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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 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 and/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 (topical treatments and antibiotics) have failed. The PRAC also recommended changes to the product information and other measures to reduce the risk of thromboembolism (the formation of blood clots in the blood vessels).

The PRAC recommendations will be considered by the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh), a regulatory body representing EU Member States, which will take a final position.

Why are Diane 35 and other medicines containing cyproterone acetate 2 mg and ethinylestradiol 35 micrograms being reviewed?

The EMA started the review of these medicines in February 2013 following the decision by the French National Agency for the Safety of Medicine and Health Products (ANSM) to suspend Diane 35 and its generics in France within three months. The French decision followed a national review by ANSM of the benefits and risks of these medicines which highlighted serious thromboembolic events. Although the risk of thromboembolism of these medicines has been known for many years, ANSM considered this risk to outweigh the benefits of these medicines in treating acne. In addition, it noted that these medicines are widely used off-label as a contraceptive.

What are the PRAC conclusions?

The PRAC assessed all available data on the risk of thromboembolism as well as the benefits of Diane 35 and other medicines containing cyproterone acetate 2 mg and ethinylestradiol 35 micrograms. Stakeholders (healthcare professionals, patients and the general public) were also able to submit relevant information to support the assessment, and a group of experts including patient representation was also convened to provide advice.

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7129
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

The PRAC confirmed the known risk of venous thromboembolism (VTE, formation of blood clots in the veins) with Diane 35 and other medicines containing cyproterone acetate 2 mg and ethinylestradiol 35 micrograms. The PRAC concluded that the risk of VTE with these medicines is 1.5 to 2 times higher than for COCs containing levonorgestrel and may be similar to the risk with contraceptives containing gestodene, desogestrel or drospirenone. The PRAC noted that, in terms of effectiveness, the available data support the use of Diane 35 and other medicines containing cyproterone acetate 2 mg and ethinylestradiol 35 micrograms in the treatment of moderate to severe acne related to androgen sensitivity and/or hirsutism, in women of reproductive age. Furthermore the PRAC concluded that in the treatment of alopecia the benefits did not outweigh the risks.

The PRAC therefore 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.

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 as well as a study on the effectiveness of the recommended risk minimisation measures.

What will happen next?

The PRAC recommendations will be considered by the CMDh at its next meeting of 27 to 29 May 2013. The CMDh will adopt a final position on the marketing authorisations for medicines containing cyproterone acetate 2 mg and ethinylestradiol 35 micrograms. The final CMDh position, together with advice for patients and healthcare professionals, will be made public.

Healthcare professionals should be aware of the risk of thromboembolism. Once the procedure is finalised, healthcare professionals in countries where these medicines are marketed will receive a letter with detailed information on the appropriate actions to be taken. Patients who have any questions should speak to their doctor or pharmacist.

More about the medicine

Medicines containing cyproterone acetate 2 mg and ethinylestradiol 35 micrograms have been approved via national procedures and are available on prescription under various trade names in all EU Member States except Cyprus. Diane 35 was first authorised in 1985. These medicines work by blocking the effects of a class of hormones called androgens. Authorised uses differ between EU Member States and include acne and other conditions caused by androgens such as hirsutism and alopecia.

More about the procedure

The review of medicines containing cyproterone acetate 2 mg and ethinylestradiol 35 micrograms was initiated in February 2013 at the request of France, under Article 107i of Directive 2001/83/EC, also known as the urgent Union procedure.

The review has been carried out by the Pharmacovigilance Risk Assessment Committee (PRAC), the Committee responsible for the evaluation of safety issues for human medicines, which has made a set of recommendations. As these medicines are all authorised nationally, the PRAC recommendation will now be forwarded to the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh), which will adopt a final position on whether their marketing authorisations should be maintained, changed, suspended or withdrawn. The CMDh is a medicines regulatory body representing the EU Member States.

If the CMDh position is agreed by consensus, the agreement will be directly implemented by the Member States where the medicines are authorised. Should the CMDh position be adopted by majority vote, the CMDh position will be sent to the European Commission, for the adoption of an EU-wide legally binding decision.