

## Direct Healthcare Professional Communication

10<sup>th</sup> December 2018

### **Retinoids (Acitretin, Adapalene, Alitretinoin, Bexarotene, Isotretinoin, Tretinoin and Tazarotene) – update on teratogenicity and neuropsychiatric disorders**

Dear Healthcare Professional,

In agreement with the European Medicines Agency and the Health Products Regulatory Authority (HPRA), the companies listed below 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***

Suspected adverse reactions should be reported to the HPRA using a Yellow Card obtained either from the HPRA, or electronically via the website at [www.hpra.ie](http://www.hpra.ie). Adverse reactions can also be reported to the HPRA by calling (01) 676 4971.

The oral retinoids, acitretin, alitretinoin and isotretinoin, will be subject to additional monitoring in the EU. The marketing authorisation holders of these medicinal products will conduct a drug utilisation study to evaluate and quantify the effectiveness of the Pregnancy Prevention Programme.

### ***Company contact point***

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

Company	Product name	INN	Email	Phone	Fax
Roche Products (Ireland) Limited	Roaccutane ▼	isotretinoin	ireland.drug_surveillance_centre@roche.com	+353 (0)1 4690700	+353 (0)1 4690793
Mylan IRE Healthcare Limited	Treclin	tretinoin	info.uk@mylan.co.uk	+44 (0)1707 853000	N/A
Teva Pharmaceuticals Ireland	Neotigason ▼	acitretin	medinfo@tevauk.com	+44 (0)20 7540 7117	+44 (0)20 7540 7349
Galderma (UK) Limited	Differin	adapalene	medinfo.uk@galderma.com	+44 1923 208950	+44 1923 208998
	Epiduo	adapalene			
Eisai Limited	Targretin	bexarotene	EUMedInfo@eisai.com	+44 (0)845 676 1400	N/A
	Panretin	alitretinoin			

▼ 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. Details of how to report can be found in the section call for reporting.

The relevant product information is available on [www.medicines.ie](http://www.medicines.ie), [www.hpra.ie](http://www.hpra.ie) or [www.ema.europa.eu/ema](http://www.ema.europa.eu/ema).

Yours sincerely,



Dr. Michal Starnawski  
Medical Director (Roche)



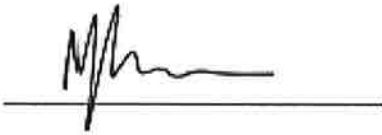
Balwant Heer

EEA QPPV & VP Global Product Safety and Risk Management (Mylan)



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John Holmes  
Director Medical Services UK & Ireland (Teva)



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Dr Navin Chohan  
Medical Director UK & Ireland (Galderma)



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Shaeed Chowdhury  
Medical Director, UK & Ireland (Eisai)

## **Annex - Conditions of the 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 1 month before initiating therapy, throughout treatment, and for 1 month (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 should stop taking acitretin, alitretinoin or isotretinoin immediately and consult a doctor urgently if she becomes pregnant or thinks she may be pregnant.