Ref:06/2023/PLD
23 Nov 2023

Oral Retinoids (acitretin, alitretinoin, and isotretinoin) - Pregnancy Prevention Program: Reminder of the risk minimisation measures

Dear Healthcare Professional,

Laboratoires Bailleul S.A., NeoFarma Pharmaceuticals Limited, and Rowex Ltd in agreement with the European Medicines Agency and the Malta Medicines Authority would like to reinforce the following:

Summary

- **Oral retinoids are highly teratogenic and must not be used during pregnancy. Therefore, a pregnancy prevention program (PPP) is in place.**

- **Recent studies revealed a low level of adherence to the PPP measures and pregnancies continue to occur in women exposed to oral retinoids. HCP must bear in mind that:**

  - **Women of childbearing potential are required to undergo medically supervised pregnancy tests just before, ideally monthly during and 1 month after stopping treatment with isotretinoin and alitretinoin. For acitretin after stopping treatment, periodically medically supervised pregnancy test should be conducted with 1-3 monthly intervals for 3 years.**

  - **Women of childbearing potential must use effective contraception, without interruption, for at least 1 month before initiating therapy, throughout the entire treatment, and for 1 month after stopping treatment with isotretinoin and alitretinoin & for 3 years after stopping treatment with acitretin.**

  - **This applies for all women of childbearing potential even sexually inactive patients (unless following the criteria in the SmPC and the educational materials, the prescriber considers that there are compelling reasons to indicate that there is no risk of pregnancy) and those with amenorrhea.**

  - **Women that become pregnant must stop taking acitretin, alitretinoin or isotretinoin immediately and consult a doctor urgently.**

Background on the safety concern:

In June 2018, following the European Article 31 referral on retinoid-containing medicinal products, the PPP was strengthened, Risk Minimization Measures (RMMs) were updated, and the Pharmacovigilance Risk Assessment Committee (PRAC) imposed/ recommended the conduct of a drug utilization study (DUS) and a survey to assess the effectiveness of the updated RMMs.

The DUS "Evaluation of the effectiveness of pregnancy prevention programme (PPP) for oral retinoids (acitretin, alitretinoin, and isotretinoin): a European before-after drug utilisation study (DUS) using secondary data" was conducted between July 2014 and December 2020 and divided in three periods: pre-referral to PRAC (July 2014 to June 2016), post-referral but prior to the implementation of risk minimisation measures (July 2016 to when educational materials were distributed in each country) and post-implementation (from when the distribution of educational materials began to December 2020), to evaluate the changes in the prescribing and monitoring practices following the update of the PPP.

The survey "Prescriber and Patient/Caregiver Survey: Effectiveness measures to investigate awareness, knowledge, and adherence to the Risk Minimization Measures (RMMs) of the Pregnancy Prevention Program (PPP) for oral retinoids (acitretin, alitretinoin, and isotretinoin)" was conducted in 2021 to assess

healthcare professionals' (HCPs) and patients'/caregivers' awareness, knowledge, and adherence to the PPP.

The results of the DUS showed that contraceptive use and pregnancy testing remain low, pregnancies are occurring in women exposed to oral retinoids more often than what would be acceptable, and most of these pregnancies result in termination.

The results of the survey demonstrated that both HCPs and patients/caregivers were aware about the RMMs of the PPP, that retinoids are teratogenic, should not be used during pregnancy, and that contraception and regular pregnancy tests would be required. However, the adherence to these RMMs were not adequate, with differences noted between participating countries. HCPs did not adequately comply with medically supervised pregnancy testing and ensuring effective contraception as required by the PPP during treatment and following discontinuation of treatment.

Call for reporting

Healthcare providers and patients are encouraged to report adverse reactions in accordance with the national spontaneous reporting system for Adverse Drug Reactions (ADRs). Report forms can be downloaded from www.medicinesauthority.gov.mt/adrportal and posted to Malta Medicines Authority Post-licensing, Sir Temi Zammit Buildings, Malta Life Sciences Park, San Ġwann SĠN 3000, or sent by email to: postlicensing.medicinesauthority@gov.mt. Please report the product name and relevant details.

Adverse events should also be reported:

Company contact point

Company	Product Name	Email	Phone
Laboratoires Bailleul S.A. Local representative Metropolis Pharma	Contracne 10 mg, 20 mg soft capsules	vigilances@bailleul.com	Office hours +356 2143 3330 Out of office hours +356 9942 6611
NeoFarma Pharmaceuticals Limited	A-CNOTREN 10 mg, 20 mg soft capsules	info@neofarma.com.mt	+356 20109494
Rowex Ltd	Isotretinoin 10 mg, 20 mg soft capsules	pv@rowa-pharma.ie	+35679829369

Yours faithfully,

Post-Licensing Directorate
Medicines Authority

Disclaimer
This Direct Healthcare Professional Communication has been submitted to you on behalf of Laboratoires Bailleul S.A., NeoFarma Pharmaceuticals Limited, and Rowex Ltd.

The MMA receives the relevant contact details from both the Medical Council and the Pharmacy Council. Should you wish to amend your details including address, you are asked to contact the Medical Council or Pharmacy Council directly, as may apply.