



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 March 2018
EMA/165360/2018

Updated measures for pregnancy prevention during retinoid use

Warning on possible risk of neuropsychiatric disorders also to be included for oral retinoids

The European Medicines Agency (EMA) has completed its review of retinoid medicines, and confirmed that an update of measures for pregnancy prevention is needed. In addition, a warning on the possibility that neuropsychiatric disorders (such as depression, anxiety and mood changes) may occur will be included in the prescribing information for oral retinoids (those taken by mouth).

Retinoids include the active substances acitretin, adapalene, alitretinoin, bexarotene, isotretinoin, tazarotene and tretinoin. They are taken by mouth or applied as creams or gels to treat several conditions mainly affecting the skin, including severe acne and psoriasis. Some retinoids are also used to treat certain forms of cancer.

The review confirmed that oral retinoids can harm the unborn child and must not be used during pregnancy. In addition, the oral retinoids acitretin, alitretinoin and isotretinoin, which are used to treat conditions mainly affecting the skin, must be used in accordance with the conditions of a new pregnancy prevention programme by women able to have children.

Topical retinoids (those applied to the skin) must also not be used during pregnancy, and by women planning to have a baby.

More information is available below.

Regarding the risk of neuropsychiatric disorders, the limitations of the available data did not allow to clearly establish whether this risk was due to the use of retinoids. However, considering that patients with severe skin conditions may be more vulnerable to neuropsychiatric disorders due to the nature of the disease, the prescribing information for oral retinoids will be updated to include a warning about this possible risk. Available data suggest that topical retinoids do not carry a risk of neuropsychiatric side effects, and therefore no additional warnings need to be added to the prescribing information.

The review of retinoids was carried out by EMA's Pharmacovigilance Risk Assessment Committee (PRAC), which assessed the available data including published literature, post-marketing reports of side effects and additional information collected from stakeholder meetings and written submissions.



The EMA's Committee for Medicinal Products for Human use (CHMP) has now endorsed the PRAC recommendations and adopted the Agency's final opinion. The CHMP opinion will be sent to the European Commission, which will take a final legally binding decision valid across the EU.

Information for patients

- Retinoid medicines, used mainly to treat conditions affecting the skin such as severe acne, are harmful to the unborn baby if taken during pregnancy.
- Oral (taken by mouth) retinoids must not be used during pregnancy.
- In addition, the oral retinoids acitretin, alitretinoin and isotretinoin must not be taken by women able to have children unless the conditions of a special pregnancy prevention programme are met.
- The pregnancy prevention programme for acitretin, alitretinoin and isotretinoin will include:
 - pregnancy tests before, during and after stopping treatment;
 - the need to use at least one effective method of contraception during and after treatment;
 - an 'acknowledgement form' to confirm that appropriate advice has been given to patients;
 - a 'patient reminder card' stating that the medicine must not be used during pregnancy, and including information about pregnancy testing and the need to use effective contraception.
- The above information will also be included in the package leaflet, and a boxed warning will be added to the outer packaging.
- Topical (applied to the skin) retinoids are less likely to cause harm to the unborn child. However, as a precaution, they must not be used during pregnancy and by women planning to have a baby.
- With oral retinoids, there may be a possible risk of disorders such as depression and anxiety. Warnings will be included in the package leaflet of oral retinoids, as well as signs and symptoms that patients and their families should look out for (such as changes in mood or behaviour).
- Patients who have any questions should speak to their doctor or pharmacist.

Information for healthcare professionals

A review of available data on teratogenicity and neuropsychiatric disorders with retinoid medicines has concluded that there is the need to strengthen the recommendations for pregnancy prevention and to raise awareness about possible neuropsychiatric risks.

- Oral retinoids (acitretin, alitretinoin, bexarotene, isotretinoin and tretinoin) are highly teratogenic and must not be used during pregnancy.
- Acitretin, alitretinoin and isotretinoin must be used in accordance with the conditions of a pregnancy prevention programme (PPP) for all women of childbearing potential. These include:
 - an assessment of each woman's potential for becoming pregnant;
 - pregnancy tests before starting treatment, during treatment and after treatment;
 - the need for at least one effective method of contraception during and after treatment;
 - a 'risk acknowledgement form' for patients and prescribers to go through and confirm that appropriate advice has been given and understood.

- For bexarotene and oral tretinoin it is considered that, in the light of the target population and an oncological indication subject to specialist care in the hospital setting, the implementation of a PPP is not necessary.
- Updated educational material will be provided to guide the discussion about the risks of oral retinoids before prescribing acitretin, alitretinoin and isotretinoin to women of childbearing potential.
- For topical retinoids (adapalene, alitretinoin, isotretinoin, tazarotene and tretinoin), the available data show that systemic absorption is negligible following topical application and that these products are unlikely to cause fetal harm. However, as a precaution, topical retinoids are contraindicated in pregnant women and in women planning a pregnancy.
- Cases of depression, depression-aggravated anxiety and mood alterations have been reported rarely in patients taking oral retinoids. Evidence from published literature and individual case reports is conflicting, and many published studies have a number of limitations. On this basis, it has not been possible to identify a clear increase in the risk of neuropsychiatric disorders in people who take oral retinoids compared to those that do not.
- However, since severe skin disorders themselves increase the risk of psychiatric disorders, a warning about this possible risk is being included in the product information for oral retinoids.
- Patients taking oral retinoids should be advised that they may experience changes in their mood and/or behaviour and that they and their families should be alert to this, and speak to their doctor if this occurs.
- Patients treated with oral retinoids should be monitored for signs and symptoms of depression and referred for appropriate treatment, if necessary. Particular care should be taken in patients with history of depression.
- For topically applied retinoids (adapalene, alitretinoin, isotretinoin, tazarotene and tretinoin), systemic absorption is negligible, and unlikely to result in psychiatric disorders.
- Further information will be available at national level in due course as the recommendations are implemented.

More about the medicine

Retinoids are vitamin A derivatives that are available as capsules to be taken by mouth or as creams and gels to be applied to the skin. Retinoids taken by mouth are used to treat various forms of severe acne, severe hand eczema that does not respond to treatment with corticosteroids, severe forms of psoriasis and other skin conditions, and certain types of cancer. Retinoids applied to the skin are used to treat various skin conditions including mild to moderate acne.

The following retinoids have been authorised nationally in a number of Member States of the EU and are covered by this review: acitretin, adapalene, alitretinoin, isotretinoin, tazarotene and tretinoin. Alitretinoin has also been authorised centrally as Panretin for the treatment of skin lesions in AIDS patients with Kaposi's sarcoma (a type of skin cancer). Bexarotene has been authorised centrally as Targretin for the treatment of cutaneous T-cell lymphoma (CTCL, a rare cancer of the lymph tissue).

More about the procedure

The review of retinoid medicines was initiated on 8 July 2016 at the request of the United Kingdom, under [Article 31 of Directive 2001/83/EC](#).

The review was first 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. The PRAC recommendations were sent to the Committee for Medicinal Products for Human Use (CHMP), responsible for questions concerning medicines for human use, which adopted the Agency's opinion.

The CHMP opinion will now be forwarded to the European Commission, which will issue a final legally binding decision applicable in all EU Member States in due course.