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Direct Healthcare Professional Communication

Retinoids (Acitretin, Adapalene, Alitretinoin, Bexarotene, Isotretinoin, Tazarotene and Tretinoin) - Update on teratogenicity and neuropsychiatric disorders

Dear Healthcare professional,

Actavis International Ltd, Central Procurement & Supplies Unit (CPSU), Eisai Ltd, Galderma International, Genus Pharmaceuticals Ltd, Laboratoires Bailleul S.A. and Neofarma Pharmaceuticals Limited in agreement with the European Medicines Agency and the Malta Medicines Authority 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 be used in accordance with the conditions of a Pregnancy Prevention Programme (PPP) for all women of childbearing potential.
- Discuss the risks of oral retinoid-containing medicines with women before prescribing acitretin, alitretinoin and isotretinoin, using the revised and streamlined educational materials.
- Topical retinoids are also contraindicated in pregnant women and in women planning a pregnancy as a precaution.

Neuropsychiatric disorders

- Cases of depression, depression-aggravated anxiety, and mood alterations have been reported rarely in patients taking oral retinoids.
- Advise patients taking oral retinoids that they may experience changes in their mood and/or behaviour and that they and their families should be alert to this and should speak to their doctor if this occurs.
- Monitor all patients treated with oral retinoids for signs and symptoms of depression and refer for appropriate treatment, if necessary. Special care should be taken in patients with history of depression.

Background on the safety concern

Retinoid-containing medicinal products are available in oral and topical forms and are widely used to treat various forms of acne, severe chronic hand eczema unresponsive to corticosteroids, severe forms of psoriasis and keratinisation disorders. Tretinoin may also be used to treat promyelocytic leukaemia, and bexarotene is used in the treatment of skin manifestations of advanced stage cutaneous T-cell lymphoma. Following a recent in-depth review of all relevant data, the Pharmacovigilance Risk Assessment Committee has strengthened information provided to patients and healthcare professionals (through the product information and educational materials) on teratogenicity and neuropsychiatric disorders.

Teratogenic risk

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

Use of acitretin, alitretinoin and isotretinoin in women of child bearing potential must be in accordance with the conditions of a Pregnancy Prevention Programme (PPP). For bexarotene and oral tretinoin, it is considered that in light of the oncological indications, subject to specialist care in the hospital setting and the target population, the currently existing measures are appropriate and therefore the implementation of a PPP is not necessary.

The review also evaluated the available data on the safety of the topical retinoids (adapalene, alitretinoin, isotretinoin, tazarotene and tretinoin) during pregnancy. The data show that systemic exposure is negligible following topical application and these products are unlikely to result in adverse foetal outcomes. However, it is also recognised that humans are amongst the most sensitive species with respect to retinoid toxicity. On this basis, it was considered that a precautionary approach is advisable and that use of topical retinoids should be contraindicated during pregnancy and in women planning a pregnancy.

Neuropsychiatric disorders

Depression, depression-aggravated anxiety, and mood alterations have been reported in patients treated with oral retinoids. The available evidence from published literature and individual case reports shows conflicting study results and the published studies suffer from a number of limitations. Therefore, it has not been possible to identify a clear increase in risk of psychiatric disorders in people who take oral retinoids compared to those that do not. Furthermore, it is recognised that patients with severe skin disorders are themselves at an increased risk of psychiatric disorders. It is recommended that patients who are 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 this happens. Any patient who shows signs of depression should be referred for appropriate treatment, as necessary. Special attention should be given to patients treated with oral retinoids with a history of depression and all patients should be monitored for signs of depression.

The review also evaluated the available data in relation to the topical retinoids (adapalene, alitretinoin, isotretinoin, tazarotene and tretinoin). The data support that following topical application systemic exposure is negligible and unlikely to result in a risk of psychiatric disorders.

The product information will be updated to include the results of this review. The educational materials for oral retinoids are going to be prepared and distributed to prescribing physicians, dispensing pharmacists and patients.

Call for reporting

Healthcare professionals are reminded to continue to report suspected adverse reactions associated with retinoid containing medicines in accordance with the national spontaneous reporting system. Any suspected adverse reactions and medication errors can be reported via the national Adverse Drug Reactions (ADRs) reporting system. Report forms can be downloaded from www.medicinesauthority.gov.mt/adrportal and posted to Post-licensing directorate, Medicines Authority, Sir Temi Żammit Buildings, Malta Life Sciences Park, San Ġwann SĠN 3000, Malta or sent by email to postlicensing.medicinesauthority@gov.mt

Company contact point

If you have further questions or require additional information please contact:

Company/ MAH	Product name	Email	Phone
Genus Pharmaceuticals Ltd.	Acitretin 25mg capsules	*Medical Information Team* thorntonross@medinformation.co.uk *Regulatory Team* reg@thorntonross.com	*Telephone* +44 (0)1484842217 *Medical Information Direct Line* +44 (0)1484 848164 *Customer Care direct line* +44 (0)1484 848200
CPSU	Tretinoin 10mg soft capsules	richard.despott@gov.mt	+356 23439150
Actavis International Ltd.	Decutan 10mg soft capsules Decutan 20mg soft capsules Neotigason 10mg Neotigason 25mg	PHVMALTA@actavis.com	+30 211 8805166
Galderma International	Differin Cream Differin Gel Epiduo Gel	aparis@prohealth.com.mt	+356 23385313
Eisai Ltd. *Local representative* Associated Drug Co. Ltd	Panretin Gel Targretin Capsules	kzammit@adc.com.mt	+356 22778000
Laboratoires Bailleul S.A. *Local representative* Metropolis Pharma	Contracne 10 mg, soft capsule Contracne 20 mg, soft capsule Ketrel 0,05%, cream	vigilances@bailleul.com	*Office hours* +356 2143 3330 *Out of office hours* +356 9942 6611
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Yours faithfully,

Post-Licensing Directorate
Medicines Authority

Disclaimer

This Direct Healthcare Professional Communication has been submitted to you on behalf of Actavis International Ltd, Central Procurement & Supplies Unit (CPSU), Eisai Ltd, Galderma International, Genus Pharmaceuticals Ltd, Laboratoires Bailleul S.A. and Neofarma Pharmaceuticals Limited together with local representatives

Annex – Conditions of the Pregnancy Prevention Programme (PPP) for the oral retinoids acitretin, alitretinoin and isotretinoin

- The Pregnancy Prevention Programme for oral retinoids has been streamlined and harmonised to provide clear and concise information for both healthcare professionals and patients. Any use of acitretin, alitretinoin and isotretinoin in female patients at risk of pregnancy should be in the context of a Pregnancy Prevention Programme. The conditions of the Pregnancy Prevention Programme require prescribers to ensure that every female patient understands that: **oral retinoids pose a risk to an unborn baby and should not be taken during pregnancy;**
- she must use effective contraception without interruption for at least one month before initiating therapy, throughout treatment and for 1 month (1-3 monthly intervals within 3 years for acitretin) after stopping treatment;
- she understands the need and accepts to undergo regular follow-up and pregnancy testing before, ideally monthly during treatment and 1 month after stopping treatment (1–3 monthly intervals within 3 years after stopping acitretin)
- she must stop taking acitretin, alitretinoin or isotretinoin immediately and consult a doctor urgently if she becomes pregnant or thinks she may be pregnant.