8015850-9093

For the use of a Registered Medical Practitioner or a Hospital or a Laboratory

TORFIX

(Rifaximin Tablets)

COMPOSITION

Each film coated tablet contains:

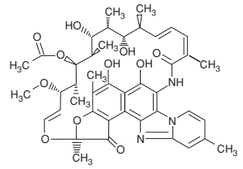
Rifaximin 200 mg

Colours: Sunset Yellow FCF & Titanium Dioxide I.P.

DESCRIPTION

Torfix Tablets for oral administration are film-coated and contain 200 mg of Rifaximin. Torfix Tablets contain rifaximin, a semi-synthetic, non systemic antibiotic. The chemical name for rifaximin is (2S,16Z,1 8E, 20S,21S,22R,23R,24R,25S,26S,27S,28E)5,6,21,23,25-pentahydroxy-27-methoxy2,4,11,16,20,22,24,26-octamethyl-2,7-(epoxypenta deca[1,11,13]trienimino)benzofuro[4,5-e]pyrido[1,2-a]benzimidazole-1,15(2H)-dione,25-acetate. The empirical formula is $C_{43}H_{51}N_3O_{11}$ and its molecular weight is 785.9.

The Chemical formula of rifaximin is as follows.



INDICATIONS

Torfix Tablets are indicated for the treatment of patients (> 12 years of age) with travelers' diarrhea caused by noninvasive strains of Escherichia coli. Torfix Tablets 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.

CLINICAL PHARMACOLOGY

Pharmacokinetics

Absorption: Rifaximin can be administered with or without food. Systemic absorption of rifaximin was low in both the fasting state and when administered within 30 minutes of a high-fat breakfast.

Table 1 : Effect of Food on the Mean ± S.D.

Pharmacokinetic Parameters Following a Single 400-mg Dose of Rifaximin (N = 14)

Parameter	Fasting	Fed
C_{max} (ng/mL)	3.80 ± 1.32	9.63 ± 5.93
T_{max} (h)	1.21 ± 0.47	1.90 ± 1.52
Half Life (h)	5.85 ± 4.34	5.95 ± 1.88
AUC (ng.h/mL)	18.35 ± 9.48	34.70 ± 9.23
% Excreted in Urine	0.023 ± 0.009	0.051 ± 0.017

14C-Rifaximin was administered as a single dose to 4 healthy male subjects. The mean overall recovery of radioactivity in the urine and feces of 3 subjects during the 168 hours after administration was 96.94 ± 5.64% of the dose. Radioactivity was excreted almost exclusively in the feces (96.62 ± 5.67% of the dose), with only a small proportion of the dose (mean 0.32% of the dose) excreted in urine. Analysis of fecal extracts indicated that rifaximin was being excreted as unchanged drug. The amount of radioactivity in urine (< 0.4% of the dose) suggests that rifaximin is poorly absorbed from the gastrointestinal tract and is almost exclusively and completely excreted in feces as unchanged drug. Mean rifaximin pharmacokinetic parameters were Cmax 4.3 ± 2.8 ng/mL and AUCt 19.5 ± 16.5 ng•h/mL with a median Tmax of 1.25 hours. Systemic absorption of rifaximin (200 mg three times daily) was also evaluated in 13 subjects with shigellosis on Days 1 and 3 of a three-day course of treatment. Rifaximin 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, AUC0-last estimates were 6.95 ± 5.15 ng•h/mL on Day 1 and 7.83 ± 4.94 ng•h/mL on Day 3. Rifaximin is not suitable for treating systemic bacterial infections because less than 0.4% of the drug is absorbed after oral administration

Distribution

Animal pharmacokinetic studies have demonstrated that 80% to 90% of orally administered rifaximin is concentrated in the gut with less than 0.2% in the liver and kidney, and less than 0.01% in other tissues. In adults with infectious diarrhea treated with rifaximin 800 mg daily for three days, concentrations of rifaximin in stools averaged ~8000 µg/g the day after treatment ended.

Metabolism

In vitro drug interactions studies have shown that rifaximin, at concentrations ranging from 2 to 200 ng/mL, did not inhibit human hepatic cytochrome P450 isoenzymes: 1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1, and 3A4. In an in vitro hepatocyte induction model, rifaximin was shown to induce cytochrome P450 3A4 (CYP3A4), an isoenzyme which rifampin is known to induce. Two clinical drug-drug interaction studies using midazolam and an oral contraceptive containing ethinyl estradiol and norgestimate demonstrated that rifaximin did not alter the pharmacokinetics of these drugs (see Drug-Drug Interactions).

Excretion

Rifaximin is excreted primarily in the feces. After oral administration of 400 mg 14C-rifaximin to healthy volunteers, approximately 97% of the dose was recovered in feces, almost entirely as unchanged drug, and 0.32% was recovered in the urine.

SPECIAL POPULATIONS

Geriatric: The pharmacokinetics of rifaximin in patients > 65 years of age has not been studied.

Pediatric:

The pharmacokinetics of rifaximin has not been studied in pediatric patients of any age.

Gender:

The effect of gender on the pharmacokinetics of rifaximin has not been studied.

Renal Insufficiency:

The pharmacokinetics of rifaximin in patients with impaired renal function has not been studied.

Hepatic Insufficiency:

Mean peak rifaximin plasma concentrations of 13.5 µg/mL were detected in hepatic encephalopathy patients administered rifaximin 800 mg three times daily for 7 days. Less than 0.1% of the administered dose was recovered after 7 days. Because of the limited systemic absorption of rifaximin, no specific dosing adjustments are recommended for patients with hepatic insufficiency.

Drug-Drug Interactions

In an in vitro hepatocyte induction model, rifaximin was shown to induce cytochrome P450 3A4 (CYP3A4), an isoenzyme which rifampin is known to induce. Two clinical drug-drug interaction studies were conducted using midazolam and an oral contraceptive containing ethinyl estradiol and norgestimate to assess the effect of rifaximin on the pharmacokinetics of these drugs. The midazolam study was an open-label, randomized, crossover, drug-interaction trial designed to assess the effect of rifaximin 200 mg administered orally (PO) every 8 hours (Q8H) for 3 days and every 8 hours for 7 days, on the pharmacokinetics of a single dose of either midazolam 2 mg intravenous (IV) or midazolam 6 mg PO. No significant difference was observed in the metrics of systemic exposure or elimination of IV or PO midazolam or its major metabolite, 1'- hydroxymidazolam, between midazolam alone or together with rifaximin. Therefore, rifaximin was not shown to significantly affect intestinal or hepatic CYP3A4 activity.

The oral contraceptive study utilized an open-label, crossover design in 28 healthy female subjects to determine if rifaximin 200 mg PO administered Q8H for 3 days altered the pharmacokinetics of a single

dose of an oral contraceptive containing 0.07 mg ethinyl estradiol and 0.50 mg norgestimate. Results showed that the pharmacokinetics of single doses of ethinyl estradiol and norgestimate were not altered by rifaximin.

Microbiology

Rifaximin acts by binding to the beta-subunit of bacterial DNAdependent 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 the following pathogen in clinical studies of infectious diarrhea as described in the

INDICATIONS :

Escherichia coli (enterotoxigenic and enteroaggregative strains).

Susceptibility Tests

In vitro susceptibility testing was performed according to the National Committee for Clinical Laboratory Standards (NCCLS) agar dilution method M7-A61. However, the correlation between susceptibility testing and clinical outcome has not been determined.

DOSAGE AND ADMINISTRATION

Torfix Tablets can be administered orally with or without food. For travelers' diarrhea, the recommended dose is one 200 mg tablet taken three times a day for 3 days.

ADVERSE EFFECTS

Some of the common side effects observed are : Nausea , Flatulence, Constipation, Vomiting , Pyrexia, Headache, Abdominal Pain, Rectal Tenesmus, Defecation Urgency etc.. Some of the rare side effects (may or may not be associated with drug) observed in some patients are: lymphocytosis, neutropenia, tinitus, motion sickness, loss of taste, hot flashes, edema, urticaria, puritus etc.

DRUG INTERACTIONS

Although in vitro studies demonstrated the potential of rifaximin to interact with cytochrome P450 3A4 (CYP3A4), a clinical drug-drug interaction study demonstrated that rifaximin did not significantly affect the pharmacokinetics of midazolam either presystemically or systemically. An additional clinical drug-drug interaction study showed no effect of rifaximin on the presystemic metabolism of an oral contraceptive containing ethinyl estradiol and norgestimate. Therefore, clinical interactions with drugs metabolized by human cytochrome P450 isoenzymes are not expected.

WARNINGS

Torfix Tablets were not found to be effective in patients with diarrhea complicated by fever and/or blood in the stool or diarrhea due to pathogens other than Escherichia coli. Torfix Tablets are not effective in cases of travelers' diarrhea due to Campylobacter jejuni. The effectiveness of Torfix Tablets in travelers' diarrhea caused by Shigella spp. and Salmonella spp. has not been proven.

Torfix Tablets should not be used in patients where Campylobacter jejuni, Shigella spp., or Salmonella spp. may be suspected as causative pathogens.

Torfix Tablets should be discontinued if diarrhea symptoms get worse or persist more than 24-48 hours and alternative antibiotic therapy should be considered.

Pseudomembranous colitis has been reported with nearly all antibacterial agents and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by Clostridium difficile is the primary cause of "antibiotic-associated colitis." After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone.

In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against Clostridium difficile.

PRECAUTIONS

General

The use of antibiotics may promote the overgrowth of nonsusceptible organisms. Should superinfection occur during therapy, appropriate measures should be taken. Torfix Tablets should be discontinued if diarrhea persists more than 24-48 hours or worsens, or if patients have fever and/or blood in the stool that they should seek medical care.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies were not conducted. Rifaximin was not genotoxic in the bacterial reverse mutation assay, chromosomal aberration assay, rat bone marrow micronucleus assay, and the CHO/HGPRT mutation assay. There was no effect on fertility in male or female rats following the administration of rifaximin at doses up to 300 mg/kg (approximately 5 times the clinical dose, adjusted for body surface area).

Pregnancy

There are no adequate and well controlled studies in pregnant women. Torfix Tablets should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

Use during lactation

It is not known whether rifaximin is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for adverse reactions in nursing infants from Torfix Tablets, a decision should be made whether to dis-continue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

The safety and effectiveness of Torfix Tablets in pediatric patients less than 12 years of age have not been established.

Geriatric Use

Clinical studies of Torfix Tablets did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently than younger subjects.

OVERDOSE

No specific information is available on the treatment of overdosage with Torfix Tablets. In clinical studies at doses higher than the recommended dose (> 600 mg/day), adverse events were similar to the recommended dose (200 mg taken three times a day) and to placebo. In the case of over-dosage, discontinue Torfix Tablets, treat symptomatically, and institute supportive measures as required.

CONTRAINDICATIONS

Torfix Tablets are contraindicated in patients with a hypersensitivity to rifaximin, any of the rifamycin antimicrobial agents, or any of the components in Torfix Tablets.

EXPIRY DATE

Do not use later than date of expiry.

STORAGE

Store in a cool and dry place.

Keep out of reach of children.

PRESENTATION

Torfix is available in strip of 10 tablets.

torrent

Marketed by :

TORRENT PHARMACEUTICALS LTD.

Indrad-382 721, Dist. Mehsana, INDIA.

Manufactured by :

LUPIN LTD.

EPIP, SIDCO, Kartholi, Bari Brahmana,

Jammu, J&K -181133, INDIA.

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