29 October 2012
EMA/PRAC/519417/2012
Patient Health Protection

Pharmacovigilance Risk Assessment Committee (PRAC)

Draft agenda of meeting **29-31 October 2012**

Explanatory notes

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

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

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

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

A safety signal is information on a new or incompletely documented adverse event that is potentially caused by a medicine and that warrants further investigation. Signals are generated from several sources such as 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 Agenda)

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

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becomes available.

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

A PSUR is a report providing an evaluation of the benefit-risk balance of a medicine, which is submitted by marketing authorisation holders at defined time points following a medicine's authorisation.
PSURs 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 Agenda)

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

Product-related pharmacovigilance inspections
(Item 8 of the PRAC Agenda)
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.europa.eu

Chair: June Raine – Vice-Chair: Almath Spooner

29 October 2012, 13:00 – 19:00, room 3/A

30 October 2012, 09:00 – 19:00, room 3/A

31 October 2012, 09:00 – 17:00, room 3/A

1. Introduction

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

1.2. Adoption of agenda of the meeting of 29-31 October 2012

Status: for adoption

Document: PRAC Agenda Rev.3 due for publication on 29 October 2012

1.3. Minutes of the previous PRAC meeting on 1-3 October 2012

Status: for adoption

Document: PRAC Final Minutes to be published on 06 November 2012

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

2.1. Newly triggered procedures

None

2.2. Ongoing Procedures

None

2.3. Procedures for finalisation

None

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

3.1. Newly triggered Procedures

3.1.1. Codeine (NAPs)

- Risk of fatal or life-threatening drug toxicity in CYP2D6 ultra-rapid metabolisers - Article 31 of Directive 2001/83/EC for codeine-containing medicines used for pain in children

Status: *for follow-up discussion and agreement of a revised scope*

Regulatory details:

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

3.1.2. Diclofenac (NAPs)

- Risk of thrombotic events - Article 31 of Directive 2001/83/EC for diclofenac-containing products for systemic use

Status: *for initial discussion and for Rapporteur appointment*

Regulatory details:

PRAC Rapporteur: *to be appointed*
PRAC Co-Rapporteur: *to be appointed*

3.2. Ongoing Procedures

None

3.3. Procedures for finalisation

None

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

None

4. Signals assessment and prioritisation

4.1. New signals detected from EU spontaneous reporting systems

4.1.1. **Cetuximab - ERBITUX** (CAP)

- Signal of cytokine release syndrome (CRS)

Status: *for initial discussion*

Regulatory details:

PRAC Rapporteur: Ulla Wandel Liminga (SE)

4.1.2. **Filgrastim, pegfilgrastim** - **NEULASTA, BIOGRASTIM, FILGRASTIM HEXAL FILGRASTIM RATIOPHARM, NIVESTIM, RATIOGRASTIM, TEVAGRASTIM, ZARZIO** (CAPs)

- Signal of systemic capillary leak syndrome (SCLS) and cytokine release syndrome (CRS)

Status: *for initial discussion*

Regulatory details:

PRAC Rapporteur (overall): *to be appointed*

4.1.3. **Nomegestrol acetate / estradiol – ZOELY** (CAP)

- Signal of deep vein thrombosis

Status: *for initial discussion*

Regulatory details:

PRAC Rapporteur: Isabelle Robine (FR)

4.1.4. **Sugammadex – BRIDION** (CAP)

- Signal of bradycardia and cardiac arrest

Status: *for initial discussion*

Regulatory details:

PRAC Rapporteur: Kirsti Villikka (FI)

4.1.5. **Tolvaptan – SAMSCA** (CAP)

- Signal of dehydration

Status: *for initial discussion*

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)

4.1.6. **Vitamin K antagonists**: **warfarin, phenprocoumon** (NAPs)

- Signal of interaction with Goji berries (*Lycium barbarum*)

Status: *for initial discussion and for Rapporteur appointment*

Regulatory details:

PRAC Rapporteur: *to be appointed*

4.2. New signals detected from other sources

None

4.3. Signals follow-up and prioritisation

4.3.1. **Fluoroquinolones: Ciprofloxacin - enoxacin - flumequin - lomefloxacin - levofloxacin - moxifloxacin - ofloxacin - pefloxacin - prulifloxacin – rufloxacin - norfloxacin** (NAPs)

- Signal of retinal detachment

Status: *for discussion and for Rapporteur appointment*

Regulatory details:

PRAC Rapporteur: *to be appointed*

4.3.2. **Human albumin solutions** (NAPs)

- Signal of increased risk of mortality in patients with severe traumatic brain injury and in patients with burns

Status: *for discussion and Rapporteur appointment*

Regulatory details:

PRAC Rapporteur: *to be appointed*

4.3.3. **Hydroxyethyl starch** (NAPs)

- Signal of increased risk of mortality in patients with severe sepsis versus Ringer's acetate

Status: *for discussion and Rapporteur appointment*

Regulatory details:

PRAC Rapporteur: *to be appointed*

4.3.4. **Olmesartan** (NAPs)

- Signal of increased risk of fatal events from cardiovascular causes in patients with type 2 diabetes at increased cardiovascular risk

Status: *for discussion and Rapporteur appointment*

Regulatory details:

PRAC Rapporteur: *to be appointed*

See also 9.1.1.

4.3.5. Pandemic influenza vaccine – PANDEMRIX (CAP)

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

Status: *for follow-up discussion and for agreement of recommendation to CHMP*

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)

4.3.6. Short-acting beta agonists: **hexoprenaline - fenoterol - ritodrine - salbutamol - terbutaline** (NAPs)

- Signal of maternal cardiovascular adverse drug reactions following use in tocolysis

Status: *for discussion and Rapporteur appointment*

Regulatory details:

PRAC Rapporteur: *to be appointed*

5. Risk Management Plans

5.1. Medicines in the pre-authorisation phase

None

5.2. Medicines already authorised

5.2.1. Anidulafungin - **ECALTA** (CAP)

- Evaluation of the updated RMP in the context of a stand-alone RMP

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

Regulatory details:

PRAC Rapporteur: Sabine Straus (NL)
PRAC Co-Rapporteur: Doris Stenver (DK)

5.2.2. Bortezomib – VELCADE (CAP)

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

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

Regulatory details:

PRAC Rapporteur: Carmela Macchiarulo (IT)
PRAC Co-Rapporteur: Kirsti Villika (FI)

5.2.3. Dabigatran– PRADAXA (CAP)

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

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

Regulatory details:

PRAC Rapporteur: Doris Stenver (DK)
PRAC Co-Rapporteur: Isabelle Robine (FR)

5.2.4. Darunavir – PREZISTA (CAP)

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

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

Regulatory details:

PRAC Rapporteur: Menno van der Elst (NL)

PRAC Co-Rapporteur: Julie Williams (UK)

5.2.5. Fampridine – FAMPYRA (CAP)

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

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

Regulatory details:

PRAC Rapporteur: Sabine Straus (NL)
PRAC Co-Rapporteur: Martin Huber (DE)

5.2.6. Imatinib – GLIVEC (CAP)

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

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

Regulatory details:

PRAC Rapporteur: Dolores Montero (ES)
PRAC co-Rapporteur: Isabelle Robine (FR)

5.2.7. Ipilimumab – YERVOY (CAP)

- Evaluation of the updated RMP in the context of a 90 day-Type II variation, extension of indication

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

Regulatory details:

PRAC Rapporteur: Sabine Straus (NL)
PRAC Co-Rapporteur: Dolores Montero (ES)

5.2.8. Raltegravir – ISENTRESS (CAP)

- Evaluation of the updated RMP in the context of 60 day-Type II variations

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

Regulatory details:

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

5.2.9. Sunitinib – SUTENT (CAP)

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

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

Regulatory details:

PRAC Rapporteur: Carmela Macchiarulo (IT)
PRAC Co-Rapporteur: Doris Stenver (DK)

6. Assessment of Periodic Safety Update Reports (PSURs)

None

7. Post-authorisation Safety Studies (PASS)

7.1. Post-authorisation safety studies protocols

None

7.2. Results of post-authorisation safety studies

None

8. Product related pharmacovigilance inspections

8.1. List of planned pharmacovigilance inspections

None

8.2. On-going or concluded pharmacovigilance inspection

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

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

9.1. Safety related variations

9.1.1. Telmisartan - KINZALMONO, MICARDIS, PRITOR (CAP)
Telmisartan/HCT - KINZALKOMB, MICARDISPLUS, PRITORPLUS (CAP)
Telmisartan/amlodipine - ONDUARP, TWYNSTA (CAP)

- Safety-related type II variation upon CHMP request

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

Regulatory details:

PRAC Rapporteur (lead for worksharing variation): Carmela Macchiarulo (IT)

9.2. Renewals of the Marketing Authorisation

9.2.1. Ambrisentan - VOLIBRIS (CAP)

- Renewal of the Marketing Authorisation after first 5 years

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

Regulatory details:

PRAC Rapporteur: Dolores Montero (ES)
PRAC Co-Rapporteur: Jana Mlada (CZ)

9.2.2. Prepandemic Influenza Vaccine (H5n1) (Split Virion, Inactivated, Adjuvanted) - **PREPANDRIX** (CAP)

- Renewal of the Marketing Authorisation after first 5 years

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

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)
PRAC Co-Rapporteur: Sabine Straus (NL)

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

None

9.4. Other requests

9.4.1. Aclidinium Bromide – EKLIRA GENUAIR, BRETARIS GENUAIR (CAP)

- Drug utilisation study protocol requested as a RMP measure by the CHMP

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

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)
PRAC Co-Rapporteur: Adam Przybylkowski (PL)

9.4.2. Epoetins: **Darbepoetin-alfa - ARANESP** (CAP), **Epoetin-beta - NEORECORMON** (CAP), **Epoetin-zeta - RETACRIT SILAPO** (CAP)**, Epoetin alfa – BINOCRIT** (CAP)**, ABSEAMED** (CAP)**, EPOETIN ALFA HEXAL** (CAP)**, Epoetin theta – EPORATIO** (CAP)**, Methoxy polyethylene glycol-epoetin beta – MIRCERA** (CAP)

- Evaluation of a proposal for a joint post authorisations safety study on target haemoglobin levels in chronic kidney disease patients

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

Regulatory details:

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

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

10.1. Renewals of the Marketing Authorisation

None

10.2. Safety related variations of the marketing authorisation

10.2.1. Granisetron (NAPs)

- Risk of QT prolongation and Torsade de Pointes

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

Regulatory details:

PRAC Rapporteur: *to be appointed*

10.2.2. Ondansetron (NAPs)

- Risk of QT prolongation and Torsade de Pointes

Status*: for discussion*

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)

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

None

11. Organisational, regulatory and methodological matters

11.1. Mandate and organisation of the PRAC

11.1.1. PRAC Rapporteurship

Status: *for discussion*

11.1.2. Rules of Procedure of the PRAC

Status: *for information*

11.2. Pharmacovigilance audits and inspections

11.2.1. Pharmacovigilance Systems and their Quality Systems

None

11.2.2. Pharmacovigilance System Master File

None

11.2.3. Pharmacovigilance Inspections

Status: *for consultation*

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

11.3.1. Periodic Safety Update Reports

None

11.3.2. PSURs Repository

None

11.3.3. Union Reference Date List

11.3.3.1. Consultation on the draft List, version November 2012

Status: *for discussion and agreement of the list*

11.4. Signal Management

11.4.1. Signal Management

None

11.5. Adverse Drug Reactions reporting and additional reporting

11.5.1. Management and Reporting of Adverse Reactions to Medicinal Products

None

11.5.2. Additional Monitoring

11.5.2.1. Standardised statements for medicinal products under additional monitoring and for the encouragement of Adverse Drug Reactions (ADR) reporting for all medicinal products

Status: *for discussion and endorsement of the standardised statements*

11.5.3. List of Product under Additional Monitoring

11.5.3.1. Creation and maintenance of the List

Status: *for discussion*

11.6. EudraVigilance Database

None

11.7. Risk Management Plans and Effectiveness of risk Minimisations

11.7.1. Implementation of summary of Risk Management Plan

Status: *for discussion*

11.8. Community Procedures

None

11.9. Risk communication and Transparency

None

11.10. Continuous pharmacovigilance

None

11.11. Inter Status with EMA Committees and Working Parties

None

11.12. Inter Status within the EU regulatory network

None

11.13. Contacts of the PRAC with external parties and interStatuss of the EMA with interested parties

None

12. Any other business

None