הודעה על החמרה (מידע בטיחות) בעלון לרופא

**תאריך \_\_\_\_\_\_14.10.12\_\_\_\_\_\_\_\_\_**

**שם התכשיר באנגלית ומספר הרישום \_\_\_\_ Fluconazol (140 93 31445 00)\_**

**שם בעל הרישום \_\_\_\_\_\_\_BIOAVENIR LTD\_\_\_\_\_\_\_\_\_\_\_**

טופס זה מיועד לפרוט ההחמרות בלבד!

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| **ההחמרות המבוקשות** | | |
| **פרק בעלון** | **טקסט נוכחי** | **טקסט חדש** |
| **Special warnings and precautions for use** | ... | ...  Use in Pregnancy:  There are no adequate and well-controlled studies of fluconazole in pregnant women.  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. These reported anomalies are similar to those seen in animal studies. If this medicine is used during pregnancy, or if the patient becomes pregnant while taking the medicine, the patient should be informed of the potential hazard to the fetus (See Section 4.6, 'Pregnancy and lactation'). |
| **Pregnancy and lactation** | Use during pregnancy: There are no adequate and well controlled studies in pregnant women. There have been reports of multiple congenital abnormalities, in infants whose mothers were being treated for three or more months with high dose (400 – 800 mg/day) fluconazole therapy for coccidioidomycosis. The relationship between fluconazole and these events is unclear. Accordingly, use in pregnancy should be avoided, except in patients with severe or potentially life-threatening fungal infection, in whom fluconazole may be used if the anticipated benefit outweighs the possible risk to the fetus. Fluconazole should not be used in women of childbearing potential, unless adequate contraception is employed.  Use during lactation: Fluconazole is found in human breast milk at concentrations similar to plasma, hence its use in nursing mothers is not recommended. | Teratogenic Effects  **Pregnancy 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. These reported anomalies are similar to those seen in animal studies. If this medicine is used during pregnancy, or if the patient becomes pregnant while taking the medicine, the patient should be informed of the potential hazard to the fetus. (See Section 4.4, 'Special warnings and precautions for use')  Human Data  Several published epidemiologic studies do not suggest an increased risk of congenital anomalies associated with low dose exposure to fluconazole in pregnancy (most subjects received a single oral dose of 150 mg). A few published case reports describe a distinctive and rare pattern of birth defects among infants whose mothers received high-dose (400-800 mg/day) fluconazole during most or all of the first trimester of pregnancy. The features seen in these infants include: brachycephaly, abnormal facies, abnormal calvarial development, cleft palate, femoral bowing, thin ribs and long bones, arthrogryposis, and congenital heart disease. These effects are similar to those seen in animal studies.  Animal Data  Fluconazole was administered orally to pregnant rabbits during organogenesis in two studies at doses of 5, 10, and 20 mg/kg and at 5, 25, and 75 mg/kg, respectively. Maternal weight gain was impaired at all dose levels (approximately 0.25 to 4 times the 400 mg clinical dose based on BSA), and abortions occurred at 75 mg/kg (approximately 4 times the 400 mg clinical dose based on BSA); no adverse fetal effects were observed.  In several studies in which pregnant rats received fluconazole orally during organogenesis, maternal weight gain was impaired and placental weights were increased at 25 mg/kg. There were no fetal effects at 5 or 10 mg/kg; increases in fetal anatomical variants (supernumerary ribs, renal pelvis dilation) and delays in ossification were observed at 25 and 50 mg/kg and higher doses. At doses ranging from 80 to 320 mg/kg (approximately 2 to 8 times the 400 mg clinical dose based on BSA), embryolethality in rats was increased and fetal abnormalities included wavy ribs, cleft palate, and abnormal cranio-facial ossification. These effects are consistent with the inhibition of estrogen synthesis in rats and may be a result of known effects of lowered estrogen on pregnancy, organogenesis, and parturition.  **Nursing Mothers**  Fluconazole is secreted in human milk at concentrations similar to maternal plasma concentrations. Caution should be exercised when fluconazole is administered to a nursing woman. |