Faxim
(Rifaximin)

TABLETS

COMPOSITION

FAXIM 200mg TABLETS

Each film coated tablet contains: Rifaximin (B.P).....200mg

FAXIM 550mg TABLETS

Each film coated tablet contains: Rifaximin (B.P).....550mg

DESCRIPTION

FAXIM tablets contain rifaximin, a non-aminoglycoside semisynthetic, non-systemic antibiotic derived from rifamycin SV. Rifaximin is a structural analog of rifampin. The chemical name for rifaximin is (2S,16Z,18E,20S,21S,22R,23R,24R,25S,26S,27S,28E)-5,6,21,23,25-pentahydroxy-27-methoxy-2,4,ll,16,20,22,24,26-octamethyl-2,7-(epoxypentadeca-[l,ll,13]trienimino)benzofuro[4,5-e]pyrido[l,2-a]-benzimidazole-l,15(2H)-dione,25-acetate. The empirical formula is $C_{43}H_{51}N_3O_{11}$and its molecular weight is 785.9.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Rifaximin is a non-aminoglycoside semi-synthetic antibacterial derived from rifamycin SV. Rifaximin acts by binding to the beta-subunit of bacterial DNA-dependent RNA polymerase resulting in inhibition of bacterial RNA synthesis. Escherichia coli has been shown to develop resistance to rifaximin in vitro. However, the clinical significance of such an effect has not been studied.

Rifaximin is a structural analog of rifampin. Organisms with high rifaximin minimum inhibitory concentration (MIC) values also have elevated MIC values against rifampin. Cross-resistance between rifaximin and other classes of antimicrobials has not been studied.

Rifaximin has been shown to be active against Escherichia coli (enterotoxigenic and enteroaggregative strains). For HE, rifaximin is thought to have an effect on the gastrointestinal flora

PHARMACOKINETICS

ABSORPTION ORAL: <0.4%

TRAVELERS' DIARRHEA

Systemic absorption of rifaximin (200mg three times daily) was evaluated in 13 subjects challenged with shigellosis on Days 1 and 3 of a three-day course of treatment. Rifaximin plasma concentrations and exposures were low and variable. There was no evidence of accumulation of rifaximin following repeated administration for 3 days (9 doses). Peak plasma rifaximin concentrations after 3 and 9 consecutive doses ranged from 0.81 to 3.4 ng/mL on Day 1 and 0.68 to 2.26 ng/mL on Day 3. Similarly, $AUC_{0.last}$ estimates were 6.95 ± 5.15 ng_h/mL on Day 1 and 7.83 ± 4.94 ng_h/mL on Day 3.FAXIM is not suitable for treating systemic bacterial infections because of limited systemic exposure after oral administration.

HEPATIC ENCEPHALOPATHY

After a single dose and multiple doses of rifaximin 550mg in healthy subjects, the mean time to reach peak plasma concentrations was about an hour. The pharmacokinetic (PK) parameters were highly variable and the accumulation ratio based on AUC was 1.37. The PK of rifaximin in patients with a history of HE was evaluated after administration of FAXIM, 550mg two times a day. The PK parameters were associated with a high variability and mean rifaximin exposure (AUC_t) in patients with a history of HE (147 ng_h/mL) was approximately 12-fold higher than that observed in healthy subjects following the same dosing regimen (12.3 ng_h/mL). When PK parameters were analyzed based on Child-Pugh Class A, B, and C, the mean (AUC_t) was 10-, 13-, and 20-fold higher, respectively, compared to that in healthy subjects

DISTRIBUTION

80% to 90% in the gut. Half-life elimination: ~6 hours. Rifaximin is moderately bound to human plasma proteins. In vivo, the mean protein binding ratio was 67.5% in healthy subjects and 62% in patients with hepatic impairment when rifaximin 550mg was administered.

METABOLISM AND EXCRETION

In a mass balance study, after administration of 400mg 14C-rifaximin orally to healthy volunteers, of the 96.94% total recovery, 96.62% of the administered radioactivity was recovered in feces almost exclusively as the unchanged drug and 0.32% was recovered in urine mostly as metabolites with 0.03% as the unchanged drug. Rifaximin accounted for 18% of radioactivity in plasma. This suggests that the absorbed rifaximin undergoes metabolism with minimal renal excretion of the unchanged drug. The enzymes responsible for metabolizing rifaximin are unknown. Excretion: Feces (~97% as unchanged drug); urine (<1%). In a separate study, rifaximin was detected in the bile after cholecystectomy in patients with intact gastrointestinal mucosa, suggesting biliary excretion of rifaximin.

INDICATIONS AND USAGE

TRAVELERS' DIARRHEA

FAXIM 200mg is indicated for the treatment of patients (≥ 12 years of age) with travelers' diarrhea caused by noninvasive strains of Escherichia coli.

LIMITATIONS OF USE

FAXIM should not be used in patients with diarrhea complicated by fever or blood in the stool or diarrhea due to pathogens other than Escherichia coli.

HEPATIC ENCEPHALOPATHY

FAXIM 550mg is indicated for reduction in risk of overt hepatic encephalopathy (HE) recurrence in patients ≥ 18 years of age.

In the trials of FAXIM for HE, 91% of the patients were using lactulose concomitantly. Differences in the treatment effect of those patients not using lactulose concomitantly could not be assessed. FAXIM has not been studied in patients with MELD (Model for End-Stage Liver Diease) scores > 25, and only 8.6% of patients in the controlled trial had MELD scores over 19. There is increased systemic exposure in patients with more severe hepatic dysfunction.

DOSAGE AND ADMINISTRATION

DOSAGE FOR TRAVELERS' DIARRHEA

The recommended dose of FAXIM is one tablet (200mg) taken orally

three times a day for 3 days. FAXIM can be administered orally, with or without food.

DOSAGE FOR HEPATIC ENCEPHALOPATHY
The recommended dose of FAXIM is one tablet (550mg) taken orally two times a day, with or without food.

ADVERSE REACTIONS SIGNIFICANT
>10%:
Cardiovascular: Peripheral edema (15%), Central nervous system: Dizziness (13%), fatigue (12%)
Hepatic: Ascites (11%). Gastrointestinal: Nausea (14%)

2% to 10%:
Cardiovascular: Chest pain (>2% to 5%), hypotension (>2% to 5%. Central nervous system: Headache (10%), depression (7%), fever (6%), amnesia (>2% to 5%), attention disturbance (>2% to 5%), confusion (>2% to 5%), hypoesthesia (>2% to 5%), pain (>2% to 5%), tremor. Dermatological: Pruritus (9%), rash (5%), cellulitis (>2% to 5%). Endocrine and metabolism: Hyper-/hypoglycemia (>2% to 5%), hyperkalemia (>2% to 5%), hyponatremia (>2% to 5%). Gastrointestinal: Abdominal pain (6% to 9%), anorexia (>2% to 5%), dehydration (>2% to 5%), esophageal varices (>2% to 5%), weight gain (>2% to 5%), xerostomia (>2% to 5%). Hematologic: Anemia (8%). Neuromuscular & skeletal: Muscle spasms (9%), arthralgia (6%), myalgia (>2% to 5%). Respiratory: Nasopharyngitis (7%), dyspnea (6%), epistaxis(>2% to 5%), pneumonia (>2% to 5%), rhinitis (>2% to 5%), upper respiratory tract infection (>2% to 5%). Miscellaneous: Influenza-like illness (>2% to 5%)
<2% (Limited to important or life-threatening): Abnormal dreams, allergic dermatitis, anaphylaxis, angioneurotic edema (including tongue and facial edema with dysphagia), CDAD, dysuria, exfoliative dermatitis, flushing, hematuria, hypersensitivity reactions, insomnia, lymphocytosis, monocytosis, motion sickness, neutropenia, polyuria, proteinuria, sunburn, tinnitus, urticaria.

CONTRAINDICATIONS
Hypersensitivity to rifaximin, other rifamycin antibiotics, or any component of the formulation.

WARNINGS/PRECAUTIONS
CONCERNS RELATED TO ADVERSE EFFECTS:
Superinfection: Prolonged use may result in fungal or bacterial superinfection, including C. difficile-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

DISEASE-RELATED CONCERNS
Diarrhea: Appropriate use: Efficacy has not been established for the treatment of diarrhea due to pathogens other than E. coli, including C. jejuni, Shigella, and Salmonella; consider alternative therapy if symptoms persist or worsen after 24-48 hours of treatment; avoid use in diarrhea with fever or blood in the stool.
Hepatic impairment: Efficacy for prevention of encephalopathy has not been established in patients with a Model for End-Stage Liver Disease (MELD) score >25; use caution in patients with severe hepatic impairment (Child-Pugh class C).

OTHER WARNINGS/PRECAUTIONS:
Appropriate use: Not for treatment of systemic infections; <1% is absorbed orally.

DRUG INTERACTIONS
BCG: Antibiotics may diminish the therapeutic effect of BCG. Risk X: Avoid combination.

PREGNANCY RISK FACTOR C
PREGNANCY IMPLICATIONS
Due to the limited oral absorption of rifaximin (<0.4%), exposure to the fetus is expected to be extremely low.

LACTATION
Excretion in breast milk unknown/not recommended.

DIETARY CONSIDERATIONS
May be taken with or without food.

INSTRUCTIONS
Store below 30°C. Protect from heat, light & moisture. Keep all medicines out of the reach of children. To be sold on the prescription of a registered medical practitioner only.

PRESENTATION
FAXIM Tablets 200mg & 550mg are available in Alu-Alu pack of 1x10 tablets.

فیکسِم ٹیبلیٹس
(ریفاکسیمین)

ہدایات: دوا کو **30°** سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔ گرمی، روشنی اور نمی سے محفوظ رکھیں۔
تمام دوائیں بچوں کی پہنچ سے دُور رکھیں۔ صرف مستند ڈاکٹر کے نسخہ پر فروخت کریں۔

Manufactured by:
STANDPHARM PAKISTAN (PVT) LTD
20 Km Ferozepur Road Lahore, Pakistan.