Four-week limit for use of high-strength estradiol creams

Share

Press release 04/10/2019

EMA’s safety committee ([PRAC](https://www.ema.europa.eu/en/glossary/prac)) has recommended limiting 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 measure is intended to minimise the risk of side effects caused by estradiol absorbed into the bloodstream from creams applied inside the vagina to treat symptoms of vaginal atrophy in women who have been through menopause.

The [PRAC](https://www.ema.europa.eu/en/glossary/prac) has reviewed available data on the safety and effectiveness of high-strength estradiol-containing creams, including data on the amount of estradiol in the blood. These data showed that in postmenopausal women who had used these creams, the levels of estradiol in the blood were higher than normal postmenopausal levels. The [PRAC](https://www.ema.europa.eu/en/glossary/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 the absence of safety data for long-term use of high-strength estradiol creams, the [PRAC](https://www.ema.europa.eu/en/glossary/prac) recommended that these creams should only be used for a single treatment period of a maximum of 4 weeks.

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](https://www.ema.europa.eu/en/glossary/prac) recommendations will now be sent to the [CMDh](https://www.ema.europa.eu/en/glossary/cmdh)1 to make a decision about their implementation. The [CMDh](https://www.ema.europa.eu/en/glossary/cmdh" \t "_blank" \o "Coordination Group for Mutual Recognition and Decentralised Procedures - Human -  the group responsible for the examination and coordination of questions relating to the marketing authorisation of human medicines in two or more Member States in accordance with the mutual recognition or decentralised procedure.   More information can be found under 'Coordination Group for Mutual Recognition and Decentralised Procedures - Human (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 such as blood clots, strokes and certain types of cancer if these creams are used for extended periods.
* Do not use high-strength estradiol cream if you are already taking another HRT (hormone replacement therapy) medicine.
* If you have any questions about your treatment, talk to your doctor or pharmacist.

**Information for healthcare professionals**

* High-strength estradiol creams 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 (100 micrograms/gram) for intravaginal use show substantial 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 i.e. 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 a female hormone estradiol, used to replace natural estradiol hormone, 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% w/w) was initiated on 11 April 2019 at the request of the European Commission, under [Article 31 of Directive 2001/83/EC](https://www.ema.europa.eu/en/human-regulatory/post-authorisation/referral-procedures).

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 EU Court of Justice 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 new review has been carried out by the [Pharmacovigilance Risk Assessment Committee](https://www.ema.europa.eu/en/glossary/pharmacovigilance-risk-assessment-committee) ([PRAC](https://www.ema.europa.eu/en/glossary/prac)), the Committee responsible for the evaluation of safety issues for human medicines, which made a set of recommendations.

Because these medicines are all authorised at national level, the [PRAC](https://www.ema.europa.eu/en/glossary/prac) recommendations will now be sent to the Co-ordination Group for [Mutual Recognition](https://www.ema.europa.eu/en/glossary/mutual-recognition) and [Decentralised Procedures](https://www.ema.europa.eu/en/glossary/decentralised-procedure" \t "_blank" \o "The procedure for authorising medicines in more than one European Union Member State in parallel. It can be used for medicines that do not need to be authorised via the centralised procedure and have not already been authorised in any Member State.   For more information, see the European Commission's Volume 2A -  Procedures for marketing authorisation -  Chapter 2 -  Mutual recognition.) – Human ([CMDh](https://www.ema.europa.eu/en/glossary/cmdh" \t "_blank" \o "Coordination Group for Mutual Recognition and Decentralised Procedures - Human -  the group responsible for the examination and coordination of questions relating to the marketing authorisation of human medicines in two or more Member States in accordance with the mutual recognition or decentralised procedure.   More information can be found under 'Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh)'.)), to make a decision about their implementation. The [CMDh](https://www.ema.europa.eu/en/glossary/cmdh" \t "_blank" \o "Coordination Group for Mutual Recognition and Decentralised Procedures - Human -  the group responsible for the examination and coordination of questions relating to the marketing authorisation of human medicines in two or more Member States in accordance with the mutual recognition or decentralised procedure.   More information can be found under 'Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh)'.) is responsible for ensuring harmonised safety standards for medicines authorised via national procedures across the EU, Iceland, Lichtenstein and Norway.