August 2025

HPRA DRUG SAFETY NEWSLETTER

120TH EDITION

In this edition

Oral retinoids (acitretin and isotretinoin): Psychiatric disorders and pregnancy prevention programme reminder

Key Messages

- **Psychiatric disorders:**
  - Psychiatric disorders have been reported in patients treated with oral retinoids.
  - Healthcare professionals are reminded that all patients should be monitored for signs of depression and referred for appropriate treatment if necessary. Particular care should be taken in patients with a history of depression.
- **Pregnancy prevention programme:**
  - Oral retinoids are highly teratogenic and associated with a high frequency of severe and life-threatening birth defects, as well as increased incidence of spontaneous abortion.
  - Healthcare professionals are reminded that use of oral retinoids is strictly contraindicated in pregnancy and in women of childbearing potential unless the conditions of the pregnancy prevention programme (PPP) are met.
  - Recent studies conducted in several other European countries suggested variability in adherence to key PPP conditions; pregnancies continue to occur in women treated with oral retinoids.

Oral retinoids, including acitretin and isotretinoin*, are authorised in Ireland to treat various dermatological conditions, including severe forms of acne, psoriasis, congenital ichthyosis, keratosis follicularis and lichen planus.

This article highlights key points from regulatory recommendations concerning the use of these products. A reminder of existing warnings related to psychiatric disorders as well as findings from studies evaluating the effectiveness of pregnancy prevention programmes** implemented for oral retinoids are included. For full details, please refer to the product information for the specific medicine, including the Summary of Product Characteristics.*

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Psychiatric disorders

Product information for oral retinoids includes a warning on psychiatric disorders.

The warning followed EU-wide reviews of this safety concern in 2003 and again in 2018. The 2018 review acknowledged the limitations of the available data, including that the body of evidence did not allow for a clear establishment of whether reports of psychiatric disorders were due to the use of oral retinoids. However, given the intended patient population and considering that patients with severe skin conditions may be more vulnerable to psychiatric disorders due to the nature of the disease, the product information for oral retinoids includes a warning about this possible risk and provides advice to healthcare professionals and patients.

A further routine review of national and EU-level pharmacovigilance data from recent years indicates that psychiatric adverse reactions associated with oral retinoids continue to be reported. This includes cases of completed suicide associated with isotretinoin. Therefore, the HPRA is highlighting the existing warning to reinforce awareness amongst healthcare professionals of the importance of discussing potential psychiatric risks with patients before, during, and in the case of isotretinoin, after treatment.

Information for Healthcare professionals

- Cases of depression, depression aggravated, anxiety, mood alterations and psychotic symptoms have been reported in patients taking systemic retinoids.
- Additionally, aggressive tendencies, suicidal ideation, suicide attempts, and suicide have been reported in patients treated with isotretinoin.
- All patients should be monitored for signs of depression and referred for appropriate treatment if necessary.
- Particular care is advised in patients with a history of depression.
- Awareness by family or friends may be useful in detecting mental health deterioration.
- For patients treated with isotretinoin, discontinuation of treatment may be insufficient to alleviate symptoms, and further psychiatric or psychological evaluation may be necessary.
- Refer patients to the package leaflet that comes with the medicine pack or is accessible online when prescribing these medicines and discuss any questions or concerns that they may have.

Pregnancy prevention programme

A pregnancy prevention program is in place for oral retinoids approved for use in Ireland, which incorporates strengthened measures recommended following a 2018 EU-wide review. To evaluate the strengthened measures, companies marketing these medicines had to conduct a drug utilisation study (DUS) along with a survey of healthcare professionals and patients or caregivers.

Studies on the effectiveness of strengthened measures

Results of the survey, conducted in seven European countries (France, Germany, Greece, Norway, Poland, the UK and Spain), indicate that both healthcare professionals and patients/caregivers are aware of the teratogenic risks of oral retinoids and the conditions of the pregnancy prevention programme.

However, the survey findings, together with the DUS (conducted in France, Germany, Sweden and Spain), suggest that these medicines may not always be prescribed and used in full alignment with the conditions of the pregnancy prevention programme, particularly with respect to medically supervised pregnancy testing and contraceptive use. Furthermore, pregnancies continued to occur in women treated with oral retinoids.

These results must be interpreted in the context of the studies' limitations, including the possibility of incomplete information on markers of adherence in the data sources used, leading to an underestimation of actual compliance within the DUS and response biases, which may impact the generalisability of the survey findings.

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In Ireland, a separate survey[1] evaluating the awareness, knowledge, and practice of specialists, GPs, and community pharmacists following the implementation of the strengthened pregnancy prevention measures for isotretinoin was conducted in 2019. Amongst survey respondents, the results of the survey were as follows:

- High awareness amongst all healthcare professional groups that isotretinoin is contraindicated in women of childbearing potential unless the conditions of the pregnancy prevention program are fulfilled.
- Lower awareness among GPs and community pharmacists that exposure during pregnancy can cause spontaneous abortions, as well as severe foetal malformations.
- Limited provision and utilisation of the patient reminder card to support patient counselling for women of childbearing potential.

Key conditions of the pregnancy prevention programme

Oral retinoids are powerful human teratogens that can induce a high frequency of severe and life-threatening birth defects. They are also associated with an increased incidence of spontaneous abortion.

Oral retinoids are strictly contraindicated in pregnant women and in women of childbearing potential unless the conditions of the pregnancy prevention programme are met. If pregnancy does occur during or after treatment (after one month for isotretinoin/after three years for acitretin), there is a great risk of very severe and serious malformations of the foetus. Oral retinoids are also contraindicated in women who are breastfeeding due to the potential for side effects in the exposed child.

If pregnancy occurs in a woman treated with oral retinoids, treatment must be stopped, and the patient should be referred to a physician specialised or experienced in teratology for evaluation and advice.

To minimise these risks, the pregnancy prevention programme includes an assessment of the potential for pregnancy in females of childbearing potential. Prescribers must discuss the following information with females of childbearing potential:

- **Teratogenicity:** Prescribers must ensure that women of childbearing potential understand the teratogenic risk and the need to follow the conditions of the pregnancy prevention programme while taking oral retinoids. Patients should understand the need to rapidly consult their doctor if there is a risk of pregnancy.
- **Contraception:** Prescribers must ensure women of childbearing potential understand the importance of consistent and correct use of effective contraception. Effective contraception should be used before, during and after treatment, unless the prescriber considers there are compelling reasons to indicate there is no risk of pregnancy.
- **Follow-up visits, pregnancy testing and monthly prescriptions:** Prescribers must ensure women of childbearing potential understand the need for regular follow-up visits and negative pregnancy test results before, during and after the end of treatment (for 1 month after isotretinoin, and periodically for 3 years after acitretin). To support this, prescriptions should ideally be limited to 30 days.

Contraception

Female patients must be provided with comprehensive information on pregnancy prevention and if they are not using effective contraception, they should be provided with/referred for contraceptive advice.

Individual circumstances should be evaluated in each case when choosing the contraception method, involving the patient in the discussion, to guarantee her engagement and compliance with the chosen measures.

As a minimum requirement, female patients of childbearing potential must be in agreement to use at least one highly effective method of contraception (e.g. a user-independent form such as an intra-uterine device or implant), or two complementary user-dependent forms of contraception (e.g. an oral hormonal contraceptive and barrier method). Contraception should be used for at least 1 month prior to starting treatment, throughout treatment and continue for at least 1 month after stopping treatment with isotretinoin, and for at least 3 years after stopping treatment with acitretin, due to the persisting risk.

These conditions apply to all females of childbearing potential, including those with amenorrhea or who are not currently sexually active, unless the prescriber considers there are compelling reasons to indicate there is no risk of pregnancy, as provided for in product information.*

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Prescription duration and dispensing

To support regular follow-up, including pregnancy testing and monitoring, the prescription duration for women of childbearing potential should be limited to 30 days. Ideally, pregnancy testing, issuing a prescription, and dispensing should occur on the same day. Dispensing of isotretinoin and acitretin should occur within a maximum of 7 days of the prescription.

Male patients

Healthcare professionals should remind male patients that they must not share their medication with anyone, particularly not females. Available data suggest the levels of oral retinoid in the semen of men taking isotretinoin or acitretin are too low to be associated with teratogenic effects.

Other precautions

Healthcare professionals should remind patients never to share their oral retinoids with another person, and to return any unused medicine to their pharmacist at the end of treatment.

Patients should not donate blood during therapy and for 1 month following discontinuation of isotretinoin, and 3 years following discontinuation of acitretin, due to the potential risk to the foetus if given to a pregnant transfusion recipient.

Educational materials to support implementation

To support prescribers and pharmacists in implementing the pregnancy prevention programme, educational materials are available. These materials aim to reinforce warnings about teratogenicity, provide guidance on contraception, and outline requirements for pregnancy testing. These materials include:

- **Physician checklist/acknowledgement form:** This form must be completed by the physician and patient at initial and follow-up visits for all female patients prescribed acitretin or isotretinoin to confirm that appropriate advice to prevent oral retinoid exposure during pregnancy has been provided and understood.
- **Pharmacist checklist:** This form is used to provide guidance on the appropriate dispensing of isotretinoin and acitretin to both male and female patients.
- **Patient reminder card:** The prescriber and pharmacist should ensure all patients (male and female) are provided with the patient reminder card each time acitretin or isotretinoin is prescribed or dispensed, and check for patient understanding. The card is now included as part of the medicine pack. If broken bulk dispensing cannot be avoided, the patient should be provided with a copy of the package leaflet and the patient reminder card.

Educational materials for acitretin and isotretinoin medicines are available on the HPRA website. To access them, search using the 'Find a Medicine' and select the medicine or the educational material ('EdM') symbol.

References:

1 *Hughes JE, Buckley N, Looney Y, Kirwan G, Mullooly M, Bennett KE. Evaluating awareness, knowledge and practice of healthcare professionals following implementation of a revised pregnancy prevention programme for isotretinoin in Ireland: A multi-stakeholder cross-sectional study. Pharmacoepidemiol Drug Saf. 2023 Feb;32(2):137-147*

* *Further details, including the approved product information and educational materials, of currently authorised oral retinoid products, containing isotretinoin or acitretin, are available from www.hpra.ie.*

** *A Direct Healthcare Professional Communication (DHPC) has been issued to remind healthcare professionals of the necessary precautions and measures in place.*

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Product information updates recommended by the Pharmacovigilance Risk Assessment Committee

The HPRA highlights a selection of recommendations made by The Pharmacovigilance Risk Assessment Committee (PRAC) to update product information for medicines in clinical use. The approved product information comprises the Summary of Product Characteristics (SmPC) and Package Leaflet (PL) and is available at www.hpra.ie. The PRAC, in which the HPRA participate, is responsible for assessing and monitoring the safety of medicines. Healthcare professionals are reminded to check the HPRA or EMA websites regularly for current product information concerning medicines.

Angiotensin II receptor antagonists: Risk of intestinal angioedema

Angiotensin II receptor blockers (ARBs) are indicated in the treatment of hypertension. Some are also used in the management of heart failure and in diabetic nephropathy.

- A new warning in product information will reflect that intestinal angioedema has been reported in patients treated with ARBs. Patients presented with abdominal pain, nausea, vomiting, and diarrhoea.
- Symptoms resolved after discontinuation of ARBs.
- If intestinal angioedema is diagnosed, ARBs should be discontinued, and appropriate monitoring should be initiated until complete resolution of symptoms has occurred.

Metformin: Caution in patients with known or suspected mitochondrial diseases

Metformin is indicated for the treatment of type 2 diabetes mellitus, particularly in overweight patients, when dietary management and exercise alone do not provide adequate glycaemic control.

- A new warning in product information will reflect that metformin-containing products are not recommended in patients with mitochondrial diseases such as MELAS (Mitochondrial Encephalopathy with Lactic Acidosis and Stroke-like episodes) syndrome or MIDD (Maternally Inherited Diabetes and Deafness).
- The use of metformin-containing products is not recommended in these patients due to the risk of lactic acidosis exacerbation and neurological complications, which may lead to worsening of the disease.
- In case of signs and symptoms suggestive of MELAS syndrome or MIDD after the intake of metformin, treatment with metformin should be withdrawn immediately and prompt diagnostic evaluation should be performed.

Anakinra (Kineret): Risk of systemic amyloidosis following prolonged high-dose exposure in patients with NOMID/CINCA

Kineret is indicated for the treatment of rheumatoid arthritis, cryopyrin-associated periodic syndrome, Still's disease, Familial Mediterranean Fever and COVID-19.

- In patients with NOMID/CINCA* who received high doses of Kineret over extended periods of time and presented with injection site amyloid deposits, isolated cases of systemic interleukin-1 receptor antagonist protein (AIL1RAP) amyloidosis have been reported during post-marketing use.
- In patients with confirmed injection site amyloid deposits, observation for symptoms of systemic amyloidosis, including monitoring for proteinuria, is recommended.

** Neonatal-onset-multisystem inflammatory disease (NOMID)/Chronic Infantile Neurological, Cutaneous, Articular Syndrome (CINCA)*

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Vedolizumab (Entyvio): Risk of increased liver enzymes, hepatitis, and hypersensitivity reactions in patients switching from subcutaneous to intravenous formulation

Entyvio is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis, Crohn's disease, and chronic pouchitis, depending on the formulation (subcutaneous or intravenous), in patients who have had an inadequate response with, lost response to, or were intolerant to prior therapies.*

- Product information will reflect that liver enzyme increases, with a frequency of 'common' and hepatitis, with a frequency of 'very rare', are adverse reactions of vedolizumab based on post-marketing experience.
- The warnings in relation to hypersensitivity reactions will reflect that cases have been reported after switching patients from subcutaneous to intravenous formulations.
- Healthcare professionals are reminded that patients need to be observed for signs of hypersensitivity reactions and that administration of vedolizumab must be discontinued immediately and appropriate treatment initiated if a severe infusion-related reaction, anaphylactic reaction or other severe reactions occur.

** Refer to the product information for more information relating to the indications.*

Direct Healthcare Professional Communications published on the HPRA website since the last Drug Safety Newsletter

PRODUCT	SAFETY ISSUE
Epilim (valproate)	Annual educational material redistribution, including an updated annual risk acknowledgement form.

Reporting suspected adverse reactions

Healthcare professionals are encouraged to report suspected adverse reactions to the HPRA via the available options at http://www.hpra.ie/report, which include an online report form.

All reports submitted to the HPRA are reviewed and stored on the HPRA's national adverse reaction database. They are subsequently submitted to the EMA's EudraVigilance database, where they are available for analysis and to support early detection and monitoring of possible safety signals.

Reporting suspected adverse reactions, even those known to occur in association with a medicine, adds to knowledge about the frequency and severity of these reactions and can help to identify patients who are most at risk.

A privacy notice relating to the processing of personal data collected by the HPRA in relation to adverse reaction reports is available at www.hpra.ie

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