

Direct Healthcare Professional Communication

June 2019

Retinoids▼ (Acitretin, Adapalene, Alitretinoin, Bexarotene*, Isotretinoin, Tretinoin*, and Tazarotene): risk of teratogenicity and neuropsychiatric disorders

Updated Pregnancy Prevention Programme (PPP) materials to support safe use of oral acitretin, alitretinoin, and isotretinoin in women of childbearing potential

Dear Healthcare professional,

Marketing authorisation holders of retinoid medicines (see list below), in agreement with the European Medicines Agency and the Medicines and Healthcare product Regulatory Agency, would like to inform you of the following:

Summary

Teratogenicity

- Oral retinoids are highly teratogenic and must not be used during pregnancy
- The oral retinoids acitretin, alitretinoin, and isotretinoin must only be used in accordance with the conditions of a Pregnancy Prevention Programme (PPP) in women and girls of childbearing potential – materials to support the PPP for each product have been updated (see links below) and hard copies are being sent to prescribers and pharmacists
- Please dispose of your existing items and replace with the updated versions
- As a precaution and because a risk cannot be excluded, topical retinoids are also contraindicated in pregnant women and in women planning a pregnancy

Neuropsychiatric disorders

- Cases of newly diagnosed depression, worsening of existing depression, and anxiety have been reported with oral retinoids
- Advise patients taking oral retinoids that they may experience changes in their mood and/or behaviour and that they should speak to their doctor if their mood is affected
- Patients should be encouraged to let family and friends know they are taking a retinoid medicine so they can look out for any change in mood
- Monitor all patients treated with oral retinoids for signs of depression or suicidal ideation and refer for appropriate treatment, if necessary. Special care should be taken in patients with history of depression

* The oral retinoids bexarotene and tretinoin are licensed for oncology indications and formal PPP materials are not required.

Background on the safety concern

Retinoid-containing medicinal products are available in oral and topical forms. They are widely used to treat a range of conditions, mainly those affecting the skin such as severe acne, severe chronic hand eczema unresponsive to corticosteroids, and severe forms of psoriasis.

Following a recent in-depth review of all the available data on the effectiveness of pregnancy prevention measures and the risk of neuropsychiatric reactions, updated Pregnancy Updated Prevention Programme materials are available (a prescriber checklist, a patient card to be given to the patient by the prescriber, and a pharmacist checklist) and up-to-date and consistent advice is available in the Summary of Product Characteristics on the risk of teratogenicity and neuropsychiatric reactions associated with all oral retinoids.

Teratogenic risk – oral retinoids

Oral retinoids (acitretin, alitretinoin, bexarotene, isotretinoin, and tretinoin) are highly teratogenic.

There is an extremely high risk that foetal exposure to isotretinoin will result in life-threatening congenital abnormalities. Any use of oral acitretin, alitretinoin, and isotretinoin in women and girls of childbearing potential must be in accordance with the conditions of a Pregnancy Prevention Programme.

Oral tretinoin (Vesanoid) is indicated for promyelocytic leukaemia and oral bexarotene (Targretin) is indicated for cutaneous of T Cell lymphoma; these two products do not have associated Pregnancy Prevention Programme materials due to the oncological indications. However, the Summary of Product Characteristics for both products emphasise they must not be used in pregnancy and for oral tretinoin states that that pregnancy prevention measures should be considered depending on the severity of the disease and urgency of treatment.

The Pregnancy Prevention Programme materials for oral retinoids have been streamlined and harmonised to provide clear and concise information for both healthcare professionals and patients. The conditions of the Pregnancy Prevention Programme require prescribers to ensure that every woman and girl taking oral retinoids understands that:

- oral retinoids are highly likely to harm an unborn baby and should not be taken during pregnancy;
- any use of acitretin, alitretinoin, and isotretinoin in women and girls of childbearing potential should be in accordance with a Pregnancy Prevention Programme;
- she must consistently and correctly use one highly effective method of contraception (ie, a user-independent form) or two complementary user-dependent forms of contraception, for at least 1 month before the start of treatment, throughout the treatment period, and for at least 1 month (3 years for acitretin) after stopping treatment;
- she needs regular follow-up and pregnancy testing (ideally monthly) and that negative pregnancy test results will need to be obtained before, during and 1 month after the end of treatment (3 years for acitretin with 1–3 monthly intervals recommended). The dates and results of pregnancy tests should be documented.
- she should consult a doctor urgently if she becomes pregnant or thinks she may be pregnant.

New PPP materials – oral retinoids

The materials now consist of a

- prescriber checklist for dermatologists or prescribing GPs with an extended role in dermatology or dermatology specialist nurses
- a patient card to be given to the patient by the dermatologist, prescribing GP or dermatology specialist nurses.
- a pharmacist checklist to act as an aide memoire for when dispensing retinoids

New materials are available in electronic form at <https://www.medicines.org.uk/emc> and hard copy distribution has started.

Teratogenic risk – topical retinoids

Systemic exposure is thought to be negligible following application of topical retinoids (topical adapalene, alitretinoin, isotretinoin, tazarotene, and tretinoin) during pregnancy. However, as a precaution, use of topical retinoids is contraindicated during pregnancy. Women should be advised not to use topical retinoids if they are planning a pregnancy.

Neuropsychiatric disorders – oral retinoids

Depression, worsening of existing depression and anxiety, and mood alterations have been reported in patients taking oral retinoids. However, it has not been possible to identify a clear increase in the risk of psychiatric disorders in people taking oral retinoids compared to those that do not.

It is recommended that patients taking oral retinoids are advised of the possibility that they may experience changes in their mood and behaviour and that they should speak to their doctor if their mood is affected. Any patient who shows signs of depression should be referred for appropriate treatment, as necessary. Special attention should be paid to patients treated with oral retinoids with a history of depression and all patients should be monitored for signs of depression or suicidal ideation.

Advise the patient to tell their family and friends that they are taking a retinoid and that it might affect their mood and so to look out for any changes in mood or behaviour.

Neuropsychiatric disorders – topical retinoids

For topical retinoids (adapalene, alitretinoin, isotretinoin, tazarotene, and tretinoin), data reviewed show systemic exposure is negligible following topical application and is unlikely to result in an increased risk of psychiatric disorders.

Call for reporting

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.

Please continue to report suspected adverse drug reactions (ADRs) to the MHRA through the Yellow Card Scheme. It is easiest and quickest to report ADRs online via the Yellow Cards website - <https://yellowcard.mhra.gov.uk/> or via the Yellow Card app available from the Apple App Store or Google Play Store.

Alternatively, prepaid Yellow Cards for reporting are available by writing to FREEPOST YELLOW CARD (no other address details necessary); by emailing yellowcard@mhra.gov.uk; at the back of the British National Formulary (BNF); by telephoning the Commission on Human Medicines (CHM) free phone line: 0800-731-6789; or by downloading and printing a form from the Yellow Card website.

Company contact point

The following Marketing Authorisation Holders will be acting as contact points for Risk Minimisation materials for the named medicinal products as part of a work-sharing arrangement.

Isotretinoin	Roche Products Limited Hexagon Place, 6 Falcon Way, Shire Park, Welwyn Garden City, Hertfordshire, AL7 1TW	Medical Information: +44 (0)800 328 1629 medinfo.uk@roche.com For ordering hard copy materials: +44 (0)370 703 0602 oralisotretinoinppp@linney.com
Acitretin	Teva UK Limited Field House, Station Approach, Harlow, Essex, CM20 2FB	Medical Information: +44 (0)207 540 7117 medinfo@tevauk.com
Alitretinoin	Stiefel, a GSK company Stockley Park West, Uxbridge, Middlesex, UB11 1BT	Medical Information: +44 (0)800 221 441 ukmedinfo@gsk.com For ordering hard copy materials: www.gskpro.com/en-gb/resources/