

# FDA Drug Safety Communication: Use of long-term, high-dose Diflucan (fluconazole) during pregnancy may be associated with birth defects in infants

## Safety Announcement

**[8-03-2011]** The U.S. Food and Drug Administration (FDA) is informing the public that chronic, high doses (400-800 mg/day) of the antifungal drug Diflucan (fluconazole) may be associated with a rare and distinct set of birth defects in infants whose mothers were treated with the drug during the first trimester of pregnancy. This risk does not appear to be associated with a single, low dose of fluconazole 150 mg to treat vaginal yeast infection (candidiasis).

There are several published case reports of birth defects in infants whose mothers were treated with high-dose fluconazole (400-800 mg/day) for serious and life-threatening fungal infections during most or all of the first trimester (see [Data Summary](#) below).<sup>1-4</sup> The features seen in these infants are listed in [Table 1](#).

Based on this information, the pregnancy category for fluconazole indications (other than vaginal candidiasis) has been changed from category C to category D. The pregnancy category for a single dose of fluconazole 150 mg to treat vaginal candidiasis has not changed and remains category C.

Pregnancy category D means there is positive evidence of human fetal risk based on human data but the potential benefits from use of the drug in pregnant women with serious or life-threatening conditions may be acceptable despite its risks.

**Healthcare professionals should be aware of the potential risks with long-term, high-dose use of fluconazole and counsel patients if the drug is used during pregnancy or if a patient becomes pregnant while taking the drug.**

### Facts about Diflucan (fluconazole)

- Used to treat yeast infections of the vagina, mouth, throat, esophagus, and other organs.
- Used to treat meningitis caused by a certain type of fungus.
- Used to prevent yeast infections in patients who are likely to become infected because they are being treated with chemotherapy or radiation therapy before a bone marrow transplant.
- The dose of fluconazole for vaginal candidiasis is a single dose of 150 mg and is lower than for other indications.

### **Additional Information for Patients**

- Use of long-term, high-dose (400-800 mg/day) fluconazole during the first three months of pregnancy (first trimester) may be associated with a rare and distinct set of birth defects in infants.
- A single dose of fluconazole 150 mg to treat vaginal yeast infection during pregnancy does not appear to be associated with the birth defects.
- Patients should notify their healthcare professional if they are pregnant or become pregnant while taking fluconazole.
- Side effects from the use of fluconazole should be reported to the FDA MedWatch program, using the information in the "Contact Us" box at the bottom of the page.

### **Additional Information for Healthcare Professionals**

- The pregnancy category for a single 150 mg dose of fluconazole for vaginal candidiasis is category C based on data from animal studies that showed an adverse effect on the fetus. There are no adequate and well-controlled studies of fluconazole in pregnant women. Available human data do not suggest an increased risk of congenital anomalies following a single maternal dose of 150 mg.
- The pregnancy category for fluconazole use for indications other than vaginal candidiasis is now category D. A few published case reports describe a rare pattern of distinct congenital anomalies in infants exposed in utero to high-dose maternal fluconazole (400-800 mg/day) during most or all of the first trimester.
- The features seen in these infants include brachycephaly, abnormal facies, abnormal calvarial development, cleft palate, femoral bowing, thin ribs and long bones, arthrogyposis, and congenital heart disease. These effects are similar to those seen in animal studies.
- If fluconazole is used during pregnancy, or if a patient becomes pregnant while taking fluconazole, the patient should be informed of the potential risk to the fetus.
- Adverse events involving fluconazole should be reported to the FDA MedWatch program using the information in the "Contact Us" box at the bottom of this page.

### **Data Summary**

There are several case reports published in the medical literature that describe rare and distinct congenital anomalies in infants whose mothers were treated with chronic high-dose (400-800 mg/day) fluconazole for fungal infections in the first trimester of pregnancy.<sup>1-4</sup> Four reports involved maternal use of chronic high-dose intravenous fluconazole for coccidioidal meningitis and one report involved a human immunodeficiency virus (HIV)-positive mother who received chronic high-dose oral fluconazole for vaginal candidiasis. Cases associated with high-dose fluconazole use all shared some characteristics with the autosomal recessive genetic disorder known as Antley-Bixler syndrome. This combination of congenital anomalies occurs rarely in the general population, and is similar to anomalies seen in animals following in utero fluconazole exposure.

Chronic high-dose fluconazole may be teratogenic in humans when used in the first trimester of pregnancy; however, the magnitude of this potential human teratogenic risk is unknown. The five reports

of distinct and rare congenital anomalies following chronic, high-dose in utero exposure to fluconazole suggest a possible drug threshold effect for a fluconazole embryopathy.

The available data in the medical literature do not suggest an association between low-dose oral fluconazole use in the first trimester of pregnancy and congenital anomalies.<sup>5-11</sup> The few published epidemiological studies of in utero exposure to low doses of fluconazole (most patients received a single oral dose of 150 mg) showed no consistent pattern of anomalies among affected infants; however, most of these studies were too small to accurately detect an increased risk for major birth defects overall.<sup>7,9-11</sup> In addition, none of these studies were large enough to accurately detect an increased risk for a rare or unique birth defect or syndrome.

**Table 1.**

<b>Features Seen in Infants Exposed to long-term, high-dose Diflucan (fluconazole) in utero</b>
short, broad head
abnormal looking face
abnormal development of the skullcap
oral cleft (opening in the lip or palate)
bowing of the thigh bones
thin ribs and long bones
muscle weakness and joint deformities
Congenital (present at birth) heart disease

**References**

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