LAPIDOT MEDICAL

22.06.2020

רופא/ה רוקח/ת נכבד/ה,
ברצוננו להודיעך על עדכון בעלון לרופא

Fluconazole B.Braun 2 mg/ml solution for infusion

חומר פעיל :

Each 50 ml solution for infusion contains	**100 mg of fluconazole.**
Each 100 ml solution for infusion contains	**200 mg of fluconazole.**
Each 200 ml solution for infusion contains	**400 mg of fluconazole.**

Each ml contains 2 mg of fluconazole.

להלן עדכונים בעלון לרופא (טקסט מסומן ירוק משמעותו עדכון, טקסט מסומן צהוב משמעותו החמרה, ~~טקסט~~ משמעותו מחיקה):

Doctor leaflet

4.2. Posology and method of administration

[…]

Method of administration

Intravenious use

Fluconazole may be administered either orally or by intravenous infusion, the route being dependent on the clinical state of the patient. On transferring from the intravenous to the oral route, or *vice versa*, there is no need to change the daily dose.

The physician should prescribe the most appropriate pharmaceutical form and strength according to age, weight and dose. The capsule formulation is not adapted for use in infants and small children. Oral liquid formulations of fluconazole are available that are more suitable in this population.

4.4 Special warnings and precautions for use

[….]

Cardiovascular system

Some azoles, including fluconazole, have been associated with prolongation of the QT-interval on the electrocardiogram. Fluconazole causes QT prolongation via the inhibition of Rectifier Potassium Channel current (Ikr). The QT prolongation caused by other medicinal products (such as amiodarone) may be amplified via the inhibition of cytochrome P450(CYP) 3A4. During post-marketing surveillance there have been very rare cases of QT prolongation and *torsades de pointes* in patients taking fluconazole. These reports included seriously ill patients with multiple confounding risk factors such as structural heart disease, electrolyte abnormalities and concomitant treatment that may have been contributory. Patients with

hypokalemia and advanced cardiac failure are at an increased risk for the occurrence of life threatening ventricular arrhythmias and *torsades de pointes*.
Fluconazole should be administered with caution in patients with these potentially pro-arrhythmic conditions. Co-administration of other medicinal products known to prolong the QT interval and which are metabolized via the cytochrome P450 (CYP) 3A4 are contraindicated (see sections 4.3 and 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

[…]

- **Halofantrine:**
  Fluconazole can increase halofantrine plasma concentration due to an inhibitory effect on CYP3A4. Concomitant use of fluconazole and halofantrine has the potential to increase the risk of cardiotoxicity (prolonged QT interval, *torsades de pointes*) and consequently sudden heart death. This combination should be avoided (see section 4.4).

Concomitant use that should be used with caution:

[….]

- **Hydrochlorothiazide:**
  In a pharmacokinetic interaction study, co-administration of multiple-dose hydrochlorothiazide to healthy volunteers receiving fluconazole increased plasma concentration of fluconazole by 40%. An effect of this magnitude should not necessitate a change in the fluconazole dose regimen in subjects receiving concomitant diuretics

[….]

- **Anticoagulants:**
  In post-marketing experience, as with other azole antifungals, bleeding events (bruising, epistaxis, gastrointestinal bleeding, hematuria, and melena) have been reported, in association with increases in prothrombin time in patients receiving fluconazole concurrently with warfarin. During concomitant treatment with fluconazole and warfarin the prothrombin time was prolonged up to 2-fold, probably due to an inhibition of the warfarin metabolism through CYP2C9. In patients receiving coumarin-type or indanedioneanticoagulants concurrently with fluconazole the prothrombin time should be carefully monitored. Dose adjustment of antifungals may be necessary.
  [….]
- **Olaparib:**
  Moderate inhibitors of CYP3A4 such as fluconazole increase olaparib plasma concentrations; concomitant use is not recommended. If the combination cannot be avoided, limit the dose of olaparib to 200 mg twice daily.
  [….]
- **Tofacitinib:**
  Exposure of tofacitinib is increased when tofacitinib is coadministered with medications that result in both moderate inhibition of CYP3A4 and strong inhibition of CYP2C19 (e.g., fluconazole). Therefore, it is recommended to reduce tofacitinib dose by 50 % when used concomitantly.

4.6 Fertility, pregnancy and lactation

Pregnancy

An observational study has suggested an increased risk of spontaneous abortion in women treated with fluconazole during the first trimester.

There have been reports of multiple congenital abnormalities (including brachycephalia, ears dysplasia, giant anterior fontanelle, femoral bowing and radiohumeral synostosis) in infants whose mothers were treated for at least three or more months with high doses (400-800 mg daily) of fluconazole for coccidioidomycosis. The relation between fluconazole use and these events is unclear.

[…]

Breast-feeding

Fluconazole passes into breast milk to reach concentrations lower than those in plasma. Breast-feeding may be maintained after a single use of a standard dose 150 mg fluconazole or less. Breast-feeding is not recommended after repeated use or after high dose of fluconazole. The developmental and health benefits of breast-feeding should be considered along with the mother's clinical need for fluconazole and any potential adverse effects on the breast-fed child from fluconazole or from the underlying maternal condition.

Studies in animals have shown reproductive toxicity (see section 5.3).

~~Data from several hundred pregnant women treated with standards doses (< 200 mg/day) of fluconazole, administered as a single or repeated dose in the first trimester, show no increased risk of undesirable effects in the foetus.~~

Fluconazole in standard doses and short-term treatments should not be used in pregnancy unless clearly necessary.

Fluconazole in high dose and/or in prolonged regimens should not be used during pregnancy except for potentially life-threatening infections.

[…]

4.8 Undesirable effects

[….]

*including Fixed Drug Eruption

Paediatric Population:

The pattern and incidence of adverse reactions and laboratory abnormalities recorded during paediatric clinical trials are comparable to those seen in adults.

Reporting suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

https://sideeffects.health.gov.il/

Not known
Drug reaction with eosinophilia and systemic symptoms

(DRESS)

5.2. Pharmacokinetic properties

[…]

Pharmacokinetics during lactation

A pharmacokinetic study in ten lactating women, who had temporarily or permanently stopped breast-feeding their infants, evaluated fluconazole concentrations in plasma and breast milk for 48 hours following a single 150 mg dose of fluconazole. Fluconazole was detected in breast milk at an average concentration of approximately 98% of those in maternal plasma. The mean peak breast milk concentration was 2.61 mg/L at 5.2 hours post-dose. The estimated daily infant dose of fluconazole from breast milk (assuming mean milk consumption of 150 ml/kg/day) based on the mean peak milk concentration is 0.39 mg/kg/day, which is approximately 40% of the recommended neonatal dose (<2 weeks of age) or 13% of the recommended infant dose for mucosal candidiasis.

6.3 Shelf life

Unopened

The expiry date of the product is indicated on the packaging materials.

העלון לרופא נשלח למאגר התרופות שבאתר משרד הבריאות www.health.gov.il לצורך העלאתו לאתר וניתן לקבלם מודפסים על ידי פניה לבעל הרישום LAPIDOT MEDICAL IMPORT AND MARKETING LTD Ltd, רח' השיטה 8, פארק התעשיה קיסריה 3088900 ישראל.

בברכה
גאי וגנר
רוקח ממונה