EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

What are safety communications and how to review them

Training session for patients and consumers – 25 November 2014

Presented by: Federica Castellani
Stakeholder and Communication Division

What are safety communications?

Information addressed to the public that conveys an important, emerging message on the use of a medicine already authorised.

Examples:

- withdrawal or suspension from the market for safety reasons;
- restriction of use, new contraindications or warnings;
- product defects leading to safety concerns.

Key objectives of safety communications

Good information

- Provides timely evidence-based information on the safe and effective use of medicines;
- Facilitates changes to healthcare practices (including self-medication practices) where necessary;
- Changes attitudes, decisions and behaviours in relation to the use of medicines;
- Supports risk minimisation behaviour;
- Facilitates informed decisions on the rational use of medicines.

When do we communicate?

Majority of safety communications will relate to a 'referral' procedure:

> 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 European Medicines Agency is requested to conduct a scientific assessment of a particular medicine or class of medicines on behalf of the European Union.

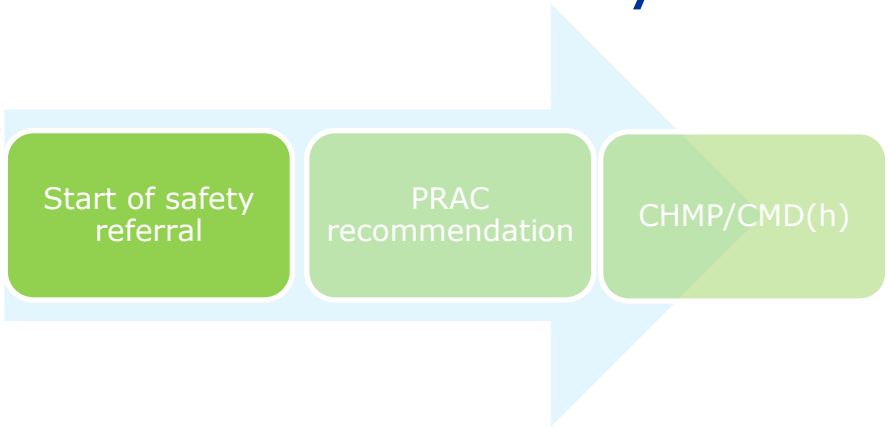
Communication about safety referrals

PRAC: Pharmacovigilance Risk Assessment Committee, responsible for the evaluation of safety issues for human medicines

CHMP: Committee for Medicinal Products for Human Use, responsible for all questions concerning medicines for human use

CMD(h): Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human, a medicines regulatory body representing the EU Member States

Communication about safety referrals



'EMA announcement of start of referral':

- Brief, lay-language document to explain why the review was started
- Published together with other documents (notification, list of questions, timetable)

Start of review of combined hormonal contraceptives containing chlormadinone, desogestrel, dienogest, drospirenone, etonogestrel, gestodene, nomegestrol, norelgestromin or norgestimate

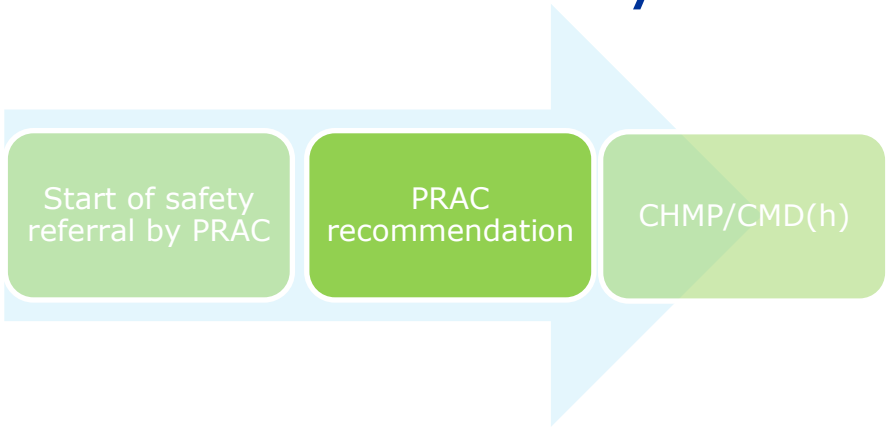
The European Medicines Agency (EMA) has started a review of several combined hormonal contraceptives authorised in the EU. Combined hormonal contraceptives contain two types of hormones, an oestrogen and a progestogen. The review includes all contraceptives containing the following progestogens: chlormadinone, desogestrel, dienogest, drospirenone, etonogestrel, gestodene, nomegestrol, norelgestromin and norgestimate.

The review of these contraceptives was requested by the French medicines agency ANSM following concerns in France about the risk of venous thromboembolism (VTE or blood clots in veins). The risk of VTE with combined hormonal contraceptives is known to depend on both the level of oestrogen and the type of progestogen they contain. While the overall risk with these products is low, the risk is known to be higher for some progestogens than the risk associated with the progestogen levonorgestrel.

The EMA will now review all available data on the risk of VTE with these contraceptives and issue an opinion on whether any changes are needed to their prescribing advice across the EU. The review will also cover the risk of arterial thromboembolism (blood clots in arteries, which can potentially cause a stroke or heart attack). This risk is very low and is not currently known to be higher with any particular type of progestogen.

Previous EMA reviews of combined oral contraceptives[1,2] concluded that that their absolute risk of VTE is low and extensive information on the risk and its management is included in their product information.

Communication about safety referrals



'Summary of PRAC recommendation'

- Should ensure that the public understands the process and what 'PRAC recommendation' means (not the final EMA opinion) and what happens next.
- As procedure is still ongoing, it does not contain detailed recommendation for patients and healthcare professionals

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PRAC confirms that benefits of all combined hormonal contraceptives (CHCs) continue to outweigh risks

Committee recommends that women and prescribers be better informed of the known risk of thromboembolism and alert for signs and symptoms

The EMA's Pharmacovigilance Risk Assessment Committee (PRAC) has reviewed the risk of venous thromboembolism (VTE or blood clots in veins) with combined hormonal contraceptives (CHCs). The PRAC concluded that the benefits of CHCs in preventing unwanted pregnancies continue to outweigh their risks.

There is no reason for women who have been using CHCs without any problem to stop taking them on the basis of this review. It is important that women are made aware of the risk of VTE and its signs and symptoms, and that doctors take into consideration a woman's individual risk factors when prescribing a contraceptive.

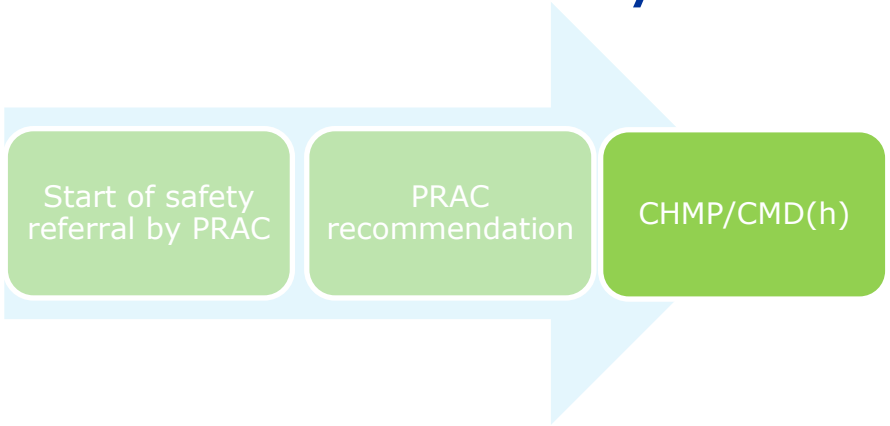
This review has confirmed that the risk of VTE with all CHCs is small and has shown that there are small differences between the CHCs depending on the type of progestogen they contain. It has reinforced the importance of ensuring good information for women who use these medicines and for the healthcare professionals providing advice and clinical care.

When prescribing a CHC, doctors should assess a woman's individual risk for blood clots regularly, as the risk changes over time. Risk factors include among others smoking, being overweight, increasing age, having migraines, family history of VTE and having given birth in the previous few weeks. Doctors should also consider how the risk of VTE compares with other CHCs.

It is important that women and doctors remain alert for the signs and symptoms of thromboembolism, which may include severe pain or swelling in the legs, sudden unexplained breathlessness, rapid breathing or cough, chest pain, and face, arm or leg weakness or numbness. In case a woman develops any of these signs and symptoms she should seek medical advice immediately.

The PRAC recommendation will now be forwarded to the Committee for Medicinal Products for Human Use (CHMP) which is expected to adopt an EMA final opinion at its plenary meeting of 18-21 November 2013.

Communication about safety referrals



'EMA public health communication'

- Composed of three sections:
  - Summary of the issue (for press and general public)
  - Information to patients
  - Information to healthcare professionals

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Benefits of combined hormonal contraceptives (CHCs) continue to outweigh risks – CHMP endorses PRAC recommendation

Product information to be updated to help women make informed decisions about their choice of contraception

The European Medicines Agency has now completed its review of combined hormonal contraceptives (CHCs), particularly of the risk of venous thromboembolism (VTE or blood clots in veins) associated with their use. The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) has concluded that the benefits of CHCs in preventing unwanted pregnancies continue to outweigh their risks, and that the well-known risk of VTE with all CHCs is small.

The review has reinforced the importance of ensuring that clear and up-to-date information is provided to women who use these medicines and to the healthcare professionals giving advice and clinical care.

The product information of CHCs will be updated to help women make informed decisions about their choice of contraception together with their healthcare professional. It is important that women are made aware of the risk of VTE and its signs and symptoms, and that doctors take into consideration a woman's individual risk factors when prescribing a contraceptive. Doctors should also consider how the risk of VTE with a particular CHC compares with other CHCs (see table below).

The review also looked at the risk of arterial thromboembolism (ATE, blood clots in arteries, which can potentially cause a stroke or heart attack). This risk is very low and there is no evidence for a difference in the level of risk between products depending on the type of progestogen.

The CHMP opinion, in agreement with the previous recommendation by the Pharmacovigilance Risk Assessment Committee (PRAC), will now be sent to the European Commission for the adoption of a legally binding decision to update the product information of all CHCs throughout the EU.

Information to patients

- This Europe-wide review looked at the benefits and risks of combined hormonal contraceptives (CHCs), particularly the risk of blood clots associated with these medicines. It confirmed that the benefits of CHCs outweigh the risk of blood clots, which has been known for many years and is very low.
- If you have been taking CHCs without any problem, there is no reason for you to stop taking them on the basis of this review. But it is important that you are aware of the risk of blood clots associated with these medicines, even though it is very low.

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- The risk of blood clots in the veins varies between CHCs, depending on the type of progestogen (a hormone) they contain, and ranges from 5 to 12 cases of blood clots per 10,000 women who use them for a year (see table below). This compares with 2 cases of blood clots in the veins each year per 10,000 women who are not using CHCs.
- You should also be aware of the factors that increase your risk of a clot and be aware of how these may change over time. Risk factors include being very overweight, increasing age, having a member of your family who has had a blood clot at a relatively young age (e.g. below 50), having migraine or being immobilised for a long time (e.g. because of an illness or injury). Your risk of a blood clot is also higher in the first year of using a CHC.
- You should discuss with your doctor or nurse what is the most appropriate type of contraception for you.
- When taking CHCs, you should be alert for the signs and symptoms of blood clots, which may include severe pain or swelling in the legs, sudden unexplained breathlessness, rapid breathing or cough, chest pain, and weakness or numbness of the face, arm or leg. If you develop any of these signs and symptoms you should seek medical advice immediately.
- If you have any questions or concerns, speak with your doctor, pharmacist or nurse.

Information to healthcare professionals

- The EU-wide review of combined hormonal contraceptives (CHCs) has confirmed that the known risk of venous thromboembolism (VTE) with all low-dose CHCs (ethinylestradiol < 50 mcg) is small.
- Differences exist between CHCs in their risk of VTE depending on the type of progestogen they contain. Currently available data indicate that CHCs containing the progestogens levonorgestrel, norethisterone or norgestimate have the lowest risk of VTE (see table below).
- When prescribing a CHC, careful consideration should be given to the individual woman's current risk factors, particularly those for VTE, and the difference in risk of VTE between products. CHCs are contraindicated if a woman has one serious or multiple risk factors that put her at high risk of blood clots.
- There is no evidence for differences between low-dose CHCs in their risk of arterial thromboembolism (ATE).
- Because a woman's individual risk factors will change over time, there is a need to regularly re-assess the suitability of her contraceptive.
- It is also important to raise awareness of the signs and symptoms of VTE and ATE when prescribing a CHC.
- Healthcare professionals should always consider the possibility of a CHC-associated thromboembolism when presented with a woman who has symptoms.

How do we prepare safety communications?

- The basis is the CHMP/PRAC assessment report
- Several stages of drafting and review
- Input from several internal and external experts ***including patients and consumers, and healthcare professionals***

Aim of review by patients and consumers

Ensure the message is clear and comprehensible and fulfils its needs in terms of information content

Areas to focus on:

- Clarity of rationale behind recommendations
- Relevance/clarity of advice to patients

Review of *sensitive and confidential* information. Documents sent for review are working documents that may change before publication

Example of comment received

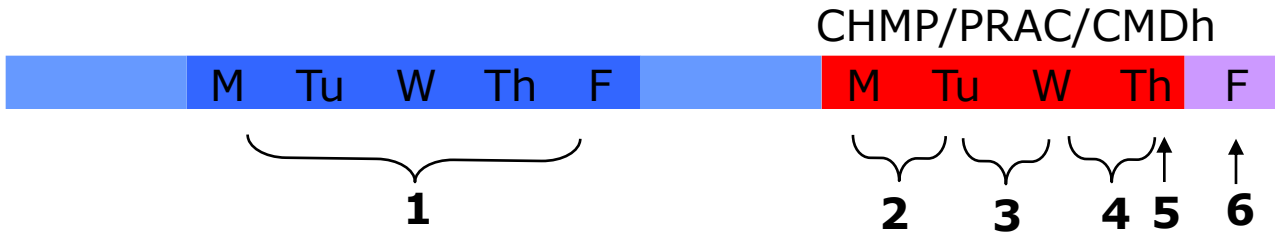
- For CHCs containing chlormadinone, dienogest and nomegestrol, the available data are insufficient to know how the risk compares with the other CHCs.

Comment [S1]: Add what the EMA/authorities are doing about that

Amended text:

- For CHCs containing chlormadinone, dienogest and nomegestrol, the available data are insufficient to know how the risk compares with the other CHCs, **but further studies are ongoing or planned.**

Timelines



1: - Internal meeting with product team to determine key message
- Prepare first draft on possible outcomes
- ***Identify and contact experts from patients and consumers***

2: - First discussion at Committee
- Update document in line with Committee's discussions

3: - Review by product team, Rapporteurs, and ***patients*** and HCPs

4. - Present documents to Committee
- Then send to company for information

5. - Final version sent to Heads of Medicines Agencies under embargo

6. - Publication (noon on Friday)

Publishing and sharing information

- All documents published on Agency website
- They are actively sent out to press mailing lists at time of publication
- ***They are sent to relevant patients' organisations for dissemination to their members***

Summary

- Safety communications are challenging:
  - short timeframe
  - limited predictability
  - views of many stakeholders to consider
- EMA communication tailored to different stakeholders (press, patients and healthcare professionals)
- Patients and consumers' views are crucial to meet communication objectives

Communication on medicines' shortages

In November 2013, the EMA started publishing a **shortages catalogue**:

- for medicine shortages that affect more than one EU country;
- where the EMA has provided recommendations to patients and healthcare professionals across the EU.

The catalogues does not give a complete overview of all medicine shortages occurring in the EU

The catalogue can be found here.

Communication on medicines' shortages

Current shortages

Document(s)	Status	First published	Last updated
Buccolam (midazolam) supply shortage	Ongoing	25/04/2014	12/09/2014
Cerezyme (imiglucerase) supply shortage	Ongoing	04/11/2013	
Fabrazyme (agalsidase beta) supply shortage	Ongoing	04/11/2013	29/10/2014
Maci (matrix applied characterised autologous cultured chondrocytes) implant supply shortage	Ongoing	04/07/2014	
Xofigo (radium-223 dichloride) supply shortage	Ongoing	17/10/2014	7/11/2014

Resolved shortages

Document(s)	Status	First published	Last updated
Enbrel (etanercept) supply shortage	Resolved	19/02/2014	07/05/2014
Increlex (macasermin) shortage resolution	Resolved	20/12/2013	

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Buccolam (midazolam) Oromucosal solution (2.5 mg; 5 mg; 7.5 mg and 10 mg prefilled syringes)	
Indication	Buccolam is used to stop a sudden and prolonged convulsive seizure (fit) in children (aged from three months to less than 18 years).
Reason for shortage	In March 2014, a routine inspection of the manufacturing site for Buccolam revealed deficiencies in its manufacturing process, which raised concerns about a potential risk of contamination with another medicine produced at the same site. Tests performed have not found any contamination of Buccolam and there is no evidence that its quality is affected but, as a precautionary measure, Buccolam has been recalled in Member States where suitable alternative treatments are available. Further production has been put on hold and transferred to a new manufacturing site. This has resulted in a temporary shortage in a number of Member States.
Member States affected[1]	Buccolam is currently marketed in Denmark, Finland, France, Germany, Ireland, Italy, Norway, Spain, Sweden and the United Kingdom. Temporary supply disruptions are affecting Finland, France, Germany, Italy and Spain.
Information to healthcare professionals	• There are problems with the supply of Buccolam (affecting all strengths) in some Member States. • In case of shortage, healthcare professionals should prescribe suitable alternatives. • Additional advice may be available from the national competent authority.
Information to parents and carers	• There are problems with the supply of Buccolam in some Member States. • Parents and carers will be informed by their healthcare professional if Buccolam is unavailable. • In case of shortage doctors will prescribe alternative treatments. • Parents or carers who have any questions should speak to their doctor or pharmacist. • Additional advice may be available from the national competent authority.
Status	Ongoing
Last updated on	10 September 2014

Thank you for your attention.