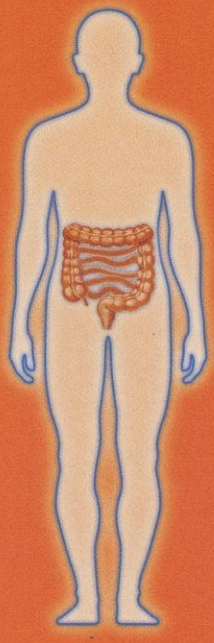
Xifaxan advertisement.

[s.l.]: [s.n.], 2003

The Point Of A Nonsystemic Antibiotic

Works In The Gut. And Only In The Gut.



XIFAXAN 200 mg Tablets TID for 3 days are indicated for the treatment of patients (≥12 years of age) with travelers' diarrhea caused by noninvasive strains of *E coli*.

- Less than 0.4% absorbed.[1]
- Superior to placebo in shortening duration of travelers' diarrhea.[1]
- Adverse events comparable to placebo.[1]
- Low risk of drug-drug interactions.[1]
- When used as directed, no clinically relevant resistance has been observed.[2,3]
- Using XIFAXAN lets you reserve systemic agents for infections that require systemic therapy.[4]

XIFAXAN Tablets should not be used in patients with diarrhea complicated by fever or blood in the stool or diarrhea due to pathogens other than *E coli*.

Safety Considerations

XIFAXAN (rifaximin) Tablets are indicated for the treatment of patients (≥12 years of age) with travelers' diarrhea caused by noninvasive strains of *Escherichia coli*. XIFAXAN 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*. XIFAXAN should be discontinued if diarrhea symptoms get worse or persist more than 24-48 hours, and alternative antibiotic therapy should be considered. *Escherichia coli* has been shown to develop resistance to rifaximin in vitro. However, the clinical significance of such an effect has not been studied.

In clinical trials, XIFAXAN was generally well tolerated. The most common side effects (vs placebo) were flatulence 11.3% (vs 19.7%), headache 9.7% (vs 9.2%), abdominal pain 7.2% (vs 10.1%), and rectal tenesmus 7.2% (vs 8.8%).

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Please see accompanying brief summary of Prescribing Information.

NONSYSTEMIC

Xifaxan™

(rifaximin) tablets 200 mg

TARGETED GI ANTIBIOTIC

Works In The Gut. And Only In The Gut.

NONSYSTEMIC

Xifaxan™

(rifaximin) tablets 200 mg

TARGETED GI ANTIBIOTIC

The following is a brief summary only; see full Prescribing Information for complete product information.

INDICATIONS AND USAGE

XIFAXAN™ Tablets are indicated for the treatment of patients (≥12 years of age) with travelers' diarrhea caused by noninvasive strains of *Escherichia coli* (see **WARNINGS**, **Microbiology**, and **CLINICAL STUDIES**).

XIFAXAN™ 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.*

CONTRAINDICATIONS

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

WARNINGS

XIFAXAN™ 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*. XIFAXAN™ Tablets are not effective in cases of travelers' diarrhea due to *Campylobacter jejuni*. The effectiveness of XIFAXAN™ Tablets in travelers' diarrhea caused by *Shigella* spp. and *Salmonella* spp. has not been proven. XIFAXAN™ Tablets should not be used in patients where *Campylobacter jejuni*, *Shigella* spp., or *Salmonella* spp. may be suspected as causative pathogens.

XIFAXAN™ 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.

Information for Patients

Patients should be advised that XIFAXAN™ Tablets may be taken with or without food. Patients should be advised that XIFAXAN™ Tablets should be discontinued if their diarrhea persists **more than 24-48 hours** or worsens, or if they have fever and/or blood in the stool that they should seek medical care (see **Patient Information**).

Drug-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 (see **Pharmacokinetics** and **Drug-Drug Interactions**).

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—Teratogenic Effects (Pregnancy Category C)

Pregnancy

Pregnancy category C: Rifaximin was teratogenic in rats at doses of 150 to 300 mg/kg (approximately 2.5 to 5 times the clinical dose, adjusted for body surface area) and in rabbits at doses of 62.5 to 1000 mg/kg (approximately 2 to 33 times the clinical dose, adjusted for body surface area). These effects include cleft palate, agnatha, jaw shortening, hemorrhage, eye partially open, small eyes, brachygnathia, incomplete ossification, and increased thoracolumbar vertebrae. There are no adequate and well-controlled studies in pregnant women. XIFAXAN™ 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 XIFAXAN™ Tablets, 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 XIFAXAN™ Tablets in pediatric patients less than 12 years of age have not been established.

Geriatric Use

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

ADVERSE REACTIONS

The safety of XIFAXAN™ Tablets 200 mg taken three times a day (TID) was evaluated in 320 patients in two placebo-controlled clinical trials with 95% of patients receiving at least three days of treatment with XIFAXAN™ Tablets. All adverse events for XIFAXAN™ Tablets 200 mg TID that occurred at a frequency ≥2% in the two placebo-controlled trials combined are provided in Table 1. (These include adverse events that may be attributable to the underlying disease.)

Table 1. All Adverse Events With an Incidence ≥2% Among Patients Receiving XIFAXAN™ Tablets, 600 mg/day, in Placebo-Controlled Studies

	Number (%) of Patients	
MedDRA Preferred Term	**XIFAXAN™Tablets, 600 mg/day (N = 320)**	**Placebo N = 228**
Flatulence	36 (11.3%)	45 (19.7%)
Headache	31 (9.7%)	21 (9.2%)
Abdominal Pain NOS	23 (7.2%)	23 (10.1%)
Rectal Tenesmus	23 (7.2%)	20 (8.8%)
Defecation Urgency	19 (5.9%)	21 (9.2%)
Nausea	17 (5.3%)	19 (8.3%)
Constipation	12 (3.8%)	8 (3.5%)
Pyrexia	10 (3.1%)	10 (4.4%)
Vomiting NOS	7 (2.2%)	4 (1.8%)

The following adverse events, presented by body system, have also been reported in <2% of patients taking XIFAXAN™ Tablets in the two placebo-controlled clinical trials where the 200 mg taken three times a day dose was used. The following includes adverse events 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 events: hypersensitivity reactions, including allergic dermatitis, rash, angioneurotic edema, urticaria, and pruritus, have been identified during foreign postapproval use of XIFAXAN™ Tablets. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to estimate their frequency or establish a causal relationship to drug exposure.

OVERDOSAGE

No specific information is available on the treatment of overdosage with XIFAXAN™ 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 overdosage, discontinue XIFAXAN™ Tablets, treat symptomatically, and institute supportive measures as required.

Rx Only

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6240.00/June 2004

REFERENCES

1. XIFAXAN complete Prescribing Information. **2.** DuPont H, Jiang ZD. Influence of rifaximin treatment on susceptibility of intestinal gram-negative flora and enterococci. *Clin Microbiol Infect Dis.* In Press. **3.** Taylor D, DuPont H, Steffen R. *Johns Hopkins Advanced Studies in Medicine: Meeting the Challenges in the Management of Infectious Diarrhea.* Nov 2003. Vol 3:S938-S963. **4.** Data on file, Salix Pharmaceuticals, Inc.

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Web site: www.salix.com
E-mail: customer.service@salix.com
8540 Colonnade Center Drive, Suite 501, Raleigh, NC 27615
Tel. 866-669-SLXP (7597) Salix Pharmaceuticals, Inc.