9 January 2015
EMA/PRAC/786812/2014
Pharmacovigilance Risk Assessment Committee (PRAC)

Pharmacovigilance Risk Assessment Committee (PRAC)

Minutes of the meeting on 1-4 December 2014

Chair: June Raine – Vice-Chair: Almath Spooner

Disclaimers

Some of the information contained in this agenda is considered commercially confidential or sensitive and therefore not disclosed. With regard to intended therapeutic indications or procedure scope listed against products, it must be noted that these may not reflect the full wording proposed by applicants and may also change during the course of the review. Additional details on some of these procedures will be published in the PRAC meeting highlights once the procedures are finalised. The start of referrals will also be announced in the meeting highlights.

Note on access to documents

Some documents mentioned in the agenda cannot be released at present following a request for access to documents under Regulation (EC) No 1049/2001 as they relate to on-going procedures for which a final decision has not yet been adopted. They will become public when adopted or considered public according to the principles stated in the Agency policy on access to documents (EMA/127362/2006).

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Explanatory notes

The Notes give a brief explanation of relevant agenda items and should be read in conjunction with the agenda.

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 agenda)

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

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

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

Assessment of Periodic Safety Update Reports (PSURs)
(Item 6 of the PRAC agenda)

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

Post-authorisation Safety Studies (PASS)
(Item 7 of the PRAC agenda)

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

Product related pharmacovigilance inspections
(Item 9 of the PRAC agenda)

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

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

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1. Introduction

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

The Chairperson opened the 1-4 December 2014 meeting by welcoming all participants.

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

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

The PRAC Chair noted that Jelena Ivanovic was to step down as alternate for Italy and thanked her for her contribution to the work of the PRAC.

1.2. Adoption of agenda of the meeting of 1-4 December 2014

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

1.3. Minutes of the previous PRAC meeting on 3-6 November 2014

The minutes were adopted with some amendments received during the consultation phase and will be published on the EMA website.

Post-meeting note: the PRAC minutes of the meeting held on 3-6 November 2014 were published on the EMA website on 12 December 2014 (EMA/PRAC/732664/2014).

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

None

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

3.1. Newly triggered Procedures

None

3.2. Ongoing Procedures

3.2.1. **Ambroxol** (NAP); **bromhexine** (NAP)

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

Regulatory details:
PRAC Rapporteur: Margarida Guimarães (PT)
PRAC Co-Rapporteurs: Jean-Michel Dogné (BE), Harald Herkner (AT)

Administrative details:
MAH(s): Boehringer Ingelheim, various

Background

A referral procedure under Article 31 of Directive 2001/83/EC is ongoing for ambroxol and bromhexine-containing medicines (see PRAC minutes 8-11 September 2014). Following receipt of an opinion from the Paediatric Committee (PDCO) and a response to the list of outstanding issues from the MAHs, the Rapporteurs prepared an assessment report for discussion at the meeting.

Summary of recommendation(s)/conclusions

One oral explanation took place at the meeting. The PRAC discussed aspects relating to paediatric use of these products based on the advice provided by the PDCO and further aspects to be clarified based on the review performed so far, and agreed a second list of outstanding issues (LoOI) to be addressed by the MAHs, together with a revised timetable for the procedure (EMA/PRAC/189079/2014 rev1).

3.2.2. **Dexibuprofen** (NAP); **ibuprofen** (NAP)

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

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

Administrative details:
MAH(s): various

Background

A referral procedure under Article 31 of Directive 2001/83/EC is ongoing for ibuprofen (and for the dextrorotatory enantiomer of ibuprofen, dexibuprofen) containing medicines (see PRAC minutes 10-13 June 2014).

A preliminary assessment of available clinical trial and epidemiological data including published and unpublished data on the risk of thrombotic events, particularly with high dose ibuprofen (2,400 mg/daily) in adults, along with new evidence on interaction between low-dose aspirin and ibuprofen/dexibuprofen, was performed by the Rapporteurs according to the agreed timelines.

Summary of recommendation(s)/conclusions

The PRAC discussed the preliminary results of the review and on this basis agreed a list of questions to be addressed by the Coxib and traditional NSAID Trialists' (CNT) Collaboration to have clarity on some aspects relating to the analysis performed in their study. Moreover the PRAC agreed a list of the

questions for the MAHs together with a revised timetable for the procedure (EMA/PRAC/332908/2014 Rev.1).

3.3. Procedures for finalisation

None

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

None

3.5. Others

None

4. Signals assessment and prioritisation[1]

4.1. New signals detected from EU spontaneous reporting systems

4.1.1. Lenalidomide – REVLIMID (CAP)

- Signal of Parkinson's disease

Regulatory details:
PRAC Rapporteur: Arnaud Batz (FR)

Administrative details:
EPITT 18135 – New signal
MAH(s): Celgene Europe Limited
Lead MS: FR

Background

Lenalidomide is an immunomodulator used for the treatment of multiple myeloma in combination with dexamethasone in certain patients and for the treatment of patients with transfusion-dependent anaemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate.

The exposure for Revlimid, a centrally authorised medicine containing lenalidomide, is estimated to have been more than 328,000 patients worldwide, in the period from first authorisation in 2007 to 2013.

During routine signal detection activities, a signal of Parkinson's disease was identified by the EMA, based on 35 cases retrieved from EudraVigilance of Parkinson's disease and Parkinsonism. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

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

Discussion

The PRAC discussed the information on the cases reporting (worsening of) Parkinson's disease (PD), including some cases with a positive dechallenge. Time to onset was variable.
The PRAC noted that worsening of Parkinson's disease symptoms has been a known adverse drug reaction (ADR) associated with the chemically related thalidomide and this is reported in its product information. Given the structural similarities and mechanism of action as well as the similar neurological reactions profile of both substances, an association of PD and lenalidomide was considered plausible. However, the PRAC agreed that further information was needed to fully assess the signal.

Summary of recommendation(s)

- The MAH for Revlimid (lenalidomide) should submit to the EMA a cumulative review of the signal in the next PSUR (DLP: 26/12/2014). The MAH should discuss separately the role of lenalidomide in reports of de novo Parkinson's disease, and in exacerbations of existing Parkinson's disease. The review should discuss whether the case reports include symptoms which represent known adverse effects of lenalidomide (e.g. tremor, impaired balance, ataxia) or whether they are characteristic Parkinsonian symptoms (i.e. include reference to resting tremor, bradykinesia, rigidity).

4.1.2. **Natalizumab – TYSABRI** (CAP)

- Signal of anaemia

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

Administrative details:
EPITT 18137 – New signal
MAH(s): Biogen Idec Ltd
Lead MS: DE

Background

Natalizumab is a monoclonal antibody used as single disease-modifying therapy in highly active relapsing-remitting multiple sclerosis for patients aged 18 years and over.

The exposure for Tysabri, a centrally authorised medicine containing natalizumab, is estimated to have been more than 370,000 patient-years worldwide in the post-marketing setting, in the period from November 2004 to June 2014.

During routine signal detection activities, a signal of anaemia was identified by the EMA, based on 10 cases retrieved from EudraVigilance and from articles published in the literature[2],[3]. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information on the suspected cases of anaemia reported in association with treatment with natalizumab. In all cases bone marrow biopsy showed pathological findings regarding

[2] Monteleone F, Buccisano F, Boffa L, Buttari F, Di Veroli A, Borriello G, Rossi S, Centonze D. Reversible hyporegenerative anemia during natalizumab treatment. Mult Scler. 2014 Sep
[3] Simone AM, Ferraro D, Vitetta F, Marasca R, Bonacorsi G, Pinelli G, Federzoni L, Nichelli PF, Sola P. Severe anaemia in a patient with multiple sclerosis treated with natalizumab. Neurology. 2014 Jul 22;83(4):374-5.

erythropoesis, suggesting that cells of the colony forming unit in the bone marrow were affected. The authors of the cases reported in the literature proposed as a suspected biological mechanism that differentiation of precursor RBC could be inhibited by natalizumab, given the presence of α4β1 integrins on their surface. Hyporegenerative anaemia could, therefore, be a haematological complication in patients treated with natalizumab.

The PRAC agreed that anaemia is frequently seen in patients with chronic inflammatory disease and respective confounding factors for the MS population should be taken into consideration, however supported gathering further information to investigate the signal.

Summary of recommendation(s)

- The MAH for Tysabri (natalizumab) should submit to the EMA, within 60 days, a cumulative review of all relevant data from all sources related to anaemia.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.1.3. Trabectedin – YONDELIS (CAP)

- Signal of capillary leak syndrome (CLS)

Regulatory details:
PRAC Rapporteur: Torbjorn Callreus (DK)

Administrative details:
EPITT 18115 – New signal
MAH(s): Pharma Mar, S.A.
Lead MS: DK

Background

Trabectedin is an antineoplastic agent used for the treatment of advanced soft-tissue sarcoma in selected patients and in combination with pegylated liposomal doxorubicin (PLD) for the treatment of patients with relapsed platinum-sensitive ovarian cancer.

The exposure for Yondelis, a centrally authorised medicine containing trabectedin, is estimated to have been more than 35,000 patients worldwide, in the period from first authorisation in 2007 to 2013.

During routine signal detection activities, a signal of capillary leak syndrome (CLS) was identified by the EMA, based on 6 cases retrieved from EudraVigilance. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information on the suspected cases of systemic capillary leak syndrome (SCLS) reported and commented that the disorder is usually identified following end-organ damage, leading to misclassification as reporters would report the clinical manifestations rather than the mechanism for it. A delayed diagnosis or misdiagnosis might increase patient morbidity and may adversely affect outcome.
The short time to onset of the reaction after the first or the second cycle of trabectedin suggested a compatible temporal relationship with the treatment. The progression and context of the events suggested the possible complications of CLS. The PRAC discussed possible confounders and agreed that further information was necessary to fully investigate the signal.

Summary of recommendation(s)

- The MAH for Yondelis (trabectedin) should submit to the EMA, within 60 days, a cumulative review of cases of CLS in association with trabectedin.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.2. New signals detected from other sources

None

4.3. Signals follow-up and prioritisation

4.3.1. Interferon alfa-2a (NAP)
Interferon alfa-2b – INTRONA (CAP)
Interferon beta-1a – AVONEX (CAP), **REBIF** (CAP)
Interferon beta-1b - BETAFERON (CAP), **EXTAVIA** (CAP)
Peginterferon alfa-2a - **PEGASYS** (CAP)
Peginterferon alfa-2b - **PEGINTRON** (CAP), **VIRAFERONPEG** (CAP)

- Signal of pulmonary arterial hypertension

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

Administrative details:
EPITT 18059 – Follow-up September 2014
MAH(s): Biogen Idec (Avonex), Merck Serono Europe Limited (Rebif), Bayer Pharma AG (Betaferon), Novartis Europharm Ltd (Extavia), Merck Sharp & Dohme Limited (IntronA, PegIntron, ViraferonPeg), Roche Registration Ltd (Pegasys, Roferon-A)

Background

For background information, see PRAC minutes of 8-11 September 2014.

The Rapporteur(s) performed an assessment of the signal of pulmonary arterial hypertension (PAH) with interferons (IFNs) alfa and beta products including PSUR and EudraVigilance (EV) data, together with the analysis by Savale et al[4] and other published clinical and non-clinical data as agreed by the PRAC at the September 2014 meeting, which was presented for PRAC discussion.

Discussion

The PRAC discussed the available evidence and noted that the retrospective study by Savale et al[4] suggests a possible role of IFN in the development of PAH, in particular when considering haemodynamic data. The role of IFN was also suspected in further published cases in various indications. Non-clinical data in sheep suggest that IFN elevates pulmonary artery pressure[5], while a recent study in mice and rats suggest that IFN alfa may reverse experimental pulmonary

[4] Savale L, Sattler C, Günther S, Montani D, Chaumais MC, Perrin S, Jaïs X, Seferian A, Jovan R, Bulifon S, Parent F, Simonneau G, Humbert M, Sitbon O. Pulmonary arterial hypertension in patients treated with interferon. Eur Respir J. 2014 Oct 16
[5] Hanaoka M, Kubo K, Hayano T, Koizumi T, Kobayashi T. Interferon-á elevates pulmonary blood pressure in sheep—the role of thromboxane cascade Eur J Pharmacol. 1999 Apr 9; 370(2):145-51

hypertension[6]. Amongst PSUR and EV data for individual products, there were cases without confounding factors as well as cases of positive dechallenge and rechallenge. However, the number of cases with sufficient information for assessment was small compared to the large exposure of the products.

Based on these data, the PRAC agreed that a causal relationship between the use of IFN and development of PAH could not be excluded and that the product information of interferon alfa and beta containing products should reflect this risk.

Summary of recommendation(s)

- The MAHs of interferon alfa and beta–containing products should submit to the EMA within 30 days comments on the wording proposed by the PRAC to reflect in the product information the risk of pulmonary arterial hypertension.
- The PRAC will assess the MAHs' responses within a 60 day timetable.

Post-meeting note: following a request from MAHs which was considered justified, the PRAC agreed for a modification of the timetable for submission of responses by 60 days.

4.3.2. Vildagliptin – **GALVUS** (CAP), **JALRA** (CAP), **XILIARX** (CAP) **Vildagliptin, metformin - EUCREAS** (CAP), **ICANDRA** (CAP), **ZOMARIST** (CAP)

- Signal of rhabdomyolysis

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

Administrative details:
EPITT 17959 – Follow-up June 2014
MAH(s): Novartis Europharm Ltd

Background

For background information, see PRAC minutes of 10-13 June 2014.
The MAH for Galvus (vildagliptin) and Eucreas (vildagliptin/metformin) had been requested to submit a variation to include 'rhabdomyolysis' in the product information.
The MAH replied to the request with a 'response to Health Authority questions - review of rhabdomyolysis' providing additional data which was assessed by the Rapporteur.

Discussion

The PRAC discussed the assessment of the response received, that included all cumulative cases in clinical trials, post-marketing safety databases and cases described in the literature relating to rhabdomyolysis, as well as epidemiological data. A review of the plausible biological mechanism for the development of rhabdomyolysis was also considered.
The PRAC concluded that the evidence to support an increased risk of rhabdomyolysis in association with vildagliptin was limited and insufficient. However, considering that there was a higher proportion of patients who experienced myalgia while on statin use in the vildagliptin group compared to placebo in clinical trials, that in a large proportion of post-marketing cases myalgia was described, and that

[6] Bauer EM, Zheng H, Lotze MT, Bauer PM. Recombinant human interferon alpha 2b prevents and reverses experimental pulmonary hypertension. PLoS One. 2014 May 16;9(5):e96720. doi: 10.1371/journal.pone.0096720. eCollection 2014

literature findings suggested that musculoskeletal disorders are strongly associated with gliptin, the PRAC therefore concluded that myalgia should be included in the product information for vildagliptin. Some changes to the RMP of relevant medicines were also considered necessary.

Summary of recommendation(s)

- The MAH for Galvus (vildagliptin) and Eucreas (vildagliptin/metformin) should submit a variation to the EMA within 2 months to include 'myalgia' in SmPC section 4.8. In the next PSUR for vildagliptin and vildagliptin/metformin (DLP: 28/02/2015), events of muscle events/myopathy/rhabdomyolysis should be closely monitored.
- In the RMP for Galvus and Eucreas, the important potential risk should be updated to include rhabdomyolysis specifically 'muscle events/myopathy/rhabdomyolysis, in particular with current statin use'.

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

- Signal of inhibitor development in previously untreated patients (PUP)

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

Administrative details:
EPITT 18134 – Follow-up November 2014
MAH(s): Bayer Pharma AG

Background and Summary of recommendation(s)

Following discussion at the 3-6 November 2014 meeting of the PRAC and in preparation for further review in January 2015, the PRAC agreed that further clarity was needed on aspects of the analysis performed in the recently published study 'Factor VIII brand and the incidence of factor VIII inhibitors in previously untreated UK children with severe haemophilia A, 2000-2011' (Blood, 2014, Collins et al., 2014). The EMA will support contact with the relevant researchers and follow-up discussion will take place at the January 2015 PRAC meeting.

5. Risk Management Plans

5.1. Medicines in the pre-authorisation phase

The PRAC provided advice to the CHMP on the proposed RMPs for a number of products (identified by active substance below) that are under evaluation for initial marketing authorisation. Information on the PRAC advice will be available in the European Public Assessment Reports (EPARs) to be published at the end of the evaluation procedure.

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

5.1.1. Ceritinib

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

Administrative details:
Product number(s): EMEA/H/C/003819
Intended indication(s): Treatment of non-small cell lung cancer (NSCLC)

5.1.2. Human papillomavirus vaccine [types 6, 11, 16, 18, 31, 33, 45, 52, 58] (recombinant, adsorbed)

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

Administrative details:
Product number(s): EMEA/H/C/003852
Intended indication(s): Treatment of human papillomavirus (HPV) diseases

5.1.3. Naltrexone, bupropion

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

Administrative details:
Product number(s): EMEA/H/C/003687
Intended indication(s): Management of obesity

5.2. Medicines already authorised

RMP in the context of a variation[7] – PRAC-led procedure

See Annex 14

RMP in the context of a variation – CHMP-led procedure

5.2.1. Bortezomib – VELCADE (CAP)

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

Regulatory details:
PRAC Rapporteur: Carmela Macchiarulo (IT)

Administrative details:
Procedure number(s): EMEA/H/C/000539/II/0072
Procedure scope: Extension of indication for the use of bortezomib in combination with rituximab, cyclophosphamide, doxorubicin and prednisone for the treatment of adult patients with previously untreated mantle cell lymphoma. Consequently, the MAH proposed updates of SmPC sections 4.1, 4.2, 4.4, 4.8 and 5.1 and the package leaflet
MAH(s): Janssen-Cilag International N.V.

Background

Velcade is a centrally authorised product containing bortezomib, a proteasome inhibitor used as an antineoplastic agent for the treatment of selected adult patients with multiple myeloma.

The CHMP is evaluating an extension of the therapeutic indication for Velcade, to include use of bortezomib in combination with rituximab, cyclophosphamide, doxorubicin and prednisone for the treatment of adult patients with previously untreated mantle cell lymphoma.
The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this extension of indication.

[7] In line with the revised variation regulation for submissions as of 4 August 2013

Summary of advice

- The RMP version 29.1 for Velcade (bortezomib) submitted in the context of the extension of indication variation under evaluation by the CHMP was considered acceptable.

RMP evaluated in the context of a PSUR procedure

See also Bromfenac – YELLOX 6.1.3. , Piperaquine, artenimol , dihydroartemisinin – EURARTESIM 15.1.24. , Tafamidis – VYNDAQEL 15.1.31. , Turoctocog alfa – NOVOEIGHT 15.1.33. , Ulipristal acetate – ELLAONE 15.1.34.

RMP evaluated in the context of PASS results

See also Human papillomavirus vaccine [types 6, 11, 18] (recombinant, adsorbed) – GARDASIL, SILGARD 16.1.10. , Insulin degludec – TRESIBA 16.1.10. , Ivacaftor – KALYDECO 16.1.14. , Telaprevir – INCIVO 16.1.19.

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

See Annex 14

RMP evaluated in the context of a stand-alone RMP procedure

None

Others

Bisphosphonates, denosumab and risk of osteonecrosis of the jaw (ONJ): consultation with Scientific Advisory Group (SAG) Oncology, see under 12.13.2.1.

6. Periodic Safety Update Reports (PSURs)

6.1.1. **Azacitidine – VIDAZA** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
Procedure number(s): EMEA/H/C/000978/PSUV 0029
MAH(s): Celgene Europe Limited

Background

Azacitidine is an antineoplastic agent indicated for the treatment of adult patients who are not eligible for haematopoietic stem cell transplantation with intermediate-2 and high-risk myelodysplastic syndromes (MDS), with chronic myelomonocytic leukaemia (CMML) or with acute myeloid leukaemia (AML) under certain conditions.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Vidaza (azacitidine) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to add necrotising fasciitis as an undesirable effect with an unknown frequency, together with a warning to ensure that appropriate treatment is promptly initiated and therapy with azacitidine is discontinued. Therefore the current terms of the marketing authorisation(s) should be varied[8].
- In the next PSUR, the MAH should provide a detailed analysis on possible preventive measures to lower the risk of tumour lysis syndrome in patients initiating azacitidine and propose to update the product information as warranted.
- In addition, the MAH should include necrotising fasciitis as a safety concern in the RMP at the next regulatory opportunity and consider implementing a targeted follow-up questionnaire as part of the routine pharmacovigilance activities to gain further clinical information on reported cases to aid causality assessment.

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

6.1.2. Boceprevir – VICTRELIS (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Arnaud Batz (FR)

Administrative details:
Procedure number(s): EMEA/H/C/002332/PSUV 0031
MAH(s): Merck Sharp & Dohme Limited

Background

Boceprevir is a protease inhibitor indicated for the treatment of chronic hepatitis C (CHC) genotype 1 infection in combination with peginterferon alfa and ribavirin under certain conditions.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Victrelis (boceprevir) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to add the drug-drug interaction between boceprevir and maraviroc when they are concomitantly administered as this increases maraviroc exposure warranting its dose-adjustment. In addition, renal impairment and

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

decreased glomerular filtration rate should be added as an undesirable effect with an unknown frequency. Therefore the current terms of the marketing authorisation(s) should be varied[9].

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC. The frequency of submission of the subsequent PSURs should be changed from 6-monthly to yearly and the list of Union reference dates (EURD list) will be updated accordingly.

6.1.3. Bromfenac – YELLOX (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Torbjorn Callreus (DK)

Administrative details:
Procedure number(s): EMEA/H/C/001198/PSUV 0010 (with RMP version 8.0)
MAH(s): Croma-Pharma GmbH

Background

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

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Yellox (bromfenac) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to add a warning on possible rebound of macular oedema following cessation of treatment. Therefore the current terms of the marketing authorisation(s) should be varied[10].
- In the next PSUR, the MAH should closely monitor any reported adverse drug reactions where the duration of treatment has exceeded the recommended 2 weeks.

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

6.1.4. Fentanyl – EFFENTORA (CAP), INSTANYL (CAP), PECFENT (CAP), NAP

- Evaluation of a PSUSA[11] procedure

Regulatory details:
PRAC Rapporteur: Arnaud Batz (FR)

[9] Update of SmPC sections 4.5 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion
[10] Update of SmPC section 4.4. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion
[11] PSUR single assessment, referring to CAP, NAP

Administrative details:
Procedure number(s): EMEA/H/C/PSUSA/00001369/201404
MAH(s): Teva Pharma B.V. (Effentora), Takeda Pharma A/S (Instanyl), Archimedes Development Limited (PecFent), various

Background

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

Based on the assessment of the individual PSURs, part of the PSUR single assessment procedure (PSUSA), the PRAC reviewed the benefit-risk balance of transmucosal fentanyl-containing products and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of transmucosal fentanyl-containing products in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated as necessary to include recommendations to discontinue treatment with transmucosal fentanyl if the patient no longer experiences breakthrough pain episodes and to closely monitor patients if discontinuation of all opioid therapy is required, in order to manage the risk of abrupt withdrawal effects. In addition, a warning relating to the drug-drug interaction with partial opioid agonist/antagonists should be added as it may induce withdrawal symptoms in opioid dependant patients. The lactation section should be also revised to specify that breastfeeding should not be restarted until at least 5 days after the last administration of fentanyl. In addition, withdrawal syndrome, pyrexia and insomnia should be added as undesirable effects with unknown frequencies. Finally, miosis should be added to the pharmacodynamic properties section as a secondary pharmacological effect. Therefore the current terms of the marketing authorisations should be varied[12].
- In the next PSUR, MAHs should provide a detailed review of cases of off-label use and, a review of cases related to brain lesion, as preclinical data have revealed brain lesions in animals administered high doses of fentanyl citrate.
- MAH Takeda should provide a detailed analysis of the two cases of cardiopulmonary arrest reported with positive rechallenge in the paediatric population.
- MAH Teva should provide a detailed analysis of the potential for medication error due to similar packaging of different strengths of Effentora. In addition, the MAH should provide further details on the marketing withdrawal of Actiq in Norway.

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

6.1.5. Ferumoxytol – RIENSO (CAP)

- Evaluation of a PSUR procedure

[12] Update of SmPC sections 4.2, 4.5, 4.6, 4.8 and 5.1. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

Administrative details:
Procedure number(s): EMEA/H/C/002215/PSUV 0015
MAH(s): Takeda Pharma A/S

Background

Ferumoxytol is a colloidal iron-carbohydrate complex indicated for the intravenous treatment of iron deficiency anaemia in adult patients with chronic kidney disease (CKD).

The PRAC is currently reviewing the benefit-risk balance of Rienso (ferumoxytol), a centrally authorised medicine, in the framework of the assessment of a PSUR procedure due for PRAC recommendation in January 2015.

Summary of conclusions

The PRAC Rapporteur provided an update to the Committee. In line with GVP module VII on PSURs, an oral explanation will be held at the January 2015 PRAC meeting. The PRAC endorsed a list of questions to be addressed by the MAH in an oral explanation.

6.1.6. Insulin lispro – **HUMALOG** (CAP), **LIPROLOG** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/000088/PSUV 0128, EMEA/H/C/000393/PSUV 0095
MAH(s): Eli Lilly Nederland B.V.

Background

Insulin lispro is a fast-acting human insulin analogue indicated for the treatment of diabetes mellitus and for the initial stabilisation of diabetes mellitus under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Humalog and Liprolog, centrally authorised medicines containing insulin lispro, and issued a recommendation on its marketing authorisations.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Humalog and Liprolog (insulin lispro) in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation(s) should be maintained.
- The MAH should submit to EMA within 90 days detailed reviews of incorrect dose administered and administration errors, fatal cases, cases of hypersensitivity reactions and cases of neoplasms.
- In the next PSUR, the MAH should provide a refined review of identified and potential risks and detailed reviews of medication errors and lack of drug effect cases as well as of fatal cases.

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

6.1.7. **Mitotane – LYSODREN** (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/000521/PSUV 0016
MAH(s): Laboratoire HRA Pharma, SA

Background

Mitotane is an antineoplastic agent indicated for the symptomatic treatment of advanced (unresectable, metastatic or relapsed) adrenal cortical carcinoma (ACC).

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Lysodren (mitotane) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to add the interaction between mitotane and any substances metabolised through cytochrome P450 3A4 as well as a warning on the need to periodically monitor liver enzymes following reporting of cases of hepatotoxicity, liver damage and autoimmune hepatitis, especially during the first months of treatment or when it is necessary to increase the dose. In addition, the posology and warning sections are to be updated to add information on the service organised by the MAH for testing plasma levels of mitotane. Therefore the current terms of the marketing authorisation(s) should be varied[13].
- In the next PSUR, the MAH should provide a detailed discussion on the seriousness of the interaction between mitotane and spironolactone when administered concomitantly. This should be reflected in the RMP accordingly. In addition, ophthalmological disorders and hypothyroidism should be considered as identified instead of potential risks. Finally, the PRAC concluded that there is not enough evidence to include neuro-psychological retardation in paediatric patients as an important identified risk.

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

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

- Evaluation of a PSUR procedure

[13] Update of SmPC sections 4.2, 4.4 and 4.5. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

Regulatory details:
PRAC Rapporteur: Veerle Verlinden (BE)

Administrative details:
Procedure number(s): EMEA/H/C/000254/PSUV 0101, EMEA/H/C/000993/PSUV 0029
MAH(s): Genzyme Europe BV

Background

Sevelamer is a non-absorbed phosphate binding poly (allylamine hydrochloride) polymer indicated for the control of hyperphosphataemia in adult patients receiving haemodialysis or peritoneal dialysis under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Renagel and Renvela, centrally authorised medicines containing sevelamer, and issued a recommendation on its marketing authorisations.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Renagel and Renvela (sevelamer) in the approved indication(s) remains favourable.
- With regard to Renvela (sevelamer carbonate), the current terms of the marketing authorisation(s) should be maintained.
- With regard to Renagel (sevelamer hydrochloride), the product information should be updated to add acidosis, increased serum chloride levels as an undesirable effect with an uncommon frequency. Therefore the current terms of the marketing authorisation(s) should be varied[14].
- With the next PSUR, the MAH should submit an updated RMP to list hypersensitivity reactions, including angioedema and anaphylactic reactions as an important potential risk, or at the next regulatory opportunity.

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

6.1.9. Sunitinib – SUTENT (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Carmela Macchiarulo (IT)

Administrative details:
Procedure number(s): EMEA/H/C/000687/PSUV 0052
MAH(s): Pfizer Limited

Background

Sunitinib is a tyrosine kinase receptor inhibitor indicated for the treatment of gastrointestinal stromal tumour (GIST), metastatic renal cell carcinoma (MRCC) and pancreatic neuroendocrine tumours (pNET) under certain conditions.

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

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Sutent (sunitinib) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to add a warning to ensure that sunitinib is used with caution in patients who are taking medicinal products that can prolong the QT interval. Therefore the current terms of the marketing authorisation(s) should be varied[15].
- In the next PSUR, the MAH should provide a detailed analysis of the literature case of exacerbation of Crohn's disease during sunitinib treatment and discuss the possible influence of sunitinib on this exacerbation[16]. In addition, the MAH should monitor the effect of interaction on the level of transporters 1-11 and discuss the drug-drug interaction on the level of transporters (P-glycoprotein and ATP-binding cassette sub-family G member 2 (ABCG2)) based on the available literature.

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

6.1.10. Temoporfin – FOSCAN (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
Procedure number(s): EMEA/H/C/000318/PSUV 0037
MAH(s): Biolitec Pharma Ltd

Background

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

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

Summary of recommendation(s) and conclusions

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

[15] Update of SmPC section 4.4. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion
[16] Boers-sonderen MJ, Mulder SF, Nagtegaal ID, et al. Severe exacerbation of Crohn's disease during sunitinib treatment. Eur J GastroenterolHepatol. 2014;26(2):234-6

- The current terms of the marketing authorisation(s) should be maintained.
- The MAH should ensure by December 2015 at the latest that all EU markets are switched to 3 mg and 6 mg vials. The MAH should complete the relevant process to replace the 20 mg vials by smaller vials with national reimbursement agencies in Belgium, France and Italy.
- In the next PSUR, the MAH should provide detailed reviews of cases reporting concomitant use of oral anticoagulants and temoporfin and of cases of brain oedema. In addition, the MAH should provide a detailed review of cases of off-label use.

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

6.2. Follow-up to PSUR procedures[17]

6.2.1. **Paclitaxel – ABRAXANE** (CAP)

- Evaluation of a follow-up to a PSUR procedure

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
Procedure number(s): EMEA/H/C/000778/LEG 029
Procedure scope: MAH's response to PRAC recommendation on PSUV/0066, as adopted in September 2014
MAH(s): Celgene Europe Limited

Background

Following the evaluation of the most recently submitted PSUR for the above mentioned medicine, the PRAC requested the MAH to submit further data relating to the potential underdosage of paclitaxel due to residual drug contained in the solution in the infusion system after completion of the intravenous (IV) administration (see PRAC Minutes September 2014). The responses were assessed by the Rapporteur for further PRAC advice.

Summary of advice/conclusions

- In the next PSUR (DLP: 06/01/2015), the MAH should provide a detailed review of the cases of dose interruption in the clinical trial, including the amount of drug that remained in the line as well as of the cases where no interruption occurred with details on the practice of flushing the IV line following drug administration. In addition, the MAH should provide a calculation of the amount of paclitaxel lost from the dose administered if the infusion line is not flushed after IV administrations, stability data with commonly used diluents for flushing as well as further information relating to flushing from the studies submitted as part of the initial marketing authorisation application. As a consequence, the MAH should propose to update the product information as warranted, and discuss the need to take additional measures to ensure healthcare professionals are adequately informed about the need for flushing of the infusion line post-administration.

[17] Follow up as per the conclusions of the previous PSUR procedure, assessed outside of the next PSUR procedure

7. Post-authorisation Safety Studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)[18]

7.1.1. **Aprotinin** (NAP)

- Evaluation of an imposed PASS protocol

Regulatory details:
PRAC Rapporteur: Veerle Verlinden (BE)

Administrative details:
Procedure number(s): EMEA/H/N/PSP/0004
Procedure scope: Evaluation of a protocol for a non-interventional post-authorisation safety study of pattern of use of Nordic aprotinin
MAH(s): Disphar International B.V (Nordic Group)

Background

For background information, see PRAC minutes 6-9 October 2014. The Rapporteur assessed the proposed study protocol in accordance with the agreed timetable.

Endorsement/Refusal of the protocol

The PRAC, having reviewed the draft protocol version 1, considered that the study is non-interventional but that the design of the study did not fulfil the study objective.

Amongst other aspects, clarifications are needed on the study setting, the protocol should include only treatments on-label as main objectives, the study objectives should be revised and the study protocol should clarify that the data collection will be performed in a completely retrospective way based on chart reviews.

The PRAC therefore recommended that:

- The MAH should submit a revised PASS protocol within 30 days to the EMA. A 30 day-assessment timetable will be applied.

7.1.2. **Cyproterone, ethinylestradiol** (NAP)

- Evaluation of an imposed PASS protocol

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

Administrative details:
Procedure number(s): EMEA/H/N/PSP/0006
Procedure scope: Evaluation of a protocol for a drug utilisation study (database DUS) following EC decision dated 25 July 2013 on a referral procedure (EMEA/H/107i/1357)
MAH(s): Bayer (Diane 35)

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

Background

For background, see PRAC Minutes April 2014, September 2014 and October 2014; the Rapporteur assessed a protocol for a database DUS, submitted by one of the MAHs for review by the PRAC, according to the agreed timetable.

Endorsement/Refusal of the protocol

The PRAC, having reviewed the draft protocol version 4.0 considered that it could be approvable pending some modifications to be implemented, including a description of any concomitant combined hormonal contraceptive (CHC) use, which is contraindicated, and justification for use of a selected population over the total population of the selected database.

The PRAC therefore recommended that:

- The MAH should submit a revised PASS protocol within 60 days to the EMA. A 60 day-assessment timetable will be applied.

7.1.3. **Flupirtine** (NAP)

- Evaluation of an imposed PASS protocol

Regulatory details:
PRAC Rapporteur: Valerie Strassmann (DE)

Administrative details:
Procedure number: EMEA/H/N/PSP/0005.2
Procedure scope: Evaluation of a revised protocol for a non-interventional post-authorisation safety study to evaluate the effectiveness of the risk minimisation measures for the use of flupirtine 100 mg immediate-release capsules in daily practice
MAH(s): Meda Pharma (Flupigil, Metanor)

Background

For background information, see PRAC minutes 10-13 June 2014. The Rapporteur assessed the proposed study protocol in accordance with the agreed timetable.

Endorsement/Refusal of the protocol

The PRAC, having reviewed the draft protocol version 3, considered that while the study design was considered acceptable in principle, some revisions of the study protocol were needed including a revision of the timelines to take into account the dissemination of educational material, a DHPC in each country, amendment of the research question and objectives to reflect comparisons before and after the referral, and other remaining aspects.

The PRAC therefore recommended that:

- The MAH should submit a revised PASS protocol within 30 days to the EMA. A 60 days-assessment timetable will be applied.

7.2. Protocols of PASS non-imposed in the marketing authorisation(s)[19]

See Annex 16

7.3. Results of PASS imposed in the marketing authorisation(s)[20]

None

7.4. Results of PASS non-imposed in the marketing authorisation(s)[21]

7.4.1. Palivizumab – SYNAGIS (CAP)

- Evaluation of PASS results

Regulatory details:
PRAC Rapporteur: Torbjorn Callreus (DK)

Administrative details:
Procedure number(s): EMEA/H/C/000257/II/0098 (without RMP)
Procedure scope: Submission of the final study report for study A11-632, an observational study carried out to assess the risk of autoimmune and allergic diseases in high risk children exposed to palivizumab, in fulfilment of the Post Authorisation Measure (REC) FU2 032.4
MAH(s): AbbVie Ltd.

Background

Synagis is a centrally authorised medicine containing palivizumab, a humanised IgG1κ monoclonal antibody directed to an epitope in the A antigenic site of the fusion protein of respiratory syncytial virus (RSV), indicated for the prevention of serious lower-respiratory-tract disease, requiring hospitalisation caused by RSV in children at high risk for RSV disease.

A final study report for study A11-632, an observational study carried out to assess the risk of autoimmune and allergic diseases in high risk children exposed to palivizumab was submitted by the MAH and assessed by the Rapporteur.

Summary of advice

The PRAC noted that the results suggested that exposure to palivizumab in early childhood might increase the risk of developing asthma in the patients treated. This effect was markedly reduced compared to what was initially estimated, following additional and better adjusted analyses performed on the results. The PRAC also noted, as shown in previous studies, that severe RSV infection in early childhood predisposes to later development of asthma and considered that the observed effect may be due to insufficient adjustment, and that the observed associations are likely to be affected by residual confounding by indication. However, the PRAC agreed that an update of the product information was necessary to reflect these findings[22].

[19] In accordance with Article 107m of Directive 2001/83/EC, supervised by PRAC in accordance with Article 61a (6) of Regulation (EC) No 726/2004
[20] In accordance with Article 107p-q of Directive 2001/83/EC
[21] In accordance with Article 61a (6) of Regulation (EC) No 726/2004, in line with the revised variations regulation for any submission as of 4 August 2013
[22] Section 4.8 of the SmPC: "In an observational, post-marketing, database study, a small increase in the frequency of asthma was observed among preterm palivizumab recipients; however, the causal relationship is uncertain."

7.4.2. Tigecycline – TYGACIL (CAP)

- Evaluation of PASS results

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

Administrative details:
Procedure number(s): EMEA/H/C/000644/II/0089 (without RMP)
Procedure scope: Submission of the final PASS study report, including the response to the assessment by the PRAC on ANX 58.4 - the outcome of the previously submitted progress report to delete the obligation to conduct a PASS study, as currently stated in Annex II. Editorial updates are made to the SmPC and package leaflet
MAH(s): Pfizer Limited

Background

Tygacil is a centrally authorised medicine containing tigecycline, an antibacterial for systemic use indicated for the treatment of complicated skin and soft-tissue infections, excluding diabetic foot infections and complicated intra-abdominal infections.

As part of the conditions to the marketing authorisation (revised at the time of the last five year-renewal procedure), the MAH for Tygacil was requested to perform a non-interventional PASS aimed at collecting information on how Tygacil is prescribed and at monitoring the identified risk of superinfection and potential risks of off-label use and lack of efficacy. This study, aiming at measuring the effectiveness of the risk minimisation measures (RMM) introduced in 2011, had been conducted and a study report is assessed by the Rapporteur.

Summary of advice

The PRAC noted that the proportion of patients with off-label indications had decreased after the RMM were put in place and the treatment patterns were aligned with Tygacil recommended use. However, it seemed that the incidence of superinfection and reports of lack of efficacy have increased after implementation of the RMM. However, the number of cases was considered very limited to identify any trend by treatment characteristics (and still lower than the incidence reported in clinical trials).

- Therefore, the PRAC considered that this study showed that the recommended RMM had been effective. As a result of the finalisation of the PASS study, Annex II of the marketing authorisation is to be updated. No changes in the RMP were considered necessary.

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

See Annex 16

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

See Annex 17

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

9. Product related pharmacovigilance inspections

9.1. List of planned pharmacovigilance inspections

9.1.1. Risk-based programme for routine pharmacovigilance inspections of marketing authorisation holders connected with human centrally authorised products

The PRAC agreed the list of planned pharmacovigilance inspections 2014-1017, second revision, reviewed according to a risk based approach. This list is subsequently due for agreement at CHMP.

9.2. On-going or concluded pharmacovigilance inspection

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

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

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

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

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

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

Administrative details:
Procedure number(s): EMEA/H/C/000721/II/0061
Procedure scope: Update of SmPC section 4.6 on pregnancy outcomes in women exposed to the vaccine during pregnancy to reflect the outcome of study EPI-HPV-018 (an observational cohort) and other available data on safety during pregnancy. The package leaflet is amended accordingly
MAH(s): GlaxoSmithKline Biologicals

Background

Cervarix is a vaccine for use from the age of 9 years for the prevention of premalignant genital (cervical, vulvar and vaginal) lesions and cervical cancer causally related to certain oncogenic human papillomavirus (HPV) (types 16, 18).

Cervarix is not recommended for use in pregnancy, because safety has not been established in pregnant women; however, unintended exposure prior to the onset of pregnancy or during pregnancy is possible in the population recommended for vaccination.

The RMP for Cervarix provides detailed actions in place to further generate data in pregnancy following vaccination with Cervarix in women who were enrolled in active clinical trials and in pregnant women who have been inadvertently exposed to the vaccine in the post marketing setting (i.e. spontaneous reports and post marketing surveillance studies, including a pregnancy registry).

The MAH submitted a type II variation, based on new safety data obtained from the observational cohort study EPI-HPV-018, to update the product information on pregnancy outcomes in women

exposed to the vaccine during pregnancy, which was assessed by the Rapporteur. A PRAC advice was requested on the assessment of this variation.

Summary of advice

Based on the review of the available information, the PRAC agreed that the clinical data in pregnant women collected as part of pregnancy registries, epidemiological studies and inadvertent exposure during clinical trials were reassuring but insufficient to conclude whether or not vaccination with Cervarix affects the risk of adverse pregnancy outcomes including spontaneous abortion.

The PRAC agreed that, as a precautionary measure, it is preferable to avoid the use of Cervarix during pregnancy. A detailed wording proposal was agreed for inclusion in the product information.

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

None

10.3. Other requests

None

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

11.1. Safety related variations of the marketing authorisation

None

11.2. Renewals of the Marketing Authorisation

None

11.3. Other requests

11.3.1. **Ciprofloxacin** for systemic use (NAP)

- PRAC consultation on a PSUR work-sharing procedure upon Norway's request

Regulatory details:
Lead member: Ingebjorg Buajordet (NO)

Administrative details:
Procedure number: NO/H/PSUR/0010/002
Procedure scope: PSUR work-sharing procedure and request for PRAC advice on the need for contraindication for concomitant use of ciprofloxacin and agomelatine
MAH(s): Bayer HealthCare

Background

Ciprofloxacin is a fluoroquinolone antibiotic indicated for uncomplicated and complicated infections caused by ciprofloxacin susceptible pathogens.

During the current PSUR work-sharing procedure for ciprofloxacin for systemic use, some potential signals had arisen. Norway, as the P-RMS, requested the advice of the PRAC on aspects concerning the assessment of these signals in the context of this ongoing procedure.

Summary of advice

Based on the review of the available information, the PRAC agreed that further scientific evidence should be reviewed on the potential consequences of a pharmacokinetic interaction between agomelatine and ciprofloxacin; and in particular, the background on the evidence assessed in support of the current labelling of agomelatine should be investigated.

The PRAC recommended that drug rash with eosinophilia and systemic symptoms (DRESS) syndrome should be added to the list of serious skin reactions in the product information for ciprofloxacin.

Information on a signal of rhabdomyolysis, should be further investigated within the ongoing procedure.

11.3.2. Influenza vaccine (surface antigen, inactivated, adjuvanted) – FLUAD (NAP)

- PRAC consultation on a batch suspension of use upon Italy's request

Regulatory details:
Lead member: Carmela Macchiarulo (IT)

Administrative details:
Procedure number: *Not applicable*
Procedure scope: Suspension of use of two batches of Fluad following reports of serious adverse events after flu vaccination
MAH(s): Novartis Vaccines and Diagnostics (Fluad)

Background

Fluad vaccine is a surface antigen, inactivated, adjuvanted, seasonal influenza vaccine for intramuscular administration. Fluad is indicated for active immunisation against influenza in the elderly (65 years of age and older), especially for those with an increased risk of associated complications (i.e. patients affected by underlying chronic diseases including diabetes, cardiovascular and respiratory diseases).

During the current season on 27 November 2014 the use of two batches (batches 142701 and 143301) of Fluad was suspended in Italy as a precautionary measure owing to four reported serious cases of adverse events observed in a short time after Fluad administration. The Italian Rapporteur presented all available information on the reported serious adverse events which included fatal cases for advice by the PRAC on the review performed.

Summary of advice

Based on the review of the available information the PRAC agreed that the reports mainly concerned events in elderly patients with multiple co-morbidities. Moreover most patients for whom vaccination is recommended are at risk of serious morbidity or death.
The PRAC took into account the likely high population exposure to the vaccine over the previous two months, the background mortality rate in the general population aged 65 years and older, as well as the lack of a consistent clinical pattern amongst the serious adverse events leading to a fatal outcome.

The PRAC considered that the reports were unrelated to vaccination and concluded that, based on the available data, there was no evidence of a causal link between Fluad and the adverse events reported.

Post-meeting note: on 24 December 2014 , IT circulated an updated review to the PRAC. The conclusions of the previous assessment were confirmed.

12. Organisational, regulatory and methodological matters

12.1. Mandate and organisation of the PRAC

12.1.1. PRAC meeting under the Latvian presidency of the council of the EU

At the organisational matters teleconference on 18 December 2014, the PRAC was presented a draft agenda for the PRAC meeting under the Latvian presidency of the council of the EU (to be held in Germany), which will be a joint one with the Paediatric Committee (PDCO) aiming at improving safety during the pre- and post-marketing lifecycle of paediatric medicines and at promoting safer and better medicines for children.

12.2. Pharmacovigilance audits and inspections

12.2.1. Pharmacovigilance Inspections

- Risk Management plans-related issues identified as part of pharmacovigilance inspections

A representative from MHRA (UK Medicines Agency) presented a review of experience in performing inspections for pharmacovigilance related matters and in particular inspections of measures included in the RMP.
In discussion, the PRAC reflected upon the use of inspections in the framework of improving the implementation of recommended risk minimisation measures; discussed the benefits of targeting inspections to particular areas; and also on the options available to address inspection findings. The experience gained so far will be taken into account for future assessors' and inspectors' training to be organised.

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

12.3.1. Periodic Safety Update Reports

- PSUR Single Assessment (PSUSA) procedures for nationally approved products (NAP) only

The PRAC was presented with the template for the assessment report for the EU PSUR single assessment (PSUSA) for NAPs only. The PRAC agreed to use it in a pilot phase in January - March 2015. The PRAC was informed that the same template was also agreed at the level of the CMDh. The template will be revised in 2Q 2015 as necessary.

12.3.2. Union Reference Date List

- Consultation on the draft list, version December 2014

The PRAC endorsed the draft revised EURD list version December 2014 reflecting the PRAC comments impacting the DLP and PSUR submission frequencies of the substances/combinations. The PRAC endorsed the newly allocated Rapporteurs for upcoming PSUSAs in accordance with the principles previously endorsed by the PRAC (see PRAC Minutes April 2013).

Post-meeting note: following the PRAC meeting in December 2014, the updated EURD list was adopted by the CHMP and CMDh at their December 2014 meeting and published on the EMA website on 22/12/2014, see:

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

12.4. Signal Management

12.4.1. Signal Management

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

In December 2014, the SMART Working Group was briefed on the emerging safety issues (ESI) new definition and the different steps of the process including the roles of the stakeholders. The new definition of ESI is currently under discussion and is planned to be incorporated in draft GVP Module XII entitled 'Continuous pharmacovigilance and action on authorised medicinal products' currently being drafted. All MSs are encouraged to review and comment on the proposals. The SMART WG also noted the publication of a paper by Pacurariu et al[24] describing the signals evaluated by PRAC during its first 18 months of activity.

12.5. Adverse Drug Reactions reporting and additional reporting

12.5.1. Management and Reporting of Adverse Reactions to Medicinal Products

- EU individual case safety report (ICSR) implementation guide

The PRAC adopted the EU Individual Case Safety Report (ICSR) implementation guide EMA/51938/2013 (based on the standard ISO ICSR 27953-2:2011 and the ICH E2B(R3) implementation guide) which describes the additional EU specific requirements to generate a valid ICSR and specifies the technical requirements and the process of transmission of safety and acknowledgement messages through the EudraVigilance gateway and describes the obligations that stakeholders have to adhere to in this process to assure a successful electronic communication. The document will be available on the EMA website.

12.5.2. Additional Monitoring

None

12.5.3. List of Product under Additional Monitoring

- Consultation on the draft list, version December 2014

The PRAC was informed of the updates made to the list of products under additional monitoring.

Post-meeting note: The updated additional monitoring list was published on 17/12/2014 on the EMA website (see: Home>Human Regulatory>Human medicines>Pharmacovigilance>Signal management>List of medicines under additional monitoring)

12.6. EudraVigilance Database

None

[24] A Description of Signals During the First 18 Months of the EMA Pharmacovigilance Risk Assessment Committee Alexandra C. Pacurariu, Preciosa M. Coloma, Anja van Haren, Georgy Genov, Miriam C. J. M. Sturkenboom, Sabine M. J. M. Straus; Drug Saf DOI 10.1007/s40264-014-0240-1

12.7. Risk Management Plans and Effectiveness of risk Minimisations

None

12.8. Post-authorisation Safety Studies

12.8.1. Post-Authorisation Safety Studies

- Non-imposed PASS protocols – proposal for a revised assessment process

Following discussion in November 2014, the PRAC discussed a revised proposal for the assessment and regulatory handling of protocols for non-imposed, non-interventional PASS. The proposal aims to integrate advice on such protocols with advice on life-cycle development of medicines including clinical trials, non-clinical studies and pharmaceutical development by leveraging the scientific advice procedure, with SAWP reporting to PRAC its advice on non-interventional PASS. The PRAC noted the proposal. An implementation pilot plan is expected early 2015.

12.8.2. PASS feasibility study reports

- Clarification on regulatory handling of feasibility study reports for IV iron-containing medicinal products

The PRAC was informed of upcoming submissions of a PASS feasibility report conducted jointly by several MAHs of intravenous (IV) iron-containing products in relation to the PASS imposed as a condition of the marketing authorisations during the Article 31 referral procedure concluded in 2013 (EMEA/H/A-31/1322). The EMA secretariat explained that the PASS being imposed after 2 July 2012 will be supervised by the PRAC; however, the PASS feasibility study report as such does not fall within the scope of Article 107n (protocol) or 107q (results) of Directive 2001/83/EC as included as part of the condition to the marketing authorisation(s). Therefore, the PASS feasibility study report should be submitted by MAH(s) to the concerned Member States where the product(s) is/are authorised. One of the Member States expressed the intention to request advice from the PRAC on this feasibility study report.

12.9. Community Procedures

None

12.10. Renewals, conditional renewals, annual reassessments

12.10.1. Five-year renewal procedure process

- Update to Committees on the changes to the renewal procedure process

The PRAC was presented the revised process for the handling of the five-year renewal procedure to be implemented at the level of the CHMP and PRAC. The key points include the use of a single assessment report template (CHMP/PRAC) prepared jointly by the CHMP Rapporteur and PRAC Rapporteur, and completion following a 90 day-procedural timetable, i.e. routinely within 90 days with routine involvement of the PRAC Rapporteur but not routine PRAC input (only when required and based on escalation criteria). Ulla Wändel Liminga (SE) volunteered to participate in the preparation of the new template for the joint assessment report. A further update will be given in due course.

12.11. Risk communication and Transparency

12.11.1. Public Participation in Pharmacovigilance

None

12.11.2. Safety Communication

- Benefit-risk communication to users of medicines - how can regulators best meet the information needs of patients and healthcare professionals

The EMA secretariat informed the PRAC of the publication on the EMA website of the report, presentations and video of the workshop 'benefit-risk communication to users of medicines - how can regulators best meet the information needs of patients and healthcare professionals':

http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/events/2014/07/event_detail_001032.jsp&mid=WC0b01ac058004d5c3

12.12. Continuous pharmacovigilance

- Effects tables as part of the procedures evaluated by the PRAC

The PRAC was given an update on the preliminary recommendations and outcome of a pilot phase where effects tables were presented to the PRAC. The utility of effects tables for assessments performed by the PRAC was discussed, and next steps proposed. The PRAC supported further exploration of the use of effects tables but agreed that this might pose challenges for observational data. An update will be given to PRAC in Q2 2015.

12.12.1. Incident Management

None

12.13. Interaction with EMA Committees and Working Parties

12.13.1.1. Paediatric committee (PDCO)

- Setting-up of a joint PRAC-PDCO Working Group (WG)

At the organisational matters teleconference on 18 December 2014, the PRAC was presented a draft mandate for a virtual and joint PDCO/PRAC working group. The purpose of this working group is to feed information on paediatric safety issues at both committees and share experience or provide insights of the therapeutic context. The aim of this working group is to optimise the interactions between both committees. The composition of the working group includes members from both committees and EMA Secretariat representatives who will meet by teleconference on an ad hoc basis only, when input from either committee has been clearly identified. The PRAC endorsed the draft mandate.

12.13.2. Working Parties

None

12.13.2.1. Scientific Advisory Group (SAG) Oncology

- Bisphosphonates, denosumab: effectiveness of risk minimisation measures: consultation of the SAG oncology on the risk of osteonecrosis of the jaw (ONJ)

The PRAC discussed a report from the Scientific Advisory Group for Oncology (SAG-O) on the effectiveness of risk minimisation measures regarding the risk of osteonecrosis of the jaw (ONJ) with bisphosphonates and denosumab. It was concluded that it may be beneficial to enhance the current risk minimisation measures regarding ONJ. Following the SAG-O advice and the conclusions of previous reviews performed, the PRAC concluded that the magnitude of ONJ risk seems greater for zoledronic acid and denosumab compared with other, less potent bisphosphonates.
Furthermore, the ONJ risk seems higher in patients treated within the oncology indications, where mainly parenteral formulations are used, compared to the osteoporosis indications where mostly oral formulations are used, although both zoledronic acid and denosumab are also approved for use in osteoporosis as parenteral formulations.
Therefore regulatory action should focus on the parenteral formulations of zolendronic acid, denosumab, pamidronic acid, ibandronic acid and neridronic acid. These parenteral formulations are mainly administered in hospital/outpatient clinics where patients may not have the same access to an awareness of the product information as patients treated with oral formulations. The PRAC supported the proposal to review the appropriateness of the risk minimisation measures in place within the ongoing and upcoming PSUR/PSUSA procedures for the concerned products. This should include a review of whether the product information is adequate with respect to current knowledge on ONJ and consideration of implementing of a patient reminder card as an additional risk minimisation measure. For the latter, consultation with patient representatives was recommended.

The PRAC Rapporteurs will present a detailed action plan together with a proposal for key safety messages for the product information and a patient reminder card, taking into account the patient's individual benefit-risk balance and the magnitude of the risk of ONJ, at the PRAC plenary meeting in February 2015.

12.14. Interaction within the EU regulatory network

12.14.1. Policy on Scientific Publication and Representation

At the organisational matters teleconference on 18 December 2014, the EMA secretariat presented the principles of the existing policy published on the EMA website:
http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/10/WC500004627.pdf

The review process for scientific publications coming from Committee members was discussed. Members were encouraged to provide any feedback or comments on the policy by the end of January 2015.

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

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

None

12.16. Others

None

13. Any other business

13.1. Marketing authorisation application (MAA) process

- Update to Committees about changes to the MAA process

The PRAC was presented with a schedule for the implementation of the revised RMP assessment process in the framework of the MAA procedures. A review of the necessary templates, processes and steps for the revision of the different templates and an action plan related to implementation was also presented. Further discussion will take at the next meeting of the PRAC in the context of a further progress report.

13.2. Medication error

13.2.1. Update on EMA medication error action plan

The EMA secretariat presented an update on the action plan on medication errors and draft guidance developed by the EU regulatory network. The key deliverables include two good practice guides, one on risk minimisation and prevention of medication errors and one on recording, coding, reporting and assessment of medication errors. An addendum for risk minimisation strategies for medication errors with high strength/fixed dose combination insulins is also under preparation by a dedicated PRAC drafting group. Before a wider consultation with stakeholders scheduled in Q2/2015, the PRAC members were invited to provide comments on the guidance and guides. As a next step the draft guidance will be subject to consultation with the EC's Patient Safety and Quality of Care Working Group (PSQCWG) in relation to aspects of collaboration with national patient safety organisations.

13.2.2. Communication on prevention of medication errors

At the organisational matters teleconference on 18 December 2014, the PRAC was presented with a proposal for streamlining EMA public communication on medication errors in order to encompass medication errors evaluated by both the PRAC and CHMP (i.e. when non-routine measures are recommended) in a consistent manner. The EMA plans to use the current communication tools to communicate on medication errors for medicines assessed by the PRAC where additional risk minimisation measures are recommended to reduce the risk of medication errors for a medicine or where a DHPC has been agreed at EU level which specifically addresses medication errors. All of these documents will be prepared by the EMA secretariat in close collaboration with EMA scientific committee members and rapporteurs. The PRAC supported this initiative which will be implemented as of January/February 2015.

13.3. Guidance to applicants on responses to questions received from EMA Scientific Committees during the evaluation within the centralised procedure

The topic was deferred to the January 2015 PRAC meeting.

14. ANNEX I Risk Management Plans

14.1. Medicines in the pre-authorisation phase

As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of the RMP for the below mentioned medicines under evaluation for

initial marketing authorisation application. Information on the medicines containing the below listed active substance will be made available following the CHMP opinion on their marketing authorisation.

14.1.1. Allogenic human heterologous liver cells

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

Administrative details:
Product number(s): EMEA/H/C/003750, *ATMP, Orphan*
Intended indication(s): Treatment of urea cycle disorders (UCD)
Applicant: Cytonet GmbH & Co KG

14.1.2. Aripiprazole

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

Administrative details:
Product number(s): EMEA/H/C/004021, *Generic*
Intended indication(s): Treatment of schizophrenia

14.1.3. Ceftolozane, tazobactam

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

Administrative details:
Product number(s): EMEA/H/C/003772
Intended indication(s): Treatment of complicated intra-abdominal infections and complicated urinary tract infections in adults

14.1.4. Ciclosporin

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

Administrative details:
Product number(s): EMEA/H/C/002066
Intended indication(s): Treatment of keratitis

14.1.5. Dalbavancin

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

Administrative details:
Product number(s): EMEA/H/C/002840
Intended indication(s): Treatment of tissue infections (cSSTI)

14.1.6. Dasiprotimut-T

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

Administrative details:
Product number(s): EMEA/H/C/002772, *Orphan*
Intended indication(s): Treatment of non-Hodgkin’s lymphoma (FL)
Applicant: Biovest Europe Ltd

14.1.7. Ex vivo autologous corneal epithelial cells including stem cells

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

Administrative details:
Product number(s): EMEA/H/C/002450, *ATMP, Orphan*
Intended indication(s): Treatment of limbal stem cell deficiency
Applicant: Chiesi Farmaceutici S.p.A.

14.1.8. Isavuconazole

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

Administrative details:
Product number(s): EMEA/H/C/002734
Intended indication(s): Treatment of invasive aspergillosis and for the treatment of mucormycosis

14.1.9. Levofloxacin

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

Administrative details:
Product number(s): EMEA/H/C/002789
Intended indication(s): Treatment of chronic pulmonary infections

14.1.10. Liraglutide

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

Administrative details:
Product number(s): EMEA/H/C/003780
Intended indication(s): Treatment of obesity

14.1.11. Phenylephrine hydrochloride, ketorolac trometamol

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

Administrative details:
Product number(s): EMEA/H/C/003702
Intended indication(s): Maintenance of intraoperative mydriasis, prevention of intraoperative miosis and reduction of acute postoperative ocular pain in intraocular lens replacement (ILR) in adults

14.1.12. Pregabalin

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

Administrative details:
Product number(s): EMEA/H/C/004024, *Generic*
Intended indication(s): Treatment of neuropathic pain, epilepsy and generalised anxiety disorder (GAD)

14.1.13. Pregabalin

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

Administrative details:
Product number(s): EMEA/H/C/003962, *Generic*
Intended indication(s): Treatment of neuropathic pain, epilepsy and generalised anxiety disorder (GAD)

14.1.14. Pregabalin

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

Administrative details:
Product number(s): EMEA/H/C/004078, *Generic*
Intended indication(s): Treatment of epilepsy and generalised anxiety disorder (GAD)

14.1.15. Pregabalin

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

Administrative details:
Product number(s): EMEA/H/C/004010, *Generic*
Intended indication(s): Treatment of neuropathic pain, epilepsy and generalised anxiety disorder (GAD)

14.1.16. Pregabalin

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

Administrative details:
Product number(s): EMEA/H/C/004070, *Generic*
Intended indication(s): Treatment of epilepsy and generalised anxiety disorder (GAD)

14.1.17. Pregabalin

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

Administrative details:
Product number(s): EMEA/H/C/003900, *Generic*
Intended indication(s): Treatment of epilepsy and generalised anxiety disorder (GAD)

14.1.18. Safinamide

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

Administrative details:
Product number(s): EMEA/H/C/002396
Intended indication(s): Treatment of Parkinson's disease (PD)

14.1.19. Sevelamer

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

Administrative details:
Product number(s): EMEA/H/C/003968
Intended indication(s): Control of hyperphosphataemia in adult patients receiving haemodialysis or peritoneal dialysis

14.2. Medicines already authorised

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

RMP in the context of a variation[25] – PRAC-led procedure

14.2.1. Aliskiren – RASILEZ (CAP)
aliskiren, amlodipine – RASILAMLO (CAP)
aliskiren, hydrochlorothiazide – RASILEZ HCT (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Carmela Macchiarulo (IT)

Administrative details:
Procedure number(s): EMEA/H/C/000780/WS0588/0094, EMEA/H/C/002073/WS0588/0095, EMEA/H/C/000964/WS0588/0064
Procedure scope: Revised RMP to update the following information: the timelines for initiation, completion and submission of study reports of on-going or planned studies together with update to some of objectives of the planned long-term safety and efficacy study
MAH(s): Novartis Europharm Ltd

14.2.2. Elvitegravir, cobicistat, emtricitabine, tenofovir – STRIBILD (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002574/II/0036/G
Procedure scope: Grouped variations to update the RMP with 1) information on applications recently finalised and studies recently concluded, 2) due date for a category 3 study (GS-US-236-0140), 3) agreed change in due date for a category 3 study (GS-US-236-0141)
MAH(s): Gilead Sciences International Ltd

14.2.3. Fentanyl – INSTANYL (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Arnaud Batz (FR)

Administrative details:
Procedure number(s): EMEA/H/C/000959/II/0028
Procedure scope: Revised RMP to add a planned study to evaluate the effectiveness of the educational material approved in July 2013 as requested by PRAC and addition of new potential risks as requested by PRAC following the assessment of the latest PSUR and RMP
MAH(s): Takeda Pharma A/S

14.2.4. Ibritumomab tiuxetan – ZEVALIN (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Torbjorn Callreus (DK)

Administrative details:
Procedure number(s): EMEA/H/C/000547/II/0043

[25] In line with the revised variation regulation for submissions as of 4 August 2013

Procedure scope: Update of the RMP to reflect the completion and analysis of study SAG 307722
MAH(s): Spectrum Pharmaceuticals B.V.

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

- Evaluation of an RMP in the context of a variation

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

Administrative details:
Procedure number(s): EMEA/H/C/000966/WS0638/0028, EMEA/H/C/000957/WS0638/0031
Procedure scope: Update of the RMP (version 8)
MAH(s): Sanofi Pasteur MSD SNC

14.2.6. Nilotinib – TASIGNA (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Doris Stenver (DK)

Administrative details:
Procedure number(s): EMEA/H/C/000798/II/0071
Procedure scope: Update of the RMP (version 13)
MAH(s): Novartis Europharm Ltd.

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

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Procedure number(s): EMEA/H/C/000832/II/0074
Procedure scope: Update of obligations to conduct post-authorisation non-clinical studies including timings for key data planned to further elucidate the potential role of Pandemrix in the onset of narcolepsy
MAH(s): GlaxoSmithKline Biologicals

14.2.8. Pegfilgrastim – NEULASTA (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/000420/II/0082
Procedure scope: Updated RMP (version 3) to address the PRAC recommendation concerning capillary leak syndrome and cytokine release syndrome
MAH(s): Amgen Europe B.V.

14.2.9. Teduglutide – REVESTIVE (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Torbjorn Callreus (DK)

Administrative details:
Procedure number(s): EMEA/H/C/002345/II/0009
Procedure scope: Update of the RMP to reflect the use of nursing services as a risk minimisation effort to decrease adverse events of fluid overload
MAH(s): NPS Pharma Holdings Limited

14.2.10. Telaprevir – INCIVO (CAP)

- Evaluation of an RMP in the context of a variation

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

Administrative details:
Procedure number(s): EMEA/H/C/002313/II/0033
Procedure scope: Revised RMP (version 7.0) to include the MAH's request for a waiver for doing the second-wave survey of the effectiveness of the rash educational programme in 2015
MAH(s): Janssen-Cilag International N.V.

RMP in the context of a variation – CHMP-led procedure

14.2.11. Caffeine – PEYONA (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Jan Neuhauser (AT)

Administrative details:
Procedure number(s): MEA/H/C/001014/II/0013
Procedure scope: Update of SmPC section 4.8 to reflect the results of a European non-interventional post-authorisation study to assess drug utilisation and safety of caffeine citrate in the treatment of premature infants affected by apnoea. This study addresses a post-authorisation measure in the RMP. Section 4 of the package leaflet is updated accordingly
MAH(s): Chiesi Farmaceutici S.p.A.

14.2.12. Colagenase clostridium histolyticum – XIAPEX (CAP)

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

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

Administrative details:
Procedure number(s): EMEA/H/C/002048/II/0044
Procedure scope: Update of the SmPC with a new indication in the treatment of adult men with Peyronie's disease with a palpable plaque and curvature deformity. The package leaflet is updated accordingly
MAH(s): Swedish Orphan Biovitrum AB (publ)

14.2.13. Empagliflozin – JARDIANCE (CAP)

- Evaluation of an RMP in the context of a variation

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

Administrative details:
Procedure number(s): EMEA/H/C/002677/II/0002
Procedure scope: Update of SmPC section 4.5 to reflect the results of an in vitro study investigating the inhibition of UGT2B7, UGT1A3, UGT1A8, and UGT1A9. The RMP was updated to reflect the finalisation of the study and the results
MAH(s): Boehringer Ingelheim International GmbH

14.2.14. Epoetin beta – NEORECORMON (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Valerie Strassmann (DE)

Administrative details:
Procedure number(s): EMEA/H/C/000116/II/083
Procedure scope: Submission of measures to minimise the potential risk of retinopathy of prematurity (RoP) as requested in the PSUR procedure covering the period 2007-2010
MAH(s): Roche Registration Ltd

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

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
Procedure number(s): EMEA/H/C/002493/II/0008/G
Procedure scope: Extension of indication to include prophylactic treatment of patients with von Willebrand disease (VWD). In addition the MAH is providing data to support treatment of paediatric patients with VWD
MAH(s): CSL Behring GmbH

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

- Evaluation of an RMP in the context of a variation

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

Administrative details:
Procedure number(s): EMEA/H/C/000721/II/0061
Procedure scope: Update of SmPC section 4.6 on pregnancy outcomes in women exposed to the vaccine during pregnancy to reflect the outcome of study EPI-HPV-018 (an observational cohort) and other available data on safety during pregnancy. The package leaflet is amended accordingly
MAH(s): GlaxoSmithKline Biologicals

See also 10.1.1.

14.2.17. Insulin degludec – TRESIBA (CAP)

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

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

Administrative details:
Procedure number(s): EMEA/H/C/002498/II/0011
Procedure scope: Extension of indication to children aged from 1 to 18 years. Update to SmPC sections 4.1, 4.2, 4.8 and 5.1. The package leaflet is updated accordingly. In addition, update of the section 2 of the package leaflet in line with the existing information in SmPC section 4.2
MAH(s): Novo Nordisk A/S

14.2.18. Insulin degludec, liraglutide – XULTOPHY (CAP)

- Evaluation of an RMP in the context of a variation

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

Administrative details:
Procedure number(s): EMEA/H/C/002647/II/0001/G
MAH(s): Novo Nordisk A/S

14.2.19. Ipilimumab – YERVOY (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
Procedure number(s): EMEA/H/C/002213/II/0028/G
MAH(s): Bristol-Myers Squibb Pharma EEIG

14.2.20. Lapatinib – TYVERB (CAP)

- Evaluation of an RMP in the context of a variation

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

Administrative details:
Procedure number(s): EMEA/H/C/000795/II/0037
Procedure scope: Update of SmPC section 5.1 with information on lapatinib effect on central nervous system (CNS) metastasis further to comparative data on the incidence of CNS metastases from studies EGF108919 (COMPLETE), EGF105485 (TEACH) and EGF106708 (ALTTO) (SOB 002.4). Annex II is also updated further to the fulfilment of the specific obligation
MAH(s): Glaxo Group Ltd

14.2.21. Lenalidomide – REVLIMID (CAP)

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

Regulatory details:
PRAC Rapporteur: Arnaud Batz (FR)

Administrative details:
Procedure number(s): EMEA/H/C/000717/X/0073/G

Procedure scope: Extension of indication for the continuous treatment of adult patients with previously untreated multiple myeloma who are not eligible for transplant A line extension application to add the following strength: 20 mg (21 capsules pack)
MAH(s): Celgene Europe Limited

14.2.22. Palonosetron – ALOXI (CAP)

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

Regulatory details:
PRAC Rapporteur: Almath Spooner (IE)

Administrative details:
Procedure number(s): EMEA/H/C/000563/II/0038
Procedure scope: Extension of indication to paediatric patients 1 month of age and older for the prevention of nausea and vomiting associated with moderately and highly emetogenic cancer chemotherapy for the IV formulation, based on the paediatric studies PALO-10-14 and PALO-10-20 and update of SmPC sections 5.1 and 5.2 of the oral formulation to reflect those studies
MAH(s): Helsinn Birex Pharmaceuticals Ltd.

14.2.23. Perampanel – FYCOMPA (CAP)

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

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002434/II/0016
Procedure scope: Extension of indication as adjunctive treatment of primary generalised tonic-clonic seizures in patients with epilepsy aged 12 years and older. SmPC sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 and the package leaflet are updated accordingly
MAH(s): Eisai Europe Ltd.

14.2.24. Pertuzumab – PERJETA (CAP)

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

Regulatory details:
PRAC Rapporteur: Doris Stenver (DK)

Administrative details:
Procedure number(s): EMEA/H/C/002547/II/0010
Procedure scope: Extension of indication of the use of pertizumab in combination with trastuzumab and docetaxel as part of a neoadjuvant treatment for patients with locally advanced, inflammatory or early stage HER2-positive breast cancer suitable for neo-adjuvant therapy
MAH(s): Roche Registration Ltd

14.2.25. Pramipexole – OPRYMEA (CAP)

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

Regulatory details:
PRAC Rapporteur: Doris Stenver (DK)

Administrative details:
Procedure number(s): EMEA/H/C/000941/X/0017
Procedure scope: Addition of new strengths 2.62 mg and 3.15 mg prolonged-release tablets
MAH(s): Krka d.d. Novo mesto

14.2.26. Prucalopride – RESOLOR (CAP)

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

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Procedure number(s): EMEA/H/C/001012/II/0034
Procedure scope: Extension of indication to the male population for the treatment of symptomatic treatment of chronic constipation in whom laxatives fail to provide adequate relief
MAH(s): Shire Pharmaceuticals Ireland Ltd.

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

14.2.27. Insulin glargine – LANTUS (CAP)

- Evaluation of an RMP on the context of a five year-renewal of the marketing authorisation

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

Administrative details:
Procedure number(s): EMEA/H/C/000284/R/0096
MAH(s): Sanofi-aventis Deutschland GmbH

15. ANNEX I Assessment of Periodic Safety Update Reports (PSURs)

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

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

15.1. Evaluation of PSUR procedures

15.1.1. Aflibercept – EYLEA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Arnaud Batz (FR)

Administrative details:
Procedure number(s): EMEA/H/C/002392/PSUV 016
MAH(s): Bayer Pharma AG
For adoption: PRAC PSUR AR, PRAC recommendation

15.1.2. Apixaban – ELIQUIS (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/002148/PSUV 022
MAH(s): Bristol-Myers Squibb / Pfizer EEIG

15.1.3. Caffeine – PEYONA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Jan Neuhauser (AT)

Administrative details:
Procedure number(s): EMEA/H/C/001014/PSUV 014
MAH(s): Chiesi Farmaceutici S.p.A.

15.1.4. Canagliflozin – INVOKANA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Valerie Strassmann (DE)

Administrative details:
Procedure number(s): EMEA/H/C/002649/PSUV 007
MAH(s): Janssen-Cilag International N.V.

15.1.5. Capecitabine – CAPECITABINE MEDAC (CAP), ECANSYA (CAP), XELODA (CAP), NAP

- Evaluation of a PSUSA[26] procedure

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

Administrative details:
Procedure number(s): EMEA/H/C/PSUSA/00000531/201404
MAH(s): Medac Gesellschaft fuer klinische Spezialpraeparate m.b.H (Capecitabine Medac), Krka d.d. Novo mesto (Ecansya), Roche Registration Ltd (Xeloda)

15.1.6. Capsaicin – QUTENZA (CAP), NAP

- Evaluation of a PSUSA[27] procedure

Regulatory details:
PRAC Rapporteur: Magda Pedro (PT)

Administrative details:
Procedure number(s): EMEA/H/C/PSUSA/00000533/201405

[26] PSUR single assessment, referring to CAP, NAP
[27] PSUR single assessment, referring to CAP, NAP

MAH(s): Astellas Pharma Europe B.V., various

15.1.7. Characterised viable autologous cartilage cells expanded ex vivo expressing specific marker proteins – CHONDROCELECT (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/000878/PSUV 011
MAH(s): TiGenix NV

15.1.8. Cholera vaccine (inactivated, oral) – DUKORAL (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/000476/PSUV 046
MAH(s): Crucell Sweden AB

15.1.9. Conestat alfa – RUCONEST (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Procedure number(s): EMEA/H/C/001223/PSUV 020
MAH(s): Pharming Group N.V

15.1.10. Decitabine – DACOGEN (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Patrick Maison (FR)

Administrative details:
Procedure number(s): EMEA/H/C/002221/PSUV 014
MAH(s): Janssen-Cilag International N.V.

15.1.11. Emtricitabine, tenofovir disoproxil – TRUVADA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Procedure number(s): EMEA/H/C/000594/PSUV 108
MAH(s): Gilead Sciences International Ltd

15.1.12. Fidaxomicin – DIFICLIR (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/002087/PSUV 020
MAH(s): Astellas Pharma Europe B.V.

15.1.13. Fluticasone furoate, vilanterol – RELVAR ELLIPTA (CAP), REVINTY ELLIPTA (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/002673/PSUV 006, EMEA/H/C/002745/PSUV 002
MAH(s): Glaxo Group Ltd

15.1.14. Follitropin beta – FERTAVID (CAP), PUREGON (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/001042/PSUV 024, EMEA/H/C/000086/PSUV 082
MAH(s): Merck Sharp & Dohme Limited

15.1.15. Fulvestrant – FASLODEX (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/000540/PSUV 044
MAH(s): AstraZeneca UK Ltd.

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

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/000703/PSUV 052, EMEA/H/C/000732/PSUV 048
MAH(s): Sanofi Pasteur MSD SNC, Merck Sharp & Dohme Limited

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

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/000966/PSUV 027, EMEA/H/C/000957/PSUV 030
MAH(s): Sanofi Pasteur, Sanofi Pasteur MSD SNC

15.1.18. Laronidase – ALDURAZYME (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Procedure number(s): EMEA/H/C/000477/PSUV 052
MAH(s): Genzyme Europe BV

15.1.19. Lidocaine, prilocaine – FORTACIN (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/002693/PSUV 001
MAH(s): Plethora Solutions Ltd.

15.1.20. Linagliptin – TRAJENTA (CAP)
linagliptin, metformin – JENTADUETO (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/002110/PSUV 016, EMEA/H/C/002279/PSUV 022
MAH(s): Boehringer Ingelheim International GmbH

15.1.21. Methylthioninium – METHYLTHIONINIUM CHLORIDE PROVEBLUE (CAP), NAP

- Evaluation of a PSUSA[28] procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/PSUSA/00002029/201405
MAH(s): Provepharm SAS

[28] PSUR single assessment, referring to CAP, NAP

15.1.22. Mycophenolate – CELLCEPT (CAP), NAP

- Evaluation of a PSUSA[29] procedure

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Procedure number(s): EMEA/H/C/PSUSA/00002099/201405
MAH(s): Roche Registration Ltd

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

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Procedure number(s): EMEA/H/C/001206/PSUV 040, EMEA/H/C/001212/PSUV 010, EMEA/H/C/000822/PSUV 0056
MAH(s): GlaxoSmithKline Biologicals

15.1.24. Piperaquine, artenimol, dihydroartemisinin – EURARTESIM (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/001199/PSUV 014 (with RMP version 12.0)
MAH(s): Sigma-Tau Industrie Farmaceutiche Riunite S.p.A.
For adoption: PRAC PSUR AR, PRAC recommendation

15.1.25. Pixantrone – PIXUVRI (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002055/PSUV 018
MAH(s): CTI Life Sciences Limited

15.1.26. Radium-223 – XOFIGO (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

[29] PSUR single assessment, referring to CAP, NAP

Administrative details:
Procedure number(s): EMEA/H/C/002653/PSUV 005
MAH(s): Bayer Pharma AG

15.1.27. Rilpivirine – EDURANT (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
Procedure number(s): EMEA/H/C/002264/PSUV 014
MAH(s): Janssen-Cilag International N.V.

15.1.28. Saxagliptin, metformin – KOMBOGLYZE (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/002059/PSUV 017
MAH(s): Bristol-Myers Squibb/AstraZeneca EEIG

15.1.29. Shingles (herpes zoster) vaccine (live) – ZOSTAVAX (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/000674/PSUV 078
MAH(s): Sanofi Pasteur MSD SNC

15.1.30. Sildenafil – REVATIO (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/000638/PSUV 063
MAH(s): Pfizer Limited

15.1.31. Tafamidis – VYNDAQEL (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Arnaud Batz (FR)

Administrative details:
Procedure number(s): EMEA/H/C/002294/PSUV 018 (with RMP version 8.0)
MAH(s): Pfizer Limited

15.1.32. Tolvaptan – SAMSCA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/000980/PSUV 019
MAH(s): Otsuka Pharmaceutical Europe Ltd

15.1.33. Turoctocog alfa – NOVOEIGHT (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/002719/PSUV 001(with RMP version 3.0)
MAH(s): Novo Nordisk A/S

15.1.34. Ulipristal – ELLAONE (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/001027/PSUV 032 (with RMP version 14.0)
MAH(s): Laboratoire HRA Pharma, SA

15.1.35. Varenicline – CHAMPIX (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Doris Stenver (DK)

Administrative details:
Procedure number(s): EMEA/H/C/000699/PSUV 054
MAH(s): Pfizer Limited

15.2. Follow-up to PSUR procedures[30]

15.2.1. Pregabalin – LYRICA (CAP)

- Evaluation of a follow-up to a PSUR procedure

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
Procedure number(s): EMEA/H/C/000546/LEG 046

[30] Follow-up as per the conclusions of the previous PSUR procedure, assessed outside of the next PSUR procedure

Procedure scope: MAH's response to PRAC recommendation on PSUV/0069 as adopted in September 2014
MAH(s): Pfizer Limited

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

Since all comments received on the assessment of these studies were addressed before the plenary meeting, the PRAC endorsed the conclusion of the Rapporteurs on the assessment of the relevant protocol or study report for the medicines listed below without further plenary discussion.

16.1.1. Adefovir dipivoxil –HEPSERA (CAP)

- Evaluation of interim PASS results

Regulatory details:
PRAC Rapporteur: Arnaud Batz (FR)

Administrative details:
Procedure number(s): EMEA/H/C/000485/MEA 070
Procedure scope: Interim report on the antiretroviral pregnancy registry
MAH(s): Gilead Sciences International Ltd

16.1.2. Aliskiren – RASILEZ (CAP)
aliskiren, amlodipine – RASILAMLO (CAP)
aliskiren, hydrochlorothiazide – RASILEZ HCT (CAP)

- Evaluation of interim PASS results

Regulatory details:
PRAC Rapporteur: Carmela Macchiarulo (IT)

Administrative details:
Procedure number(s): EMEA/H/C/000780/WS0581/0093, EMEA/H/C/002073/WS0581/0094, EMEA/H/C/000964/WS0581/0063 (without RMP)
Procedure scope: Submission of the final study report for the non-interventional study CSPP100A2414: cohort study to assess various safety outcomes in aliskiren initiators using US claims data
MAH(s): Novartis Europharm Ltd

16.1.3. Aripiprazole – ABILIFY MAINTENA (CAP)

- Evaluation of interim PASS results

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

Administrative details:
Procedure number(s): EMEA/H/C/002755/MEA 005
Procedure scope: PASS study report on the results of the analysis of EPS-related events to be presented in the RMP
MAH(s): Otsuka Pharmaceutical Europe Ltd

16.1.4. Autologous peripheral-blood mononuclear cells activated with prostatic acid phosphatase granulocyte-macrophage colony-stimulating factor (sipuleucel-T) – PROVENGE (CAP)

- Evaluation of an imposed PASS protocol

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

Administrative details:
Procedure number: EMEA/H/C/002513/ANX 001
Procedure scope: Evaluation of a PASS protocol to establish and keep an observational EU-based registry therapy in men with metastatic castrate-resistant prostate cancer (mCRPC) to evaluate overall survival, the risk of ischemic stroke or myocardial infarction following treatment with Provenge and other identified and potential risks (observational study P13-1)
MAH(s): Dendreon UK Ltd

16.1.5. Cobicistat – TYBOST (CAP)

- Evaluation of a PASS protocol

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002572/MEA 012.1
Procedure scope: Evaluation of the MAH's response to MEA-012 (draft procedure protocol and a feasibility assessment for drug utilisation study) as adopted in April 2014
MAH(s): Gilead Sciences International Ltd

16.1.6. Deferasirox – EXJADE (CAP)

- Evaluation of an imposed PASS protocol

Regulatory details:
PRAC Rapporteur: Arnaud Batz (FR)

Administrative details:
Procedure number: EMEA/H/C/000670/ANX 038.5
Procedure scope: Evaluation of MAH's responses to ANX 038.4 as adopted by PRAC in July 2014 including a revised PASS protocol for study CICL670E2422: observational cohort study in paediatric non transfusion dependant-thalassaemia (NTDT) patients over 10 years
MAH(s): Novartis Europharm Ltd

16.1.7. Etravirine – INTELENCE (CAP)

- Evaluation of interim PASS results

Regulatory details:
PRAC Rapporteur: Patrick Maison (FR)

Administrative details:
Procedure number(s): EMEA/H/C/000900/MEA 049
Procedure scope: First annual report on study TMC125-EPPICC (pharmacovigilance study to define the long-term safety profile of etravirine in HIV-1-infected children and adolescents in Europe)
MAH(s): Janssen-Cilag International N.V.

16.1.8. Fidaxomicin – DIFICLIR (CAP)

- Evaluation of a PASS protocol

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

Administrative details:
Procedure number(s): EMEA/H/C/002087/MEA 004
Procedure scope: Evaluation of a revised PASS protocol for a drug utilisation study (DUS) of the use of oral fidaxomicin (clinical study 2819-CL-2002)
MAH(s): Astellas Pharma Europe B.V.

16.1.9. Florbetaben (^{18}F) – NEURACEQ (CAP)

- Evaluation of a PASS protocol

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002553/MEA 001.1
Procedure scope: Evaluation of a revised PASS protocol for a non-interventional prospective observational multicentre, multi-country registry to observe usage pattern, safety and tolerability of florbetaben (^{18}F) in clinical practice (study FBB-01_03_13)
MAH(s): Piramal Imaging Limited

16.1.10. Human papillomavirus vaccine [types 6, 11, 18] (recombinant, adsorbed)– GARDASIL (CAP), SILGARD (CAP)

- Evaluation of PASS results

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

Administrative details:
Procedure number(s): EMEA/H/C/000703/WS0643/0053 (with RMP), EMEA/H/C/000732/WS0643/0049 (with RMP)
Procedure scope: Submission of the final pregnancy registry report in order to address MEA 65 (Gardasil) and MEA 64 (Silgard) on submission of annual pregnancy registry reports and a consequential update of the RMP (version 8)
MAH(s): Sanofi Pasteur MSD SNC

16.1.11. Infliximab – INFLECTRA (CAP), REMSIMA (CAP)

- Evaluation of interim PASS results

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002778/MEA 008, EMEA/H/C/002576/MEA 008
Procedure scope: Annual safety report on post-marketing surveillance to evaluate safety and efficacy in Korea
MAH(s): Hospira UK Limited, Celltrion Healthcare Hungary Kft

16.1.12. Insulin degludec – TRESIBA (CAP)

- Evaluation of PASS results

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

Administrative details:
Procedure number(s): EMEA/H/C/002498/II/0012 (with RMP)

Procedure scope: Final study report for a study/survey with the objective of investigating the impact of red-green colour blindness on the ability to discriminate between the packages and the prefilled pen devices of the two different strengths as well as bolus insulin products marketed in colour schemes relevant in red-green colour blindness
MAH(s): Novo Nordisk A/S

16.1.13. Insulin glargine – LANTUS (CAP)
Insulin glulisine – APIDRA (CAP)

- Evaluation of a PASS protocol

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

Administrative details:
Procedure number(s): EMEA/H/C/000284/MEA 051.1, EMEA/H/C/000557/MEA 037.1
Procedure scope: Revised PASS protocol related to a packaging differentiation study UK SoloStar differentiation study: test in patients with Type 1 or Type 2 diabetes in the UK, to evaluate the ease of differentiating between SoloStar pens containing different types of insulin, following list of questions adopted at PRAC in June 2014
MAH(s): Sanofi-aventis Deutschland GmbH

16.1.14. Ivacaftor – KALYDECO (CAP)

- Evaluation of PASS results

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

Administrative details:
Procedure number(s): EMEA/H/C/002494/II/0032 (with RMP)
Procedure scope: Submission of the final PopPK report (including data from all completed studies that had enrolled patients aged 6-11 years [including Study 110 and Study 111]) to fulfil post-authorisation measure MEA 010
MAH(s): Vertex Pharmaceuticals (U.K.) Ltd.

16.1.15. Lipegfilgrastim – LONQUEX (CAP)

- Evaluation of a PASS protocol

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002556/MEA 004.1
Procedure scope: Evaluation of the MAH's responses to MEA-004 (PASS study XM22-ONC-50002, drug utilisation study) request for supplementary information (RSI) as adopted in May 2014
MAH(s): Sicor Biotech UAB

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

- Evaluation of interim PASS results

Regulatory details:
PRAC Rapporteur: Magda Pedro

Administrative details:
Procedure number(s): EMEA/H/C/002380/MEA/003.5, EMEA/H/C/000626/MEA/003.11
Procedure scope: Annual status report for PASS SP854 (TRUST)

MAH(s): UCB Manufacturing Ireland Ltd.

16.1.17. Sodium, magnesium, potassium sulphates for bowel preparation (NAP)

- Evaluation of an imposed PASS protocol

Regulatory details:
PRAC Rapporteur: Arnaud Batz (FR)

Administrative details:
Procedure number: EMEA/H/N/PSP/0007.1
Procedure scope: Evaluation of a revised protocol for a multi-centre European observational drug utilisation study (DUS) of post-commitment BLI800 to assess drug utilisation in the real life setting in a representative sample of the European target population
MAH(s): Ipsen Pharma (Eziclen, Izinova)

16.1.18. Telaprevir – INCIVO (CAP)

- Evaluation of PASS results

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

Administrative details:
Procedure number(s): EMEA/H/C/002313/II/0034 (with RMP)
Procedure scope: Submission of a study report (HIV/HCV co-infection study, VX-950HPC3008) and a revised RMP to update the information on the mentioned study. Update of SmPC sections 4.2, 4.4, 4.8 and 5.1 in accordance with the results of study VX-950HPC3008. In addition, the MAH took the opportunity to change in the SmPC the word 'subjects' into 'patients' in the description of the C211 study description (section 5.1). The package leaflet is updated accordingly
MAH(s): Janssen-Cilag International N.V.

16.1.19. Tenofovir – VIREAD (CAP)

- Evaluation of a PASS protocol

Regulatory details:
PRAC Rapporteur: Arnaud Batz (FR)

Administrative details:
Procedure number(s): EMEA/H/C/000419/MEA 265.3
Procedure scope: Evaluation of an updated PASS protocol for the HIV post-authorisation safety study: GS-EU-104-1402
MAH(s): Gilead Sciences International Ltd

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

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

17.1.1. Alipogene tiparvovec – GLYBERA (CAP)

- PRAC consultation on an annual reassessment of the marketing authorisation

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002145/S/0039 (without RMP)
MAH(s): UniQure Biopharma B.V.

17.1.2. Cholic acid – ORPHACOL (CAP)

- PRAC consultation on an annual reassessment of the marketing authorisation

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Procedure number(s): EMEA/H/C/001250/S/0008 (without RMP)
MAH(s): Laboratoires CTRS – Boulogne Billancourt

17.1.3. Delamanid – DELTYBA (CAP)

- PRAC consultation on a conditional renewal of the marketing authorisation

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002552/R/0004 (without RMP)
MAH(s): Otsuka Novel Products GmbH

17.1.4. Ofatumumab – ARZERRA (CAP)

- PRAC consultation on a conditional renewal of the marketing authorisation

Regulatory details:
PRAC Rapporteur: Doris Stenver (DK)

Administrative details:
Procedure number(s): EMEA/H/C/001131/R/0033 (without RMP)
MAH(s): Glaxo Group Ltd

17.1.5. Tocofersolan – VEDROP (CAP)

- PRAC consultation on an annual reassessment of the marketing authorisation

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Procedure number(s): EMEA/H/C/000920/S/0012 (without RMP)
MAH(s): Orphan Europe S.A.R.L.

ANNEX II – List of participants:

Including any restrictions with respect to involvement of members / alternates / experts following evaluation of declared interests for the 1 - 4 December 2014 meeting.

PRAC member PRAC alternate	***Country***	***Outcome restriction following evaluation of e-DoI for the meeting***	***Topics on the current Committee Agenda for which restriction applies*** ***Product/ substance***
June Munro Raine	Chair	Full involvement	
Jan Neuhauser	Austria	Full involvement	
Jean-Michel Dogné	Belgium	Cannot act as Rapporteur or Peer Reviewer for:	interferon alfa-2b;interferon beta-1a, Interferon beta-1b, peginterferon alfa-2a, peginterferon alfa-2b; aflibercept; radium-223; Cyproterone, ethinylestradiol; ciprofloxacin
Veerle Verlinden	Belgium	Full involvement	
Yuliyan Eftimov	Bulgaria	Full involvement	
Viola Macolić Šarinić	Croatia	Full involvement	
Nectaroula Cooper	Cyprus	Full involvement	
Eva Jirsová	Czech Republic	Full involvement	
Doris Stenver	Denmark	Full involvement	
Torbjörn Callreus	Denmark	Full involvement	
Maia Uusküla	Estonia	Full involvement	
Kirsti Villikka	Finland	Full involvement	
Terhi Lehtinen	Finland	Full involvement	
Arnaud Batz	France	Cannot act as Rapporteur or Peer Reviewer for:	telaprevir; bortezomib; canagliflozin; decitabine; rilpivirine; etravirine
Martin Huber	Germany	Full involvement	
Valerie Strassmann	Germany	Full involvement	
Leonidas Klironomos	Greece	Cannot act as Rapporteur or Peer Reviewer for:	apixaban; sildenafil; sunitinib; tafamidis; varenicline; pregabalin; tigecycline
Julia Pallos	Hungary	Cannot act as Rapporteur or Peer Reviewer for:	pregabalin; sevelamer
Almath Spooner	Ireland	Full involvement	
Ruchika Sharma	Ireland	Full involvement	
Carmela Macchiarulo	Italy	Full involvement	
Jelena Ivanovic	Italy	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
Andis Lacis	Latvia	Full involvement	
Jolanta Gulbinovic	Lithuania	Full involvement	
Sabine Straus	Netherlands	Full involvement	
Menno van der Elst	Netherlands	Full involvement	
Ingebjørg Buajordet	Norway	Full involvement	
Karen Pernille Harg	Norway	Full involvement	
Adam Przybylkowski	Poland	Full involvement	
Margarida Guimarães	Portugal	Full involvement	
Roxana Stroe	Romania	Full involvement	
Tatiana Magálová	Slovakia	Full involvement	
Gabriela Jazbec	Slovenia	Full involvement	
Dolores Montero Corominas	Spain	Full involvement	
Miguel-Angel Maciá	Spain	Full involvement	
Qun-Ying Yue	Sweden	Full involvement	
Ulla Wändel Liminga	Sweden	Full involvement	
Julie Williams	UK	Full involvement	
Rafe Suvarna	UK	Full involvement	

Independent scientific experts nominated by the European Commission	Country	Outcome restriction following evaluation of e-DoI for the meeting:	Topics on the current Committee Agenda for which restriction applies Product/ substance
Jane Ahlqvist Rastad	Not applicable	Full involvement	
Marie Louise De Bruin		Full involvement	
Stephen Evans		Cannot act as Rapporteur or Peer reviewer for:	pandemic influenza vaccine (H1N1) (split viron, inactivated, adjuvanted); human papillomavirus vaccine [types 16, 18] (recombinant, adjuvanted, adsorbed); lapatinib; fluticasone furoate, vilanterol; pandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted); prepandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted; ofatumumab
Brigitte Keller-Stanislawski		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*
Lennart Waldenlind		Full involvement	

Health care professionals and patients members	*Country*	*Outcome restriction following evaluation of e-DoI for the meeting:*	*Topics on the current Committee Agenda for which restriction applies* *Product/substance*
Filip Babylon	Not applicable	Full involvement	
Albert van der Zeijden		Cannot act as Rapporteur or Peer Reviewer in relation to any medicinal product from the relevant companies for which his institution receives grants as listed in the published Declaration of Interest (16-05-2014) http://www.ema.europa.eu/docs/en_GB/document_library/contacts/avanderzeijden_DI.pdf	

Additional European experts participating at the meeting for specific Agenda items	*Country*	*Topics on the current Committee Agenda for which restriction applies* *Product/ substance*
Christelle Bizimungu	Belgium	No restrictions were identified for the participation of European experts attending the PRAC meeting for discussion on specific agenda items
Jonathan Douxfils	Belgium	
Miranda Vroenhove	Belgium	
Mette Madsen	Denmark	
Elisabeth Penninga	Denmark	
Corinne Fechant	France	
Thomas Grüger	Germany	
Tania Meier	Germany	
Vahid Taravati	Germany	
Luca Pani	Italy	
Quirine Fillekes	Netherlands	
Jan Schellens (SAG chair)	Netherlands	
Elena Moštenická	Slovakia	

Additional European experts participating at the meeting for specific Agenda items	*Country*	*Topics on the current Committee Agenda for which restriction applies* *Product/ substance*
Jana Nováková	Slovakia	
Ferrán Catalá	Spain	
César de la Fuente	Spain	
Pilar Rayón	Spain	
Alexandra Vasconcelos	Portugal	
Charlotte Backman	Sweden	
Darius Matusevicius	Sweden	
Elina Rönnemaa	Sweden	
Philip Bryan	United Kingdom	
Claire Davies	United Kingdom	
Anya Sookoo	United Kingdom	

ANNEX III – List of abbreviations

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

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