- **Drug interactions and contraindications:**
- **Rifampin**, an **inducer** of CYP450 system, can **shorten** the **duration** of **action** of **ketoconazole and the other azoles.**
- **CONTRAINDICATIONS :** coadministration with **ergot** derivatives or **cisapride** is contraindicated due to risk of **potentially fatal cardiac arrhythmias.**

Ketoconazole and amphotericin B should not be used together, because the decrease in ergosterol in the fungal membrane reduces the fungicidal action of amphotericin B .

Finally, ketoconazole is **teratogenic** in animals, **and it should not be given during pregnancy (C).**

DOSAGE FORMS

- **Aerosol, topical [foam] : 2% (50 g, 100 g)**
- **Cream, topical : 2% (15 g, 30 g, 60 g)**
- **Gel, topical : 2% (15 g) [contains dehydrated alcohol 34%]**
- **Shampoo, topical: 1% (120 mL), 2% (120 mL)**
- **Tablet : 200 mg (LFTs monitoring)**

- **Azole = Triazole = Fluconazole**
- **Fluconazole** is ***clinically important*** because of its **lack of the endocrine side effects of ketoconazole and its excellent penetrability into the CSF of both normal and inflamed meninges.** Fluconazole is employed ***prophylactically,*** with some success, for reducing fungal infections in recipients ***of bone marrow transplants.***

- **Mechanism of action: Like Ketoconazole**
- Fluconazole is effective against all forms of **mucocutaneous candidiasis.**
- Fluconazole is **administered orally or intravenously. Its absorption is excellent** and, **unlike that of ketoconazole, *is not dependent on gastric acidity.***
- **Binding to plasma proteins is minimal.**

- The drug **is excreted via the kidney**, ***and doses must be reduced in patients with compromised renal function.***

- **Concentrations** measured in the **urine, tears, and skin are approximately 10 times the plasma concentration,** only **10% of elimination is due to metabolism**, the remainder being **excreted** in **urine** and **sweat.**

- Fluconazole **has no endocrinologic effects**, because it ***does not inhibit the cytochrome P450 system*** responsible for the synthesis of androgens.

- Fluconazole **is secreted in human milk** at **concentrations similar to plasma.**

- Fluconazole therapy **has been associated with QT interval prolongation.**

- **Side effects: Nausea, vomiting, and rashes. Hepatitis is rare.**
- **Fluconazole is teratogenic, as are other azoles, and should not be used in pregnancy (C).**

- **A dosage of 500–600 mg/day** may be used **for systemic or severe infections**, and, in **urgent infections** such as meningitis caused by yeast, **800 mg/day have been used**. **Pediatric doses are measured at 6 –12 mg/kg/day.**

- **Azole = Triazole = Voriconazole**
- It is available for **IV** administration and **orally** administration and is approximately **0.95 bioavailable.**
- **Voriconazole is approved for the *treatment of invasive aspergillosis* and seems to have replaced amphotericin B as the treatment of choice for this indication.**

- **Voriconazole penetrates tissues well, including the CNS. *Elimination* is primarily by *metabolism* through the CYP450 2C19, 2C9, and 3A4 enzymes.**
- **One unique problem is a transient visual disturbance that occurs within 30 minutes of dosing.**
- **DOSAGE FORMS**
- **Injection, powder for reconstitution: 200 mg**
- **Powder for oral suspension: 200 mg/5ml**
- **Tablet: 50 mg, 200 mg**

- **ADVERSE REACTIONS**
- **Hallucinations**, Fever , chills , headache
- **Hypokalemia**
- Nausea , vomiting , abdominal pain .

- **CONTRAINDICATIONS** :
- Hypersensitivity to voriconazole or any component of the formulation.
- coadministration with barbiturates (long acting), carbamazepine, ergot alkaloids, rifampin, rifabutin.

- **DRUG INTERACTIONS :**
- **Calcium channel blockers: Serum levels** may be **increased**, including felodipine, nifedipine, and verapamil).
- **Omeprazole:** Voriconazole may **increase** omeprazole serum levels. In patients taking **≥ 40 mg** of omeprazole per day, **dose** of omeprazole **should be reduced by half.**
- **Warfarin:** Anticoagulant effects may be **increased**; monitor INR.

- **Echinocandins:**
- **Caspofungin, micafungin, and anidulafungin.**
- Echinocandins interfere with the synthesis of the **fungal cell wall** by **inhibiting the synthesis of β(1,3)-D-glucan**, leading to lysis and cell death. This **drug's** spectrum is **limited** to **Aspergillus and Candida species.**
- ***Caspofungin is not active by the oral route.***
- **DOSAGE FORMS**
- **Injection, powder for reconstitution: 50 - 70 mg**