RIXMIN 550 Tablets (Rifaximin)

Composition

RIXMIN 550 Tablets
Each tablet contains:
Rifaximin..... 550 mg

Dosage Form

Tablet for oral use

Pharmacology

Pharmacodynamics

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.

For hepatic encephalopathy (HE), rifaximin is thought to have an effect on the gastrointestinal flora.

Susceptibility Tests
In vitro susceptibility testing was performed according to the National Committee for Clinical Laboratory Standards (NCCLS) agar dilution method M7-A6. However, the correlation between susceptibility testing and clinical outcome has not been determined.

Pharmacokinetics

Absorption
After a single dose and multiple doses of rifaximin 550 mg 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 rifaximin, 550 mg two times a day. The PK parameters were associated with a high variability and mean rifaximin exposure (AUCτ) 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 ngh/mL). When PK parameters were analyzed based on Child-Pugh Class A, B, and C, the mean AUCτ was 10-, 13-, and 20-fold higher, respectively, compared to that in healthy subjects (Table 1).

Table 1: Mean (± S.D.) PK Parameters of Rifaximin at Steady-State in Patients with a History of HE

by Child-Pugh Class[1]

	Healthy Subjects (n = 14)	Child-Pugh Class		
		A (n = 18)	B (n = 7)	C (n = 4)
AUC_{tau} (ng h/mL)	12.3 ± 4.8	118 ± 67.8	161 ± 101	246 ± 120
C_{max} (ng/mL)	3.4 ± 1.6	19.5 ± 11.4	25.1 ± 12.6	35.5 ± 12.5
T_{max} 2 (h)	0.8 (0.5, 4.0)	1 (0.9, 10)	1 (0.97, 1)	1 (0, 2)

1 Cross-study comparison with PK parameters in healthy subjects
2 Median (range)

Food Effect in Healthy Subjects
A high-fat meal consumed 30 minutes prior to rifaximin dosing in healthy subjects delayed the mean time to peak plasma concentration from 0.75 to 1.5 hours and increased the systemic exposure (AUC) of rifaximin by 2-fold (Table 2).

Table 2: Mean (± S.D.) PK Parameters After Single-Dose Administration of Rifaximin Tablets 550 mg in Healthy Subjects Under Fasting and Fed Conditions (N = 12) Parameter Fasting Fed

Parameter	Fasting	Fed
C_{max} (ng/mL)	4.1 ± 1.5	4.8 ± 4.3
T_{max} 1 (h)	0.8 (0.5, 2.1)	1.5 (0.5, 4.1)
Half-life (h)	1.8 ± 1.4	4.8 ± 1.3
AUC (ng h/mL)	11.1 ± 4.2	22.5 ± 12

[1]Median (range)

Distribution
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 550 mg was administered.

Metabolism and Excretion
In a mass balance study, after administration of 400 mg ^{14}C-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.

In a separate study, rifaximin was detected in the bile after cholecystectomy in patients with intact gastrointestinal mucosa, suggesting biliary excretion of rifaximin.

Specific Populations

Hepatic Impairment
The systemic exposure of rifaximin was markedly elevated in patients with hepatic impairment compared to healthy subjects. The mean AUC in patients with Child-Pugh Class C hepatic

impairment was 2-fold higher than in patients with Child-Pugh Class A hepatic impairment.

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

Indications

RIXMIN 550 Tablets are indicated for reduction in the risk of overt HE recurrence in patients ≥18 years of age.

Dosage and Administration

The recommended dose of **RIXMIN 550 Tablets** taken orally is two times a day, with or without food.

Contraindications

Rifaximin is contraindicated in patients with a hypersensitivity to rifaximin, any of the rifamycin antimicrobial agents, or any of the components in rifaximin. Hypersensitivity reactions have included exfoliative dermatitis, angioneurotic edema, and anaphylaxis.

Warnings and Precautions

General

***Clostridium difficile*-Associated Diarrhea**
Clostridium difficile-associated diarrhea (CDAD) has been reported with the use of nearly all antibacterial agents, including rifaximin, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon, which may lead to overgrowth of *C. difficile*.

C. difficile produces toxins A and B, which contribute to the development of CDAD. Hypertoxin-producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over 2 months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

Development of Drug-Resistant Bacteria
Prescribing rifaximin for travelers' diarrhea in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Severe (Child-Pugh C) Hepatic Impairment
There is increased systemic exposure in patients with severe hepatic impairment. Animal toxicity studies did not achieve systemic exposures that were seen in patients with severe hepatic impairment. The clinical trials were limited to patients with MELD scores

Drug Interactions

In vitro drug interaction studies have shown that rifaximin, at concentrations ranging from 2 to 200 ng/mL, did not inhibit human hepatic cytochrome (CY) P450 isoenzymes, 1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1 and 3A4.

Rifaximin is not expected to inhibit these enzymes in clinical use.

In an In vitro study, rifaximin was shown to induce CYP3A4 at the concentration of 0.2 µM. An In vitro study suggests that rifaximin is a substrate of P-glycoprotein (P-gp). In the presence of the P-gp inhibitor, verapamil, the efflux ratio of rifaximin was reduced greater than 50% In vitro. The effect of P-gp inhibition on rifaximin was not evaluated in vivo. The inhibitory effect of rifaximin on the P-gp transporter was observed in an In vitro study. The effect of rifaximin on the P-gp transporter was not evaluated in vivo.

However, in patients with normal liver function, rifaximin at the recommended dosing regimen is not expected to induce CYP3A4. It is unknown whether rifaximin can have a significant effect on the pharmacokinetics of concomitant CYP3A4 substrates in patients with reduced liver function who have elevated rifaximin concentrations.

Midazolam
The effect of rifaximin 200 mg administered orally every 8 hours for 3 days and for 7 days on the pharmacokinetics of a single dose of either midazolam 2 mg intravenous or midazolam 6 mg orally was evaluated in healthy subjects. No significant difference was observed in the metrics of systemic exposure or elimination of intravenous or oral 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 for the 200 mg, three-times-a-day dosing regimen.

After rifaximin 550 mg was administered three times a day for 7 days and 14 days to healthy subjects, the mean AUC of single midazolam 2 mg orally was 3.8% and 8.8% lower, respectively, than when midazolam was administered alone. The mean C_{max} of midazolam was also decreased by 4-5% when rifaximin was administered for 7-14 days prior to midazolam administration. This degree of interaction is not considered clinically meaningful. The effect of rifaximin on CYP3A4 in patients with impaired liver function who have elevated systemic exposure is not known.

Oral Contraceptives Containing 0.07 mg Ethinyl Estradiol and 0.5 mg Norgestimate
The oral contraceptive study utilized an open-label, crossover design in 28 healthy female subjects to determine if rifaximin 200 mg orally administered three times a day for 3 days (the dosing regimen for travelers' diarrhea) altered the pharmacokinetics of a single dose of an oral contraceptive containing 0.07 mg ethinyl estradiol and 0.5 mg norgestimate. Results showed that the pharmacokinetics of single doses of ethinyl estradiol and norgestimate were not altered by rifaximin.

Effect of rifaximin on oral contraceptives was not studied for rifaximin 550 mg twice a day, the dosing regimen for HE.

Renal Impairment

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

Hepatic Impairment

Following administration of rifaximin 550 mg twice daily to patients with a history of HE, the systemic exposure (i.e., AUCτ) of rifaximin was about 10-, 3-, and 20-fold higher in those patients with mild (Child-Pugh A), moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment, respectively, compared to that in healthy volunteers. No dosage adjustment is recommended because rifaximin is presumably acting locally. Nonetheless, caution should be exercised when rifaximin is administered to patients with severe hepatic impairment.

Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. Rifaximin has been shown to be teratogenic in rats and rabbits at doses that caused maternal toxicity.Rifaximin tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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 rifaximin, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

The safety and effectiveness of rifaximin 550 mg for HE has not been established in patients

Geriatric Use

In the controlled trial with rifaximin 550 mg for HE, 19.4% were aged 65 years and over, while 2.3% were 75 years and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but the greater sensitivity of some older individuals cannot be ruled out.

Undesirable Effects

Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described below reflect exposure to rifaximin 550 mg in 348 patients, including 265 exposed for 6 months and 202 exposed for more than a year (mean exposure was 364 days). The safety of rifaximin 550 mg taken two times a day for reducing the risk of overt HE recurrence in adult patients was evaluated in a 6-month placebo controlled clinical trial (n = 140) and in a long-term follow-up study (n = 280). The population studied had a mean age of 56.26 (range: 21-82) years; approximately 20% of the patients were ≥65 years old, 61% were male, 86% were White, and 4% were Black. In the trial, 91% of patients were taking lactulose concomitantly. All adverse reactions that occurred at an incidence ≥5% and at a higher incidence in rifaximin 550 mg-treated subjects than in the placebo group in the 6-month trial are provided in Table 3. (These include adverse events that may be attributable to the underlying disease).

Table 3: Adverse Reactions Occurring in ≥5% of Patients Receiving Rifaximin and at a Higher Incidence Than Placebo

MedDRA Preferred Term	Rifaximin Tablets 550 mg Twice Daily n = 140	Placebo n = 159
	Number (%) of Patients	
Edema peripheral	21 (15%)	13 (8%)
Nausea	20 (14%)	21 (13%)
Dizziness	18 (13%)	13 (8%)
Fatigue	17 (12%)	18 (11%)
Ascites	16 (11%)	15 (9%)
Muscle spasms	13 (9%)	11 (7%)
Pruritus	13 (9%)	10 (6%)
Abdominal pain	12 (9%)	13 (8%)
Abdominal distension	11 (8%)	12 (8%)
Anemia	11 (8%)	6 (4%)
Cough	10 (7%)	11 (7%)
Depression	10 (7%)	8 (5%)
Insomnia	10 (7%)	11 (7%)
Nasopharyngitis	10 (7%)	10 (6%)
Abdominal pain upper	9 (6%)	8 (5%)
Arthralgia	9 (6%)	4 (3%)
Back pain	9 (6%)	10 (6%)
Constipation	9 (6%)	10 (6%)
Dyspnea	9 (6%)	7 (4%)
Pyrexia	9 (6%)	5 (3%)
Rash	7 (5%)	6 (4%)

The following adverse reactions, presented by body system, have also been reported in the placebo-controlled clinical trial in greater than 2% but less than 5% of patients taking rifaximin 550 mg orally two times a day for HE. The following includes adverse events occurring at a greater incidence than placebo, regardless of causal relationship to drug exposure.

Ear and Labyrinth Disorders: Vertigo.

Gastrointestinal Disorders: Abdominal pain lower, abdominal tenderness, dry mouth, esophageal variceal bleed, stomach discomfort.

General Disorders and Administration Site Conditions: Chest pain, generalized edema, influenza-like illness, pain NOS.

Infections and Infestations:*Cellulitis, pneumonia, rhinitis, upper respiratory tract infection NOS.*

Injury, Poisoning and Procedural Complications: Contusion, fall, procedural pain.

Investigations: Weight increased.

Metabolic and Nutritional Disorders: Anorexia, dehydration, hyperglycemia, hyperkalemia,

hypoglycemia, hyponatremia.

Musculoskeletal, Connective Tissue and Bone Disorders: Myalgia, pain in extremity.

Nervous System Disorders: Amnesia, disturbance in attention, hypoesthesia, memory impairment, tremor.

Psychiatric Disorders: Confusional state.

Respiratory, Thoracic and Mediastinal Disorders: Epistaxis.

Vascular Disorders: Hypotension.

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of rifaximin. Because these reactions are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These reactions have been chosen for inclusion due to either their seriousness, frequency of reporting or causal connection to rifaximin.

Infections and Infestations
Cases of *C. difficile*-associated colitis have been reported.

General
Hypersensitivity reactions, including exfoliative dermatitis, rash, angioneurotic edema (swelling of face and tongue and difficulty swallowing), urticaria, flushing, pruritus and anaphylaxis have been reported. These events occurred as early as within 15 minutes of drug administration.

Overdosage

No specific information is available on the treatment of overdosage with rifaximin. In clinical studies at doses higher than the recommended dose (>600 mg/day for travelers diarrhea or >1,100 mg/day for HE), adverse reactions were similar in subjects who received doses higher than the recommended dose and placebo.

In the case of overdosage, discontinue rifaximin, treat symptomatically, and institute supportive measures as required.

Storage and Handling Instructions

Store in a cool and dry place.

Packaging Information

RIXMIN 550 Tablets: Strip of 10 tablets

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