RIXMIN Tablets (Rifaximin)

Composition

RIXMIN 200 Tablets
Each tablet contains:
Rifaximin ....................... 200 mg

Dosage Form

Tablet

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.

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.

Pharmacokinetics

Absorption

Systemic absorption of rifaximin (200 mg 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 (nine doses). Peak plasma rifaximin concentrations after three and nine 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, the AUC\textsubscript{0-last} estimates were 6.95 ± 5.15 ngh/mL on day 1, and 7.83 ± 4.94 ngh/mL on day 3. Rifaximin is not suitable for treating systemic bacterial infections because of limited systemic exposure after oral administration.

Effect of Food 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 1: Effect of Food on the Mean ± S.D. Pharmacokinetic Parameters Following a Single 550 mg Dose of Rifaximin (N = 14)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Fasting</th>
<th>Fed</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td>4.1 ± 1.5</td>
<td>4.8 ± 1.4</td>
</tr>
<tr>
<td>$T_{\text{max}}$ (hour)</td>
<td>0.8 ± 0.8</td>
<td>4.3 ± 1.5</td>
</tr>
<tr>
<td>Half-life (hour)</td>
<td>(0.5, 2.1)</td>
<td>(0.5, 4.1)</td>
</tr>
<tr>
<td>AUC (ng/h/mL)</td>
<td>1.8 ± 1.4</td>
<td>4.1 ± 1.4</td>
</tr>
<tr>
<td></td>
<td>11.1 ± 4.2</td>
<td>± 4.2</td>
</tr>
<tr>
<td></td>
<td>1.3 ± 22.5</td>
<td>± 12</td>
</tr>
</tbody>
</table>

1 Median (range)

Rifaximin can be administered with or without food.

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 the feces, almost entirely as unchanged drug, and 0.32% was recovered in the 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.

Special Populations

Geriatric: The pharmacokinetics of rifaximin in patients who are 65 years of age or older has not been studied.

Pediatric: The pharmacokinetics of rifaximin has not been studied in pediatric patients.

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

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

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.

Indications

For the treatment of adult patients with infectious diarrhea.

Dosage And Administration

For infectious diarrhea, the recommended dose of RIXMIN 200 Tablets is one tablet taken three times a day for 3 days.
### Contraindications

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

### Warnings And Precautions

#### General

Rifaximin was 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*. Discontinue rifaximin if diarrhea symptoms get worse or persist for more than 24 to 48 hours and consider alternative antibiotic therapy.

#### Drug-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. 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.

An *in vitro* study suggests that rifaximin is a substrate of P-glycoprotein. In the presence of the P-glycoprotein inhibitor, verapamil, the efflux ratio of rifaximin was reduced greater than 50% *in vitro*. The effect of P-glycoprotein inhibition on rifaximin was not evaluated *in vivo*.

The inhibitory effect of rifaximin on the P-glycoprotein transporter was observed in an *in vitro* study. The effect of rifaximin on the P-glycoprotein transporter was not evaluated *in vivo*.

#### 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 dosing regimen of 200 mg, three times a day.

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\text{max} of midazolam was also decreased by 4% to 5% when rifaximin was administered for 7 to 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.
The effect of rifaximin on oral contraceptives was not studied for rifaximin 550 mg twice a day, the dosing regimen for hepatic encephalopathy.

**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 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.

### 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 hepatic encephalopathy, the systemic exposure (i.e., AUC?) of rifaximin was about 10-, 13-, 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 in pediatric patients has not been established.

### Geriatric Use

Clinical studies of rifaximin did not include a sufficient number of subjects aged 65 years and over to determine whether they respond differently than younger subjects.
In the controlled trial with rifaximin 550 mg for hepatic encephalopathy, 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 elderly 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.

**Diarrhea**

The safety of rifaximin 200 mg taken three times a day was evaluated in patients with travelers' diarrhea consisting of 320 patients in two placebo-controlled clinical trials, with 95% of patients receiving 3 or 4 days of treatment with rifaximin. The population studied had a mean age of 31.3 (18 to 79) years, of which approximately 3% were ≥65 years old, 53% were male, and 84% were White while 11% were Hispanic.

Discontinuations due to adverse reactions occurred in 0.4% of patients. The adverse reactions leading to discontinuation were taste loss, dysentery, weight decrease, anorexia, nausea, and nasal passage irrigation.

All adverse reactions for rifaximin 200 mg three times daily that occurred at a frequency ≥2% in the two placebo-controlled trials combined are provided in Table 2. (These include adverse reactions that may be attributable to the underlying disease.)

#### Table 2: All Adverse Reactions with an Incidence ≥2% Among Patients Receiving Rifaximin Tablets, 200 mg Three Times Daily, in Placebo-Controlled Studies

<table>
<thead>
<tr>
<th>MedDRA Preferred Term</th>
<th>Number (%) of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifaximin Tablets, 600 mg/day</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>N = 320</td>
</tr>
<tr>
<td>Flatulence</td>
<td>36 (11%)</td>
</tr>
<tr>
<td>Headache</td>
<td>31 (10%)</td>
</tr>
<tr>
<td>Abdominal pain NOS*</td>
<td>23 (7%)</td>
</tr>
<tr>
<td>Rectal tenesmus</td>
<td>23 (7%)</td>
</tr>
</tbody>
</table>
| Adverse Reaction       | Placebo-Controlled Trials | Rifaximin  
|------------------------|---------------------------|-------------
| Defecation urgency     | 19 (6%)                   | 21 (9%)     
| Nausea                 | 17 (5%)                   | 19 (8%)     
| Constipation           | 12 (4%)                   | 8 (4%)      
| Pyrexia                | 10 (3%)                   | 10 (4%)     
| Vomiting NOS           | 7 (2%)                    | 4 (2%)      

*NOS: Not otherwise specified*

The following adverse reactions, presented by body system, have also been reported in <2% of patients taking rifaximin in the two placebo-controlled clinical trials where the 200 mg tablet was taken three times a day for travelers' diarrhea.

The following includes adverse reactions regardless of causal relationship to drug exposure:

**Blood and Lymphatic System Disorders:** Lymphocytosis, monocytosis, neutropenia.

**Ear and Labyrinth Disorders:** Ear pain, motion sickness, tinnitus.

**Gastrointestinal Disorders:** Abdominal distension, diarrhea NOS, dry throat, fecal abnormality NOS, gingival disorder NOS, inguinal hernia NOS, dry lips, stomach discomfort.

**General Disorders and Administration Site Conditions:** Chest pain, fatigue, malaise, pain NOS, weakness.

**Infections and Infestations:** Dysentery NOS, respiratory tract infection NOS, upper respiratory tract infection NOS.

**Injury and Poisoning:** Sunburn.

**Investigations:** Aspartate aminotransferase increased, blood in stool, blood in urine, weight decreased.

**Metabolic and Nutritional Disorders:** Anorexia, dehydration.

**Musculoskeletal, Connective Tissue and Bone Disorders:** Arthralgia, muscle spasms, myalgia, neck pain.

**Nervous System Disorders:** Abnormal dreams, dizziness, migraine NOS, syncope, loss of taste.

**Psychiatric Disorders:** Insomnia.

**Renal and Urinary Disorders:** Choluria, dysuria, hematuria, polyuria, proteinuria, urinary frequency.

**Respiratory, Thoracic and Mediastinal Disorders:** Dyspnea NOS, nasal passage irritation, nasopharyngitis, pharyngitis, pharyngolaryngeal pain, rhinitis NOS, rhinorrhea.

**Skin and Subcutaneous Tissue Disorders:** Clamminess, rash NOS, sweating increased.

**Vascular Disorders:** Hot flashes NOS.

### 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 hepatic encephalopathy), 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, dry place. Protect from light.

Packaging Information

RIXMIN 200 Tablets ................. Strip pack of 10 tablets

Last updated: October 2013
Last reviewed: October 2013

RIXMIN Tablets

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