European Medicines Agency recommends the suspension of Nizoral tablets

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Information on Medicinal Product

Nizoral® in tablet form (ketoconazole) is a synthetic broad-spectrum antifungal agent used to treat fungal infections of the blood (such as candidiasis, candiduria, blastomycosis, coccidioidomycosis, histoplasmosis, chromomycosis, and paracoccidioidomycosis). The mode of action of ketoconazole is by stopping the synthesis of ergosterol, which is important for fungal cell membranes. Nizoral tablets are authorised for use in Malta. Other formulations such as creams ointments and shampoos are available but these are not affected by the suspension.

Information from European Medicines Agency about the safety concern

In July 2011, France requested the Committee on Medicinal Products for Human Use (CHMP) to assess the benefits of oral ketoconazole containing products for use as antifungal treatment due to its concerns on the safety and effecitiness of this product.

The CHMP concluded that, although liver injury such as hepatitis is a known side effect of antifungal medicines, the incidence and the seriousness of liver injury with oral ketoconazole were higher than with other antifungals. The CHMP was concerned that reports of liver injury occurred early after starting treatment with recommended doses, and it was not possible to identify measures to adequately reduce this risk. The Committee also concluded that the clinical benefit of oral ketoconazole is uncertain as data on its effectiveness are limited and do not meet current standards, and alternative treatments are available. Taking into account the increased rate of liver injury and the availability of alternative antifungal treatments, the CHMP concluded that the benefits did not outweigh the risks and that the Marketing Authorisations in EU member states should be suspended.

The suspension will be effected in Malta when a final European Commission binding decision on the opinion of the CHMP is issued (in due course).

Topical formulations of ketoconazole (such as creams, ointments and shampoos) can continue to be used as the amount of ketoconazole absorbed throughout the body is very low with these formulations.

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In Malta

For Healthcare Professionals

Although the potential for hepatotoxicity is a class effect with azole antifungals, the data assessed show that the incidence and seriousness of hepatotoxicity is higher with ketoconazole than with other antifungal agents.[1] Reported cases of hepatotoxicity included hepatitis, cirrhosis and liver failure with fatal outcomes or requiring liver transplantation.

The onset of hepatotoxicity occurred generally between 1 and 6 months after starting treatment, but has also been reported earlier than 1 month after starting treatment, and at the recommended daily dose of 200 mg.

The efficacy studies on oral ketoconazole are limited and have not been carried out in line with the most recently agreed guidelines[2]. There are also inadequate data to support the efficacy of ketoconazole when other treatments have failed or are not tolerated, or resistance has been detected.

The risk minimisation measures proposed, such as limiting the treatment duration or restricting the use to patients refractory or intolerant to alternative treatments and to physicians experienced in treating rare fungal infections, were not considered sufficient to reduce the risk of hepatotoxicity to an acceptable level. Therefore;

- As oral ketoconazole is no longer recommended, doctors should review patients being treated with this medicine for fungal infections, with a view of stopping treatment or choosing an appropriate alternative treatment.
- Topical ketoconazole formulations have very low systemic absorption and may continue to be used as currently approved.
- Pharmacists should refer patients with a prescription of oral Nizoral for fungal infections to their treating doctor.

References.

1. Garcia Rodriguez *et al.* A cohort study on the risk of acute liver injury among users of ketoconazole and other antifungal drugs. *Br J Clin Pharmacol* 1999; 48(6):847-852.

2. Guideline on the clinical evaluation of antifungal agents for the treatment and prophylaxis of invasive fungal disease CHMP/EWP/1343/01 Rev. 1, Apr 2010.

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Advice for Patients

- The European Medicines Agency has recommended the suspension of oral (by mouth) ketoconazole following a review of data showing higher liver toxicity with this medicine compared with other antifungal medicines.
- If you are currently taking Nizoral tablets for fungal infections, you should speak to your doctor at a routine appointment to discuss suitable alternative treatments.
- If you are taking topical formulations of ketoconazole (such as creams, ointments and shampoos), you can continue your treatment, as the amount of ketoconazole absorbed throughout the body is very low with these formulations.
- If you have any questions, you should contact your doctor or pharmacist.

For more information please visit www.ema.europa.eu

Reporting Adverse Drug Reactions

Healthcare professionals and patients are encouraged to report any adverse events or medication errors with Nizoral. Suspected Adverse Drug Reactions (side effects) may be reported using the Medicines Authority yellow card scheme or online at **http://www.medicinesauthority.gov.mt/adrportal** or to the marketing authorisation holder or their local representatives.

Dr John J Borg PhD (Bristol)

Post-licensing director

Healthcare professionals and patients are encouraged to regularly check the Medicines Authority website for product safety updates as these are issued on an ongoing basis.

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