The PRAC – Roles and challenges
Focus on RMPs and RMAs

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Content

- Context of the new Pharmacovigilance legislation
- The PRAC – An overall overview
- What's the role of the PRAC in the evaluation of RMPs?
- RMP Effectiveness: What does it mean and how is it evaluated?

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Burden of adverse drug reactions

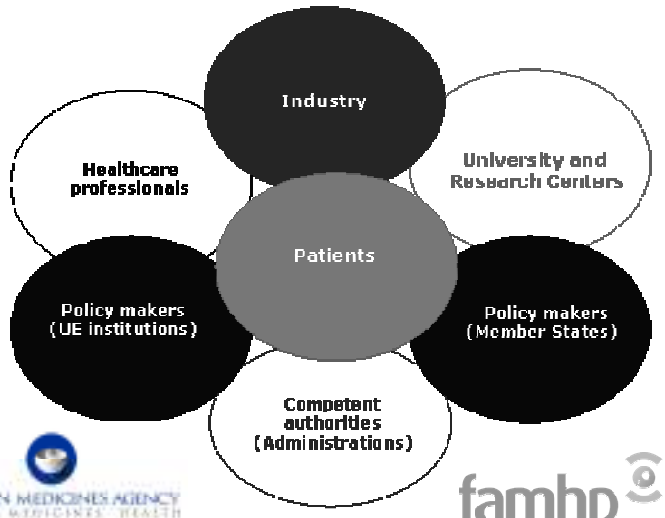
- Despite all the benefits of modern medicines, evidence continues to mount that adverse reactions to medicines are a common, yet often preventable, cause of illness, disability and even death.
  - 5% of all hospital admissions are for ADRs,
  - ADRs are the 5th most common cause of hospital death
  - Estimated 197,000 deaths per year in EU from ADRs
  - EU Societal cost of ADRs Euro 79 Billion / year

Why is Pharmacovigilance needed?

- Limitations of clinical trials performed before drug approval (phase I-, II-, III-trials)
  - "too few": on average 1.500 patients*
  - "too simple": selected population
  - "too median-aged": not too young, not too old
  - "too narrow": well-defined indications
  - "too brief": exposure and follow-up

*If a medicine has a risk that only occurs once in every 5,000 patients you would have to give the medicine to 15,000 patients during the trials to be reasonably sure of identifying it.

Key players



New legislation at EU level

- The European Commission has reviewed the current system and proposed new EU pharmacovigilance legislation*, in order to continue to improve patient safety through better monitoring.
- This new legislation was adopted by the European Parliament and European Council in December 2010 and entered into force in July 2012.

*Regulation (EU) No 1235/2010 and Directive 2010/84/EU of the European Parliament and of the Council

New legislation at EU level

- The legislation was the **biggest change to the regulation of human medicines** in the European Union (EU) since 1995.
- It has significant implications for applicants and holders of EU marketing authorisations.
- The European Medicines Agency (EMA), together with the European Member States, is responsible for implementing much of the new legislation.

Better vigilance for public health protection

Overview of the new European Union pharmacovigilance legislation

New legislation at EU level

- Key benefits:

It is estimated that these measures could save up to approximately 5,000 lives, while providing savings to society of some €2.5 billion per year in the EU.

New legislation at EU level

- Risk management plans
  - RMP mandatory for all applications…but proportionate to risks
  - Broader vision: risk => benefit/risk

OLD LEGISLATION	NEW LEGISLATION
If needed, a detailed description of the risk management system	The risk management plan describing the risk management system. Proportionate: -to risks -to the need for post-authorization safety data

New legislation at EU level

- PASS/PAES:
  - PASS requested by CA at time of authorization or later
    - MA granted subject to condition to conduct PASS
    - After the granting of a MA, if concerns about risks
  - PAES requested by CA at time of authorization or later
    - MA granted subject to condition to conduct PAES: where questions relating to some aspects of the efficacy of the product are identified and can only be answered after the product is marketed
    - After the granting of a MA: the CA may require a MAH to conduct a PAES when the understanding of the disease or the clinical methodology indicate that previous efficacy evaluations could be significantly changed

New legislation at EU level

- **GVP modules**
  - In the past, the European Commission drew up pharmacovigilance guidelines in accordance with Article 106 of Directive 2001/83/EC of the European Parliament and the Council, known as ***volume 9A***.
  - With the application of the new pharmacovigilance legislation as of July 2012, volume 9A has now been replaced by the ***good-pharmacovigilance-practice (GVP) guideline***, published by the Agency.

New legislation at EU level

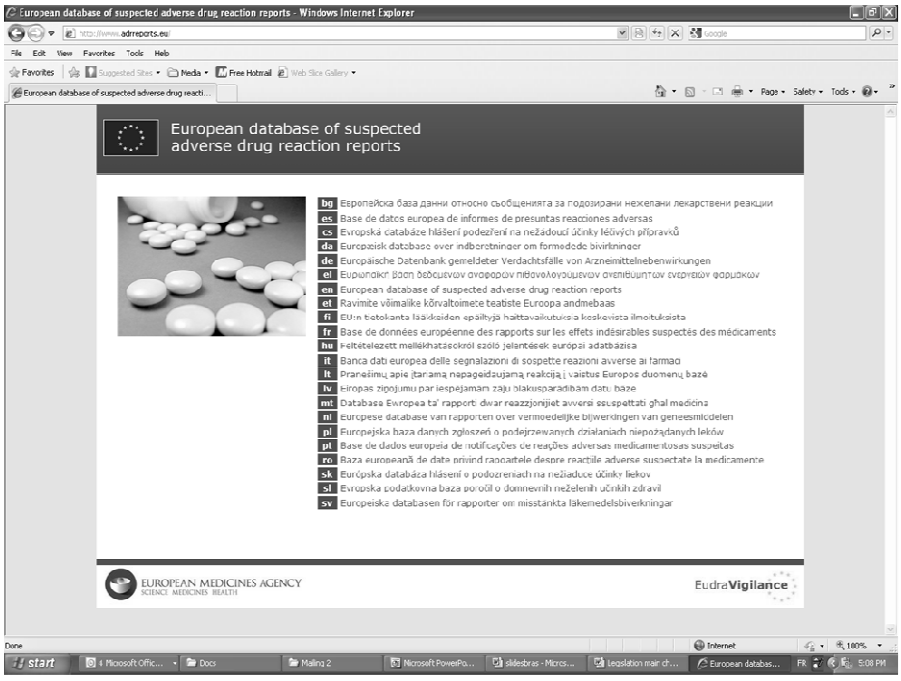
- More implication of patients and HCPs
  - Information on use of medicines in real life
  - Patient reporting
  - Representatives of HCPs and patients in PRAC
  - Adaptating information to the needs of HCPs and patients (link with assessment of impact of RMA)

New legislation at EU level

- More transparency
  - European and national (safety) web portals
    - summaries of RMP (national MA)
    - list of medicinal products referred to in Article 23 of Reg.
    - information on the different ways for reporting suspected ADRs, including the web-based structured forms (Reg. art. 25)
  - European medicines web-portal – Reg. art. 26:
    - agendas and minutes from each meeting of the CHMP and PRAC and the CMD(h) as regards phvig activities
    - summary of the RMP (CEP authorized products)
    - Assessment conclusions, recommendations, opinions, agreements and decisions (for PSURs, urgent union procedure, PASS) taken by CHMP, PRAC, Commission, NCA and CMD(h)

New legislation at EU level

- More transparency
  - In May 2012, the EMA launched the website 'European database of suspected adverse drug reaction reports' (http://www.adrreports.eu/) providing public access to all reports of suspected side effects that have been submitted to EudraVigilance.
  - The website is available in 22 of the official languages of the European Union.



New legislation at EU level

- Additional monitoring of certain medicinal products

- On 7 March 2013, the European Commission adopted a black triangle as the symbol to be placed on the patient information leaflets and the Summary of Product Characteristics ("SmPC") of medicinal products "subject to additional monitoring" in the European Union ("EU").
- What is the black triangle? What is its purpose?
  - The purpose of the black triangle is to attract the attention of patients and healthcare professionals to the fact that the medicinal product is subject to additional monitoring in the EU.
  - The black triangle must be accompanied by a text encouraging patients and healthcare professionals ***to report any unexpected adverse events*** experienced in the treatment with these products.

New legislation at EU level

- European list of additionally monitored medicines
  - A European list of medicines under additional monitoring is available. The Agency first published this list in April 2013, and **it is reviewed every month by the PRAC**.
  - A medicine can be included on this list when it is approved for the first time or at any time during its life cycle. A medicine remains under additional monitoring for five years or until the PRAC decides to remove it from the list.

New legislation at EU level

- European list of additionally monitored medicines
  - More information on additional monitoring is available:
    - Guideline on good pharmacovigilance practices: Module X - Additional monitoring
    - Medicines under additional monitoring: Background information (website of the EMA)

List of medicines under additional monitoring

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Document(s)	Language	Status	First published	Last updated	Effective Date
List of medicinal products under additional monitoring	(English only)		25/04/2013		

http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/document_listing/document_listing_000365.jsp&mid=WC0b01ac058067bfff

List of medicinal products under additonal monitorino

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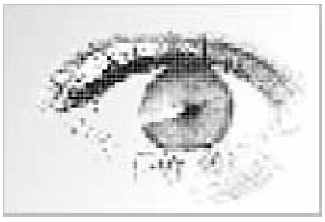
- Examples based on PRAC Minutes

PRAC overview

- The Agency has seven scientific committees that carry out the scientific evaluation of applications from pharmaceutical companies.
  - Committee for Medicinal Products for Human Use (CHMP)
  - ***Pharmacovigilance Risk Assessment Committee (PRAC)***
  - Committee for Medicinal Products for Veterinary Use (CVMP)
  - Committee for Orphan Medicinal Products (COMP)
  - Committee on Herbal Medicinal Products (HMPC)
  - Paediatric Committee (PDCO)
  - Committee for Advanced Therapies (CAT)

PRAC overview

- The Pharmacovigilance Risk Assessment Committee shall be responsible for providing **recommendations** to the **Committee for Medicinal Products for Human Use** and the **Coordination group** :
  - On any question relating to pharmacovigilance activities with respect to medicinal products for human use and
  - On risk management systems and it shall be responsible for monitoring the effectiveness of these systems



PRAC overview

Appointed by each Member State:

- 1 member + 1 alternate
- 27 + EEA countries non voting members

Appointed by the European Commission following a public call for expressions of interest:

- *1 patient organisations[1] rep + alternate*
- *1 healthcare professionals[1] rep + alternate*
- 6 members to ensure relevant expertise available

[1] *Criteria for involvement in EMA activities*

PRAC overview

Expertise…

- Drug safety in pregnancy and lactation
- Drug utilisation studies
- Medication errors leading to ADRs
- Pharmacogenetics and safety of medicines
- PhV in special populations (paediatrics, elderly)
- PhV of biological and biosimilar substances
- PhV and quality defects
- PhV of Vaccines
- Specialised clinical areas for Adverse Drug Reactions

PRAC overview

- Mandate
  - REGULATION (EU) No 1235/2010 the Mandate shall cover:
    - All aspects of the risk management of the use of medicinal products including:

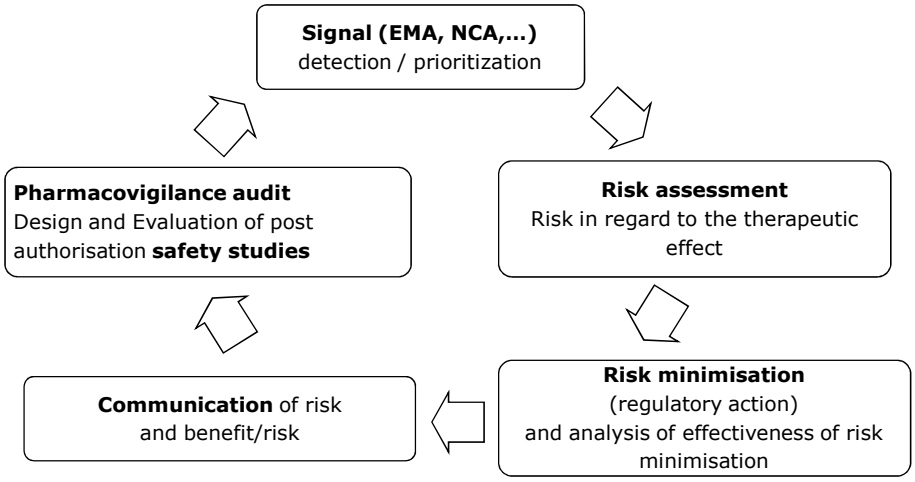
      -Detection, assessment, minimisation and communication relating to the **risk** of adverse reactions, having **due regard to the therapeutic effect of the medicinal product**,

      -The design and evaluation of post-authorisation safety studies and pharmacovigilance audit

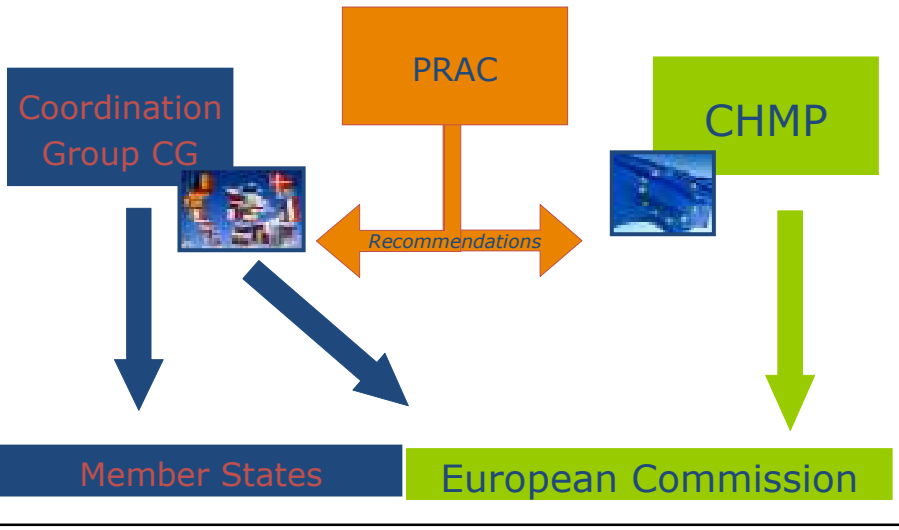
PRAC overview

- Further to the tasks already performed by the PhVWP, the PRAC will also have a strengthened role regarding:
  - Prioritisation of signals (signal rapporteurs)
  - Handling of safety issues in terms of communication and crisis management
  - Communication to the public (press releases, text for safety announcements) and management of public hearings
  - Strategic risk management: assessment of PSURs, RMPs and PASSs
  - Major role in referrals triggered by safety issues, with due regard to therapeutic use in the evaluation

PRAC overview

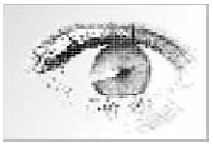


PRAC overview



PRAC overview

PRAC Rapporteurs…
Third pair of eyes…



For **complete new MAAs for CAPs** starting as of December 2012:

		Initial Authorisation Phase	Post-authorisation Phase
New MAAs as of September 2012	CHMP Rapporteur	A[1]	A[1]
	CHMP Co-Rapporteur	B[1]	B[1]
	PRAC Rapporteur	X[2]	X[2]
	PRAC Co-Rapporteur	A[1]	A[1]

[1] Status-quo with current situation

[2] X = open to all PRAC delegates, the selection criteria being the best possible scientific expertise and, where possible, from a different MS compared to the CHMP Rapporteur (A) and CHMP Co-Rapporteur (B)

PRAC overview

European Medicines Agency Annual Report 2012

1.4 | Changes to the Agency's approach to transparency

The year 2012 was also notable for the progress the Agency made in its approach to transparency. The European Parliament, in its discharge decision, highlighted the measures introduced to improve transparency.

- In July 2012, the Agency's committees started publishing their agendas and minutes. The Paediatric Committee (PDCO) was the first to publish agendas and minutes, followed by the PRAC and the Committee for Orphan Medicinal Products (COMP).

19 Jul

First meeting of the Pharmacovigilance Risk Assessment Committee

PRAC overview

Transparency…

The Pros & Cons of Organizational Transparency
Drumm McNaughton, January 14, 2013

Challenges

- risk that information may be distorted, misunderstood or misrepresented
- takes more time and resources and may slow down decision-making processes
- may open to media attack and media risk amplification
- difficult to learn how to balance transparency with keeping some information protected

PRAC overview

It's a good relationship!

- Both processes make information available although for different purposes
- When sender is trusted communication is more effective - transparency creates trust in an organisation
- Transparency is a pre-requisite for and a result of public participation, needed for strategic risk communication

Drug Saf. 2010 Dec 1;33(12):1065-79. Public pharmacovigilance communication: a process calling for evidence-based, objective-driven strategies. Bahri P

PRAC overview

- Transparency?
  - Agenda published ***before*** the PRAC meeting.
  - Minutes published ***when endorsed*** at the next PRAC.
  - ***Highlights published on Friday of the week*** of the PRAC
    - Referrals procedures
      - Letter of the referral
      - Timetable
      - List of questions (art 107i: list of questions to all stakeholders)
      - Outcome and divergent opinions
  - DoI and CV of members published

PRAC: today…

On target

-Signals
-Referrals
-RMPs and PSURs
-PASS/PAES
-Renewals,
conditional renewals
and annual reassessments

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PRAC: today…

On target

-Signals
-***Referrals***
-***RMPs*** and PSURs
-***PASS/PAES***
-Renewals,
conditional renewals
and annual reassessments

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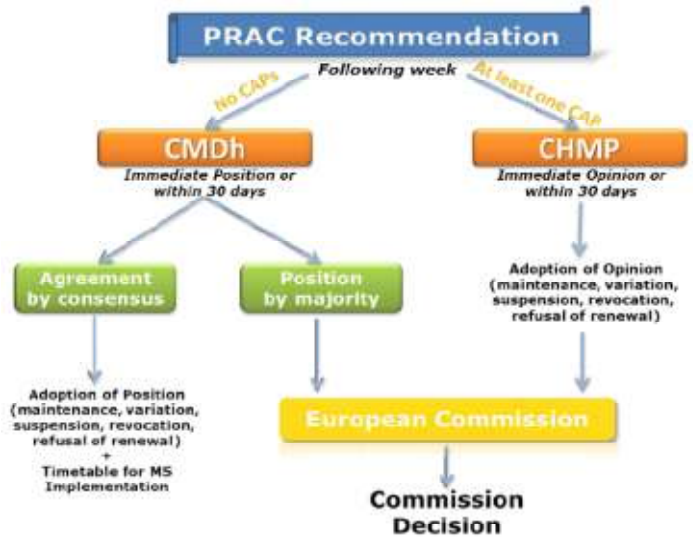
PRAC and safety referrals

- 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.
- safety-related referrals are assessed by the Pharmacovigilance Risk Assessment Committee (PRAC) and then either by the Committee for Medicinal Products for Human Use (CHMP) or, for nationally authorised medicines, by the Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh);

Safety issues	
Article 107i procedures	This type of procedure is triggered when a Member State or the European Commission **consider that urgent action is necessary** because of a **safety issue**. Situations that fall under this procedure include: -consideration for suspension or revocation of the marketing authorisation for a medicine, -the prohibition of supply of a medicine or major changes to the marketing authorisation such as deletion of indications, -reduction of the recommended dose or new contraindications. The procedure is also applicable in case of a safety issue with a class of medicines.
Safety, quality, manufacturing or efficacy issues	
Article 20 procedures	This type of procedure is triggered for medicines that have been authorised via the **centralised procedure** in case of manufacturing or safety issues.
Article 31 referrals	This type of referral is triggered when the **interest of the Community** is involved, following concerns relating to the **quality, safety or efficacy** of a medicine or a class of medicines.

PRAC and safety referrals



PRAC and safety referrals

Art. 107i

active substance	Scope	Rap	co-rap	PRAC decision	CMDh or CHMP
Diane-35	venous and arterial thrombo-embolism	NL	FR	13-16 May 2013	30 May 2013 (CMDh)
Tetrazapam	serious cutaneous toxicity	BE	FR	8-11 April 2013	(CMDh)
Flupirtine	liver problems	PT	DE	Juni 2013	CMDh

Art. 20

active substance	scope	Rap	co-rap	PRAC decision	CMDH or CHMP
laropiprant + nicotinic acid (Tredaptive	increase in the incidence of non-fatal serious adverse events	DE	NL	10 januari 2013	18 januari 2013 (CHMP)
kogenate/helixate	development of antibodies, risk for bleeding	DE	SE	Oct-13	CHMP

PRAC and safety referrals

Art. 31

active substance	scope	Rap	co-rap	PRAC decision	CMDh or CHMP
Codeine	risk of drug toxicity in ultrarapid metabolisers	ES	UK	8-11 April 2013	CMDh
COC's	venous and arterial thromboembolism	UK	FR	13-16 May 2013	CMDh
Diacerine	digestive disorders, hepatitis and serious skin disorders	ES	FR	8-11 July 2013	CMDh
Diclofenac	cardiovascular safety (thrombotic events)	DK	UK	8-11 April 2013	CMDh
HES	higher mortality in critically ill/ICU patients	SE	DE	13-16 May 2013	CMDh
SABA	use in tocolysis	UK	HU	13-16 May 2013	CMDh
Almitrine	peripheral neuropathy and weight loss	PT	FR	8-11 April 2013	CMDh
Nicotinic acid	impact on nicotinic acid containing substances after suspension of Tredaptive	HU	DK	8-11 July 2013	CMDh
Domperidone	Cardiotoxicity	FR	BE	8-11 July 2013	CMDh

Article 107(i)
NAP's +MRP/DCP's+CAP's

Initiated by →
MS/EC when **urgent action** is considered necessary
EC can initiate for NAP's
MS can initiate for CAP's

+ criteria

Time Limit →
60 days (PRAC)
Max 30 days (CHMP / CMDh)

Consultation →
HCP's
Public
MAHs
Written +/- public hearing
+/- non-public hearing
+/- oral explanation

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Article 107(i)
NAP's +MRP/DCP's+CAP's

Outcome →

PRAC recommendation
↓
CHMP Opinion (at least one CAP)
OR CMDh agreement (no CAP)
↓
Commission Decision
(CHMP - All)
(CMDh - no agreement)

- **♦ +/- Temporary measures**
- **♦ Final measures**

- **♦ Variation**
- **♦ Suspension**
- **♦ Revocation**
- **♦ Non-renewal**
- **♦PASS studies**
- **♦Risk Minimisation Measures**

Urgent Action to protect public health →
Until definitive decision may suspend marketing + use product

NO RE-EXAMINATION

PRAC april 2013 meeting

- Media concern: « Diane 35 »

Santé. La pilule «Diane 35» serait liée à quatre décès

Vu 312 fois | Publié le 27/01/2013 à 10:33 | Commenter cet article

TAGS ASSOCIES | France/Monde | Santé | Actualité | Dernières minutes

L'agence du médicament a confirmé ce dimanche quatre décès «imputables à une thrombose veineuse liée à Diane 35» à la suite d'une information du Figaro faisant état de sept décès liés à la prise de ce traitement contre l'acné du laboratoire Bayer généralement utilisé comme pilule contraceptive.

Timetable for the procedure

Procedure under Article 107i of Directive 2001/83/EC

Cyproterone acetate/ethinylestradiol (2mg/0.035mg) containing medicinal products

Procedure no: EMEA/H/A 107i/1357

Procedural step:	Date
Notification:	04 February 2013
Start of the procedure (PRAC):	February 2013 PRAC
List of questions:	08 February 2013
Submission of responses:	11 March 2013
Start of assessment:	18 March 2013
Rapporteur/co-rapporteur assessment report(s) circulated to PRAC and to CMDh[1]:	05 April 2013
First PRAC discussion:	April 2013 PRAC (8 – 11 April 2013)
Comments:	21 April 2013
Ad-hoc expert meeting:	26 April 2013
Updated rapporteur/co-rapporteur/joint assessment report(s):	02 May 2013
Oral explanation/PRAC recommendation to CMDh:	May 2013 PRAC

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Cyproterone- and ethinylestradiol-containing medicines

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Current status: Recommendation provided by Pharmacovigilance Risk Assessment Committee

Procedure started → Under evaluation → PRAC recommendation → CMDh Positive → European Commission final decision

PRAC recommendations on Diane 35

Recommendations by PRAC to be considered by CMDh for final position

During its meeting of 13 to 16 May 2013, the European Medicines Agency's (EMA's) Pharmacovigilance Risk Assessment Committee (PRAC) concluded that the benefits of Diane 35 and other medicines containing cyproterone acetate 2 mg and ethinylestradiol 35 micrograms continue to outweigh their risks for the treatment of moderate to severe acne related to androgen sensitivity or hirsutism (excessive unwanted growth of hair in women) in women of reproductive age. In addition, the PRAC recommended that these medicines, when used for the treatment of acne, should only be used when alternative treatments [illegible]

More information on cyproterone- and ethinylestradiol-containing medicines

- European Medicines Agency reiterates PRAC recommendation for Diane 35 and generics (17/05/2013)
- Meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 13-16 May 2013 (17/05/2013)

Libération

ACTUALITÉS | DÉBATS

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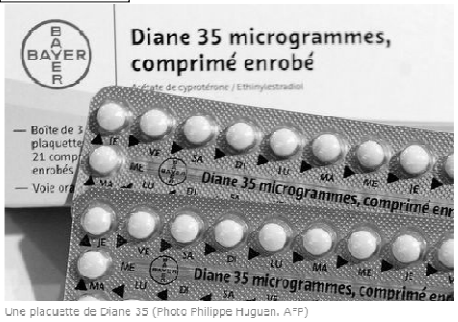
SOCIÉTÉ

SOCIÉTÉ

Diane 35: l'agence européenne ne suit pas la France sur la suspension

17 mai 2013 à 18:11



Une plaquette de Diane 35 (Photo Philippe Huguen, AFP)

Le nouvel Observateur

Diane 35: l'avis de l'Europe conforte les médecins français

par Bruno Martrette | Publié le 19 Mai 2013

Recommander 21 | +1 0 | Aa − +

L'Agence européenne du médicament évalue les bénéfices du médicament Diane 35 supérieurs aux risques. Un avis qui rejoint la position des spécialistes français.

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PRAC: List of deliverables

- CAPs and NAPs
  - **Urgent union procedure** (Dir Art 107(j))
  - Article 31 procedure (Dir Art 31)
  - Article 20 procedure (Reg Art 20)
  - PSUR single assessment (Dir Art 107(e) + Reg Art 28(5))
  - **PASS protocol** (Dir Art 107(m - o) + Reg Art 28b(1))
  - **PASS results** (Dir Art 107(p - q) + Reg Art 28b(1))
  - Signals (Dir Art 107(h) + Reg Art 28a(2))
  - PSUR reference dates (Dir Art 107(c)
  - List of products under additional monitoring (Reg Art 23(2) and (4))
  - For cause phv inspections (Dir Art 111(8) + Reg Art 56(1) and 57(i))

PRAC: List of deliverables

- CAPs
  - **RMPs and outcome of risk minimisation (Reg Art 5(2) and 28a(1))**
  - PSURs for for single CAPs (Reg Art 28(3))
  - Renewals, annual reassessment, safety type II variations (Reg Art 5(2) and 56(1)(aa))
- Non-CAPs
  - PSUR single assessment (Dir Art 107(e))
  - **RMPs, outcome of risk minimisation, renewals, safety type II variations (Reg Art 56(1) and 27(1) and Dir Art 107(h)1)**
  - Member States safety announcements (Dir Art 106(a)(3))

PRAC: RMPs

- CAPs
  - **Reg *Art 5(2)***

    'For the fulfilment of its pharmacovigilance tasks, including the approval of risk management systems and monitoring their effectiveness provided for under this Regulation, the Committee for Medicinal Products for Human Use shall rely on the scientific assessment and recommendations of the Pharmacovigilance Risk Assessment Committee

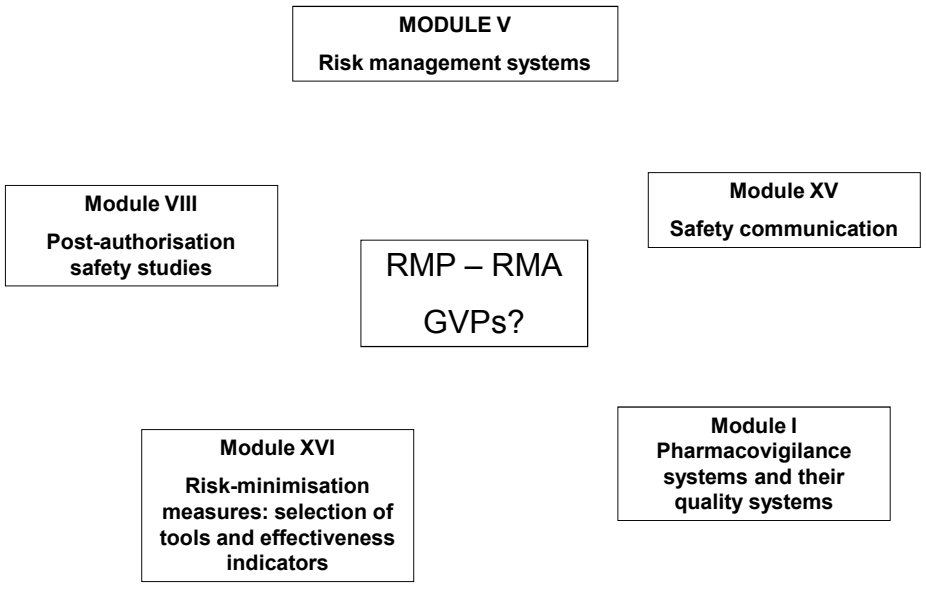
  - **Reg Art 28a(1)**

    Regarding medicinal products for human use authorised in accordance with this Regulation, the Agency shall, in collaboration with the Member States, take the following measures:

    (a) monitor the outcome of risk minimisation measures contained in risk management plans […];

    (b) assess updates to the risk management system;

    (c) […].



PRAC: RMPs

22 June 2012
EMA/838713/2011

Guideline on good pharmacovigilance practices (GVP)

Module V – Risk management systems

PRAC: RMPs

- Risk management in the EU has historically focused upon the risk reduction approach.
- The chapter on risk management systems for medicinal products for human use in Volume 9A, which this guidance replaces, was based solely on managing risks.
- However, when considering how to maximise, or indeed assess, the risk-benefit balance, **risks need to be understood in the context of benefit**.

PRAC: RMPs

- Therefore, although the legal provisions primarily relate to risks, public health will be better served by looking at both benefits and risks.
- Regulation (EU) No 1235/2010 amending Regulation (EC) No 726/2004 and Directive 2010/84/EU amending Directive 2001/83/EC, which apply from July 2012, include provisions for:
  - Post-authorisation efficacy studies, in addition to post-authorisation safety studies, to be a condition of the marketing authorisation in certain circumstances.

The principles of risk management are the same regardless of stakeholder or territory.

PRAC: RMPs

Part I	Product(s) overview
Part II	Safety specification
	Module SI Epidemiology of the indication(s) and target population(s)
	Module SII Non-clinical part of the safety specification
	Module SIII Clinical trial exposure
	Module SIV Populations not studied in clinical trials
	Module SV Post-authorisation experience
	Module SVI Additional EU requirements for the safety specification
	Module SVII Identified and potential risks
	Module SVIII Summary of the safety concerns
Part III	Pharmacovigilance plan
Part IV	Plans for post-authorisation efficacy studies
Part V	Risk minimisation measures (including evaluation of the effectiveness of risk minimisation measures)
Part VI	Summary of the risk management plan
Part VII	Annexes

PRAC: RMPs

- Situations when a risk management plan should be submitted
  - An RMP or an update, as applicable, may need to be submitted **at any time during a product's life-cycle**, i.e. during both the pre- and post-authorisation phases. Situations, in addition, where a RMP or RMP update will normally be expected include:
  - with an application involving a significant change to an existing marketing authorisation:
    - new dosage form;
    - new route of administration;
    - new manufacturing process of a biotechnologically-derived product;
    - paediatric indication;
    - other significant change in indication;
  - **at the request of the Agency or national competent authority** when there is a concern about a risk affecting the risk-benefit balance;
  - **at the time of the renewal** of the marketing authorisation if the product has an existing risk management plan.

PRAC: RMPs

Figure V.3. Requirements for new marketing applications

Type of new application	Part I	Part II-Module SI	Part II-Module SII	Part II-Module SIII	Part II-Module SIV	Part II-Module SV	Part II-Module SVI	Part II-Module SVII	Part II-Module SVIII	Part III	Part IV	Part V	Part VI	Part VII
New active substance	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Similar biological	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Informed consent[1]	✓	✓	✓	✓	✓	✓	✓	✓	✓	*	*	✓	*	✓
Generic medicine	✓								✓	*	*	✓	*	✓
Hybrid medicinal products	✓	✓	^	^	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Fixed combination	✓	✓	^	^	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
"Well established use"	✓	✓				✓	✓	✓	✓	✓	✓	✓	✓	✓
"Same active substance"	✓	✓	*	*	*	✓	✓	✓	✓	✓	✓	✓	✓	✓

[1] Application under Article 10(c) of Directive 2001/83/EC

^ May be omitted under certain circumstances

* Modified requirement

PRAC: RMPs

- PRAC Rapporteur

– For **complete new MAAs for CAPs** starting as of December 2012:

		Initial Authorisation Phase	Post-authorisation Phase
New MAAs as of September 2012	CHMP Rapporteur	A[1]	A[1]
	CHMP Co-Rapporteur	B[1]	B[1]
	PRAC Rapporteur	X[2]	X[2]
	PRAC Co-Rapporteur	A[1]	A[1]

[1] Status-quo with current situation

[2] X = open to all PRAC delegates, the selection criteria being the best possible scientific expertise and, where possible, from a different MS compared to the CHMP Rapporteur (A) and CHMP Co-Rapporteur (B)

PRAC: RMPs

- **PRAC Rapporteur**
  - **PRAC Rapporteur to take lead**
  - **Appointment made on the basis of objective criteria taking into account composition of proposed assessment team**
  - **Prepare recommendation or advice (as applicable) as per pre-defined adopted timelines**
  - **Close collaboration with CHMP Rapporteur (or CMDh lead MS/RMS)**
  - **Format of recommendation/*advice* and assessment report (if applicable) to be endorsed by PRAC in close collaboration with EMA Secretariat**

08:30	Wednesday 10 April 2013	PRAC Rapp / MS Lead
ORGAN	List of Product under Additional Monitoring	
RMPs		
Pre D-210	Avanafil - SPEDRA (CAP MAA)	PRAC Rapporteur: Miguel-Angel Mada (ES) PRAC Co-Rapporteur: Carmela Macciarulo (IT)
	Alogliptin - VIPIDIA (CAP MAA) Alogliptin, metformin - VIPDOMET (CAP MAA) Alogliptin, pioglitazone - INORESYNC (previously SYR 322-4833) (CAP MAA)	PRAC Rapporteur: Menno van der Elst (NL) PRAC Co-Rapporteur: Qun-Ying Yue (SE)
	Lomitapide - LOMITAPIDE AEGERION (CAP MAA)	PRAC Rapporteur: Sabine Straus (NL) PRAC Co-Rapporteur: Julia Dunne (UK)
	Lorcaserin - BELVIQ (CAP MAA)	PRAC Rapporteur: Julie Williams (UK) PRAC Co-Rapporteur: Qun-Ying Yue (SE)
	Somatropin - SOMATROPIN BIOPARTNERS (CAP MAA)	PRAC Rapporteur: Martin Huber (DE) PRAC Co-Rapporteur: Sabine Straus (NL)
	Modified Vaccinia Ankara virus - IMVAMEX (CAP MAA)	PRAC Rapporteur: Julia Dunne (UK) PRAC Co-Rapporteur: Brigitte Keller-Stanislawski (DE)
	Enzlutamide - XTANDI (CAP MAA)	PRAC Rapporteur: Dolores Montero (ES) PRAC Co-Rapporteur: Ulla Wändel Liminga (SE)
Pre D-180	Canagliflozin - CANAGLIFLOZIN (CAP MAA)	PRAC Rapporteur: Martin Huber (DE) PRAC Co-Rapporteur: Qun-Ying Yue (SE)
	Dabrafenib - RAFINLAR (CAP MAA)	PRAC Rapporteur: Ulla Wändel Liminga PRAC Co-Rapporteur: *to be appointed*
	Esomeprazole - NEXIUM CONTROL (CAP MAA)	PRAC Rapporteur: Jolanta Gulbinovic (LT) PRAC Co-Rapporteur: Julia Dunne (UK)
	Fluticasone furoate, vilanterol - RELVAR ELLIPTA (CAP MAA)	PRAC Rapporteur: Miguel-Angel Mada (ES) PRAC Co-Rapporteur: Almath Spooner (IE)
11:00 11:30 Coffee Break		
Pre D-120	Dapagliflozin, metformin - XIGDUO (CAP MAA)	PRAC Rapporteur: Julie Williams (UK) PRAC Co-Rapporteur: Qun-Ying Yue (SE)
	Flutemetamol F-18 - VIZAMYL (CAP MAA)	PRAC Rapporteur: Julie Williams (UK) PRAC Co-Rapporteur: Miguel-Angel Mada (ES)
	Aripiprazole monohydrate - ABILIFY MAINTENA (CAP MAA)	PRAC Rapporteur: Qun-Ying Yue (SE) PRAC Co-Rapporteur: Margarida Guimaraes (PT)
	Levetiracetam - LEVETIRACETAM HOSPIRA (CAP MAA)	PRAC Rapporteur: Jean-Michel Dogne (BE) PRAC Co-Rapporteur: Ancis Lacis (LV)
	Spheroids of human autologous matrix-associated chondrocytes - CHONDROSPHERE (CAP MAA)	PRAC Rapporteur: Brigitte Keller-Stanislawski (DE) PRAC Co-Rapporteur: Qun-Ying Yue (SE)
Other RMPs (in the context of variations or RMP in parallel of PSURs)	Retigabine - TROBALT (CAP)	PRAC Rapporteur: Doris Stenver (DK)
	Ulipristal acetate - ELLAONE (CAP)	PRAC Rapporteur: Menno van der Elst (NL)
	Human hepatitis B immunoglobulin - ZUTECTRA (CAP)	PRAC Rapporteur: Brigitte Keller-Stanislawski (DE)

PRAC: RMPs

- **Publications in the minutes**
  - **Medicines in the *pre-authorisation phase***
    - **The PRAC provided advice to the CHMP on the proposed RMPs for a number of products (identified by active substance below) that are under evaluation for initial marketing authorisation. Information on the PRAC advice will be available in the European Public Assessment Reports (EPARs) to be published *at the end of the evaluation procedure*.**
  - **Medicines already authorised (i.e. RMP in the context of a PSUR procedure)**
    - **Backgrounds and summary of advices published**

February PRAC minutes

5.2.15. Canakinumab – ILARIS (CAP)

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

Regulatory details:

PRAC Rapporteur: Brigitte Keller-Stanislawski (DE)

Background

Canakinumab is a monoclonal antibody used in the treatment of cryopyrin-associated periodic syndromes (CAPS).

The CHMP is evaluating an extension of the therapeutic indication for Ilaris, a centrally authorised product containing canakinumab, to include the treatment of active systemic juvenile idiopathic arthritis (SJIA) in selected patients. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this extension of indication.

Summary of advice

- The RMP version 7 for Ilaris (canakimumab) submitted in the context of the extension of indication variation under evaluation by the CHMP was considered acceptable provided that responses to a list of questions agreed by the PRAC are submitted before finalisation of the variation procedure by the CHMP.

PRAC: RMPs

- ***RMP part IV "Plans for post-authorisation efficacy studies"***
  - **For many medicines there will not be a need for post-authorisation efficacy studies.** However, there may be circumstances where efficacy may vary over time and also patients in whom this assumption of constant efficacy may not be true and where longer term efficacy data post authorisation is necessary.
  - The regulations on **paediatric** medicinal products (Regulation (EC) No 1901/2006)11, and **advanced therapy medicinal products** (Regulation (EC) No 1394/2007)12 provide the legal basis and specify the potential need for long term follow-up of efficacy as part of post-authorisation surveillance for certain medicinal products namely:
    - applications for a marketing authorisation that include a paediatric indication;
    - applications to add a paediatric indication to an existing marketing authorisation;
    - application for a paediatric use marketing authorisation;
    - advanced therapy medicinal products.
  - Although the legislation refers to the studies as post-authorisation efficacy studies, the fact that these efficacy issues can only be resolved **post-authorisation implies that this term includes effectiveness studies**.

PRAC: RMPs

- RMP part IV "Plans for post-authorisation efficacy studies"
  - A summary table showing an overview of the planned studies together with timelines and milestones should be provided here with the (draft) protocols for these studies included in RMP annex 8.
  - Efficacy studies which are specific obligations and/or conditions of the marketing authorisation should also be included in this part of the RMP.

Efficacy studies which are specific obligations and/or conditions of the MA

Description of Study	Milestones (may be several Per activity)	Due Date (may be several Per activity)

Other efficacy/effectiveness studies

Description of Study	Milestones (may be several Per activity)	Due Date (may be several Per activity)

PRAC: RMPs

- ***RMP Part V "Risk minimisation measures"***
  - The risk minimisation plan should provide details of the risk minimisation measures which will be taken to reduce the risks associated with individual safety concerns.
  - It is ***not possible to provide precise guidance*** on which risk minimisation activity should be used in a given situation as each safety concern needs to be considered on a ***case-by-case basis*** and will depend upon the severity of the risk, the healthcare setting, the indication, the pharmaceutical form and the target population.

PRAC: RMPs

- ***RMP Part V "Risk minimisation measures"***
  - Risk minimisation activities may consist of ***routine risk minimisation or additional risk minimisation activities***.
  - All risk minimisation measures should have a ***clearly identifiable objective***
  - All risk minimisation measures should be reviewed at regular intervals and ***their effectiveness assessed***.
  - Additional risk minimisation measures and the assessment of the effectiveness of risk minimisation measures in general is discussed in more detail in ***Module XVI…***

PRAC: RMPs

- *Routine risk minimisation activities* are those which apply to every medicinal product.
  - These relate to:
    - the summary of product characteristics;
    - the labelling;
    - the package leaflet;
    - the pack size(s);
    - the legal status of the product.

PRAC: RMPs

- *Additional risk minimisation activities* should only be suggested when essential for the safe and effective use of the medicinal product and these should be science based, and developed and provided by suitably qualified people.
- This includes:
  - Educational material
    - For centrally authorised products, the CHMP will agree the key elements of what should be included in the educational material and these key elements will become, once agreed by the European Commission, a condition of the marketing authorisation.
    - Further extensive guidance on additional risk minimisation measures is provided in ***Module XVI…***

PRAC: RMPs

- ***RMP Part V "Evaluation of the effectiveness of risk minimisation activities"***
  - When the RMP is updated, the risk minimisation plan should include an evaluation of the impact of routine and/or additional risk minimisation activities as applicable.
  - Results of any studies to assess the impact or other formal assessment(s) of risk minimisation activities should be included when available. As part of this critical evaluation, the marketing authorisation holder should make observations on factors contributing to the success or weakness of risk minimisation activities.
  - If a particular risk minimisation strategy proves ineffective, or to be causing an excessive or undue burden on patients or the healthcare system then alternative activities need to be put in place.
  - More extensive guidance on monitoring the effectiveness of risk minimisation activities is included in ***Module XVI***…

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Modules covering major pharmacovigilance processes

In total, there are 16 **GVP modules** covering major pharmacovigilance processes.

Most modules are available in their final versions. The full set of final modules is scheduled to be available during 2013.

The remaining modules below are under development and are scheduled for release for an eight-week public consultation as indicated below:

Module number	Module title	Date of release for public consultation
XI	Public participation in pharmacovigilance	Third quarter 2013
XII	Continuous pharmacovigilance, ongoing benefit-risk evaluation, regulatory action and planning of public communication	Third quarter 2013
XIV	International cooperation	Third quarter 2013
XVI	Risk-minimisation measures: selection of tools and effectiveness indicators	Second quarter 2013

Module XVI– Risk minimisation measures: selection of tools and effectiveness indicators: highlights

- This Module provides guidance on the principles for:
  - The development and implementation of additional risk minimisation measures, including examples of risk minimisation tools, and
  - The evaluation of the effectiveness of risk minimisation measures.

Module XVI– Risk minimisation measures: selection of tools and effectiveness indicators: highlights

- Educational programme
  - The aim of an educational programme is to improve the use of a medicine by positively influencing the actions of healthcare professionals and patients towards minimising risk.
  - Built on the premise that there is an actionable recommendation for targeted educational and that applying this measure is considered important for minimising an important risk and/or for optimisation of the benefit-risk profile.
  - completely separated from promotional activities and contact information of physicians or patients gathered throughout educational programmes should not be used for promotional activities.

Module XVI– Risk minimisation measures: selection of tools and effectiveness indicators: highlights

- Educational programme
  - The educational tools can
    - have several different target audiences,
    - address more than one concern
    - be delivered using a combination of tools and media (paper, audio, video, web, in-person training).

Module XVI– Risk minimisation measures: selection of tools and effectiveness indicators: highlights

- Educational programme
  - The educational tools
    - Educational tools targeting healthcare professionals
      - should be to deliver specific recommendation(s) on the use (what to do) and/or contraindication(s) (what not to do) and/or warnings (how to manage ADRs) associated with the medicine, including:
        - » i) selection of patients;
        - » ii) treatment management such as dosage, testing and monitoring;
        - » iii) special administration procedures, or the dispensing of a medicinal product.
      - Such a tool may be provided in the format of a check list, a brochure, posters.

Module XVI– Risk minimisation measures: selection of tools and effectiveness indicators: highlights

- Educational programme
  - The educational tools
    - Educational tools targeting patients and/or carers
      - A patient's educational tool could be used to provide information and to remind the patient about an important activity; E.g. A diary for posology or diagnostic procedures that need to be recorded or conducted by the patient and eventually discussed with healthcare professionals.
      - Patient alert card
        - » The aim of this tool should be to ensure that special information regarding the ***patient's current therapy and its risks (e.g. potential interactions with other therapies) is held by the patient at all times and reaches the relevant healthcare professional as appropriate***.

Annex

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the member states

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the member states

The Member States shall ensure that the following conditions or restrictions with regard to the safe and effective use of the medicinal product described below are implemented:

- The MAH shall provide an educational pack, targeting all physicians who are expected to prescribe/use Xarelto prior to the launch of the new indication for the treatment of deep vein thrombosis (DVT) and prevention of recurrent DVT and pulmonary embolism (PE) following an acute DVT in adults.
- The MAH shall provide an educational pack, targeting all physicians who are expected to prescribe/use Xarelto prior to the launch of the new indication for the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors.
- The educational pack is aimed at increasing awareness about the potential risk of bleeding during treatment with Xarelto and providing guidance on how to manage that risk.
- The content and format of the educational material, together with a communication plan, should be agreed with the MAH prior to distribution of the educational pack and launch of the new indication.

Xarelto® rivaroxaban

Annex

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the member states

- The physician educational pack should contain:
  - The Summary of Product Characteristics
  - Prescriber Guide
  - Patient Alert Cards

- The Prescriber Guide should contain the following key safety messages:
  - Details of populations potentially at higher risk of bleeding
  - Recommendations for dose reduction in at risk populations
  - Guidance regarding switching from or to rivaroxaban treatment
  - The need for intake of the 15 mg and 20 mg tablets with food
  - Management of overdose situations
  - The use of coagulation tests and their interpretation
  - That all patients should be provided with a Patient alert card and be counselled about:
    - Signs or symptoms of bleeding and when to seek attention from a health care provider.
    - Importance of treatment compliance
    - The need for intake of the 15 mg and 20 mg tablets with food
    - Necessity to carry the Patient alert card with them at all times
    - The need to inform Health Care Professionals that they are taking Xarelto if they need to have any surgery or invasive procedure.

- The Patient alert card should contain the following key safety messages:
  - Signs or symptoms of bleeding and when to seek attention from a health care provider.
  - Importance of treatment compliance
  - The need for intake of the 15 mg and 20 mg tablets with food
  - Necessity to carry the Patient alert card with them at all times
  - The need to inform Health Care Professionals that they are taking Xarelto if they need to have any surgery or invasive procedure.

Xarelto® rivaroxaban

What should I know about Xarelto®?

- Xarelto® thins the blood, which prevents you from dangerous blood clots.
- Xarelto® must be taken exactly as prescribed by your doctor. To ensure optimal protection from blood clots, **never skip a dose.**
- You must not stop taking Xarelto® without first talking to your doctor as your risk of blood clots may increase.
- Speak to your health care provider prior to any intake of other medication.
- Inform your health care providers about Xarelto® intake prior to any surgery or invasive procedure.

When should I seek advice from my health care provider?

When taking a blood thinner such as Xarelto® it is important to be aware of its possible side effects. Bleeding is the most common side effect. Do not start taking Xarelto® if you are at risk of abnormal bleeding, without first discussing this with your doctor.

Tell your health care provider right away if you have any signs or symptoms of bleeding such as the following:

- pain
- swelling or discomfort
- headache, dizziness or weakness
- unusual bruising, nosebleeds, bleeding of gums, bleeding from cuts that take a long time to stop
- menstrual flow or vaginal bleeding that is heavier than normal
- pink or brown urine, red or black stools
- coughing up blood, or vomiting blood or material that looks like coffee grounds.

How do I take Xarelto®?

- To ensure optimal protection, Xarelto®15mg and 20mg must be taken with food.

Date of preparation: November 2012
LGB.10.2012.0954

PATIENT ALERT CARD

Xarelto® 15mg
Xarelto® 20mg

- **Keep this card with you at all times**
- **Present this card to every physician or dentist prior to treatment**

I am under anticoagulation treatment with Xarelto® (rivaroxaban)

Name:
Address:
Birth date:
Blood type:
Weight:
Other medications/conditions:

In case of emergency, please notify:

Doctor's name:
Doctor's phone:
Doctor's stamp:

Please also notify:

Name:
Phone:
Relationship:

Information for health care providers:

- INR values should not be used as they are not a dependable measure of the anticoagulant activity of Xarelto®.

Module XVI– Risk minimisation measures: selection of tools and effectiveness indicators: highlights

- Controlled access programme
  - A controlled access programme consists of interventions seeking to control access to a medicinal product beyond the level of control ensured by routine risk minimisation measures (i.e. legal status).
  - Examples of requirements that need to be fulfilled before the product is prescribed and/or dispensed and/or used, included individually or in combination, in a controlled access programme may include:
    - Specific testing and/or examination of the patient to ensure compliance with strictly defined clinical criteria;
    - Prescriber and/or dispenser and /or patient documenting their receipt and understanding of information on the serious risk of the product;
    - Patient systematic follow up through enrolment in a specific data collection system (e.g. patient registry);
    - Medicines made available for dispensing only to Pharmacies who are registered and approved to dispense the product.

*Informed consent can be a special case of controlled access to a medicine.

Module XVI– Risk minimisation measures: selection of tools and effectiveness indicators: highlights

- Other risk minimisation measures
  - Pregnancy prevention programme
  - Direct Health Care Professional Communication (DHPC)
    - See GVP module V: Safety communication
      - The preparation of DHPCs involves cooperation between the marketing authorisation holder and the competent authority. Agreement between these two parties should be reached before a DHPC is issued by the marketing authorisation holder
      - In “Documents in lay language”

Module XVI– Risk minimisation measures: selection of tools and effectiveness indicators: highlights

- Effectiveness of risk minimisation measures
  - The evaluation should address different aspects of the risk minimisation:
    - The process itself (e.g. to which extent the programme has been implemented as planned),
    - its impact on knowledge and behavioral changes in the target population,
    - the outcome: to which extent the predefined objectives of risk minimisation were met, in the short and long term
  - Two indicators should be considered:
    - **Process indicators**
    - **Outcome indicators**

Module XVI– Risk minimisation measures: selection of tools and effectiveness indicators: highlights

- Process indicators: measures of the extent of implementation of the original plan
  - Reaching the target population?
  - Assessing clinical knowledge
    - In order to assess the awareness of the target audience and the level of knowledge achieved by educational interventions and/or information provision (for example via the SmPC), ***scientifically rigorous survey methods*** should be applied.

Module XVI– Risk minimisation measures: selection of tools and effectiveness indicators: highlights

- Process indicators: measures of the extent of implementation of the original plan
  - Assessing clinical action
    - In order to evaluate the effectiveness of educational interventions and/or information provisions (e.g. via the SmPC), not only clinical knowledge but also the resulting clinical actions (e.g. prescribing behaviour) should be measured.
    - ***Drug utilization studies*** by means of secondary use of electronic records should be considered as a valuable tool to quantify clinical actions if representative of the target population. The analysis of prescription records, especially when linked to other patients clinical and demographic data, may allow the evaluation of prescribing behaviour, including co-prescribing of two interacting medicinal products, compliance with laboratory monitoring recommendations, as well as patient's selection and monitoring.

Module XVI– Risk minimisation measures: selection of tools and effectiveness indicators: highlights

- Outcome indicators
  - The ultimate measure of success of a risk minimisation programme are the safety outcomes and those safety outcome should be the outcome(s) indicator, i.e. the frequency and/or severity of adverse reactions in relation to patients' exposure to the medicine outside of an interventional study setting (i.e. non-interventional setting).
    - Such an evaluation should involve the comparison of epidemiologic measures of outcome frequency such as incidence rate or cumulative incidence of an adverse reaction, obtained in the context of ***post-authorisation safety studies (PASS)***.
    - ***Comparisons of frequency before and after the implementation of the risk minimisation measures (i.e. pre-post design) should be considered (spontaneous reports not optimal, epidemiological data more relevant)***

Module XVI– Risk minimisation measures: selection of tools and effectiveness indicators: highlights

- Implementation
  - Implementation of **additional risk minimisation measures takes place at national level** and allows member states to tailor the required conditions and restrictions to any national legal requirements and local healthcare systems.
  - Annex II of the CHMP opinion will outline the key elements of any additional risk minimisation measures imposed on the applicant/marketing authorisation holder as a condition for the safe and effective use of a medicinal product. An Annex related to Article127a of Directive 2001/83/EC may describe the responsibilities of national competent authorities in ensuring that the additional risk minimisation measures are implemented in the Member States in accordance with defined key elements. Further details or key elements on any additional risk minimisation measures may be included in annex 10 of the RMP (see Module V)

Module XVI– Risk minimisation measures: selection of tools and effectiveness indicators: highlights

- Roles of the PRAC
  - Based on its scientific assessment, the PRAC should make recommendations to the CHMP or the CMDh as appropriate, regarding the need for additional risk minimisation measures and regarding the key elements that should be included in those measures.
  - The PRAC should evaluate the outcome of risk minimisation systems, including additional risk minimisation measures and make recommendations to the CHMP or the CMDh as appropriate regarding any necessary regulatory action.
  - PRAC will normally assess both protocol and results of post-authorisation safety studies which aim to evaluate the effectiveness of risk minimisation measures (see GVP Module VIII).

PRAC: RMPs

- Situations when a risk management plan should be submitted post MA, with new RMAs.
  - Examples: Referrals for all MAs
    - Art 107i Tetrazepam
      - Final PRAC recommendation: Syspension but RMP was proposed to include all RMAs, including measuring the effectiveness of RMAs.
    - Art 107i Diane 35® and generics

Timetable for the procedure

Procedure under Article 107i of Directive 2001/83/EC

Cyproterone acetate/ethinylestradiol (2mg/0.035mg) containing medicinal products

Procedure no: EMEA/H/A 107i/1357

Procedural step:	Date
Notification:	04 February 2013
Start of the procedure (PRAC):	February 2013 PRAC
List of questions:	08 February 2013
Submission of responses:	11 March 2013
Start of assessment:	18 March 2013
Rapporteur/co-rapporteur assessment report(s) circulated to PRAC and to CMDh[1]:	05 April 2013
First PRAC discussion:	April 2013 PRAC (8 – 11 April 2013)
Comments:	21 April 2013
Ad-hoc expert meeting:	26 April 2013
Updated rapporteur/co-rapporteur/joint assessment report(s):	02 May 2013
Oral explanation/PRAC recommendation to CMDh:	May 2013 PRAC

PRAC: RMPs

PRAC recommendation as published on the EMA website:

- *The PRAC concluded that medicines containing cyproterone acetate 2 mg and ethinylestradiol 35 micrograms should only be used for the treatment of moderate to severe acne related to androgen sensitivity and/or hirsutism in women of reproductive age.*
- *In addition the PRAC recommended that these medicines should only be used for the treatment of acne when alternative treatments such as topical therapy (applied to the skin) or antibiotics have failed.*
- *The product information for Diane 35 and other medicines containing cyproterone acetate 2 mg and ethinylestradiol 35 micrograms should include that these medicines are also hormonal contraceptives and therefore should not be used in combination with other hormonal contraceptives.*
- *Concomitant use with another hormonal contraceptive would expose the woman to a higher dose of oestrogen and increase her risk of VTE.*

PRAC: RMPs

PRAC recommendation as published on the EMA website:

"The PRAC also recommended a number of measures to further raise awareness amongst healthcare professionals and patients of the risk of thromboembolism, in order to allow for timely diagnosis, treatment and prevention of any complications. Measures include:

-***Educational material*** for healthcare professionals and patients on thromboembolism, and its risk factors, signs and symptoms.

In addition the PRAC recommended that the company should carry out:

-a **study on the use** of Diane 35 and other medicines containing cyproterone acetate 2 mg and ethinylestradiol 35 micrograms ***(Drug utilization study)***

-as well as a **study on the effectiveness of the recommended risk minimisation measures (PASS)**

-Within a **RMP**

-**DHCP?**

PRAC: RMPs

- Transparency
  - The Agency and Member States shall make publically available public assessment reports and summaries of risk management plans [REG Art 26(1), DIR Art 106].
  - For centrally authorised products the Agency will:
    - make public a summary of the RMP;
    - include tables relating to the RMP in the European Public Assessment Report (EPAR) including the product information and any conditions of the marketing authorisation.
  - To promote public health, the Agency will make available (either on request or via its web portal):
    - any questionnaires included in RMPs for centrally authorised products which are used to collect information on specified adverse reactions;
    - details, which may include copies, of educational material or other additional risk minimisation activities required as a condition of the marketing authorisation;
    - details of disease or substance registries requested as part of< the pharmacovigilance plan for centrally authorised products.

Conclusion: PRAC

Key player on all aspects of the risk management

Relevant expertise in pharmacovigilance matters and risk assessment need to be strengthened

- **Team work at NCAs**

Recommendations to the CHMP and CMDh

- **Major impact on the decision on the B/R assessments**
- **Level of transparency never reached**
- **Close collaboration between members from the different committees**