פייזר פי אף אי פרמצבטיקה ישראל בע"מ
רח' שנקר 9, ת.ד. 12133
הרצליה פיתוח, ישראל 46725
טל: 972-9-9700500 פקס: 972-9-9700501

יולי 2021

רופא/ה, רוקח/ת נכבד/ה,

ברצוננו להודיעך על עדכון בעלון לרופא של **Cresemba IV& Cresemba Caps :**

ISAVUCONAZOLE (AS SULFATE) 100 MG (Caps)
ISAVUCONAZOLE (AS SULFATE) 200 MG (IV)

Indicated for (IV):
Cresemba is indicated in adults for the treatment of:
Invasive aspergillosis
Mucormycosis in patients for whom amphotericin B is inappropriate

Indicated for (Caps):
Cresemba is indicated in adults for the treatment of:
Invasive aspergillosis
Mucormycosis in patients for whom amphotericin B is inappropriate
Consideration should be given to official guidance on the appropriate use of antifungal agents.

להלן העדכונים העיקריים בעלון לרופא Cresemba IV& Cresemba Caps:

5.3 Preclinical safety data

In rats and rabbits, isavuconazole at systemic exposures below the therapeutic level were associated with dose-related increases in the incidence of skeletal anomalies (rudimentary supernumerary ribs) in offspring. In rats, a dose-related increase in the incidence of zygomatic arch fusion was also noted in offspring (see section 4.6).

Administration of isavuconazonium sulfate to rats at a dose of 90 mg/kg/day (~~2.3 fold the human maintenance dose [200 mg] based on mg/m2/day~~ approximately 1.0-fold the systemic exposure at the human clinical maintenance dose of 200 mg isavuconazole) during pregnancy through the weaning period showed an increased perinatal mortality of the pups. *In utero* exposure to the active moiety isavuconazole had no effect on the fertility of the surviving pups.

Intravenous administration of ^{14}C-labelled isavuconazonium sulfate to lactating rats resulted in the recovery of radiolabel in the milk.

Isavuconazole did not affect the fertility of male or female rats treated with oral doses up to 90 mg/kg/day (~~2.3 fold the human maintenance dose [200 mg] based on mg/m2/day~~ approximately 1.0-fold the systemic exposure at the human clinical maintenance dose of 200 mg isavuconazole).

Isavuconazole has no discernible mutagenic or genotoxic potential. Isavuconazole was negative in a bacterial reverse mutation assay, was weakly clastogenic at cytotoxic concentrations in the L5178Y tk+/- mouse lymphoma chromosome aberration assay, and showed no biologically relevant or statistically significant increase in the frequency of micronuclei in an *in vivo* rat micronucleus test.

Isavuconazole has demonstrated carcinogenic potential in 2-year rodent carcinogenicity studies. Liver and thyroid tumours are likely caused by a rodent-specific mechanism that is not relevant for humans. Skin fibromas and fibrosarcomas were seen in male rats. The mechanism underlying this effect is unknown. Endometrial adenomas and carcinomas of the uterus were seen in female rats, which is likely due to a hormonal disturbance. There is no safety margin for these effects. The relevance for humans of the skin and uterine tumours cannot be excluded.
~~No carcinogenicity studies have been performed.~~

Isavuconazole inhibited the hERG potassium channel and the L-type calcium channel with an IC_{50} of 5.82 µM and 6.57 µM respectively (34- and 38-fold the human non-protein bound C_{max} at maximum recommended human dose [MRHD], respectively).The *in vivo* 39-week repeated-dose toxicology studies in monkeys did not show QTcF prolongation at doses up to 40 mg/kg/day (~~2.3 fold the human maintenance dose [200 mg] based on mg/m2/day~~ approximately 1.0-fold the systemic exposure at the human clinical maintenance dose of 200 mg isavuconazole).

Environmental risk assessment has shown that Cresemba may pose a risk for the aquatic environment.

השינויים המודגשים ברקע צהוב מהווים החמרה. כמו כן, בוצעו שינויים נוספים הכוללים תוספת מידע, השמטת מידע ועדכוני נוסח שאינם מהווים החמרה. העלונים המעודכנים זמינים באתר משרד הבריאות.

https://www.old.health.gov.il/units/pharmacy/trufot/index.asp?safa=h

לחילופין, לקבלת עלון מלא מודפס ניתן לפנות לחברת פייזר פרמצבטיקה ישראל בע"מ, שנקר 9, ת.ד. 12133 הרצליה פיתוח, 46725.

בברכה,
אורטל עבודי
רוקחת ממונה