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Benefits of Diane 35 and its generics outweigh risks in certain patient groups - PRAC recommendation endorsed by CMDh

The Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) has endorsed by majority (26:1) the recommendation of the European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC), which concluded that the benefits of Diane 35 (cyproterone acetate 2 mg / ethinylestradiol 35 micrograms) and its generics outweigh the risks, provided that several measures are taken to minimise the risk of thromboembolism (formation of blood clots in blood vessels). These medicines should be used solely in 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. Furthermore, Diane 35 and generics should only be used for the treatment of acne when alternative treatments, such as topical therapy and antibiotic treatment, have failed.

Since Diane 35 and its generics act as hormonal contraceptives, women should not take these medicines in combination with other hormonal contraceptives. Concomitant use of Diane 35 and its generics with another hormonal contraceptive will expose women to a higher dose of oestrogen and increase the risk of thromboembolism.

The risk of thromboembolism occurring with these medicines is low and well known. However, to minimise this risk, further measures should be implemented in addition to the updated product information. These include providing educational materials to prescribers and patients highlighting the risks of thromboembolism, for example a prescriber checklist to ensure that the risks, together with the signs and symptoms, are discussed with the patient.

These recommendations have been endorsed by the CMDh, a body representing EU Member States. Because the CMDh took this position by majority it will now be sent to the European Commission, which will adopt a legally binding decision.

The review of Diane 35 and its generics was triggered by the French medicines agency, the National Agency for the Safety of Medicine and Health Products (ANSM), following its decision to suspend Diane 35 and its generics in France within three months. The French decision followed a national review of the medicine by ANSM. This review highlighted serious thromboembolic events and extensive off-label use of these medicines as a contraceptive only.

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Despite the PRAC recommendation ANSM proceeded with the suspension of the marketing authorisation of these medicines in France. Once the European Commission has adopted its decision, all EU Member States where Diane 35 and its generics are authorised must follow it and ensure that all agreed risk minimisation measures, including changes to the information to prescribers and patients, are implemented.

Information to patients

- Diane 35 and its generics should only be used to treat moderate to severe acne (related to sensitivity to hormones called androgens) and/or hirsutism in women of child-bearing age. However, when used for acne, they should only be used if other treatments, such as those applied to the skin and antibiotics, have failed.
- If you are using these medicines for other conditions you should make a non-urgent appointment with your doctor to review your treatment.
- You should not stop taking these medicines before speaking to your doctor. Diane 35 and its generics act also as hormonal contraceptives and stopping them means that you will have to use another form of contraception to prevent unwanted pregnancies.
- You should always read the package leaflet and be aware that there is a low risk of blood clots with these medicines. The risk of blood clots in the veins with these medicines is 1.5 to 2 times higher than for combined oral contraceptives (COCs) containing levonorgestrel and may be similar to the risk with contraceptives containing gestodene, desogestrel or drospirenone.
- You should be aware that there are factors that can increase the risk of blood clots in blood vessels, such as increasing age, smoking, obesity and prolonged immobility. You should immediately report any relevant symptoms to your doctor, such as pain and swelling in the legs, or breathlessness and a sharp pain in the chest.
- If you have any questions you should speak to your doctor or pharmacist.

Information to healthcare professionals

Healthcare professionals should follow these recommendations:

- Diane 35 and its generics should only be used for the treatment of moderate to severe acne related to androgen-sensitivity (with or without seborrhoea) and/or hirsutism, in women of reproductive age.
- For the treatment of acne, these medicines should only be used after topical therapy or systemic antibiotic treatment has failed.
- Since Diane 35 and its generics act also as hormonal contraceptives, they should not be used in combination with other hormonal contraceptives.
- Doctors should review patients on Diane 35 and generics in line with these recommendations at their next scheduled appointment.
- Doctors should discuss with their patients the risk of thromboembolism and risk factors such as increasing age, smoking, obesity and prolonged immobility.
- Healthcare professionals will be sent a letter with further details.

These recommendations are based on a review of all available data on the risk of thromboembolism as well as the benefits of Diane 35 and its generics:

- The review confirmed the rare and known risk of thromboembolism with Diane 35 and its generics. Observational studies have shown that the risk of venous thromboembolism (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. Data on the risk of arterial thromboembolism (ATE) with Diane and its generics are sparse and indicate that this risk is lower than for VTE.
- The review also showed that the excess risk of VTE is highest during the first year of use of Diane 35 and its generics or when restarting or switching from an oral hormonal contraceptive to Diane 35 and its generics after a pill-free interval of at least one month.
- In terms of effectiveness, the available data support the use of Diane 35 and its generics in the treatment of moderate to severe acne related to androgen sensitivity and/or hirsutism, in women of reproductive age. The efficacy in moderate and severe acne with or without seborrhoea and /or hirsutism is demonstrated in more than 30 clinical trials.
- In the treatment of alopecia androgenetica and acne without androgenic features, the data on efficacy is limited.

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. Cyproterone also supresses ovulation and therefore has a contraceptive effect.

More about the procedure

The review of Diane 35 and its generics 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.

A review of these data was first conducted by the Pharmacovigilance Risk Assessment Committee (PRAC). The PRAC recommendations were sent to the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh), which adopted a final position. The CMDh is a medicines regulatory body representing the EU Member States. Its main responsibility is to resolve disagreements between Member States involved in mutual recognition or decentralised procedures, to ensure that patients have the same level of protection, no matter where they are in the EU.

As the CMDh position was adopted by majority vote and not by consensus, the CMDh position will now be sent to the European Commission, which will take a legally binding decision throughout the EU.

Further information on the PRAC recommendation and the background to this review can be found on Agency's website.