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European Medicines Agency recommends suspension of marketing authorisations for oral ketoconazole

Benefit of oral ketoconazole does not outweigh risk of liver injury in fungal infections

The European Medicines Agency's Committee on Medicinal Products for Human Use (CHMP) has recommended that the marketing authorisations of oral ketoconazole-containing medicines should be suspended throughout the European Union (EU). The CHMP concluded that the risk of liver injury is greater than the benefits in treating fungal infections.

Patients currently taking oral ketoconazole for fungal infections should make a non-urgent appointment with their doctor to discuss suitable alternative treatments. Doctors should no longer prescribe oral ketoconazole and should review patients' treatment options.

The EU-wide review of oral ketoconazole was triggered by the suspension of the medicine in France. The French medicine agency, the National Agency for the Safety of Medicine and Health Products (ANSM), concluded that the benefit-risk balance of oral ketoconazole was negative because of a high level of liver injury associated with the medicine and in view of the currently available alternative treatments, which are deemed to be safer. European legislation requires that there is a coordinated European approach when a Member State takes regulatory action in relation to a medicine that is authorised in more than one country.

Having assessed the available data on the risks with oral ketoconazole, 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. 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.

The CHMP opinion will now be sent to the European Commission for a legally binding decision.

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The European Medicines Agency is aware that ketoconazole is used off-label for treating patients with Cushing's syndrome. In order to ensure that these patients will not be left without treatment, national competent authorities may make these medicines available under controlled conditions.

Information to 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 oral ketoconazole 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.

Information to healthcare professionals

Healthcare professionals should follow these recommendations:

- 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 ketoconazole for fungal infections to their treating doctor.

The Agency's recommendations are based on a review by the Committee for Medicinal Products for Human Use (CHMP), which looked at available data on the benefits of oral ketoconazole and the risk of hepatotoxicity from pre-clinical and clinical studies, post-marketing spontaneous case reports, epidemiological studies and the scientific literature. The Committee also considered the advice from a group of experts in the treatment of infections.

- 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.

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.

More about the medicine

Ketoconazole is an antifungal medicine used to treat infections caused by dermatophytes and yeasts. Ketoconazole taken orally (by mouth) has been authorised in the EU since 1980, and later topical (on the skin) formulations, such as creams, ointments and shampoos, have become available.

Oral formulations of ketoconazole have been authorised in the EU via national procedures, and are currently available in several EU Member States under various trade names, including Nizoral and Fungoral.

More about the procedure

The review of oral ketoconazole was initiated in July 2011 at the request of France, under Article 31 of Directive 2001/83/EC. In June 2011, the French medicines agency concluded that the benefit-risk balance of oral ketoconazole was negative and suspended the existing marketing authorisations in France. Consequently, the French agency asked the EMA to carry out a full assessment of the benefit-risk balance of oral ketoconazole-containing medicines and to issue an opinion on whether their marketing authorisations should be maintained, varied, suspended or withdrawn across the EU.

The review of oral ketoconazole has been carried out by EMA's Committee for Medicinal Products for Human Use (CHMP), responsible for all questions concerning medicines for human use, which adopted the EMA's final opinion.

The CHMP opinion will be forwarded to the European Commission, which will issue a final legally binding decision in due course.

To lift the suspension, the marketing authorisation holder for oral ketoconazole will have to provide convincing data that identify a group of patients in whom the benefits of the medicine outweigh their risks.

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