EMA/20248/2020
17 January 2020

PRAC confirms four-week limit for use of high-strength estradiol creams

EMA's safety committee (PRAC) has confirmed its recommendation to limit the use of high-strength creams containing 100 micrograms/gram (0.01%) of estradiol to a single treatment period of up to 4-weeks. This follows a re-examination of its recommendation of October 2019 which was requested by one of the companies that market high-strength estradiol cream.

The PRAC reviewed available data on the safety and effectiveness of high-strength estradiol-containing creams used to treat symptoms of vaginal atrophy in women who have been through menopause. Data on these creams show that in postmenopausal women who use them, the levels of estradiol in the blood were higher than normal postmenopausal levels. The PRAC concluded that absorption of estradiol into the bloodstream is of concern and could result in similar side effects to those seen with hormone replacement therapy (HRT). The side effects of HRT taken orally or used transdermally (as patches) include venous thromboembolism (formation of blood clots in the veins), stroke, endometrial cancer (cancer of the lining of the womb) and breast cancer. In addition, there are limited safety data on long term use of high-strength estradiol creams. For these reasons, the PRAC recommended that these creams should only be used for a single treatment period of a maximum of 4 weeks.

The PRAC recommends that the prescribing information for these creams will be updated with the new recommendations. A warning that the medicine is to be used for a single treatment period of up to 4 weeks only will be placed on the outer and inner packaging and the size of the tube will be limited to 25 grams to prevent use for longer than recommended.

The PRAC recommendations will now be sent to the CMDh[1] to make a decision about their implementation. The CMDh is a body representing EU Member States as well as Iceland, Liechtenstein and Norway.

Information for patients

- High-strength estradiol creams (100 micrograms/gram) applied inside the vagina should only be used for a single treatment period of a maximum of 4 weeks. This is because the hormone estradiol in these creams can be absorbed into the bloodstream and may increase the risk of side effects.
- Do not use high-strength estradiol cream if you are already taking another HRT (hormone replacement therapy) medicine.

[1] Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

- If you have any questions about your treatment, talk to your doctor or pharmacist.

Information for healthcare professionals

- High-strength estradiol creams (100 micrograms/gram) should not be prescribed for longer than a single treatment period of 4 weeks due to the risks associated with systemic exposure to estradiol.
- Pharmacokinetic data on high-strength estradiol creams for intravaginal use show systemic exposure to estradiol, with levels higher than the normal postmenopausal range (up to five times above the upper limit of the reference postmenopausal estradiol serum levels of 10–20 pg/ml).
- Systemic exposure to estradiol could be associated with side effects similar to those of oral and transdermal HRT products such as endometrial hyperplasia/carcinoma, breast and ovarian cancer and thromboembolic events.
- High-strength estradiol creams should not be prescribed with other HRT medicines.

More about the medicines

The estradiol-containing creams covered by this review contain 100 micrograms of estradiol per gram of cream.

They are a type of topical hormone replacement therapy: they contain the female hormone estradiol, used to replace natural estradiol, which declines in the body after menopause. These high-strength estradiol creams have been authorised in the EU for a number of years to treat symptoms of vaginal atrophy in postmenopausal women. They are marketed in Austria, Bulgaria, Croatia, Czech Republic, Estonia, Germany, Hungary, Latvia, Lithuania and Slovakia under the following trade names: Linoladiol, Linoladiol N, Linoladiol Estradiol, Estradiol Wolff and Montadiol.

More about the procedure

The review of high-strength estradiol-containing creams (0.01%) was initiated on 11 April 2019 at the request of the European Commission, under Article 31 of Directive 2001/83/EC.

In 2014, EMA had completed a review of the risk of systemic absorption with high-strength estradiol creams and recommended measures to minimise it, including limiting the use of the creams for up to 4 weeks. However, in March 2019 the Court of Justice of the European Union partially annulled the conclusions of the review on procedural grounds. Although the Court of Justice did not question the scientific conclusions, the partial annulment meant that some of the measures taken to minimise the risk were invalidated.

The current review was carried out by the Pharmacovigilance Risk Assessment Committee (PRAC), the Committee responsible for the evaluation of safety issues for human medicines, which made a set of recommendations. Following a re-examination requested by one of the marketing authorisation holders, the PRAC subsequently confirmed its conclusions for high-strength estradiol creams.

Because these medicines are all authorised at national level, the PRAC recommendations will now be sent to the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh), to make a decision about their implementation. The CMDh is responsible for ensuring

harmonised safety standards for medicines authorised via national procedures across the EU, Iceland, Lichtenstein and Norway.