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Pharmacovigilance Risk Assessment Committee (PRAC)

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Minutes of the meeting on 3-6 March 2014

Chair: June Raine – Vice-Chair: Almath Spooner

Note on access to documents

Readers please note that some documents mentioned in the agenda/minutes subject to on-going procedures for which a final decision has not yet been adopted might not be released at present following a request for access to documents under Regulation (EC) No 1049/2001. 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 minutes items and should be read in conjunction with the minutes.

EU Referral procedures for safety reasons: Urgent EU procedures and Other EU referral procedures
(Items 2 and 3 of the PRAC agenda)

A referral is a procedure used to resolve issues such as concerns over the safety or benefit-risk balance of a medicine or a class of medicines. In a referral, the EMA is requested to conduct a scientific assessment of a particular medicine or class of medicines on behalf of the European Union (EU). For further detailed information on safety-related referrals please see: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000150.jsp&mid=WC0b01ac05800240d0

Signals assessment and prioritisation
(Item 4 of the PRAC Minutes)

A safety signal is information on a new or incompletely documented adverse event that is potentially caused by a medicine and that warrants further investigation. Signals are generated from several sources such as reports of adverse events from healthcare professionals or patients (so called spontaneous reports), clinical studies and the scientific literature. The evaluation of safety signals is a routine part of pharmacovigilance and is essential to ensuring that regulatory authorities have a comprehensive knowledge of a medicine's benefits and risks.
The presence of a safety signal does not mean that a medicine has caused the reported adverse event. The adverse event could be a symptom of another illness or caused by another medicine taken by the patient. The evaluation of safety signals is required to establish whether or not there is a causal relationship between the medicine and the reported adverse event.
After evaluation of a safety signal the conclusion could be that the medicine caused the adverse reaction, that a causal relationship with the adverse event was considered unlikely, or that no clear answer could be given and the signal therefore is to be further investigated. In cases where a causal relationship is confirmed or considered likely, regulatory action may be necessary and this usually takes the form of an update of the product information (the summary of product characteristics and the package leaflet).
For completeness the information on signals is complemented, when available, by information on worldwide population exposure.

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

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

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

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

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

A PASS is a study of an authorised medicinal product carried out to obtain further information on its safety, or to measure the effectiveness of risk minimisation activities that have been introduced. The results of a PASS help regulatory agencies to further evaluate the safety and benefit-risk profile of a medicine already in use.

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

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

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

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1. Introduction

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

The Chairperson opened the meeting, welcoming all participants to the 3-6 March 2014 meeting of the PRAC.

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

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 welcomed Rafe Suvarna as new alternate for the UK and Hrefna Guðmundsdóttir as alternate for Iceland.

1.2. Adoption of agenda of the meeting of 3-6 March 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 February 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 February 2014 EMA/PRAC/158631/2014 were published on the EMA website on 19 March 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. **Agents acting on the renin-angiotensin system** (CAP, NAP): **angiotensin receptor blockers** (**ARBs**), **angiotensin converting enzyme inhibitors** (**ACEi**), **direct renin inhibitors** (**aliskiren**)

- Review of the risks of dual blockade of the renin angiotensin system through concomitant use of ARBs, ACEi or aliskiren-containing medicines following the notification by Italy of a referral under Article 31 of Directive 2001/83/EC based on pharmacovigilance data

Regulatory details:
PRAC Rapporteur: Carmela Macchiarulo (IT)
PRAC Co-Rapporteurs: Margarida Guimarães (PT), Valerie Strassmann (DE), Tatiana Magálová (SK), Dolores Montero Corominas (ES), Almath Spooner (IE), Menno van der Elst (NL), Julie Williams (UK), Qun-Ying Yue (SE)

Administrative details:
Procedure number: EMEA/H/A-31/1370
EPITT 13359 – Follow up January 2014
PRAC Co-Rapporteurs (responsibility per substance): Margarida Guimarães (PT) (lisinopril); Carmela Macchiarulo (IT) (delapril, telmisartan, aliskiren, moexipril); Tatiana Magálová (SK) (spirapril, quinapril); Dolores Montero Corominas (ES) (fosinopril, irbesartan); Almath Spooner (IE) (benazepril, cilazapril, perindopril); Valerie Strassmann (DE) (ramipril, eprosartan, olmesartan); Menno van der Elst (NL) (trandolapril, losartan, azilsartan); Julie Williams (UK) (captopril, imidapril, zofenopril, candesartan); Qun-Ying Yue (SE) (enalapril, valsartan)
MAH(s): Actavis (Telmisartan Actavis, Actelsar HCT), Bayer Smith Kline Beecham (Kinzalmono, Kinzalkomb, Pritor, Pritor Plus), Boehringer Ingelheim (Micardis, Micardis Plus, Onduarp, Twynsta), Krka (Ifirmasta, Ifirmacombi, Tolura), Novartis (Copalia, Copalia HCT, Exforge, Exforge HCT, Dafiro, Dafiro HCT, Imprida), Novartis Europharm Ltd (Rasilamlo, Rasilez, Rasilez HCT, Rasitrio), Pharmathen S.A. (Sabervel), Sanofi-Winthrop / BMS (Aprovel, CoAprovel, Irbesartan Zentiva, Irbesartan HCT Zentiva, Karvea, Karvezide), Takeda (Edarbi, Ipreziv), Teva Pharma / Pharmachemie (Irbesartan Teva, Irbesartan HCT Teva, Telmisartan Teva, Telmisartan Teva Pharma), various

Background

A referral procedure under Article 31 is ongoing to review the benefit-risk of the concomitant use (dual blockade of the renin-angiotensin system) of ARBs, ACE-inhibitors or aliskiren-containing medicines (see PRAC minutes 6-10 January 2014). The Co-Rapporteurs prepared an assessment based on the data received by the MAHs for discussion at PRAC and IT as PRAC Rapporteur presented an overall assessment report.

Summary of recommendation(s)/conclusions

The PRAC discussed some aspects to be further elucidated during the course of the review and heard feed-back from the Scientific Advisory Group meeting held on 11 of February 2014.

The PRAC agreed on a second list of outstanding issues to be addressed by the MAHs and adopted a revised timetable for the procedure (EMA/PRAC/290691/2013 rev3).

3.2.2. **Bromocriptine** (NAP)

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

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)
PRAC Co-Rapporteur: Isabelle Robine (FR)

Administrative details:
Procedure number: EMEA/H/A-31/1379
MAH(s): Sanofi-aventis, Meda Pharma, various

Background

A referral procedure under Article 31 of Directive 2001/83/EC is ongoing for bromocriptine-containing medicines in the inhibition of lactation (see PRAC minutes 2-5 September 2013). The (Co-)Rapporteurs assessed the data submitted by some of the MAHs on the issue.

Summary of recommendation(s)/conclusions

The PRAC noted further aspects to be addressed during the review and agreed on a list of outstanding issues and on an updated timetable (EMA/PRAC/493206/2013 rev.1).

3.3. Procedures for finalisation

3.3.1. **Domperidone** (NAP)

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

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

Administrative details:
Procedure number: EMEA/H/A-31/1365
EPITT 15994 – Follow up January 2014
MAH(s): Janssen-Cilag, various
Oral Explanation(s): Janssen-Cilag

Background

A referral procedure under Article 31 of Directive 2001/83/EC for domperidone-containing medicines (see minutes of the PRAC 6-9 January 2014) was to be concluded. A final assessment of the data submitted was produced by the Rapporteurs according to the agreed timetable.

Discussion

The PRAC discussed the conclusion reached by the Rapporteurs. One oral explanation took place at the meeting. The review confirmed a small increased risk of serious cardiac adverse drug reactions related to the use of domperidone. A higher risk was observed in patients older than 60 years, patients taking daily doses of more than 30 mg, and those taking QT-prolonging drugs or CYP3A4 inhibitors concomitantly. Therefore the PRAC agreed on a series of risk minimisation measures including a restriction of the indication to the relief of the symptoms of nausea and vomiting in which benefit risk

remained favourable and a newly reduced dose of 10 mg up to three times daily orally for adults and adolescents weighing 35 kg or more as described in the revised product information;where the medicine is licensed in children and adolescents weighing less than 35 kg, it should be given orally at a dose of 0.25 mg per kg bodyweight up to three times daily. Moreover measuring devices should be included with liquid formulations to allow accurate dosing by bodyweight and the medicine should not normally be used for longer than one week. A revision of other parts of the product information, including the contraindications, interactions and warnings was also agreed. The PRAC also agreed on further studies to be carried out to expand the knowledge on specific aspects of the benefit-risk profile for domperidone, in particular in children.

Summary of recommendation(s)/conclusions

The PRAC adopted, by majority, the variation of the marketing authorisations for domperidone-containing medicines (and revocation for some of them: products supplying a dose of 20 mg orally, and suppositories of 10 or 60 mg are no longer recommended for use and should be withdrawn, as should combination products with cinnarizine) and adopted a recommendation to be considered by CMDh for a position– see communication 'PRAC recommends restricting use of domperidone' EMA/129231/2014. A Direct Healthcare Professional Communication (DHPC) and communication plan were also endorsed.

Twenty-nine members, voted in favour of the variation (or revocation as appropriate, see above) of the marketing authorisation of domperidone-containing products together with Iceland and Norway, while three members had divergent views[1].

3.3.2. **Zolpidem** (NAP)

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

Regulatory details:
PRAC Rapporteur: Menno van der Elst (NL)
PRAC Co-Rapporteur: Jelena Ivanovic (IT)

Administrative details:
Procedure number: EMEA/H/A-31/1377
EPITT 17427 – Follow up December 2013
MAH(s): Sanofi-aventis, various

Background

A referral procedure under Article 31 of Directive 2001/83/EC for zolpidem-containing medicines (see minutes of the PRAC 2-5 December 2013) was to be concluded. A final assessment of the data submitted was produced by the Rapporteurs according to the agreed timetable.

[1] The relevant AR containing the divergent views will be published on the EMA website once the procedure is fully concluded.

Discussion

The PRAC discussed the evidence on the risks of next-morning impaired driving ability and somnambulism in the context of the use of zolpidem for the short-term treatment of insomnia. It was agreed that to mitigate these risks the product information of zolpidem containing medicines should be updated, to include strengthened warnings and precautions and enhanced information on interactions with other medicinal products that can increase these risks. It was also recommended that there should be a rest period of at least 8 hours after zolpidem administration before performing activities that require mental alertness such as driving. The PRAC considered that the recommended daily dose should remain at 10 mg of zolpidem, and that this dose must not be exceeded; zolpidem should be taken as a single intake immediately at bedtime without being re-administered during the same night. The PRAC agreed that the available efficacy data did not provide robust evidence that a lower dose was effective on a population level. However, it also considered that there were some data indicating that in some individual patients a lower dose could be effective and therefore patients should take the lowest effective dose. This information should also be reflected in the product information. In elderly patients and in patients with reduced liver function, the recommended dose remains 5 mg of zolpidem per day.

Summary of recommendation(s)/conclusions

The PRAC adopted, by majority, the variation of the marketing authorisations for zolpidem-containing medicines and adopted a recommendation to be considered by CMDh—see communication 'PRAC recommends product information of zolpidem be updated with new advice to minimise the risk of next-morning impaired driving ability and mental alertness' EMA/129598/2014.

Thirty members, voted in favour of the variation together with Iceland and Norway, while one member had a divergent view[2].

3.4. Re-examination procedures

3.4.1. **Diacerein** (NAP)

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

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

Administrative details:
Procedure number: EMEA/H/A-31/1349
EPITT 15994 – Follow-up December 2013
MAH(s): Negma-Wockhardt, TRB Chemedica
Oral Explanation(s): Negma-Wockhardt, TRB Chemedica

Background

Following a request for a re-examination of the PRAC recommendation on diacerein-containing medicines, provided under Article 31 of Directive 2001/83/EC ,and submission of grounds for this re-

[2] The relevant AR containing the divergent views will be published on the EMA website once the procedure is fully concluded.

examination received by some of the MAHs, the PRAC was to issue a final recommendation on the Article 31 referral procedure (see PRAC minutes of the 3-6 February 2014 for background). The appointed Rapporteur and Co-Rapporteur for the re-examination procedure circulated their assessment report on these grounds for the procedure.

Summary of recommendation(s)/conclusions

The PRAC discussed the conclusions reached by the Rapporteurs. Two oral presentations by the MAHs took place at the meeting.

The PRAC agreed that available data from pre-clinical studies, clinical trials, post-marketing spontaneous case reports, and published literature have shown that the use of diacerein-containing products was associated with safety concerns such as frequent cases of severe diarrhoea and rare cases of potentially serious hepatotoxicity; also a risk of cutaneous reactions could not be excluded. However, during the re-examination, new proposals to manage these risks were considered. These included a recommendation to start treatment at half the normal daily dose, a contraindication in patients with previous or current liver disease and a clear recommendation for patients to stop treatment as soon as diarrhoea occurs. It was also proposed that diacerein should not be recommended for patients aged 65 years and above. In addition, given the gastrointestinal risk and potential risk of hepatic reactions, prescription should be restricted to specialists experienced in the treatment of osteoarthritis. Information on pruritus, rash, eczema should also be included in the product information. Finally, periodic safety update reports (PSURs) should be submitted on a yearly basis.

Provided these risk minimisation measures were put in place, the PRAC concluded that diacerein's risks could be appropriately mitigated and as a consequence, that the benefit-risk balance of the medicinal products containing diacerein would remained favourable (this means that the November 2013 recommendation to remove the medicines from the market need not be maintained).

Twenty-one members voted in favour of a variation of the marketing authorisation of diacerein containing products together with Iceland and Norway, while fourteen members had divergent views[3].

4. Signals assessment and prioritisation[4]

4.1. New signals detected from EU spontaneous reporting systems

4.1.1. **Cefepime** (NAP)

- Signal of convulsions

Regulatory details:
PRAC Rapporteur: *Margarida Guimarães (PT)*

Administrative details:
EPITT 17859 – New signal
MAH(s): Bristol-Myers Squibb, various
Lead MS: PT

[3] Martin Huber (DE), Doris Stenver (DK), Kirsti Villikka (FI), Isabelle Robine (FR), Carmela Macchiarulo (IT), Margarida Guimarães (PT), Jean-Michel Dogné (BE), Amy Tanti (MT), Julie Williams (UK), Menno van der Elst (NL), Marieke De Bruin (aaaindependent scientific expert nominated by the EC).
[4] Each signal refers to a substance or therapeutic class. The route of marketing authorisation is indicated in brackets (CAP for Centrally Authorised Products; NAP for Nationally Authorised Products including products authorised via Mutual Recognition Procedures and Decentralised Procedure). Product names are listed for reference Centrally Authorised Products (CAP) only. PRAC recommendations will specify the products concerned in case of any regulatory action required

Background

Cefepime is a cephalosporin antibiotic used in the treatment of infections caused by susceptible pathogens, including serious conditions such as bacterial meningitis in children and febrile neutropenia.

The exposure for nationally authorised medicine containing cefepime is estimated to have been more than 12 million patients worldwide, in the period from first authorisation in 1994 to 2012.

During routine signal detection activities, a signal of convulsions was identified by PT, based on an initial number of 190 cases retrieved from EudraVigilance relating to convulsions and related terms potentially ascribable to episodes of seizure activity. PT as Reference Member State for the originator cefepime-containing medicine confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information on the cases of convulsions and related terms reported and commented that cefepime, like other cephalosporins, has been associated with reports of various neurological adverse drug reactions (ADRs), namely encephalopathy, seizures (convulsions) and myoclonus, mostly in patients with renal impairment and in patients who received cefepime in higher doses than those recommended. This is reported in the current product information. However the data suggested a higher incidence of convulsions and related events than known and for risk factors beyond those currently identified. Therefore the PRAC agreed that the signal should be further investigated.

The PRAC appointed Margarida Guimarães (PT) as rapporteur for the signal.

Summary of recommendation(s)

- The MAH for the originator, nationally authorised cefepime-containing medicine should submit to the PRAC Rapporteur a cumulative review of the signal, within 60 days, including the studies with cefepime. An estimate of the use of cefepime and of the incidence of convulsions should be added.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.1.2. Cefepime (NAP)

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

Regulatory details:
PRAC Rapporteur: *to be appointed*

Administrative details:
EPITT 17866 – New signal
MAH(s): Bristol-Myers Squibb, various
Lead MS: PT

Background

Cefepime is a cephalosporin antibiotic used in the treatment of infections caused by susceptible pathogens, including more serious conditions such as bacterial meningitis in children and febrile neutropenia.

The exposure for nationally authorised medicine containing cefepime, is estimated to have been more than 12 million patients worldwide, in the period from first authorisation in 1994 to 2012.

During routine signal detection activities, a signal of DRESS was identified by PT, based on 13 cases retrieved from EudraVigilance. PT as Reference Member State for the originator, cefepime-containing medicine confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC noted that eosinophilia, drug hypersensitivity and a number of skin and systemic reactions are included in the cefepime product information but not DRESS. DRESS has been reported for other cephalosporins in the scientific literature. However the PRAC agreed that only 4 cases possibly implicate cefepime. Therefore, given the limited evidence, the PRAC agreed that prioritisation would be unjustified at this stage and that the pharmacovigilance activities currently in place were appropriate to address the signal.

Summary of recommendation(s)

- The PRAC agreed that routine pharmacovigilance was sufficient at this time to address the signal.

4.1.3. **Regorafenib – STIVARGA** (CAP)

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

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
EPITT 17813 – New signal
MAH(s): Bayer Pharma AG
Lead MS: NL

Background

Regorafenib is a protein-kinase inhibitor used as an antineoplastic agent in the treatment of adult patients with metastatic colorectal cancer who have been previously treated with, or are not considered candidates for, available therapies.

The exposure for Stivarga, a centrally authorised medicine containing regorafenib, is estimated to have been more than 18600 patients worldwide, in the period from first authorisation in 2013 to 2014.

During routine signal detection activities, a signal of hypersensitivity, drug reaction with eosinophilia and systemic symptoms (DRESS) was identified by the EMA, based on 19 cases retrieved from EudraVigilance. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information on the reported cases of hypersensitivity including DRESS the reports included cases of widespread skin eruption. Hepatic and kidney involvement with hepatitis and nephritis was described, as well as eosinophilia and thrombocytopenia. Some other cases reported either only rash or rash in combination with fever. Given these findings the PRAC agreed that the signal should be further investigated.

Summary of recommendation(s)

- The MAH for Stivarga (regorafenib) should submit to the EMA within the next PSUR (DLP 26/03/2014), a cumulative review of all cases suggestive of this suspected adverse drug reaction, from spontaneous reports, from clinical trials as well as from the literature.

4.1.4. Tacrolimus - ADVAGRAF (CAP), **MODIGRAF** (CAP), NAP
Febuxostat – **ADENURIC** (CAP)

- Signal of potential drug-drug interaction between systemic tacrolimus and febuxostat

Regulatory details:
PRAC Rapporteur: Almath Spooner (IE)

Administrative details:
EPITT 17809 – New signal
MAH(s): Astellas Pharma Europe B.V. (Advagraf, Modigraf), Menarini International Operations Luxembourg S.A. (Adenuric), various

Background

Tacrolimus is a calcineurin inhibitor used in the prophylaxis of transplant rejection in adult kidney or liver allograft recipients and for the treatment of allograft rejection resistant to treatment with other immunosuppressive medicinal products in adult patients. Febuxostat is a xanthine oxidase inhibitor authorised for the treatment of chronic hyperuricaemia in conditions where urate deposition has already occurred (including a history, or presence, of tophus and/or gouty arthritis).

During routine signal detection activities, a signal of drug-drug interaction between systemic tacrolimus and febuxostat was identified by the UK, based on an individual case reported in the United Kingdom and further cases retrieved from EudraVigilance. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information on the cases of suspected interaction between tacrolimus and febuxostat leading to an increase in tacrolimus blood concentrations. The PRAC commented that a particular underlying mechanism was not obvious, the number of cases was small in absolute terms and the detail provided was quite limited.

However, the identified time to interaction seemed plausible and positive dechallenge information (further normalisation of blood levels after febuxostat dechallenge or tacrolimus dose reduction) was present. The suspected interaction, if confirmed, could be potentially medically important as tacrolimus is a medicine with a narrow therapeutic index and maintenance of whole blood tacrolimus concentrations within the therapeutic range is required to avoid toxicity and graft rejection linked to overdosing and under dosing, respectively. The consequences of overdose are primarily renal impairment; however other manifestations of toxicity include nausea, vomiting, tremor and elevated liver enzymes. Investigation of the potential for an interaction is also clinically relevant in the context of real world use as gout is a common problem among the population of renal transplant patients with a prevalence of 2 to 13%[5] (although the use of febuxostat in organ transplant recipients is not recommended in section 4.2 of the Summary of Product Characteristic (SmPC) of Adenuric as there is no experience with febuxostat in this patients population).

[5] JASN 2000 vol.11 no. 5 974-979

Based on these considerations the PRAC concluded that it would be important to gather further information on the signal.

Summary of recommendation(s)

- The MAHs for Advagraf, Modigraf and Prograf (tacrolimus) and Adenuric (febuxostat) should submit to the EMA, within 60 days, a cumulative review of the signal, including information suggesting a potential drug–drug interaction between tacrolimus and febuxostat, from spontaneous reports (with causality assessment), literature cases and any relevant studies. The MAHs should particularly focus on exploring potential mechanisms (e.g. transporter-based drug interaction between tacrolimus and febuxostat, which could affect the absorption and/or excretion of tacrolimus, or an inhibition of cytochrome P450 CYP 3A4 by febuxostat metabolites, which could affect the metabolism of tacrolimus).
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.2. New signals detected from other sources

4.2.1. **Testosterone** (NAP)

- Signal of cardiovascular and thrombotic risks

Regulatory details:
PRAC Rapporteur: *to be appointed*

Administrative details:
EPITT 17877 – New signal
MAH(s): various
Lead MS: EE

Background

Testosterone is a naturally occurring hormone used in the EU to treat a range of conditions including use as replacement therapy in male hypogonadal disorders caused by either pituitary or testicular disorders, in hypogonadism following orchiectomy, to promote masculinisation in hypogonadal adolescent boys, and in the prevention of osteoporosis in hypogonadal men.

During routine signal detection activities, a signal of increased cardiovascular and thrombotic risk was identified by EE, following the publication of an article describing an increased risk of non-fatal myocardial infarction (MI) following testosterone therapy in men[6]. EE as lead MS for signal detection activities for testosterone confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the recently published article by Finkle et al. and questioned the appropriateness of the choice for the control group, given an apparent imbalance in the distribution of covariates. It was unclear whether measures applied to take into account such a different distribution (propensity score matching) were effective. The PRAC also discussed the results of a retrospective cohort study,

[6] PLoS One. 2014 Jan 29;9(1):e85805. doi: 10.1371/journal.pone.0085805. Increased risk of non-fatal myocardial infarction following testosterone therapy prescription in men. Finkle WD, Greenland S, Ridgeway GK, Adams JL, Frasco MA, Cook MB, Fraumeni JF Jr, Hoover RN.

conducted in the US Veterans Affairs (VA) system, in men with low testosterone levels (<300 ng/dL) who underwent coronary angiography, published in the JAMA[7]. The members commented that the study was overall well-conducted; however, information regarding the indication for use of testosterone was missing. Testosterone is used in several different indications and the paper did not clarify which testosterone uses the results apply to, and whether this was applicable to all or to a specific subpopulation of men. The PRAC also discussed the preliminary results of a search performed in EudraVigilance and noted that there were other studies in the literature on this possible association, and agreed that overall further assessment of this evidence was needed and that a benefit-risk assessment should be undertaken.

The PRAC appointed Maia Uusküla (EE) as Rapporteur for the signal.

Summary of recommendation(s)

- Based on the published literature showing a potential association between the use of testosterone and an increased risk of cardiovascular events, the PRAC has agreed that a benefit-risk assessment should be undertaken with due regard to licensed indications and pharmaceutical forms.

4.3. Signals follow-up and prioritisation

4.3.1. **Bupropion** (NAP)

- Signal of pancytopenia

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
Procedure scope: Evaluation of the MAH's responses to PRAC recommendation as adopted at PRAC in November 2013
EPITT 17727 - Follow-up November 2013
MAH(s): GlaxoSmithKline, various

Background

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

Discussion

The PRAC discussed the evidence presented, which suggested that pancytopenia was very rarely reported and that the reporting rate might very well have been within the background incidence.

However, some questions were raised on the occurrence of adverse events concerning anaemia and single cytopenias, such as thrombocytopenia and leucopenia. Effects on red cell parameters were observed at clinically relevant doses in dogs, including a decrease in total erythrocytes. The PRAC agreed that the underlying data and clinical relevance of this finding should be further investigated.

[7] JAMA. 2013 Nov 6;310(17):1829-36. doi: 10.1001/jama.2013.280386. Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels. Vigen R, O'Donnell CI, Barón AE, Grunwald GK, Maddox TM, Bradley SM, Barqawi A, Woning G, Wierman ME, Plomondon ME, Rumsfeld JS, Ho PM.

Furthermore the number of cases seen in the observational databases was higher than expected (even acknowledging that data were obtained from observational databases and not all the cases represent adverse reactions) and the reasons for this should be further clarified.

Summary of recommendation(s)

- The MAHs for of all bupropion-containing medicines should continue monitoring cases of pancytopenia in future PSURs. Furthermore the MAHs should respond to a request for supplementary information concerning effects on red cell parameters and on haematopenia with a specific focus on anaemia, leucopenia, lymphopenia and thrombocytopenia within 60 days.

4.3.2. **Goserelin** (NAP)

- Signal of long-duration flushing and hyperhidrosis

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure scope: Evaluation of the MAH's responses to PRAC recommendation as adopted at PRAC in November 2013
EPITT 17698 - Follow-up November 2013
MAH(s): Astra Zeneca, various

Background

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

Discussion

The PRAC discussed the additional information on the post-marketing cases and information from the published literature. Whilst the limitations of the post-marketing data were noted it was agreed that there were a small number of cases of hot flushes and/or hyperhidrosis which prolonged after stopping goserelin that were not explained by comorbidities/concomitant treatments or the patient's age. In addition to these cases, there was strong supporting evidence from published clinical data[8] showing that in men with prostate cancer the suppression of luteinising hormone (LH) and testosterone levels (and corresponding symptoms of sweating and hot flushes) can persist for many months after goserelin was stopped. Data showed that the recovery of hypothalamic-pituitary-testicular axis function after goserelin administration was variable and for some patients was protracted.

[8] Dearnaley DP, Norman AR, Shahidi M, Re: Time to normalization of serum testosterone after 3-month luteinizing hormone-releasing hormone agonist administered in the neoadjuvant setting: Implications for dosing schedule and neoadjuvant study consideration. (Letter). Journal of Urology 1999;162:170.
Meinhardt W, Horenblas S, Re: Time to normalization of serum testosterone after 3-month luteinizing hormone-releasing hormone agonist administered in the neoadjuvant setting: Implications for dosing schedule and neoadjuvant study consideration. (Letter) Journal of Urology 1999;162:170-171.
Nejat RJ, Rashid HH, Bagiella E, Katz AE, Benson MC, A prospective analysis of time to normalization of serum testosterone after withdrawal of androgen deprivation therapy Journal of Urology 2000;164:1891-1894.
Pickles T, Agranovich A, Berthelet E et al. Testosterone recovery following prolonged adjuvant androgen ablation for prostate carcinoma. Cancer 2002;94:362-7.

Taken together, the available evidence indicated that, in some patients, goserelin can cause flushing and hyperhidrosis that persist after cessation of treatment and for a period of time that is longer than expected. The PRAC agreed that this should be reflected in the product information.

Summary of recommendation(s)

- The MAHs for the reference, nationally authorised goserelin-containing medicines[9] should be requested to submit to the NCA within 60 days a variation to update the product information to include that hyperhidrosis and hot flushes may continue after stopping the treatment.
- The MAHs of generic products should then be requested to submit to the EMA or to the NCA, as applicable, a variation to align their product information to that of the originator.

For the full PRAC recommendations, see EMA/PRAC/144622/2014 published on the EMA website on 24/03/2014.

4.3.3. **Quetiapine** (NAP)

- Signal of suicidality in major depressive disorder (MDD) patients

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
Procedure scope: Evaluation of the MAH's responses to PRAC recommendation as adopted at PRAC in October 2013
EPITT 17709 - Follow-up October 2013
MAH(s): various

Background

For background information, see PRAC minutes of 7-10 October 2013. The MAH replied to the request for information on the signal of suicidality in major depressive disorder (MDD) patients and the responses were assessed by the Rapporteur.

Discussion

The PRAC discussed the interpretations of the results of the previously discussed General Practice Research Database (GPRD) study which was compared with the PHARMO, an epidemiological study which was completed in 2011. Furthermore data from other studies, in particular the results of a prescription-event monitoring study concluded at the end of 2013 (mPEM), and the clinical trial database were also reviewed. The PRAC discussed the strength and limitations of the evidence provided and agreed that overall there was a higher mortality rate in Seroquel XR (quetiapine) user groups, especially in MDD patients; however confounding by indication might explain at least part of these findings.

A higher mortality rate in elderly patients with dementia in comparison with elderly without dementia was also observed according to the data submitted. However, no clear conclusions can be drawn at the moment based on the currently available data on both populations. The PRAC noted that, currently,

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

use in elderly patients with dementia-related psychosis is listed as not recommended in the product information.

Given the areas to be clarified in the interpretation of the findings, and the absence of solid data on the risk of suicidality, the PRAC agreed that further investigation was necessary, and the MAH should be requested to provide additional key information including current use in patients with dementia and a number of clarifications on the results of the mPEM study. The PRAC noted that mutual recognition procedures are currently ongoing to fully assess all data of the GPRD and mPEM study reports and assessment of the requested data will be included in the assessment of the type II variation within the MRP procedure.

Summary of recommendation(s)

- The MAHs for the Seroquel XR (quetiapine),[10] should be requested to submit to the RMS (NL) within 60 days a response to a request for supplementary information agreed by the PRAC. The PRAC Rapporteur will keep the PRAC informed of the outcome of the assessment of the MRP procedure.

4.3.4. Tenofovir disoproxil fumarate – VIREAD (CAP)
efavirenz, emtricitabine, tenofovir disoproxil fumarate - ATRIPLA (CAP)
emtricitabine, rilpivirine, tenofovir disoproxil fumarate – EVIPLERA (CAP)
elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil fumarate - STRIBILD (CAP)
emtricitabine, tenofovir disoproxil fumarate - TRUVADA (CAP)
Diclofenac (NAP)

- Signal of acute kidney injury caused by co-administration of tenofovir disoproxil fumarate and diclofenac (Publication from Bickel M et al, HIV Medicine 2013)

Regulatory details:
PRAC Rapporteur (overall): Isabelle Robine (FR)

Administrative details:
Procedure scope: Evaluation of the MAH's responses to the PRAC recommendation adopted at PRAC in January 2014
EPITT 17777 - Follow-up January 2014
MAH(s): Gilead Sciences International Ltd (Eviplera, Stribild, Truvada, Viread), Bristol-Myers Squibb and Gilead Sciences Ltd. (Atripla), various

Background

For background information, see PRAC minutes of 6-9 January 2014. The MAH replied to the request for information on the signal of acute kidney injury caused by co-administration with non-steroidal anti-inflammatory drugs (NSAIDs) and the responses were assessed by the Rapporteur.

Discussion

The PRAC noted that a search in the database of the MAH for tenofovir-containing medicines found that the use of one or more NSAID up to the onset of the renal event was identified in 4.4% of the cases reported at least one renal adverse event with tenofovir. Information on the dose of NSAID was

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

reported in 38.5% of the cases. Among these, high-dose NSAID use was reported in 44%. All adequately documented cases of renal events in which NSAID use was reported involved patients at risk for renal dysfunction and/or concomitant use of nephrotoxic medications.

The PRAC agreed that overall the available data from spontaneous cases and the literature suggested that the co-administration of NSAIDs (in particular high dose or multiple NSAIDs) with tenofovir may expose patients to a risk of renal injury, especially in patients with risk factors for renal dysfunction. Therefore the PRAC considered that the available information should be reflected in the product information of tenofovir-containing products with a recommendation that if tenofovir is co-administered with an NSAID, renal function should be monitored adequately. The PRAC agreed that as the mechanism remains unclear and as there was currently insufficient evidence to support a pharmacokinetic interaction, consideration should be given to the conduct of a drug-drug interaction study.

Summary of recommendation(s)

- The MAH for tenofovir-containing medicines should be requested to submit to the EMA within 30 days a variation to update the product information as per agreed wording[11].
- The MAH should discuss the feasibility and value of performing a pharmacokinetic drug-drug interaction study involving tenofovir and individual NSAIDs to assess the effect of NSAIDs on tenofovir clearance in the next PSUR for Viread (DLP 31/03/2014).

For the full PRAC recommendations, see EMA/PRAC/144622/2014 published on the EMA website on 24/03/2014.

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 weare 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. Aclidinium, formoterol fumarate

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

Administrative details:
Product number(s): EMEA/H/C/003745, EMEA/H/C/003969
Intended indication: Maintenance bronchodilator treatment for airflow obstruction and relief of symptoms in adult patients with chronic obstructive pulmonary disease (COPD)

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

5.1.2. Bazedoxifene, oestrogens conjugated

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

Administrative details:
Product number(s): EMEA/H/C/002314
Intended indication: Treatment of oestrogen deficiency and osteoporosis

5.1.3. Faldaprevir

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

Administrative details:
Product number(s): EMEA/H/C/003720
Intended indication: Treatment of chronic genotype-1 hepatitis C virus (HCV) infection

5.1.4. Insulin degludec, liraglutide

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

Administrative details:
Product number(s): EMEA/H/C/002647
Intended indication: Treatment of type 2 diabetes mellitus

5.1.5. Insulin glargine

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

Administrative details:
Product number(s): EMEA/H/C/002835, *Biosimilar*
Intended indication: Treatment of diabetes mellitus

5.1.6. Ospemifene

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

Administrative details:
Product number(s): EMEA/H/C/002780
Intended indication: Treatment of vulvar and vaginal atrophy (VVA)

5.1.7. Peginterferon beta-1a

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

Administrative details:
Product number(s): EMEA/H/C/002827
Intended indication: Treatment of relapsing multiple sclerosis

5.1.8. Siltuximab

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

Administrative details:
Product number(s): EMEA/H/C/003708, *Orphan*
Intended indication: Treatment of multicentric Castleman's disease (MCD)

5.2. Medicines already authorised

RMP in the context of a variation[12] – PRAC-led procedure

See Annex 14.2

RMP in the context of a variation – CHMP-led

5.2.1. Belimumab – **BENLYSTA** (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/002015/II/0023
Procedure scope: Update of SmPC section 4.4 to add a warning regarding progressive multifocal leukoencephalopathy (PML)
MAH(s): Glaxo Group Ltd

Background

Belimumab is an immunosuppressant used as add-on therapy in adult patients with active, autoantibody-positive systemic lupus erythematosus (SLE) with a high degree of disease activity (e.g. positive anti-ds DNA and low complement) despite standard therapy.

The CHMP is evaluating a type II variation procedure for Benlysta, a centrally authorised product containing belimumab, to include a warning regarding progressive multifocal leukoencephalopathy (PML). The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this variation.

Summary of advice

- The RMP version 12 for Benlysta (belimumab) in the context of the variation under evaluation by the CHMP was considered acceptable provided that some amendments are included before finalisation of the variation procedure by the CHMP. PML should be included in the RMP as an important potential risk in all relevant sections of the RMP. A targeted questionnaire for suspected PML cases should be added as a routine pharmacovigilance activity.

5.2.2. Pandemic influenza vaccine (H1N1)v (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/0069
Procedure scope: Restriction of the indication to adults of 18 years of age and older in an officially declared pandemic situation caused by A (H1N1)v 2009 virus and to update SmPC sections 4.2, 4.4, 4.8 and 5.1 to reflect the totality of data on the risk of narcolepsy and an updated benefit-risk

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

assessment of Pandemrix, based on the data currently available to the MAH on H1N1 influenza disease burden, effectiveness and safety of Pandemrix and available epidemiology data on narcolepsy.

MAH(s): GlaxoSmithKline Biologicals

Background

Pandemrix is a pandemic influenza vaccine (H1N1) currently indicated for the prophylaxis of influenza caused by A (H1N1)v 2009 virus. In persons under 20 years of age, Pandemrix should only be used if the recommended annual seasonal trivalent influenza vaccine is not available and if immunisation against (H1N1)v is considered necessary. However, Pandemrix is not in use in any EU Member State.

The CHMP is evaluating a variation for Pandemrix (see also 10.1.2.) and PRAC is responsible for providing advice to the CHMP on the updates to the RMP in support of this variation which includes up-to-date post-marketing data and results of the Quebec study (see 7.4.2.).

Summary of advice

- The RMP version 17 for Pandemrix (pandemic influenza vaccine (H1N1)) submitted in the context of the restriction of indication variation under evaluation by the CHMP was considered overall acceptable. However, updates relating to the proposed restricted indication in those under 18 years of age and for use only in a pandemic were not supported and the RMP will require further revision in line with PRAC and CHMP requests.

See also under 10.1.2.

5.2.3. Saquinavir – INVIRASE (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Harald Herkner (AT)

Administrative details:
Procedure number(s): EMEA/H/C/000113/II/0104
Procedure scope: Update of SmPC sections 5.1 and 5.2 with results from a phase I clinical study investigating the effect of modified saquinavir/ritonavir dosing regimen (500 mg saquinavir/100 mg ritonavir bid) on the QTc interval, pharmacokinetics and antiviral activity in HIV-1 infected patients. This study was conducted as a post-authorisation measure required in the RMP and Annex II of the MA. In line with the results of the study, recommendations for on-treatment ECG are included in SmPC section 4.4. In addition, Annex II is updated to delete the requirement to conduct this study.

MAH(s): Roche Registration Ltd

Background

Invirase (saquinavir) is a protease inhibitor used in the treatment of HIV-1-infected adult patients. Invirase should only be given in combination with ritonavir and other antiretroviral medicinal products. The CHMP is evaluating a type II variation procedure for Invirase, to include recommendations for an ECG while under treatment. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this variation. The PRAC had previously considered that a DHPC as an additional risk minimisation measure was necessary for the safe and effective use of the medicinal product and a draft was therefore proposed by the MAH.

Summary of advice

- The RMP version 6 for Invirase (saquinavir) in the context of the variation under evaluation by the CHMP was considered acceptable. The PRAC agreed the DHPC and related communication plan addressing the modification in clinical management of patients initiating therapy with ritonavir-boosted Invirase and the newly introduced recommendations with regard to an ECG that should be performed approximately 10 days after the start of the treatment.
- Due to very low usage of Invirase (saquinavir) in some member states the need for dissemination of the DHPC will be established nationally.

RMP evaluated in the context of a PSUR procedure

See Aflibercept (ZALTRAP) under 15.1.1. , Axitinib (INLYTA) under 15.1.4. , Brentuximab vedotin (ADCETRIS) under 15.1.6. , Emtricitabine, rilpivirine, tenofovir disoproxil (EVIPLERA) under 15.1.9. , Nalmefene (SELINCRO) under 15.1.15. , Natalizumab (TYSABRI) under 15.1.16. , Nonacog alfa (BENEFIX) under 15.1.18. , Orlistat (ALLI) under 15.1.19. , Prasugrel (EFIENT) under 15.1.21.

RMP evaluated in the context of PASS results

See Human rotavirus (ROTARIX) under 16.4.5.

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

See Characterised viable autologous cartilage cells expanded ex vivo expressing specific marker proteins (CHONDROCELECT) under 17.1.2. , Everolimus (AFINITOR) under 8.1.1. , Saxagliptin (ONGLYZA) under 17, Tolcapone (TASMAR) under 17, Vinflunine (JAVLOR).

RMP in the context of a stand-alone RMP procedure

None

6. Periodic Safety Update Reports (PSURs)

6.1. Evaluation of PSUR procedures[13]

6.1.1. **Busulfan – BUSILVEX** (CAP), NAP

- Evaluation of a PSUSA[14] procedure

Status: *for discussion and agreement of recommendation to CHMP*

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

Administrative details:
Procedure number(s): PSUSA/00000464/201307
MAH(s): Pierre Fabre Médicament
Documents:

[13] Where a regulatory action is recommended (variation, suspension or revocation of the terms of Marketing Authorisation(s)), the assessment report and PRAC recommendation are transmitted to the CHMP for adoption of an opinion. Where PRAC recommends the maintenance of the terms of the marketing authorisation(s), the procedure finishes at the PRAC level
[14] PSUR single assessment, referring to CAP, NAP

For adoption: PRAC PSUR AR, PRAC recommendation

Background

Busulfan is a cytotoxic agent indicated in combination as conditioning treatment prior to conventional haematopoietic progenitor cell transplantation (HPCT) under certain conditions. Busulfan oral solution is also indicated for palliative treatment of the chronic phase of chronic granulocytic leukaemia and for producing prolonged remission in polycythaemia vera, essential thrombocythaemia and myelofibrosis.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of busulfan-containing products in the approved indication(s) remains favourable.
- Regarding busulfan for oral use, the current terms of the marketing authorisation(s) should be maintained.
- Regarding busulfan for intravenous use, the product information should be updated to include interstitial lung disease as an undesirable effect with an unknown frequency. Therefore the current terms of the marketing authorisation should be varied[15].
- In the next PSUR, the MAHs should discuss the possible risk of interaction between busulfan and deferasirox based on a recent publication by Sweiss *et al.*[16]. In addition, the MAHs should closely monitor cases of thrombotic microangiopathy, cerebral sinus thrombosis, Stevens-Johnson syndrome and decrease in skeletal growth rate in children.

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. Colistimethate sodium – COLOBREATHE (CAP)

- Evaluation of a PSUR procedure

Status: *for discussion and agreement of recommendation to CHMP*

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Procedure number(s): EMEA/H/C/001225/PSU 003
MAH(s): Forest Laboratories UK Limited
Documents:
For adoption: PRAC PSUR AR, PRAC recommendation

[15] 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
[16] Sweiss K, Patel P and Rondelli D. Deferasirox increases busulfan blood concentrations. Bone Marrow Transplantation. 2012;47:315-316

Background

Colistimethate sodium is a cyclic polypeptide antibacterial agent indicated for the management of chronic pulmonary infections due to *Pseudomonas aeruginosa* in patients with cystic fibrosis aged 6 years and older.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Colobreathe, a centrally authorised medicine containing colistimethate sodium, 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 Colobreathe (colistimethate sodium) in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAH should reflect the important identified risks (dyspnoea, lower respiratory tract infection, dysgeusia) and potential risks (hepatotoxicity) as concluded in the assessment of RMP version 4.

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 Rapporteur took the opportunity to inform the PRAC regarding an increased frequency of reporting of capsule breakage (within the turbospin inhaler device). PRAC noted that the capsule breakage rate is relatively low and that whilst this may have caused cough or dysgeusia in some patients, such reactions are also known side effects of the product itself and there is no evidence of any serious implications from capsule breakage. The PRAC considered that it would not be appropriate to set up a registry to collect further data on the rate of capsule breakage at this stage but instead that the focus should be on successfully addressing the root cause. Further assessment will be conducted at the level of the CHMP and the PRAC will be consulted as applicable.

6.1.3. Crizotinib – XALKORI (CAP)

- Evaluation of a PSUR procedure

Status: *for discussion and agreement of recommendation to CHMP*

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

Administrative details:
Procedure number(s): EMEA/H/C/002489/PSU 019
MAH(s): Pfizer Limited
Documents:
For adoption: PRAC PSUR AR, PRAC recommendation

Background

Crizotinib is a selective small-molecule inhibitor of the anaplastic lymphoma kinase (ALK) receptor tyrosine kinase indicated for the treatment of adults with previously treated ALK-positive advanced non-small cell lung cancer (NSCLC).

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Xalkori, a centrally authorised medicine containing crizotinib, 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 Xalkori (crizotinib) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to include gastrointestinal perforations as a warning and as an undesirable effect with an uncommon frequency. Therefore the current terms of the marketing authorisation should be varied[17].
- In the next PSUR, the MAH should closely monitor cases of renal dysfunction and thrombosis. In addition, the MAH should provide a detailed analysis of cases of vision disorders.

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. Peginterferon alfa-2b – **PEGINTRON** (CAP), **VIRAFERONPEG** (CAP)

- Evaluation of a PSUR procedure

Status: *for discussion and agreement of recommendation to CHMP*

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

Administrative details:
Procedure number(s): EMEA/H/C/000280/PSU 084 (PegIntron), EMEA/H/C/000329/PSU 081 (ViraferonPeg)
MAH(s): Merck Sharp & Dohme Limited
Documents:
For adoption: PRAC PSUR AR, PRAC recommendation

Background

Peginterferon alfa-2b is a recombinant interferon alfa-2b covalently conjugated with monomethoxy polyethylene glycol indicated for the treatment of chronic hepatitis C genotype 1 infection in monotherapy or combination under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of PegIntron and ViraferonPeg, centrally authorised medicines containing peginterferon alfa-2b, 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 PegIntron and ViraferonPeg (peginterferon alfa-2b) in the approved indication(s) remains favourable.
- The product information should be updated to include tongue pigmentation as an undesirable effect with an unknown frequency. Therefore the current terms of the marketing authorisations should be varied[18].

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

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

6.1.5. **Ruxolitinib – JAKAVI** (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/002464/PSU 009
MAH(s): Novartis Europharm Ltd
Documents:
For adoption: PRAC PSUR AR, PRAC recommendation

Background

Ruxolitinib is a selective inhibitor of the Janus associated kinases (JAKs) indicated for the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis (also known as chronic idiopathic myelofibrosis), post-polycythaemia vera myelofibrosis or post-essential thrombocythaemia myelofibrosis.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Jakavi, a centrally authorised medicine containing ruxolitinib, 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 Jakavi (ruxolitinib) 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 60 days additional data, including detailed information on exposure to ruxolitinib across all ongoing studies. The MAH should also provide a detailed analysis of cases of sepsis/septic shock, serious infections, opportunistic infections and related fatal cases and discuss the possible involvement of ruxolitinib in such serious infections. The MAH should submit a variation to update the product information as warranted.
- In the next PSUR, the MAH should provide a detailed analysis of ruxolitinib use in patients with hepatic impairment and update on the status of, and the safety findings in, study CINC424AFR02T (JakALLO).

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[19]

6.2.1. **Degarelix – FIRMAGON** (CAP)

- Evaluation of a follow-up to a PSUR procedure

[18] Update of SmPC sections 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion
[19] Follow up as per the conclusions of the previous PSUR procedure, assessed outside next PSUR procedure

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

Administrative details:
Procedure number(s): EMEA/H/C/000986/LEG 035
Procedure scope: Evaluation of MAH's response to PSUR#7 as adopted at PRAC/CHMP in September 2013
MAH(s): Ferring Pharmaceuticals A/S

Background

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

Summary of recommendation(s)/conclusions

- The MAH should submit to EMA within 60 days a variation to update the product information to refine the warning on injection site reactions to reflect that rare serious complications had been reported. The educational material should be updated accordingly.
- In the next PSUR, the MAH should closely review all cases of pneumonia, including interstitial pneumonia. The MAH should update the product information as warranted. In addition, the MAH should provide detailed information on cases reported in patients with renal impairment.

7. Post-authorisation Safety Studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)[20]

See Annex 16.1

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

See Annex 16.2

7.3. Results of PASS imposed in the marketing authorisation(s)[22]

None

7.4. Results of PASS non-imposed in the marketing authorisation(s)[23]

7.4.1. **Palivizumab – SYNAGIS** (CAP)

- Evaluation of PASS results

Regulatory details:
PRAC Rapporteur: Line Michan (DK)

[20] In accordance with Article 107n of Directive 2001/83/EC
[21] 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
[22] In accordance with Article 107p-q of Directive 2001/83/EC
[23] 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

Administrative details:
Procedure number(s): EMEA/H/C/000257/II/0098 (without RMP)
Procedure scope: Evaluation of final study report for study A11-632 (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 IgG1 monoclonal antibody targeting the respiratory syncytial virus (RSV) fusion protein, indicated for the prevention of serious lower respiratory-tract disease requiring hospitalisation caused by RSV in children at high risk for RSV disease; in children born at 35 weeks of gestation or less and less than six months of age at the onset of the RSV season; in children less than two years of age and requiring treatment for bronchopulmonary dysplasia within the last six months; in children less than two years of age and with haemodynamically significant congenital heart disease.

A final study report of an observational study carried out to assess the risk of autoimmune and allergic diseases in high-risk children exposed to palivizumab (study A11-632, which was performed since no long-term follow-up studies exist on the potential risk of autoimmune and allergic disease in children who receive palivizumab as passive RSV prophylaxis in infancy/early childhood) was submitted by the MAH and assessed by the Rapporteur; PRAC was to provide advice to CHMP on this final report.

Summary of advice

The PRAC acknowledged the considerable limitations of the current observational registry study. Although the data should be interpreted with caution, there was a signal of increased risk of asthma which qualified for further investigation and data from the current registry study should be further analysed. Therefore, the MAH should be requested to address a list of questions. Follow-up discussion will take place once a response has been received.

Post-meeting note: this advice was finalised via written procedure on 13 March 2013.

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

- Evaluation of PASS results

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Procedure number(s): EMEA/H/C/000832/II/0068 (without RMP)
Procedure scope: Evaluation of data from the test-negative case-control analysis of a retrospective epidemiological study conducted in Quebec, Canada, to evaluate the risk of narcolepsy associated with vaccination with Arepanrix and to follow-up cases to assess any atypical or differential clinical course and prognosis in any vaccinated vs. non-vaccinated subjects.
MAH(s): GlaxoSmithKline Biologicals

Background

Pandemrix is a pandemic influenza vaccine (H1N1) currently indicated for the prophylaxis of influenza caused by A (H1N1)v 2009 virus. In persons under 20 years of age, Pandemrix should only be used if the recommended annual seasonal trivalent influenza vaccine is not available and if immunisation against (H1N1)v is considered necessary.

A final study report of the study 'Risk of narcolepsy associated with administration of inactivated adjuvanted (AS03) A/H1N1 (2009) pandemic influenza vaccine in the province of Quebec, Canada' was submitted by the MAH including an additional test-negative case control analysis as requested by the CHMP. The Rapporteur assessed these results and the PRAC will provide advice to CHMP (see also 5.2.2.).

Summary of advice

The PRAC agreed that the submission of these additional test-negative case-control analyses indicated, as with the previous cohort and self-controlled case series analysis (SCCS), that there was a lack of power in the Quebec dataset which is related to the low number of cases identified. However, as with the previous results of the cohort and SCCS analysis, the additional case-control study results from the Quebec narcolepsy dataset appear to exclude a narcolepsy risk of similar magnitude to that seen with Pandemrix in Europe. The PRAC considered that these additional analyses from the Quebec narcolepsy study did not impact on the benefit-risk of Pandemrix, which remained positive in its authorised indication. Test-negative analysis commitment from Annex II should therefore be removed.

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[24]

See Annex 16.5

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

8.1.1. Everolimus – AFINITOR (CAP)

- PRAC consultation on a renewal of the marketing authorisation

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

Administrative details:
Procedure number(s): EMEA/H/C/001038/R/0036 (with RMP)
MAH(s): Novartis Europharm Ltd

Background

Everolimus is used in oncology for the treatment of hormone receptor-positive, HER2/neu negative advanced breast cancer, for the treatment of resectable or metastatic, well- or moderately-differentiated neuroendocrine tumours of pancreatic origin and for the treatment of patients with advanced renal cell carcinoma, whose disease has progressed on or after treatment with vascular endothelial growth factor (VEGF)-targeted therapy.

Afinitor, a centrally authorised medicine containing everolimus, was authorised in 2009.

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

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

Summary of advice

Based on the review of the available pharmacovigilance data for Afinitor and the CHMP Rapporteur's assessment report, the PRAC considered that a second five-year renewal of the marketing authorisation is warranted on the basis of insufficient number of patients exposed to Afinitor in the recently approved new indication outside of clinical trials, which precludes the adequate collection to date of pharmacovigilance data in real-world clinical use, and the ongoing post-authorisation study BOLERO-6 (CRADY2201).

9. Product related pharmacovigilance inspections

None

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. Measles, mumps, rubella and varicella vaccine – PROQUAD (CAP), M-M RVAXPRO (CAP)

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

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

Administrative details:
Procedure number(s): EMEA/H/C/WS0492 (without RMP)
Procedure scope: Update of SmPC section 4.8 to include acute disseminated encephalomyelitis (ADEM) based on a review of reports of cases of encephalopathy consistent with ADEM for measles, mumps and rubella virus vaccine live (M-M-R II / M-M-RVaxpro) and measles, mumps, rubella and varicella (Oka/Merck) virus vaccine live (ProQuad).
MAH(s): Sanofi Pasteur MSD, SNC

Background

Proquad is a vaccine used as prophylaxis against measles, mumps, rubella and varicella infection.

Following a review of reports of cases of encephalopathy consistent with acute disseminated encephalomyelitis (ADEM) a type II worksharing variation to update the product information for measles, mumps and rubella virus vaccine live (M-M-R II / M-M-RVaxpro), and measles, mumps, rubella and varicella virus vaccine live, to include ADEM is under evaluation at the CHMP. The PRAC was requested to provide advice on this variation.

Summary of advice

Based on the review of the available information, the PRAC agreed that the subsection "Encephalitis and Encephalopathy" in the product information needs to be revised and brought up-to-date with most recent knowledge, especially to include information concerning serious cases in immunocompromised children, sometimes with fatal outcome. A revised proposal should be requested to conclude on this variation.

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

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

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Procedure number(s): EMEA/H/C/000832/II/0069
Procedure scope: Restriction of the indication to adults 18 years of age and older in an officially declared pandemic situation caused by A (H1N1)v 2009 virus and to update sections 4.2, 4.4, 4.8 and 5.1 of the SmPC to reflect the totality of the data on the risk of narcolepsy and an updated benefit-risk assessment of Pandemrix, based on the data currently available to the MAH on H1N1 influenza disease burden, effectiveness and safety of Pandemrix and available epidemiology data on narcolepsy.
MAH(s): GlaxoSmithKline Biologicals

Background

Pandemrix is an pandemic influenza vaccine (H1N1) currently indicated for the prophylaxis of influenza caused by A (H1N1)v 2009 virus. In persons under 20 years of age, Pandemrix should only be used if the recommended annual seasonal trivalent influenza vaccine is not available and if immunisation against (H1N1)v is considered necessary. However, Pandemrix is not in use in any EU Member State.

PRAC advice was requested by CHMP on a variation to restrict the indication to adults 18 years of age and older in an officially declared pandemic situation caused by A (H1N1)v 2009 virus, and to make related changes in other parts of the product information including an updated warning on the risk of narcolepsy and removal of all information relating to use in those aged less than 18 years.

Summary of advice

Based on the review of the submitted data, including the MAH's assessment of epidemiological studies investigating Pandemrix and narcolepsy and an exploratory quantitative benefit-risk assessment focused on narcolepsy, the PRAC acknowledged that possible bias and confoundings in the studies were unlikely to have fully accounted for the observed risk following vaccination and that the totality of evidence supports a role of Pandemrix in the development of narcolepsy.

The PRAC agreed that, at least in theory, in its currently authorised indication (and if it were still available), Pandemrix could still offer potential benefits to individuals (e.g. elderly, immunocompromised) in a seasonal context, therefore the proposed restricted indication to adults 18 years and older and only in an officially declared pandemic situation was not considered appropriate based on the MAH's benefit-risk assessment. Moreover on the basis that no new data on benefits and risks have been presented, there was little basis to alter the conclusion on the indication and updated narcolepsy paragraph for section 4.4 of the SmPC, as previously reached by PRAC (see, PRAC minutes 10-13 June 2013). However, the PRAC agreed with the MAH's proposal to include the range of absolute risk estimates for narcolepsy in the SmPC. Further information will be requested to the MAH to clarify some remaining aspects.

See also under 5.2.2.

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. **Antidiabetics** (CAP, NAP)

- PRAC consultation on national review of the safety of insulins in patients with type 2 diabetes mellitus, on Member State's request

Status: *for discussion and agreement of advice to Member States*

Regulatory details:
Lead PRAC member: Julie Williams (UK)

Administrative details:
Procedure scope: UK's review of the safety of insulins used in the treatment of type 2 diabetic patients.
MAH(s): Eli Lilly Nederland B.V. (Humalog, Liprolog) Novo Nordisk A/S (Actrapid, Actraphane, Insulatard, Levemir, Novorapid, Novomix, Tresiba), Sanofi-aventis Deutschland GmbH (Apidra, Insuman, Insulin human Withrop, Lantus), various

Background

In 2011 and 2012 following various publications from Currie et al. including recently published research[25], the Pharmacovigilance Working Party (PhVWP) discussed a signal of possible increased risk of common diabetes-related complications and all-cause mortality in people with type 2 diabetes treated with insulin. The results of such studies showed significantly increased risks of all outcomes for patients receiving insulin, when compared with metformin monotherapy, with hazard ratios (HRs) of 1.4 for cancer, 1.8 for major adverse cardiovascular events (MACE) and 2.2 for all-cause mortality. Following an assessment by the UK, the PhVWP concluded that the ongoing European Commission-funded projects which might be suitable to incorporate some of the research questions arising from the review, should be identified with a view to confirming or refuting the signal. The Cancer Risk and Insulin Analogues (CARING) project and the Safety Evaluation of Adverse Reactions in Diabetes (SAFEGUARD) project were subsequently explored and were considered to be a source of further data.

In 2012, the MHRA convened a national Expert Working Group to investigate the signal in more detail which had been kept under ongoing monitoring. The UK requested the PRAC advice on the latest position reached by the now finalised national in-depth review.

[25] J Clin Endocrinol Metab. Feb 2013; 98(2): 668–677. Published online Jan 31, 2013. doi: 10.1210/jc.2012-3042PMCID: PMC3612791Mortality and Other Important Diabetes-Related Outcomes With Insulin vs Other Antihyperglycemic Therapies in Type 2 Diabetes- Craig J. Currie, Chris D. Poole, Marc Evans, John R. Peters, and Christopher Ll. Morgan

Summary of advice

The PRAC acknowledged that regarding the cancer signal, 3 reviews of mechanistic studies, one meta-analysis of randomized trials and observational studies, 3 clinical trials and 8 observational studies had been conducted. For insulin glargine in particular, publications of 2 non-clinical studies, one clinical trial and 7 observational studies were assessed. Regarding the signal of cardiovascular morbidity, a series of papers retrieved following a literature search were reviewed. Overall, 7 mechanistic studies, 11 randomized trials, 2 meta-analyses of randomized trials and 22 observational studies were assessed.

In addition to assessing these publications, the MHRA performed a Drug Utilisation Study using the Clinical Practice Research Datalink to examine how insulin is being used to treat type 2 diabetes in the UK, and compared this with recommendations for use of insulin described in national clinical guidance.

The PRAC stressed that the cancer risk associated with insulin use in the treatment of type 2 diabetes is the focus of highly-active and fast-moving research. Nonetheless, the currently available studies of relevance have too many methodological limitations to allow a conclusion to be reached on causality.

From the assessment of cardiovascular morbidity, although there is currently very little evidence that use of insulin in type 2 diabetes leads to a reduction in MACE, there is also no consistent evidence of cardiovascular harm from use of insulin in patients with type 2 diabetes, while acknowledging some exceptions (ACCORD trial).

Overall, no regulatory action is considered necessary. The PRAC considered that at this stage, given the limitations of the evidence currently available and in anticipation of the study results that will become available from a range of studies, no revisions are required to the RMPs for insulin-containing products.

12. Organisational, regulatory and methodological matters

12.1. Mandate and organisation of the PRAC

12.1.1. PRAC Rules of Procedure

- Revision of the Rules of Procedure

The PRAC adopted a revised version of the rules of procedure following incorporation of Regulation (EU) 1235/2010 and Directive 2010/84/EU into the Agreement on the European Economic Area ("the EEA Agreement"). The PRAC Rules of Procedure have been amended to be in line with other EMA Scientific Committees to reflect the involvement of Members nominated by the EEA-EFTA countries in the PRAC. They will be published after receiving a favourable opinion from the Commission and the EMA Management Board.

Post meeting note: the revised Rules of Procedure received a favourable opinion from the EMA Management Board at its 20 March 2014 meeting and by the EC on 9 April 2014 and will be published on the EMA website.

12.2. Pharmacovigilance audits and inspections

12.2.1. Pharmacovigilance Inspections

12.2.1.1. Union Procedure on Follow-up to Pharmacovigilance Inspections

- Union procedure on the coordination of EU pharmacovigilance inspections
- Union procedure on sharing of pharmacovigilance inspection information

The PRAC endorsed the final versions of the above mentioned document that will be published on the EMA website.

12.2.2. Pharmacovigilance audits

12.2.2.1. Pharmacovigilance Audit Facilitation Group (PAFG)

- Standardisation for preparing, performing and reporting pharmacovigilance audits to European Commission

J Pallos (HU), member of the PAFG, reminded the PRAC how GVP Module IV – Pharmacovigilance audits requires the development by NCAs of an audit strategy, a high-level document which describes how the audit activities will be delivered over a period of time. The audit strategy includes a list of audits that could be performed, outlines areas highlighted for audit, the audit topics as well as the methods and assumptions (including e.g. risk assessment) on which the audit programme is based. The PRAC discussed a draft proposal for NCA audit strategies including draft risk ratings for frequency of audits of pharmacovigilance system activities. The PRAC provided various comments and proposed that a questionnaire will be circulated to the members to collect structured feedback. Follow-up discussion will take place at the April 2014 PRAC meeting.

Post-meeting note: a questionnaire was circulated for replies by 1/4/2014.

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

12.3.1. Union Reference Date List

12.3.1.1. Consultation on the draft List, version March 2014

The PRAC endorsed the draft revised EURD list version March 2014 reflecting the PRAC comments impacting DLP and PSUR submission frequencies of the substances / combinations. This also includes upcoming PSUR single assessment (PSUSA)[26] procedures with allocated PRAC Rapporteur MS and Rapporteurs' names in accordance with the principles previously endorsed by the PRAC (see PRAC Minutes April 2013). The handling of PSURs for substances contained in Nationally Approved Products (NAPs) is due for discussion at the EMA Management Board on 19-20 March 2014. The PRAC will be updated accordingly.

Post-meeting note: following the PRAC meeting in March 2014, the updated EURD list was adopted by the CHMP at its March 2014 meeting and published on the EMA website on 01/04/2014 (see: Home>Regulatory>Human medicines>Pharmacovigilance>EU reference date and PSUR submission).

12.4. Signal Management

12.4.1. Signal Management

12.4.1.1. Feedback from Signal Management Review Technical (SMART) Working Group

The PRAC heard the monthly update on the work of the SMART Working Group. Feedback received from the European Generic medicines Association on the implementation of recommendations of the PRAC for the product information was brought to the attention of the group who will reflect on

[26] Referring to procedures with CAP, NAP

strategies to streamline current practice. The group also discussed internal Signal Management process improvement in the framework of the EMA reorganisation.

12.4.1.2. Update of the Signal Management worksharing list

The EMA Secretariat presented to the PRAC a draft updated list of active substances / medicinal products subject to work-sharing for signal management. Following consultation of Member States in recent months, new substances have been allocated to a Lead Member State while a number of previously allocated substances no longer have a Lead Member State. These changes have been reflected in the draft updated list. The list will be communicated to the CMDh for endorsement prior to publication on the EMA website.

Post-meeting note: A preliminary discussion on the draft updated list took place at the March CMDh meeting. Follow-up discussion is planned at the April meeting prior to formal endorsement of the list.

12.5. Adverse Drug Reactions reporting and additional reporting

12.5.1. Management and Reporting of Adverse Reactions to Medicinal Products

12.5.1. Individual Case Safety Report (ICSR) standard

- Draft EU ICSR Implementation Guide

The EMA secretariat presented the EU ICSR implementation guide created in consultation with the EudraVigilance Expert Working group. The draft document is scheduled to go out for a 2-month public consultation starting at the end of April 2014. PRAC members were invited to send their comments in writing by 28 March 2014. An update is planned at the April 2014 PRAC meeting.

12.5.2. Additional Monitoring

None

12.5.3. List of Product under Additional Monitoring

12.5.3.1. Consultation on the draft List, version March 2014

The PRAC was informed of the products newly added to the additional monitoring list and the updated list.

Post-meeting note: The updated additional monitoring list was published on 26/03/2014 on the EMA website (see: Home>Human Regulatory>Human medicines>Pharmacovigilance>Signal management>List of medicines under additional monitoring).

12.6. EudraVigilance Database

None

12.7. Risk Management Plans and Effectiveness of risk Minimisations

None

12.8. Post-authorisation Safety Studies

None

12.9. Community Procedures

None

12.10. Renewals, conditional renewals, annual reassessments

None

12.11. Risk communication and Transparency

12.11.1. Safety Communication

12.11.1.1. Communication on prevention of medication errors

The EMA secretariat presented a proposal for a more consistent and proactive approach for communicating on medication errors. This proposal follows a plan to strengthen existing EMA communication practice and to communicate consistently on outcomes of PRAC/CHMP assessments. PRAC made some initial comments on the content and suggested that additional relevant expert input should be considered. The proposal will be further developed.

12.11.1.2. Timing of finalisation of PRAC communication – process improvement

The EMA secretariat proposed a model for streamlining current processes for finalisation of communication material related to PRAC outcomes, which was endorsed by the PRAC with some comments. The process will be gradually introduced to validate fully its feasibility.

12.12. Continuous pharmacovigilance

None

12.13. Interaction with EMA Committees and Working Parties

12.13.1. Working Parties

12.13.2. Vaccine Working Party (VWP)

- Draft interim guidance on enhanced safety surveillance for seasonal influenza vaccines in the EU

Following discussion at the February 2014 meeting of the PRAC EMA secretariat presented a revised proposal for a draft interim guidance in accordance with the *Explanatory Note on the withdrawal of the note for guidance on harmonisation of requirements for influenza vaccines*. This document focuses on the requirements for annual enhanced safety surveillance to rapidly detect any increased local and systemic reactogenicity, or other unexpected adverse immune response that may arise during the influenza vaccine product life-cycle, e.g. due to changes in the manufacturing process.

Post meeting note: the interim guidance on enhanced safety surveillance for seasonal influenza vaccines in the EU was published on the EMA website for consultation until 28/03/2014. Following

consultation the document shall be updated and discussed at PRAC the April 2014 meeting of the PRAC.

12.13.3. EudraVigilance Working Group (EV-EWG)

- Draft Work Programme 2014

The EMA secretariat presented the draft Work Programme 2014. The PRAC endorsed the work programme and advocated strengthened links with the Working Party. A call for candidates will be launched for joint PRAC / EV-EWG membership.

12.13.4. Scientific Advisory Groups (SAG)

12.13.4.1. Inter-Committee Scientific Advisory Group for Oncology

- Call for nominations

The EMA secretariat informed the PRAC of a call for nominations for the recently created Inter-Committee Oncology Scientific Advisory Group (SAG) (replacing the existing SAG Oncology). Core members should be external clinical experts in the fields of clinical oncology, haematological oncology, paediatric oncology, or biostatistics.

12.14. Interaction within the EU regulatory network

See 12.2.2.1.

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

None

13. Any other business

13.1.1. EMA move in 2014 to new building

The PRAC received an update from the EMA secretariat on the preparation of the EMA's move to a new building in July 2014.

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 substances will be made available following the CHMP opinion on their marketing authorisation(s).

14.1.1. Dolutegravir, abacavir, lamivudine

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

Administrative details:
Product number(s): EMEA/H/C/002754
Intended indication: Treatment of human immunodeficiency virus (HIV) infection in adults and adolescents from 12 years of age who are antiretroviral treatment-naïve or are infected with HIV without documented or clinically suspected resistance to dolutegravir, abacavir, lamivudine

14.1.2. Empagliflozin

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

Administrative details:
Product number(s): EMEA/H/C/002677
Intended indication: Treatment of type 2 diabetes mellitus

14.1.3. Human fibrinogen, human thrombin

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

Administrative details:
Product number(s): EMEA/H/C/002807
Intended indication: Adjunct to haemostasis

14.1.4. Idelalisib

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

Administrative details:
Product number(s): EMEA/H/C/003843
Intended indication: Treatment of patients with relapsed chronic lymphocytic leukaemia (CLL) and refractory indolent non-Hodgkin lymphoma (iNHL)

14.1.5. Ibrutinib

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

Administrative details:
Product number(s): EMEA/H/C/003791
Intended indication: Treatment of mantle cell lymphoma, chronic lymphocytic leukaemia, small lymphocytic lymphoma

14.1.6. Mifepristone

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

Administrative details:
Product number(s): EMEA/H/C/002830
Intended indication: Treatment of signs and symptoms of endogenous Cushing's syndrome in adults

14.1.7. Nonacog gamma

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

Administrative details:
Product number(s): EMEA/H/C/003771
Intended indication: Treatment and prophylaxis of bleeding in patients with haemophilia B (congenital factor IX deficiency)

14.1.8. Perflubutane

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

Status: *for discussion and agreement of advice to CHMP*

Administrative details:
Product number(s): EMEA/H/C/002347
Intended indication: Detection of coronary artery disease (CAD)

14.1.9. Secukinumab

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

Administrative details:
Product number(s): EMEA/H/C/003729
Intended indication: Treatment of plaque psoriasis

14.1.10. Simeprevir

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

Administrative details:
Product number(s): EMEA/H/C/002777
Intended indication: Treatment of chronic hepatitis C (CHC) genotype 1 or genotype 4 infection

14.1.11. Simoctocog alfa

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

Administrative details:
Product number(s): EMEA/H/C/002813
Intended indication: Treatment and prophylaxis of bleeding

14.1.12. Tacrolimus

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

Administrative details:
Product number(s): EMEA/H/C/002655*, Hybrid*
Intended indication: Prophylaxis of transplant rejection in adult kidney allograft recipients

14.1.13. Tobramycin

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

Administrative details:
Product number(s): EMEA/H/C/002633*, Hybrid*
Intended indication: Treatment of chronic pulmonary infection

14.1.14. Trametinib

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

Administrative details:
Product number(s): EMEA/H/C/002643
Intended indication: Treatment of unresectable or metastatic melanoma with a BRAF V600 mutation

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 – PRAC led procedure

14.2.1. Dabigatran – PRADAXA (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/000829/II/0058
Procedure scope: Changes in the agreed study protocol for 1160.136 (SPAF MEA 025), a global registry program GLORIA-AF investigating patients with newly diagnosed non-valvular AF at risk for stroke receiving dabigatran
MAH(s): Boehringer Ingelheim International GmbH

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

- Evaluation of an RMP in the context of a variation

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

Administrative details:
Procedure number(s): EMEA/H/C/000898/II/0026
Procedure scope: Update of the RMP version 11
MAH(s): Omrix Biopharmaceuticals N. V.

14.2.3. Insulin glulisine – APIDRA (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/000557/II/0054

Procedure scope: Update of the RMP version 6.0
MAH(s): Sanofi-aventis Deutschland

14.2.4. **Prucalopride – RESOLOR** (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/001012/II/0030
Procedure scope: Update of the RMP version 11 and updated study protocol for a study specified in the Pharmacovigilance plan, following a request from the PRAC based on the review of the last PSUR 006 (EMEA/H/C/001012/PSU/012) and RMP vs. 10 (EMEA/H/C/1012 RMP 020)
MAH(s): Shire Pharmaceuticals Ireland Ltd.

14.2.5. **Tegafur, gimeracil, oteracil – TEYSUNO** (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/001242/II/0016
Procedure scope: Update of the RMP version 5.1 to modify the post-authorisation phase III clinical study to assess efficacy and safety of Teysuno versus an appropriate triplet comparator in the RMP (MEA 001). In addition the MAH took the opportunity to update the RMP with a new amendment for phase I study TPU-S1119 (MEA 002)
MAH(s): Nordic Group B.V.

RMP in the context of a variation – CHMP led procedure

14.2.6. **Abiraterone – ZYTIGA** (CAP)

- Evaluation of an RMP in the context of a variation

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

Administrative details:
Procedure number(s): EMEA/H/C/002321/II/0018/G
Procedure scope: Update of SmPC section 4.5 with information regarding OATP1B1 and CYP2C8 inhibition by abiraterone based on the results of drug-drug interaction studies FK10383 and 212082PCR1011 included in the RMP
MAH(s): Janssen-Cilag International

14.2.7. **Adefovir dipivoxil – HEPSERA** (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

Administrative details:
Procedure number(s): EMEA/H/C/000485/II/0064
Procedure scope: Update of SmPC section 4.4 on the risk for renal impairment and appropriate monitoring of renal function
MAH(s): Gilead Sciences International

14.2.8. Amifampridine – FIRDAPSE (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/001032/II/0026, *Orphan*
Procedure scope: Update of the SmPC based on data from a completed QTc study (specific obligation): section 4.4 to add a statement providing information on ECG morphological changes, section 4.8 to include additional terms with > 10% incidence (hypoaesthasia, paraesthesia, hyperhidrosis and cold sweat) and section 4.9 to reflect the experience with higher doses tested. In parallel, the MAH proposed to reflect results from the QTc study in section 5.1 of the SmPC. The MAH also proposed to update Annex II to delete reference to the respective specific obligation (SOB 001)
MAH(s): BioMarin Europe Ltd

14.2.9. Anidulafungin – ECALTA (CAP)

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

Status*: for discussion and agreement of advice to CHMP*

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
Procedure number(s): EMEA/H/C/000788/II/0026
Procedure scope: Update of SmPC sections 4.1, 4.4, 4.8 and 5.1 following the CHMP assessment of efficacy and safety data of Ecalta in neutropenic patients with invasive candidiasis and non-neutropenic patients with Cancida deep tissue infection (MEA 014.3)
MAH(s): Pfizer Limited

14.2.10. Ceftaroline fosamil – ZINFORO (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/002252/II/0008
Procedure scope: Evaluation of final results of a single-dose PK study of ceftaroline fosamil in children from birth to less than 12 years of age with suspected or confirmed infection (study P903-201/D3720C00006)
MAH(s): AstraZeneca AB

14.2.11. Eslicarbazepine – ZEBINIX (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

Administrative details:
Procedure number(s): EMEA/H/C/000988/II/0035
Procedure scope: Update of SmPC sections 4.4 and 4.8 to update the safety information based on a cumulative safety analyses of the available clinical data including the results of a phase III study in the approved indication
MAH(s): Bial - Portela & Cª, S.A.

14.2.12. Exenatide – BYDUREON (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/002020/II/0017/G
MAH(s): Bristol-Myers Squibb/AstraZeneca EEIG

14.2.13. Golimumab – SIMPONI (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/000992/II/0055
Procedure scope: Update of SmPC sections 4.8 and 5.1 to reflect the safety and efficacy data ts (week 256 for efficacy and week 268 for safety) for studies C0524T05, C0524T06, C0524T11, C0524T08, and C0524T09
MAH(s): Janssen Biologics B.V.

14.2.14. Human fibrogen, human thrombin – EVARREST (CAP)

- Evaluation of an RMP in the context of a variation

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

Administrative details:
Procedure number(s): EMEA/H/C/002515/II/0002/G

MAH(s): Omrix Biopharmaceuticals N. V.

14.2.15. Iloprost – VENTAVIS (CAP)

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

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

Administrative details:
Procedure number(s): EMEA/H/C/000474/X/0043
Procedure scope: Addition of a new strength: 20 microgram/ml nebuliser solution (in 30 and 168 ampoules package sizes)
MAH(s): Bayer Pharma AG

14.2.16. Pandemic influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) – FOCLIVIA (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/001208/II/0008/G

Procedure scope: Grouping of three type II variations, whereby the MAH proposes 1) update of SmPC sections 4.2, 4.8 and 5.1 with immunogenicity and safety from study V111_03 in children; 2) update of SmPC section 4.4 with data on convulsion; 3) update of SmPC sections 4.3 and 4.4 to include barium sulphate among the trace residues and an update of SmPC section 4.8 based on a cumulative review on thrombocytophenia
MAH(s): Novartis Vaccines and Diagnostics S.r.l.

14.2.17. Pasireotide – SIGNIFOR (CAP)

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

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

Administrative details:
Procedure number(s): EMEA/H/C/002052/X/0010
Procedure scope: Line extension application to add 20mg, 40mg and 60mg powder and solvent for suspension for injection in the treatment of adult patients with acromegaly for whom surgery is not an option or has not been curative, or who are inadequately controlled on treatment with other somatostatin analogues
MAH(s): Novartis Europharm Ltd

14.2.18. Ponatinib – ICLUSIG (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/002695/II/0005/G, *Orphan*
Procedure scope: Update of SmPC section 4.5 to reflect the results from study AP24534-12-107 (open-label, non-randomized, inpatient/outpatient clinical study to assess the effect of rifampicin on the Pharmacokinetics of ponatinib, when administered concomitantly in healthy subjects; Update of SmPC sections 4.4, 4.5, 5.2 to reflect the results from study AP24534-12-108 (clinical study to evaluate the effect of multiple doses of lansoprazole on the pharmacokinetics of ponatinib when administered concomitantly to healthy subjects; Update of SmPC sections 4.2, 4.4, 4.5 and 5.2 to reflect the results from study AP24534-12- 109 (evaluation of pharmacokinetics and safety of ponatinib in patients with chronic hepatic impairment and matched healthy subjects; Update of SmPC sections 4.5 to reflect the results from study ARI-001A (simcyp physiologically-based PBPK modeling to determine the impact of different ketoconazole dosing regimens on the pharmacokinetics of ponatinib due to CYP3A4 inhibition); Update of SmPC section 5.2 to reflect the results from study ARP350 (in vitro study to determine whether co-administered drugs that are highly bound to human plasma proteins can displace ponatinib from its binding sites). Submission of the results of study ARP395 (a follow up study in which plasma samples from post 24 hr collections were analyzed to determine metabolite profile); Submission of the results of study XT133050 (study on the potential for ponatinib to induce cytochrome P450 (CYP) enzymes in cultured human hepatocytes).In addition, the RMP is u[updated to reflect the data submitted and to reflect changes requested as part of variation EMEA/H/C/002695/II/002
MAH(s): Ariad Pharma Ltd

RMP in the context of a PSUR procedure

Not applicable

RMP evaluated in the context of PASS results

Not applicable

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

Not applicable

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[27]

15.1.1. Aflibercept – ZALTRAP (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/002532/PSU 006 (with RMP version 2.0)
MAH(s): Sanofi-Aventis Groupe

15.1.2. Agalsidase beta – FABRAZYME (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
Procedure number(s): EMEA/H/C/000370/PSU 061
MAH(s): Genzyme Europe BV

15.1.3. Asenapine – SYCREST (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

[27] Where a regulatory action is recommended (variation, suspension or revocation of the terms of Marketing Authorisation(s)), the assessment report and PRAC recommendation are transmitted to the CHMP for adoption of an opinion. Where PRAC recommends the maintenance of the terms of the marketing authorisation(s), the procedure finishes at the PRAC level

Administrative details:
Procedure number(s): EMEA/H/C/001177/PSU 009

15.1.4. Axitinib – INLYTA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Doris Stenver (DK)

Administrative details:
Procedure number(s): EMEA/H/C/002406/PSU 008 (with RMP version 8.0)
MAH(s): Pfizer Limited

15.1.5. Azilsartan medoxomil – EDARBI (CAP), **IPREZIV** (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/002293/PSU 005, EMEA/H/C/002517/PSU 005
MAH(s): Takeda Global Research and Development Centre (Europe) Ltd.

15.1.6. Brentuximab vedotin – ADCETRIS (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
Procedure number(s): EMEA/H/C/002455/PSU 017 (with RMP version 3.0)
MAH(s): Takeda Pharma A/S

15.1.7. Catridecacog – NOVOTHIRTEEN (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

Administrative details:
Procedure number(s): EMEA/H/C/002284/PSU 010
MAH(s): Novo Nordisk A/S

15.1.8. Dronedarone – MULTAQ (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/001043/PSU 034
MAH(s): sanofi-aventis groupe

15.1.9. Emtricitabine, rilpivirine, tenofovir disoproxil – EVIPLERA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
Procedure number(s): EMEA/H/C/002312/PSU 017 (with RMP version 6.0)
MAH(s): Gilead Sciences International Ltd

15.1.10. Human coagulation factor IX – NONAFACT (CAP), NAPs

- Evaluation of a PSUSA[28] procedure

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
Procedure number(s): EMEA/H/C/PSUSA/00001617/201307
MAH(s): Sanquin, Central Laboratory of the Netherlands Red Cross (CLB) (Nonafact), Aimafix Ixed (Kedrion SPA), Instituto Grifols (Alphanine), CSL Behring GmbH (Berinin P, Mononine), LFB Biomedicaments (Betafact), Instituto Grifols SA (Factor IX Grifols 50 UI/ml, Novix), Biotest Pharma GmbH (Haemonine), Octapharma (Octanine F)

15.1.11. Human protein C – CEPROTIN (CAP), NAP

- Evaluation of a PSUSA[29] procedure

Status: *for discussion and agreement of recommendation to CHMP*

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

Administrative details:
Procedure number(s): E EMEA/H/C/PSUSA/00002563/201307
MAH(s): Baxter AG, LFB Biomedicaments (Protexel)

15.1.12. Influenza vaccine (surface antigen, inactivated, prepared in cell cultures) – OPTAFLU (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
Procedure number(s): EMEA/H/C/000758/PSU 047
MAH(s): Novartis Vaccines and Diagnostics GmbH

15.1.13. Loxapine – ADASUVE (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

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

Administrative details:
Procedure number(s): EMEA/H/C/002400/PSU 005
MAH(s): Alexza UK Ltd.

15.1.14. Moroctocog alfa – REFACTO AF (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Doris Stenver (DK)

Administrative details:
Procedure number(s): EMEA/H/C/000232/PSU 140
MAH(s): Pfizer Limited

15.1.15. Nalmefene – SELINCRO (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

Administrative details:
Procedure number(s): EMEA/H/C/002583/PSU 005 (with RMP version 2.0)
MAH(s): H. Lundbeck A/S

15.1.16. Natalizumab – TYSABRI (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/000603/PSU 058 (with RMP version 16.0)
MAH(s): Biogen Idec Ltd

15.1.17. Nomegestrol, estradiol – IOA (CAP), **ZOELY** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

Administrative details:
Procedure number(s): EMEA/H/C/002068/PSU 007, EMEA/H/C/001213/PSU 007
MAH(s): Merck Sharp & Dohme Limited (Ioa), Theramex S.r.l. (Zoely)

15.1.18. Nonacog alfa – BENEFIX (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/000139/PSU 142 (with RMP version 8.0)
MAH(s): Pfizer Limited

15.1.19. Orlistat – ALLI (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Procedure number(s): EMEA/H/C/000854/PSU 024 (with RMP version 13)
MAH(s): Glaxo Group Ltd

15.1.20. Pioglitazone – ACTOS (CAP), **GLUSTIN** (CAP), NAP
Pioglitazone, glimepiride – TANDEMACT (CAP)
Pioglitazone, metformin – COMPETACT (CAP), **GLUBRAVA** (CAP)

- Evaluation of a PSUSA[30] procedure

Regulatory details:
PRAC Rapporteur: Almath Spooner (IE)

Administrative details:
Procedure number(s): EMEA/H/C/PSUSA/00002417/201307
MAH(s): Takeda Pharma A/S (Actos, Competact, Glubrava, Glustin, Tandemact), Cinfa Portugal (Pioglitazona Cinfa), Generis Farmaceutica (Pioglitazona Generis), Germed Farmaceutica, lda (Pioglitazona Germed), Torrent Pharma SRL (Pioglitazone Torrent), Heumann Pharma GmbH&Co Generica (Pioglitazone Torrent IT), Torrent Pharma GmbH (Pioglitazone Torrent NL), Torrent Pharma SRL (Pioglitazono Torrent LT), Terix Labs ltd (Zatrip)

15.1.21. Prasugrel – EFIENT (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Doris Stenver (DK)

Administrative details:
Procedure number(s): EMEA/H/C/000984/PSU 032 (with RMP version 9.0)
MAH(s): Eli Lilly Nederland B.V.

15.1.22. Romiplostim – NPLATE (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/000942/PSU 031
MAH(s): Amgen Europe B.V.

15.1.23. Telavancin – VIBATIV (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

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

Administrative details:
Procedure number(s): EMEA/H/C/001240/PSU 012
MAH(s): Clinigen Healthcare Ltd

15.1.24. Telbivudine – SEBIVO (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

Administrative details:
Procedure number(s): EMEA/H/C/000713/PSU 063
MAH(s): Novartis Europharm Ltd

15.1.25. Tocofersolan – VEDROP (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/000920/PSU 012
MAH(s): Orphan Europe S.A.R.L.

15.1.26. Ulipristal – ESMYA (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/002041/PSU 014
MAH(s): Gedeon Richter

15.1.27. Vemurafenib – ZELBORAF (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/002409/PSU 028
MAH(s): Roche Registration Ltd

15.1.28. Vismodegib – ERIVEDGE (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/002602/PSU 015
MAH(s): Roche Registration Ltd

15.2. Follow-up to PSUR procedures[31]

15.2.1. **Voriconazole – VFEND** (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/000387/LEG 085.1
Procedure scope: Evaluation of MAH's response to PSUR#13 as adopted at PRAC in October 2013
MAH(s): Pfizer Limited

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

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

16.1. Protocols of PASS imposed in the marketing authorisation(s)[32]

16.1.1. **Brentuximab vedotin - ADCETRIS** (CAP)

- Evaluation of an imposed PASS protocol

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
Procedure number(s): EMEA/H/C/002455/SOB/008
Procedure scope: Evaluation of PASS protocol (MA25101) for an observational cohort study of the safety of brentuximab vedotin in the treatment of relapsed or refractory CD30+ Hodgkin lymphoma and relapsed or refractory systemic anaplastic large cell lymphoma
MAH(s): Takeda Pharma A/S

16.1.2. **Defibrotide - DEFITELIO** (CAP)

- Evaluation of an imposed PASS protocol

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002393/SOB 001
Procedure scope: Evaluation of the MAH's responses to a LoQ for PASS protocol - DF VOD-2012-03-REG (patient registry to investigate the long term safety, health outcomes and patters of utilisation of deifibrotide during normal use)
MAH(s): Gentium S.p.A.

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

16.2. Protocols of PASS non-imposed in the marketing authorisation(s)[33]

16.2.1. Colistimethate sodium – COLOBREATHE (CAP)

- Evaluation of a PASS protocol

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Procedure number(s): EMEA/H/C/001225/MEA/008.1
Procedure scope: Evaluation of the MAH's responses to MEA-008 RSI as adopted in July 2013: systemic absorption study in cystic fibrosis patients. Revised protocol for a long term observational safety study for Colobreathe in cystic fibrosis patients using cystic fibrosis registries
MAH(s): Forest Laboratories UK

16.2.2. Elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil – STRIBILD (CAP)

- Evaluation of a PASS protocol

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002574/MEA/002.1
Procedure scope: Evaluation of the MAH's responses to MEA 002 PASS protocol as adopted in October 2013: prospective, observational drug utilisation study of Stribild in Adults with HIV-1 Infection (GS-EU-236-0141)
MAH(s): Gilead Sciences International Ltd

16.2.3. Fenofibrate, pravastatin – PRAVAFENIX (CAP)

- Evaluation of a PASS protocol

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

Administrative details:
Procedure number(s): EMEA/H/C/001243/MEA/007.3
Procedure scope: Evaluation of an observational study protocol: European, observational, three-year cohort study on the safety of the fixed-dose combination pravastatin 40 mg/fenofibrate 160 mg (Pravafenix) in real clinical practice (FENOPRA-IV-14-1)
MAH(s): Laboratoires SMB S.A.

16.2.4. Insulin degludec – TRESIBA (CAP)

- Evaluation of a PASS protocol

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

Administrative details:
Procedure number(s): EMEA/H/C/002498/MEA/001.1
Procedure scope: Evaluation of updated protocol for colour-blindness usability study PDS290-UT117-2013 also including the MAH's response to MEA 001 as adopted by PRAC/CHMP in October 2013
MAH(s): Novo Nordisk A/S

[33] 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

16.3. Results of PASS imposed in the marketing authorisation(s)[34]

None

16.4. Results of PASS non-imposed in the marketing authorisation(s)[35]

16.4.1. **Agomelatine – THYMANAX** (CAP), **VALDOXAN** (CAP)

- Evaluation of PASS results

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

Administrative details:
Procedure number(s): EMEA/H/C/000916/II/0020, EMEA/H/C/000915/II/0022 (without RMP)
Procedure scope: Evaluation of results from the prescription survey on the knowledge of prescribing conditions of Valdoxan/Thymanax (agomelatine) by psychiatrists and general practitioners in four European countries as requested by the CHMP (MEA 005)
MAH(s): Servier (Ireland) Industries, Les Laboratoires Servier

16.4.2. **Buprenorphine, naloxone – SUBOXONE** (CAP)

- Evaluation of PASS results

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

Administrative details:
Procedure number(s): EMEA/H/C/000697/II/0020 (without RMP)
Procedure scope: Evaluation of final PASS study report (monitoring pregnancy outcomes among pregnant opioid dependent women using medical registries)
MAH(s): RB Pharmaceuticals Ltd.

16.4.3. **Buprenorphine, naloxone – SUBOXONE** (CAP)

- Evaluation of PASS results

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

Administrative details:
Procedure number(s): EMEA/H/C/000697/II/0021 (without RMP)
Procedure scope: Evaluation of PASS study PEUS002 (surveillance of hepatic events and other serious adverse events in the UK in Suboxone users in comparison to Subutex and methadone users)
MAH(s): RB Pharmaceuticals Ltd.

16.4.4. **Buprenorphine, naloxone – SUBOXONE** (CAP)

- Evaluation of PASS results

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

Administrative details:
Procedure number(s): EMEA/H/C/000697/II/0022 (without RMP)

[34] In accordance with Article 107p-q of Directive 2001/83/EC
[35] 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

Procedure scope: Evaluation of final PASS study report PEUS003 (assessment of fatal overdose in Sweden and Denmark among buprenorphine, methadone and heroin users)
MAH(s): RB Pharmaceuticals Ltd.

16.4.5. Human rotavirus – ROTARIX (CAP)

- Evaluation of PASS results

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

Administrative details:
Procedure number(s): EMEA/H/C/000639/II/0062 (with RMP)
Procedure scope: Evaluation of final report of genetic stability study EPI-ROTA-014 VS BE – 112560 that addresses the post-approval measure ME2 005.2 in which the MAH commits to monitor for the potential occurrence of genetic drifts and shifts in the vaccine strain in post-marketing settings
MAH(s): GlaxoSmithKline Biologicals S.A.

16.5. Interim results of imposed and non-imposed PASS and results of non-imposed PASS submitted before the entry into force of the revised variations regulation[36]

16.5.1. Apixaban – ELIQUIS (CAP)

- Evaluation of interim PASS results

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

Administrative details:
Procedure number(s): EMEA/H/C/002148/MEA 012.2
Procedure scope: Evaluation of the first interim report for the following drug utilisation studies (DUS) for apixaban: study of the utilisation pattern in Sweden and study of the utilisation pattern in the Netherlands
MAH(s): Bristol-Myers Squibb / Pfizer EEIG

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 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. As per agreed criteria, the procedures were finalised at the PRAC level without further plenary discussion.

17.1.1. Certolizumab pegol – CIMZIA (CAP)

- PRAC consultation on a renewal of the marketing authorisation

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

Administrative details:
Procedure number(s): EMEA/H/C/001037/R/0040 (without RMP)

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

MAH(s): UCB Pharma SA

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

- PRAC consultation on a renewal of the marketing authorisation

Regulatory details:

PRAC Rapporteur: Brigitte Keller-Stanislawski (DE)

Administrative details:

Procedure number(s): EMEA/H/C/000878/R/0009 (with RMP version 9)
MAH(s): TiGenix NV

17.1.3. Clopidogrel – CLOPIDOGREL DURA (CAP), CLOPIDOGREL MYLAN (CAP)

- PRAC consultation on renewals of the marketing authorisations

Regulatory details:

PRAC Rapporteur: Margarida Guimarães (PT)

Administrative details:

Procedure number(s): EMEA/H/C/001132/R/0017 (without RMP), EMEA/H/C/001134/R/0027 (without RMP)
MAH(s): Mylan dura GmbH (Clopidogrel Dura), Mylan S.A.S. (Clopidogrel Mylan)

17.1.4. Clopidogrel – CLOPIDOGREL KRKA (CAP), CLOPIDOGREL KRKA D.D. (CAP), ZYLAGREN (CAP), ZYLLT (CAP)

- PRAC consultation on renewals of the marketing authorisations

Regulatory details:

PRAC Rapporteur: Margarida Guimarães (PT)

Administrative details:

Procedure number(s): EMEA/H/C/001056/R/0022 (without RMP) (Clopidogrel Krka), EMEA/H/C/001137/R/0018 (without RMP) (Clopidogrel Krka D.D.), EMEA/H/C/001138/R/0013 (without RMP) (Zylagren), EMEA/H/C/001058/R/0016 (without RMP) (Zyllt)
MAH(s): Krka d.d. Novo Mesto

17.1.5. Clopidogrel – CLOPIDOGREL TAD (CAP)

- PRAC consultation on a renewal of the marketing authorisation

Regulatory details:

PRAC Rapporteur: Margarida Guimarães (PT)

Administrative details:

Procedure number(s): EMEA/H/C/001136/R/0022 (without RMP)
MAH(s): TAD Pharma GmbH

17.1.6. Clopidogrel – CLOPIDOGREL TEVA (CAP)

- PRAC consultation on renewals of the marketing authorisations

Regulatory details:

PRAC Rapporteur: Margarida Guimarães (PT)

Administrative details:
Procedure number(s): EMEA/H/C/001053/R/0029 (without RMP)
MAH(s): Teva Pharma B.V.

ANNEX II – List of participants:

Including any restrictions with respect to involvement of members / alternates / experts following evaluation of declared interests for the 3-6 March 2014 meeting.

PRAC members and alternates	***Country***	***Outcome restriction following evaluation of e-DoI for the meeting***	***Topics on the current Committee Agenda for which restriction applies*** ***Product/ substance***
Aleksandra Martinovic	Austria	Cannot act as Rapporteur or Peer reviewer for:	agents acting on the renin-angiotensin system, dabigatran
Harald Herkner	Austria	Full involvement	
Jean-Michel Dogné	Belgium	Cannot act as Rapporteur or Peer reviewer for:	agents acting on the renin-angiotensin system, regorafenib, iloprost
Veerle Verlinden	Belgium	Full involvement	
Yuliyan Eftimov	Bulgaria	Full involvement	
Maria Popova-Kiradjieva	Bulgaria	Full involvement	
Viola Macolić Šarinić	Croatia	Full involvement	
Nectaroula Cooper	Cyprus	Full involvement	
Zena Gunther	Cyprus	Full involvement	
Jana Mladá	Czech Republic	Full involvement	
Line Michan	Denmark	Full involvement	
Doris Stenver	Denmark	Full involvement	
Katrin Kiisk	Estonia	Full involvement	
Maia Uusküla	Estonia	Full involvement	
Terhi Lehtinen	Finland	Full involvement	
Kirsti Villikka	Finland	Full involvement	
Isabelle Robine	France	Full involvement	
Martin Huber	Germany	Full involvement	
Valerie Strassmann	Germany	Full involvement	
Julia Pallos	Hungary	Full involvement	
Guðrún Kristín Steingrímsdóttir	Iceland	Full involvement	
Almath Spooner	Ireland	Full involvement	
Ruchika Sharma	Ireland	Full involvement	
Jelena Ivanovic	Italy	Full involvement	
Carmela Macchiarulo	Italy	Full involvement	
Andis Lacis	Latvia	Full involvement	
Jolanta Gulbinovic	Lithuania	Full involvement	
Jacqueline Genoux-Hames	Luxembourg	Full involvement	
Amy Tanti	Malta	Full involvement	
Sabine Straus	Netherlands	Full involvement	
Menno van der Elst	Netherlands	Full involvement	
Ingebjørg Buajordet	Norway	Full involvement	
Karen Pernille Harg	Norway	Full involvement	
Kamila Czajkowska	Poland	Full involvement	
Margarida Guimarães	Portugal	Full involvement	
Roxana Stroe	Romania	Full involvement	

PRAC members and alternates	*Country*	*Outcome restriction following evaluation of e-DoI for the meeting*	*Topics on the current Committee Agenda for which restriction applies* *Product/ substance*
Tatiana Magálová	Slovakia	Full involvement	
Gabriela Jazbec	Slovenia	Full involvement	
Miguel-Angel Macia	Spain	Full involvement	
Dolores Montero Corominas	Spain	Full involvement	
Ulla Wändel Liminga	Sweden	Full involvement	
Qun-Ying Yue	Sweden	Full involvement	
June Munro Raine	Chair	Full involvement	
Julie Williams	United Kingdom	Full involvement	
Rafe Suvarna	United Kingdom	Full involvement	

Independent scientific experts nominated by the European Commission	**Country**	**Outcome restriction following evaluation of e-DoI for the meeting:**	**Topics on the current Committee Agenda for which restriction applies** ***Product/ substance***
Jane Ahlqvist Rastad	Not applicable	Full involvement	
Marie Louise De Bruin		Full involvement	
Stephen Evans		Cannot act as Rapporteur or Peer reviewer for:	bupropion, belimumab, pandemic influenza vaccine (H1N1)v (split virion, inactivated, adjuvanted), orlistat, human rotavirus
Birgitte Keller-Stanislawski		Full involvement	
Herve Le Louet		Full involvement	
Lennart Waldenlind		Full involvement	

Additional European experts participating at the meeting for specific Agenda items	Country	
Stefan Bonne	Belgium	No restrictions were identified for the participation of European experts attending the PRAC meeting for discussion on specific agenda items
Brune De Schuiteneer	Belgium	
Jamila Hamdani	Belgium	
Cécile Lescrainier	Belgium	
Javier Sawchik	Belgium	
Romana Hašková	Czech Republic	
Nathalie Dumarcet	France	
Gaëlle Guyader	France	
Caroline Semaille	France	
Massimo Cirillo	Italy	
Giuseppe Rosano	Italy	
Jacoline Bouvy	Netherlands	
Cristel Loeb	Netherlands	
Jarno Hoekman	Netherlands	
Maarten Simoons	Netherlands	
Maria Vanenburg	Netherlands	
Tamar Wohlfarth	Netherlands	
Charlotte Backman	Sweden	
Anne Ambrose	United Kingdom	
Julie Beynon	United Kingdom	
Phil Bryan	United Kingdom	
Claire Doe	United Kingdom	
Raquel Rogers	United Kingdom	
Catherine Tregunno	United Kingdom	

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		Full involvement	
Marco Greco		Full involvement	
Kristen Myhr		Full involvement	

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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