a Drug Utilisation Study to collect data on the pattern of use of pioglitazone in clinical practice in the context of regulatory milestones which may have influenced the use of pioglitazone in Europe, including the lifting of the contraindication and additions of the indication of pioglitazone with insulin and the suspension of rosiglitazone. In addition following introduction of additional risk minimisation measures at the conclusion of the Article 20 procedure for pioglitazone in July 2011, the MAH was requested to evaluate drug utilisation data taking into account the timing of implementation of new risk minimisation measures.

The results of the drug utilisation studies conducted with the Clinical Practice Research Datalink CPRD and PHARMO database network have provided useful information on the pattern of use of pioglitazone in clinical practice. Among other findings, the studies report indicated an increased incidence of heart failure in patients treated with insulin as a co-medication compared to non-insulin users treated with

pioglitazone in everyday medical practice. Additionally, the incident rate of heart failure observed in elderly patients was higher than in non-elderly patients treated with pioglitazone in clinical practice.

The product information for pioglitazone and recently implemented risk minimisation measures address and reinforce the increased risk of heart failure in patients using insulin concomitantly and the age-related risks of pioglitazone, including heart failure. The CHMP requested PRAC advice on the adequacy of the risk minimisation measures, particularly with reference to heart failure and use in the elderly and in those using insulin concomitantly.

In the context of the discussion a researcher from the Aarhus University Hospital connected via teleconference presented preliminary results from a registered European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) study with the title: 'Monitoring the effectiveness of risk minimisation in patients treated with pioglitazone-containing products'. The study concluded that the number of new users of pioglitazone-containing products decreased slightly in all countries examined after a DHPC was sent out - as recommended by the CHMP - to inform of the decision of restricting use of the drug to patients without known risk factors for bladder cancer, history of bladder cancer, investigated macroscopic haematuria, advanced age (dose adjustment) smoking. The interim report on the study results is available on the ENCePP website.

Summary of advice

In considering the above mentioned findings, the PRAC noted that the product information for pioglitazone and the additional risk minimisation measures (including educational materials) address the identified risk of heart failure. The product information includes warnings relating to the increased risk of heart failure in patients using insulin concomitantly and the age-related risks of pioglitazone, including heart failure. The PRAC also noted that the results of these studies show that the number of patients being initiated on pioglitazone therapy has fallen and a minority of patients appear to be initiated as first line therapy, suggesting adherence to the labelled indications in clinical practice.

- Based on the results of the drug utilisation studies considered in the context of the previously known information on the heart failure risk and existing warnings, the MAH should provide to the EMA in the next PSUR (with a data lock point of 31 January 2013) an explicit specific benefit-risk evaluation for concomitant use of pioglitazone with insulin in elderly patients; available information on exposure and drug utilisation should also be presented.
- Such evaluations should be submitted to the EMA in the next PSURs to be considered by the PRAC: one in February 2013 and the second with DLP of 31 January 2013.

8. Product related pharmacovigilance inspections

8.1. List of planned pharmacovigilance inspections

None

8.2. On-going or concluded pharmacovigilance inspection

None

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

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

9.1.1. Denosumab – PROLIA (CAP)

- PRAC consultation on a safety-related type II variation upon CHMP request

Regulatory details:

PRAC Rapporteur: Ulla Wändel Liminga (SE)

Background

Prolia, a centrally authorised medicine containing denosumab, is a monoclonal antibody indicated for the treatment of postmenopausal osteoporosis and bone loss in patients undergoing hormone ablation therapy (HALT) for cancer.

The CHMP is evaluating a type II variation for Prolia to update the product information to reflect that rare cases of atypical femoral fracture have been reported following use of denosumab (the PRAC also noted that a variation will also be submitted for Xgeva, another centrally authorised medicine containing denosumab). A DHPC was proposed as an additional risk minimisation measure in order to inform prescribers of this safety concern and the subsequent changes to the product information. The CHMP requested PRAC advice on the assessment of this variation.

Summary of advice

- Information about the risk of atypical fractures of the femur should be included in the Prolia (denosumab) product information. ADR frequencies in the product information should be calculated based on events per total number of subjects. Such updates should be submitted in the framework of a subsequent variation.
- The next PSUR should consider whether criteria used to define atypical fractures in cases where information is missing from the reports lead to an underestimation of the number of cases.
- The PRAC agreed that there is a need for a DHPC as an additional risk minimisation measure to communicate this safety concern to prescribers.

9.1.2. Zonisamide – ZONEGRAN (CAP)

- PRAC consultation on a type II variation, extension of indication upon CHMP request

Regulatory details:

PRAC Rapporteur: Almath Spooner (IE)

Background

Zonegran, a centrally authorised anti-epileptic drug (AED) containing zonisamide, is indicated as adjunctive therapy in the treatment of adults with partial seizures with or without secondary generalisation, and as monotherapy in the treatment of partial seizures with or without secondary generalisation in adults with newly diagnosed epilepsy.

A type II variation is under evaluation by the CHMP to extend the indication as adjunctive therapy in specific types of seizures to adolescents and children aged 6 years and above.

The CHMP requested PRAC advice on the need for additional post-authorisation pharmacovigilance activities relating to use in children (aged 6 years and above) and adolescents.

Summary of advice

- The MAH should submit to the EMA a proposal(s) for an intensive monitoring or active surveillance scheme (e.g. via sentinel sites) to address potential safety concerns in the paediatric population.
- The MAH should submit to the EMA a proposal(s) for a drug utilisation study (ideally a retrospective database study) with the objective of evaluating adherence to routine risk minimisation measures as recommended in the product information for Zonegran (zonisamide) for the paediatric population.
- The PRAC recommended that routine risk minimisation advice in the SmPC should clearly state the need for monitoring height and weight in the paediatric population.

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

9.2.1. Doripenem – DORIBAX (CAP)

- PRAC consultation on a renewal procedure of the marketing authorisation

Regulatory details:

PRAC Rapporteur: Qun-Ying Yue (SE)

Background

Doripenem is a synthetic carbapenem antibacterial agent used in adults for the treatment of nosocomial pneumonia, complicated intra-abdominal infections and complicated urinary tract infections.

Doribax, a centrally authorised medicine containing doripenem, was authorised in 2008.

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

Summary of advice

- Based on the review of the risk management system for Doribax (doripenem), and the CHMP Rapporteur's assessment report, the PRAC concluded that no relevant safety concerns had arisen from the assessment of this renewal procedure. However the PRAC considered the procedure could only be finalised if satisfactory clarification is given on the current status of the discussion regarding the European Committee of Antimicrobial Susceptibility Testing (EUCAST) clinical breakpoints, as agreed in the Article 20 of Regulation (EC) No 726/2004 referral procedure for Doribax concluded in June 2012[12].

[12] The CHMP had agreed to ask the MAH to liaise with the EUCAST to consider the need to revise the clinical breakpoints for Doripenem.

9.2.2. Icatibant – **FIRAZYR** (CAP)

- PRAC consultation on a renewal procedure of the marketing authorisation

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

Background

Icatibant is a selective competitive antagonist at the bradykinin type 2 (B2) receptor and used for symptomatic treatment of acute attacks of hereditary angioedema (HAE) in adults with C1-esterase-inhibitor deficiency.

Firazyr, a centrally authorised medicine containing icatibant, was authorised in 2008.The MAH submitted an application for renewal of the marketing authorisation for opinion by the CHMP. The PRAC is responsible for providing advice to the CHMP on this renewal with regard to safety and risk management aspects.

Summary of advice

Based on the review of the risk management system for Firazyr (icatibant), and the CHMP Rapporteur's assessment report, the PRAC concluded that no relevant safety concerns had arisen from the assessment of this first renewal procedure. The current RMP was considered adequate.

9.2.3. Lapatinib – **TYVERB** (CAP)

- PRAC consultation on a renewal procedure of the conditional marketing authorisation

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

Background

Lapatinib is an inhibitor of the intracellular tyrosine kinase receptor used for the treatment of patients with breast cancer, whose tumours overexpress HER2 (ErbB2), in combinations therapy.

Tyverb, a centrally authorised product containing lapatinib, was authorised under conditional marketing authorisation in 2008. The MAH submitted a renewal of the marketing authorisation for opinion by the CHMP. The PRAC is responsible for providing advice to the CHMP on this renewal with regard to safety and risk management.

Summary of advice

Based on the review of the available information on the status of the fulfilment of Specific Obligations, the safety data submitted and the CHMP Rapporteur assessment report, the PRAC considered that the MAH should provide within the next PSUR a review of the reported cases listed under the SOC Central Nervous System and discuss whether these adverse events are possible adverse reactions associated with lapatinib.

9.2.4. Mecasermin – **INCRELEX** (CAP)

- PRAC consultation on an annual reassessment of the marketing authorisation

Regulatory details:

PRAC Rapporteur: Kirsti Villikka (FI)

Background

Mecasermin is human insulin-like growth factor-1 (rhIGF-1) used for the long-term treatment of growth failure in children and adolescents from 2 to 18 years with severe primary insulin-like growth factor-1 deficiency (primary IGFD).

Increlex, a centrally authorised product containing mecasermin, was authorised under exceptional circumstances in 2007. The MAH submitted an annual reassessment of the marketing authorisation under exceptional circumstances for evaluation by the CHMP. The PRAC is responsible for providing advice to the CHMP on this procedure with regard to safety and risk management.

Summary of advice

Based on the review of the available information on the status of the fulfilment of Specific Obligations and safety data submitted, the PRAC considered that the annual re-assessment procedure for Increlex could be finalised without any amendments to the Specific Obligations.

9.2.5. Methylnaltrexone bromide – RELISTOR (CAP)

- PRAC consultation on a renewal procedure of the marketing authorisation

Regulatory details:

PRAC Rapporteur: Martin Huber (DE)

Background

Methylnaltrexone is a peripheral opioid receptor antagonists used for the treatment of opioid-induced constipation in selected patients.

Relistor, a centrally authorised medicine containing methylnaltrexone, was authorised in 2008.

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

Summary of advice

Based on the review of the risk management system for Relistor (methylnaltrexone) and the CHMP Rapporteur's assessment report, the PRAC concluded that no relevant safety concerns had arisen from the assessment of this first renewal procedure. The PRAC considered that the renewal procedure could be finalised, pending the update of the RMP.

9.2.6. Nicotinic acid / laropiprant – PELZONT (CAP), TREDAPTIVE (CAP), TREVACLYN (CAP)

- PRAC consultation on renewal procedures of the marketing authorisations

Regulatory details:

PRAC Rapporteur: Martin Huber (DE)

Background

The MAH for Tredaptive (nicotinic acid / laropiprant) had submitted an application for renewal of the marketing authorisation for opinion by the CHMP. The PRAC is responsible for providing advice to the CHMP on this renewal with regard to safety and risk management aspects.

Summary of advice

See also 2.1.1.

Due to the preliminary results of HPS2-THRIVE provided to the authorities in December 2012, showing that the primary efficacy endpoint was not met but known and new adverse events occurred more often in the niacotinic acid/laropiprant group than in the placebo group, the PRAC considered that the benefit-risk balance for nicotinic acid/laropiprant is not favourable in the approved indication. The PRAC issued a recommendation to the CHMP for suspension of the marketing authorisation of products containing nicotinic acid/laropiprant.

In order to proceed with the assessment of the renewal, the MAH would need to provide convincing data to identify a patient population in which the efficacy of nicotinic acid/laropiprant can be demonstrated, and in which the benefit clearly outweighs the risks, taking into account the new results identified by the HPS2-THRIVE study.

9.2.7. Pixantrone dimaleate – PIXUVRI (CAP)

- PRAC consultation on a renewal procedure of the conditional marketing authorisation

Regulatory details:
PRAC Rapporteur: Julia Dunne (UK)

Background

Pixantrone is a cytotoxic aza-anthracenedione used as monotherapy for the treatment of adult patients with multiply- relapsed or refractory aggressive non-Hodgkin B-cell lymphomas (NHL).

Pixuvri, a centrally authorised product containing pixantrone, was authorised under a conditional marketing authorisation in 2012. The MAH submitted the first renewal of the conditional marketing authorisation for opinion by the CHMP. The PRAC is responsible for providing advice to the CHMP on this conditional renewal with regard to safety and risk management.

Summary of advice

Based on the review of the available information on the status of the fulfilment of Specific Obligations, the safety data submitted and the CHMP Rapporteur assessment report, the PRAC advised that no amendments to the Specific Obligations were currently required.

9.2.8. Pramipexole – OPRYMEA (CAP)

- PRAC consultation on a renewal procedure of the marketing authorisation

Regulatory details:
PRAC Rapporteur: Doris Stenver (DK)

Background

Pramipexole is a dopamine agonist used for treatment of the signs and symptoms of idiopathic Parkinson's disease.

Oprymea, a centrally authorised generic medicine containing pramipexole, was authorised in 2008. The MAH submitted the first renewal of the marketing authorisation for opinion by the CHMP. The PRAC is responsible for providing advice to the CHMP on this conditional renewal with regard to safety and risk management.

Summary of advice

Based on the review of the risk management system for Oprymea (pramipexole) and the CHMP Rapporteur's assessment report, the PRAC concluded that no relevant safety concerns had arisen from the assessment of this first renewal procedure. The PRAC considered that the MAH should address some outstanding issues, including the update of the product information to bring it in line with the reference medicinal product, before finalisation of the renewal procedure at CHMP level.

9.2.9. Ranolazine – RANEXA (CAP)

- PRAC consultation on a renewal procedure of the marketing authorisation

Regulatory details:

PRAC Rapporteur: Qun-Ying Yue (SE)

Background

Ranolazine is used as add-on therapy for the symptomatic treatment of patients with stable angina pectoris who are inadequately controlled by or intolerant to first-line anti-anginal therapies (such as beta- blockers and/or calcium antagonists).

Ranexa, a centrally authorised medicine containing ranolazine, was authorised in 2008.

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

Summary of advice

Based on the review of the risk management system for Ranexa (ranolazine) and the CHMP Rapporteur's assessment report, the PRAC concluded that no relevant safety concerns had arisen from the assessment of this first renewal procedure. The PRAC considered that the renewal procedure could be finalised, provided the MAH presents an overview of published literature relevant to the approved indication (or to exploratory studies under way) assessing the potential impact on the benefit/risk for the approved indication or dose for Ranexa.

9.2.10. Sitagliptin / metformin hydrochloride – EFFICIB (CAP), **JANUMET** (CAP), **VELMETIA** (CAP)

- PRAC consultation on a renewal procedure of the marketing authorisation

Regulatory details:

PRAC Rapporteur: Menno van der Elst (NL)

Background

The combination sitagliptin a DPP4 inhibitor and metformin, a biguanide, is used in the treatment of type II diabetes mellitus.

Efficib, Janumet and Velmetia, centrally authorised medicines containing sitagliptin / metformin, were authorised in 2008.

The MAH submitted applications for the renewal of the marketing authorisation for each medicinal product for opinion by the CHMP. The PRAC is responsible for providing advice to the CHMP on these with regard to safety and risk management aspects.

Summary of advice

Based on the review of the risk management system for Efficib, Janumet and Velmetia (sitagliptin / metformin) and the CHMP Rapporteur's assessment report, the PRAC concluded that no relevant safety concerns had arisen from the assessment of these first renewal procedures. Therefore the PRAC considered that the renewal procedures could be finalised.

9.3. Timing and message content in relation to MS safety announcements

None

9.4. Other requests

See Insulin glargine 7.2.1. ; Pioglitazone 7.2.2.

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

10.1. Renewals of the Marketing Authorisation

None

10.2. Safety related variations of the Marketing Authorisation

None

10.3. Other requests

10.3.1. Mycobacterium bovis BCG (Bacillus Calmette-Guerin) **vaccine**, Danish strain 1331, live attenuated - **BCG VACCINE SSI** (NAP)

- PRAC consultation on a stand-alone RMP procedure upon a Member State's request

Regulatory details:

PRAC Rapporteur: *to be appointed*

Background and discussion

In 2012 the PhVWP discussed a safety concern raised by Latvia on an increasing number of cases of severe (suppurative) lymphadenitis that required surgical treatment (lymph node extirpation in under general anaesthesia) in the paediatric population following administration of BCG Vaccine SSI. The

PhVWP recommended that the MAH respond to a number of questions and submit a RMP to address an increase in the number of surgically treated cases of BCG lymphadenitis.

LV assessed the responses of the MAH and requested the PRAC advice on the current risk minimisation proposed. In the meantime LV informed the committee that a DHCP and educational brochure on the correct injection technique of the BCG Vaccine SSI were distributed to provide advice on correct administration procedures and management of lymphadenitis in Latvia.

In the context of this discussion RO gave a presentation regarding a recent increase in reports received by the National Public Health Institute in Romania reporting lymphadenitis following vaccination with BCG vaccines confirming that the reports are in the process of being transmitted to EudraVigilance. The PRAC noted the recommendations agreed by the World Health Organization and the European Centre for Disease Protection and Control on the matter (WHO and ECDC recommend immediate resumption of BCG vaccination programme in Romania).

The PRAC agreed that in addition to the evaluation of the RMP, there was a need to review more comprehensively relevant quality and manufacturing data as well as pharmacovigilance data to gather information on quality and safety aspects of the vaccine and to evaluate further the cause of the increase in reports of surgically treated cases of lymphadenitis. DK as reference member state for the BCG vaccine SSI and the member state responsible for the batch release certification will produce a list of points to be addressed for the February 2013 meeting. At the same meeting a PRAC Rapporteur will be appointed for any follow-up action.

PRAC advice will be discussed and agreed on the basis of the assessment provided.

11. Organisational, regulatory and methodological matters

11.1. Mandate and organisation of the PRAC

None

11.2. Pharmacovigilance audits and inspections

None

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

11.3.1. Periodic Safety Update Reports

None

11.3.2. PSUR Repository

None

11.3.3. Union Reference Date List

- Consultation on the draft List, version January 2013

The PRAC was consulted on the EURD list version January 2013. It was agreed that PRAC members should give input on the few outstanding issues by 11 January 2013. The process to be followed for the monthly maintenance of the list was explained by the EMA secretariat and responses from the committee members were to be sent in writing.

The responses received will be integrated into the list for consideration and adoption by CMDh and CHMP at their January 2013 meetings. Any unresolved issues will be brought back to the PRAC at its February 2013 meeting.

Post-meeting note: the process for the monthly update will be implemented without amendment.

11.4. Signal Management

11.4.1. Signal Management

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

The PRAC received an updated on the SMART WG Work plan including the mandate of the group, its objectives and the operational organisation based on 3 work streams (WST): tools and processes, operational best practice guidance and methodological, including statistical guidance. The PRAC will be receiving periodic updates on the progress of the work and deliverables.

11.5. Adverse Drug Reactions reporting and additional reporting

None

11.6. EudraVigilance Database

None

11.7. Risk Management Plans and Effectiveness of Risk Minimisation

11.7.1. Risk Management Systems

None

11.7.2. Tools, Educational Materials and Effectiveness Measurement for Risk Minimisation

None

11.7.2.1. RMP Flowchart

The EMA secretariat presented a set of criteria for rationalising plenary discussion time - relating to RMP assessments - at the meetings of the PRAC, in line with the most recent recommendations from the EMA MB on the need for careful management of resources vis-à-vis the workload (See minutes of the 77th meeting of the EMA MB). These criteria had been developed by the EMA in collaboration with Member States through the Governance structure for the Implementation of the Pharmacovigilance legislation.

The EMA Secretariat emphasised that the PRAC will be involved in the assessment of all RMP procedures for centrally authorised products. The criteria address circumstances relating to the need for in-depth Committee advice on assessment of RMPs for both centrally and non-centrally authorised products and aim to allocate discussion time at the PRAC plenary in a risk-proportionate way. The criteria, in establishing the need for plenary discussion, take into consideration different factors according to the type of application, the nature of the comments received on the assessment performed by the Rapporteurs, the need for specific input and advice, and whether the RMP discusses an emerging safety issue or includes a proposal to remove an additional risk minimisation measure or proposes additional pharmacovigilance activities.

It is expected that the criteria will result in some procedures being allocated extended time for discussion. In contrast, others will be allocated less, or even no, time for discussion at the plenary in case of more administrative updates.

The PRAC agreed to use the criteria for the February 2013 meeting as a pilot phase in order to gain experience and evaluate the need for any refinement.

11.8. Post-authorisation Safety Studies

None

11.9. Community Procedures

None

11.10. Risk communication and Transparency

11.10.1. Public Participation in Pharmacovigilance

None

11.10.2. Safety Communication

- Guideline on good pharmacovigilance practices (GVP) Module XV on safety communication

EMA secretariat presented the updated GVP module XV on safety communications. It now incorporates feedback received during public consultation. The scope has been modified to clarify that although safety communication is a broader term, the module focuses on the communication of new emergent safety information. Among the different tools and channels described, the text places particular emphasis on Direct Health Care Professional Communications (DHPCs). The MAHs are to submit proposals for DHPC communication plans to the Agency according to criteria listed in the GVP Module. The Agency will coordinate the review within its scientific committees/ groups (i.e. involvement of PRAC and finalisation by CHMP or CMDh). The PRAC will always be involved when the safety concern is or has been discussed at the PRAC and the DHPC will be part of the PRAC assessment. The CHMP or CMDh will input following PRAC review where applicable.

If a DHPC relates to an issue not discussed by the PRAC (e.g. a shortage not linked to safety), there will be no need for PRAC advice.

11.11. Continuous pharmacovigilance

None

11.12. Interaction with EMA Committees and Working Parties

11.12.1. Committees

None

11.12.2. Working Parties

11.12.2.1. Patients and Consumers Working Party (PCWP)

- PCWP Work Plan for 2013

The PRAC adopted the work plan of the PCWP which will be published on the EMA website. A nomination for a PRAC member to attend the PCWP meeting in order to strengthen the interaction will be agreed once representatives from civil societies are appointed to the PRAC.

11.13. Interaction within the EU regulatory network

None

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

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

None

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

The PRAC endorsed the transfer of the evaluation of the D:A:D data and responsibility for regulatory representation in the HAART Oversight Committee from CHMP to PRAC, the CHMP being in agreement. Roles and responsibilities were explained to the members as well as an outline of this prospective multi-cohort study of HIV-infected persons under active follow-up. Follow-up will be given at the March 2013 PRAC meeting.

11.14.3. Other Drug Regulatory Authorities outside the EU

- International pharmacovigilance teleconferences and non-EU DRA and PRAC observerships to PRAC

The EMA secretariat presented a proposal for the participation of experts from other national competent authorities outside the EU as observers, and for a monthly pharmacovigilance teleconference with other medicines agencies. The PRAC welcomed efforts to facilitate international collaboration in the area of pharmacovigilance among regulatory authorities. Members were invited to provide comments in writing and a follow-up discussion will take place at the 4-7 February 2013 meeting of the PRAC.

12. Any other business

12.1. PRAC Rapporteurs appointment principles for re-examination procedures of the initial marketing authorisation application

- Appointment (and role) of PRAC Rapporteurs for re-examinations

The appointment and role of the PRAC Rapporteur in re-examination procedures were outlined to the Committee. PRAC involvement will focus on specific elements relating to the RMP and any other specific points highlighted for PRAC consideration in the CHMP Re-Examination Rapporteurs Assessment report, and will result in PRAC advice to be forwarded to the CHMP. In case of a positive opinion resulting from the re-examination, the PRAC Rapporteur will be responsible for the finalisation of the RMP. EMA will work on an amendment to the current procedural advice on these aspects and the PRAC will be updated accordingly.

ANNEX I – List of abbreviations

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

www.ema.europa.eu

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ANNEX II – List of participants: *including any restrictions with respect to involvement of members / alternates / experts following evaluation of declared interests for the 7-10 January 2013 meeeting.*

PRAC member PRAC alternate	Country	Outcome restriction following evaluation of e-DoI for the meeting	Topics on the current Committee Agenda for which restriction applies Product / substance
Harald Herkner	Austria	Full involvement	
Jean-Michel Dogne	Belgium	Cannot act as Rapporteur or Peer-reviewer for:	regorafenib, octocog alfa
Maria Popova-Kiradjieva	Bulgaria	Full involvement	
Christos Petrou	Cyprus	Full involvement	
Eva Jirsova	Czech Republic	Full involvement	
Line Michan	Denmark	Full involvement	
Doris Stenver	Denmark	Full involvement	
Maia Uuskula	Estonia	Full involvement	
Terhi Lehtinen	Finland	Involvement in discussions only with respect to procedures involving the following products i.e. no part in final deliberations and voting as appropriate as regards these medicinal products. - Cannot act as Rapporteur for these products.	pramipexole, votrioxetine, tiotropium
Kirsti Villikka	Finland	Full involvement	
Isabelle Robine	France	Full involvement	
Martin Huber	Germany	Full involvement	
Leonidas Klironomos	Greece	Cannot act as Rapporteur or Peer reviewer:	etanercept, pneumococcal polysaccharide conjugate vaccine, pegaptanib, tygecycline, sildenafil
Julia Pallos	Hungary	Full involvement	
Gudrun Kristin Steingrimsdottir	Iceland	Full involvement	
Almath Spooner	Ireland	Full involvement	
Fernanda Ferrazin	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	

PRAC member PRAC alternate	*Country*	*Outcome restriction following evaluation of e-DoI for the meeting*	*Topics on the current Committee Agenda for which restriction applies* *Product / substance*
Margarida Guimaraes	Portugal	Full involvement	
Nicolae Fotin	Romania	Involvement in discussions only with respect to procedures involving the following products i.e. no part in final deliberations and voting as appropriate as regards these medicinal products. - Cannot act as Rapporteur for these products.	fidaxomycin, tygecycline, tobramycin, doripenem
Anna Marekova	Slovakia	Full involvement	
Milena Radoha-Bergoc	Slovenia	Full involvement	
Miguel-Angel Macia	Spain	Full involvement	
Dolores Montero	Spain	Full involvement	
Qun-Ying Yue	Sweden	Full involvement	
Ulla Wandel Liminga	Sweden	Full involvement	
June Munro Raine	United Kingdom	Full involvement	
Julia Dunne	United Kingdom	Full involvement	
Julie Williams	United kingdom	Full involvement	

Independent scientific experts nominated by the European Commission	**Country**	**Outcome restriction following evaluation of e-DoI for the meeting:**	**Topics on the current Committee Agenda for which restriction applies** *Product / substance*
Marie Louise (Marieke) De Bruin	Not applicable	Cannot act as Rapporteur or Peer reviewer:	etanercept, pneumococcal polysaccharide conjugate vaccine, pegaptanib, tygecycline, sildenafil, lapatinib, ambrisentan
Stephen Evans		Cannot act as Rapporteur or Peer reviewer:	etanercept, pneumococcal polysaccharide conjugate vaccine, pegaptanib, tygecycline, sildenafil
Birgitte Keller-Stanislawski		Full involvement	
Herve Le Loue		Involvement in discussions only with respect to procedures involving the following products i.e. no part in final deliberations and voting	etanercept

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*
		as appropriate as regards these medicinal products. - Cannot act as Rapporteur for these products.	
Lennart Waldenlind		Full involvement	

Additional European experts participating at the meeting for specific Agenda items	Country	
Diederica Claeys	Belgium	No restrictions were identified for the participation of European experts attending the PRAC meeting for discussion on specific agenda items
Jamila Hamdani	Belgium	
Walter Janssens	Belgium	
Veerle Verlinden	Belgium	
Vera Ehrenstein	Denmark	
Rikke Jensen	Denmark	
Katja Ivanitskiy	Finland	
Arnaud Batz	France	
Florence Cardona	France	
Sara Miranda	France	
Christelle Saussier	France	
Christine Diesinger	Germany	
Tania Meier	Germany	
Yvonne Looney	Ireland	
Zane Neikena	Latvia	
John J Borg	Malta	
Charlotte Backman	Sweden	
Filip Josephson	Sweden	
Karl-Mikael Kalkner	Sweden	