20 December 2013
EMA/796289/2013

European Medicines Agency recommends restricting use of estradiol-containing creams Linoladiol N and Linoladiol HN

Benefits continue to outweigh risks with new restrictions

The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) has concluded that Linoladiol N and Linoladiol HN, two high-strength estradiol-containing creams used for topical treatment of diseases of the genital area in women who have been through the menopause, may continue to be used with certain restrictions.

The CHMP recommended that Linoladiol N may continue to be used for the treatment of vaginal atrophy due to a lack of oestrogen when previous topical, lower dose oestrogen treatment has failed. For Linoladiol HN, which also contains a weak corticosteroid, prednisolone, the CHMP recommended limiting the use to the treatment of mild, inflammatory skin diseases of the external genital area.

For both creams, the CHMP recommended limiting treatment to a duration of four weeks to minimise the risk of side effects. The CHMP acknowledged that the creams have been used for a long time without serious risks to public health. However, due to the relatively high concentration of estradiol in these creams, there is a risk of estradiol being absorbed systemically (throughout the body). When used long-term, the risks with these creams could be similar to those associated with the use of estradiol in systemic hormone replacement therapy (HRT), which include venous thromboembolism (formation of blood clots in the veins), stroke and endometrial cancer (cancer of the lining of the womb). The CHMP recommended that the product information of these medicines be updated to reflect current knowledge in this area.

The CHMP also recommended that Linoladiol HN should no longer be used to treat lichen sclerosus, another condition affecting the genital area, characterised by small white spots that are often itchy or sore. This is because there is no evidence supporting the use of estradiol in this condition.

The review of Linoladiol N and Linoladiol HN follows a national re-registration procedure for Linoladiol N in Germany, during which the German medicines agency, the Federal Institute for Drugs and Medical Devices (BFARM), re-assessed existing data on the benefits and risks of Linoladiol N and concluded that its benefit-risk balance was unfavourable. Because Linoladiol N is also authorised in other EU

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countries[1], the BFARM subsequently asked the CHMP to carry out an EU-wide review of this medicine. The referral was extended to include Linoladiol HN because it also contains a relatively high dose of estradiol.

The CHMP recommendation will now be sent to the European Commission for the adoption of a final, legally binding decision valid throughout the EU.

Information to patients

The estradiol-containing creams Linoladiol N and Linoladiol HN continue to be available for the treatment of certain diseases of the genital area in women who have been through the menopause. Linoladiol N can be used for vaginal atrophy when other topical treatments containing a lower amount of estradiol have failed and Linoladiol HN can be used for the treatment of mild, inflammatory skin diseases of the external female genital area. However, patients should be aware of the following recommendations:

- Linoladiol N and Linoladiol HN should not be used for more than four weeks. This is to minimise the risk of side effects. The creams contain high amounts of the hormone estradiol which are absorbed into the bloodstream in such amounts that they can affect the body as a whole. When used beyond four weeks the risks could be similar to those associated with the use of estradiol in systemic hormone replacement therapy (HRT), which include venous thromboembolism (formation of blood clots in the veins), stroke, and endometrial cancer.
- Linoladiol N should only be applied into the vagina while Linoladiol HN should be applied to the external genital area.
- In addition, the cream Linoladiol HN should no longer be used to treat lichen sclerosus, another condition affecting the genital area, characterised by small white spots that are often itchy or sore.
- If you have been taking Linoladiol N or Linoladiol HN for longer than four weeks or if you are currently taking Linoladiol HN for lichen sclerosus, you should speak to your doctor at a routine appointment to discuss suitable alternative treatments.
- If you have any questions, you should contact your doctor or pharmacist.

Information to healthcare professionals

- Linoladiol N can continue to be prescribed for the short-term treatment of vaginal atrophy. However, Linoladiol N should only be used when previous topical, lower dose oestrogen treatment has failed. Linoladiol HN can continue to be prescribed for the short-term treatment of acute, mild inflammatory skin diseases of the external genital area in postmenopausal women when weak acting corticosteroids and estradiol are indicated.
- Application beyond four weeks is not recommended, due to possible systemic exposure to estradiol during treatment. With Linoladiol HN, skin atrophy might occur, potentially further increasing systemic exposure to estradiol.
- Doctors should also review patients being treated with Linoladiol N or Linoladiol HN for longer than four weeks.

[1] Linoladiol N is marketed in Bulgaria, Czech Republic, Estonia, Germany, Hungary, Latvia, Lithuania and Slovakia. In Austria Linoladiol N is marketed as Montadiol. Linoladiol HN is marketed in Estonia, Germany, Latvia and Lithuania.

- Doctors should no longer prescribe Linoladiol HN for lichen sclerosus. Doctors should review patients being treated with Linoladiol HN for lichen sclerosus in order to choose an appropriate alternative treatment.

More about the medicine

Linoladiol N (0.01 %w/w) is a cream that contains 100 microgram of estradiol per gram. It had previously been authorised for application into the vagina or vulva to treat atrophic disorders due to oestrogen deficiency in women who have been through the menopause.

Linoladiol HN (0.005 %w/w, 0.4 %w/w) is a cream that contains 50 microgram of estradiol and 4 mg of the corticosteroid prednisolone per gram. It had previously been authorised to be applied to the vulva for short-term treatment of mild, inflamed, burning and itching skin diseases of the external female genital area when weak acting corticosteroids and estradiol are indicated. It had also been authorised in some EU Member States for the treatment of lichen sclerosus, a disease characterised by chronic (long-term) inflammation affecting the skin in the genital area.

During the menopause, the levels of the female hormone oestrogen fall, leading to the absence of menstrual periods. Symptoms include hot flushes and night sweats as well as vaginal dryness (which can be painful and irritating). Linoladiol N and Linoladiol HN are a type of 'hormone replacement therapy': they contain female hormones used to replace the ones the body no longer makes after menopause. Linoladiol N and Linoladiol HN work by replacing oestrogen in the genital area. Linoladiol HN also contains low-dose prednisolone which acts to reduce the inflammation associated with skin diseases of the external female genital area.

Lichen sclerosus is not related to oestrogen deficiency and estradiol containing products are not considered a treatment option for this condition.

Both medicines have been authorised in the EU through national procedures for over 40 years. Linoladiol N is marketed in Bulgaria, Czech Republic, Estonia, Germany, Hungary, Latvia, Lithuania and Slovakia, while Linoladiol HN is marketed in Estonia, Germany, Latvia and Lithuania.

More about the procedure

The review of the topical estradiol-containing medicines Linoladiol N and Linoladiol HN was triggered on 24 May 2012 by Germany, under Article 31 of Directive 2001/83/EC. The German medicines agency asked the CHMP to carry out a full assessment of the benefit-risk balance of these medicines and to issue an opinion on whether their marketing authorisations should be maintained, varied, suspended or withdrawn across the European Union.

The CHMP opinion will now be forwarded to the European Commission, which will issue a final decision in due course.

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