
Retinoid Containing Medicines: Pregnancy prevention recommended in women who start retinoids and prescribing information to be updated with possible risk of neuropsychiatric disorders

16.05.18 | Circular Number P05/2018

Information on Retinoid containing medicines

- 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
- Oral retinoids 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
- Topical retinoids are used to treat various skin conditions including mild to moderate acne

Most retinoids have been authorised nationally except for Panretin (alitretinoin) that has been authorised centrally for the treatment of skin lesions in AIDS patients with Kaposi's sarcoma (a type of skin cancer) and Targretin (bexarotene) that has been authorised centrally for the treatment of the visible signs on the skin of cutaneous T-cell lymphoma (CTCL, a rare cancer of the lymph tissue).

In Malta the following products are authorised through various licensing procedures:

| Active Ingredients | Product Name | Pharmaceutical Form | Classification | Authorisation Number | MAH/license holder |
|--------------------|-------------------|---------------------|----------------|----------------------|----------------------------------|
| Acitretin 10 mg | Neotigason | Capsule | POM | MA628/04101 | Actavis Group PTC ehf |
| Acitretin 25 mg | Neotigason | Capsule | POM | MA628/04102 | Actavis Group PTC ehf |
| Acitretin 25 mg | Acitretin 25mg | Capsule | POM | AA085/00601 | Genus Pharmaceuticals Limited |
| Isotretinoin 10mg | Decutan 10mg | Soft capsule | POM | MA628/17401 | Actavis Group PTC ehf |
| Isotretinoin 20mg | Decutan 20mg | Soft capsule | POM | MA628/17402 | Actavis Group PTC ehf |
| Isotretinoin 10mg | Isotretinoin 10mg | Capsule | POM | AA908/13201 | NeoFarma Pharmaceuticals Limited |

| Active Ingredients | Product Name | Pharmaceutical Form | Classification | Authorisation Number | MAH/license holder |
|---|--------------------|---------------------|----------------|----------------------|-------------------------------------|
| Isotretinoin 20mg | Isotretinoin 20mg | Capsule | POM | AA908/13202 | NeoFarma Pharmaceuticals Limited |
| Isotretinoin 10mg | Contracne 10mg | Soft capsule | POM | AA1106/00401 | Laboratoires Bailleul S.A. |
| Isotretinoin 20mg | Contracne 20mg | Soft capsule | POM | AA1106/00402 | Laboratoires Bailleul S.A. |
| Tretinoin 0.05 percent | Ketrel 0.05% cream | Cream | POM | AA1106/00101 | Laboratoires Bailleul S.A. |
| Tretinoin 10mg | Tretinoin 10mg | Soft capsule | POM | AA565/28501 | Central Procurement & Supplies Unit |
| Adapalene 0.1 percent w/w | Differine | Cream | POM | MA117/00201 | Galderma International |
| Adapalene 0.1 percent w/w | Differine | Gel | POM | MA117/00202 | Galderma International |
| Adapalene 1 mg/gm Benzoyl peroxide 25 mg/gm | Epiduo gel | Gel | POM | MA117/01202 | Galderma International |
| Alitretinoin 0.1 % gel | Panretin | Gel | POM | EU/1/00/149/001 | Eisai Ltd |
| Bexarotene 75 mg | Targretin | Soft capsules | POM | EU/1/01/178/001 | Eisai Ltd. |

Information from the EMA's review on retinoid containing medicines

The European Medicines Agency (EMA) has completed the 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.

- **Oral retinoids (taken by mouth) can harm the unborn child and must not be used during pregnancy**
- Topical retinoids (applied to the skin) are not recommended to be used during pregnancy, and by women planning to have a baby.
- The conditions of a new pregnancy prevention programme should be respected by women able to have children treated with the oral retinoids acitretin, alitretinoin and isotretinoin

- Available data on the risk of neuropsychiatric disorders are limited, but the prescribing information for oral retinoids will be updated to include a warning about this possible risk. For topical retinoids, no additional warning is required.

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

In Malta

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
- 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 foetal 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. 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 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 in due course as the recommendations are implemented in Malta

In addition, DHPC letter will be issued to HCPs in Malta in due course. Archived DHPCs can be found on the Medicines Authority website on <http://www.medicinesauthority.gov.mt/dhpc>.

Advice 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. If you are planning to have a baby, you must not use oral retinoids.
- You must not start a treatment with the oral retinoids acitretin, alitretinoin and isotretinoin unless the conditions of a special pregnancy prevention programme (PPP) are met. Information related to the PPP will be included in the package leaflet, and a boxed warning will be added to the outer packaging.
- If you are under treatment with acitretin, alitretinoin and isotretinoin, you must:
 - Do a pregnancy test before, during and after stopping treatment;
 - Use at least one effective method of contraception during and after treatment.
 - Sign an acknowledge form stating that you received all the relevant information related to the PPP from your doctor.

You will receive a patient reminder card stating that the medicine must not be used during pregnancy, including information about pregnancy testing and the need to use effective contraception.

- Topical (applied to the skin) retinoids are less likely to cause harm to the unborn child. However, as a precaution, the recommendation is not to use topical retinoids during pregnancy and by women planning to have a baby.
- If you have history of depression or you notice change in your behavior (changes in mood or behavior or signs of depression and/or anxiety), speak to your doctor or pharmacist.

For more information please see the European Medicines Agency's [webpage on the retinoids review](#)

Reporting Adverse Drug Reactions

Healthcare professionals and patients are encouraged to maintain vigilance on retinoids containing medicines. Suspected Adverse Drug Reactions (side effects) may be reported using the Medicines Authority Form (available from <http://www.medicinesauthority.gov.mt/adrportal>) and sent by mail to Medicines Authority, Sir Temi Żammit Buildings, Malta Life Sciences Park, San Ġwann SĠN 3000 or email to postlicensing.medicinesauthority@gov.mt or to the marketing authorisation holders or their local representatives.

Post-Licensing Directorate
Medicines Authority

Healthcare professionals and patients are encouraged to regularly check the Medicines Authority website for product safety updates as these are issued on an ongoing basis.

Feedback Form

The Medicines Authority thanks you for the time taken to read this safety circular. The dissemination of safety circulars is an important process whereby Regulatory Authorities can communicate important issues with respect to the safety of medicines, in order to protect and enhance public health

The Medicines Authority kindly invites your anonymous feedback about the regulatory action being communicated. This may be returned by folding this form (address side up), stapling the ends and then posting (no stamp required)

Feedback:

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Pharmacovigilance Section

Post-Licensing Directorate

Medicines Authority

Sir Temi Zammit Buildings

Malta Life Sciences Park

San Ġwann SĠN 3000