

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use XIFAXAN safely and effectively. See full prescribing information for XIFAXAN.

XIFAXAN® (rifaximin) Tablets  
Initial U.S. Approval: 2004

To reduce the development of drug-resistant bacteria and maintain the effectiveness of XIFAXAN Tablets and other antibacterial drugs, XIFAXAN Tablets should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

### INDICATIONS AND USAGE

XIFAXAN Tablets are a rifamycin antibacterial indicated for:

- The treatment of patients (≥ 12 years of age) with travelers' diarrhea caused by noninvasive strains of *Escherichia coli* (1.1)

### DOSAGE AND ADMINISTRATION

- Travelers' diarrhea: one 200 mg tablet taken orally three times a day for 3 days (2.1)
- XIFAXAN Tablets can be taken with or without food (2.2)

### DOSAGE FORMS AND STRENGTHS

- 200 mg tablets (3)

### CONTRAINDICATIONS

- History of hypersensitivity to rifaximin, or to rifamycin antimicrobial agents, or any of the components of XIFAXAN Tablets (4.1)

### WARNINGS AND PRECAUTIONS

- Travelers' Diarrhea Not Caused by *E. coli*: XIFAXAN Tablets were not found effective in diarrhea complicated by fever and/or blood in the stool or diarrhea due to pathogens other than *Escherichia coli*. If diarrhea symptoms get worse or persist for more than 24-48 hours, discontinue treatment with XIFAXAN (5.1)
- *Clostridium difficile*-Associated Diarrhea: evaluate if diarrhea occurs after therapy or does not improve or worsens during therapy (5.2)

### ADVERSE REACTIONS

Most common adverse reactions (≥ 5%) were flatulence, headache, abdominal pain, rectal tenesmus, defecation urgency and nausea (6.1)

To report suspected adverse reactions, contact Salix Pharmaceuticals at 1-866-669-7597 and [www.Salix.com](http://www.Salix.com) or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

### USE IN SPECIFIC POPULATIONS

Pregnancy: Based on animal data, may cause fetal harm (8.1)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: xxx/2010

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51 **FULL PRESCRIBING INFORMATION**

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54 **1 INDICATIONS AND USAGE**

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**1.1 Travelers' Diarrhea**

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XIFAXAN<sup>®</sup> Tablets are indicated for the treatment of patients ( $\geq 12$  years of age) with travelers' diarrhea caused by noninvasive strains of *Escherichia coli* [see *Warnings and Precautions* (5), *Clinical Pharmacology* (12.4) and *Clinical Studies* (14.1)].

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**1.2 Limitations of Use – Travelers' Diarrhea**

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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*.

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**2 DOSAGE AND ADMINISTRATION**

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**2.1 Dosage for Travelers' Diarrhea:**

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The recommended dose of XIFAXAN Tablets is one 200 mg tablet taken orally three times a day for 3 days.

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**2.2 Administration**

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XIFAXAN Tablets can be administered orally with or without food [see *Clinical Pharmacology* (12.3)].

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**3 DOSAGE FORMS AND STRENGTHS**

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XIFAXAN Tablets are pink-colored biconvex tablets and are available in the following strength:

- 200 mg – a round tablet debossed with “Sx” on one side.

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**4 CONTRAINDICATIONS**

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**4.1 Hypersensitivity**

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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.

99 **5 WARNINGS AND PRECAUTIONS**

100 **5.1 Travelers' Diarrhea Not Caused by *Escherichia coli***

101 XIFAXAN Tablets were not found to be effective in patients with diarrhea complicated by  
102 fever and/or blood in the stool or diarrhea due to pathogens other than *Escherichia coli*.

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

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

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111 **5.2 *Clostridium difficile*-Associated Diarrhea**

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

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

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

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128 **5.3 Development of Drug Resistant Bacteria**

129 Prescribing XIFAXAN Tablets in the absence of a proven or strongly suspected bacterial  
130 infection or a prophylactic indication is unlikely to provide benefit to the patient and increases  
131 the risk of the development of drug-resistant bacteria.

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133 **6 ADVERSE REACTIONS**

134 **6.1 Clinical Studies Experience**

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

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139 ***Travelers' Diarrhea***

140 The safety of XIFAXAN Tablets 200 mg taken three times a day (TID) was evaluated in  
141 320 patients in two placebo-controlled clinical trials with 95% of patients receiving three or  
142 four days of treatment with XIFAXAN Tablets. The population studied had a mean age of 31.3  
143 (18-79) years of which approximately 3% were  $\geq 65$  years old, 53% were male and 84% were  
144 White, 11% were Hispanic.

145 Discontinuations of XIFAXAN Tablets 200 mg TID due to adverse reactions occurred in  
 146 0.4% of patients. The adverse reactions leading to discontinuation were taste loss, dysentery,  
 147 weight decrease, anorexia, nausea and nasal passage irrigation.

148 All adverse reactions for XIFAXAN Tablets 200 mg TID that occurred at a frequency  $\geq$   
 149 2% in the two placebo-controlled trials combined are provided in Table 1. (These include  
 150 adverse reactions that may be attributable to the underlying disease.)  
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**Table 1. All Adverse Reactions With an Incidence  $\geq$ 2% Among Patients Receiving XIFAXAN Tablets, 200 mg Three Times Daily, in Placebo-Controlled Studies**

MedDRA Preferred Term	Number (%) of Patients	
	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%)

152 The following adverse reactions, presented by body system, have also been reported in  
 153 <2% of patients taking XIFAXAN Tablets in the two placebo-controlled clinical trials where  
 154 the 200 mg was taken three times a day for travelers' diarrhea was used. The following  
 155 includes adverse reactions regardless of causal relationship to drug exposure.  
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- 157 *Blood and Lymphatic System Disorders:* lymphocytosis, monocytosis, neutropenia
- 158 *Ear and Labyrinth Disorders:* ear pain, motion sickness, tinnitus
- 159 *Gastrointestinal Disorders:* abdominal distension, diarrhea NOS, dry throat, fecal  
 160 abnormality NOS, gingival disorder NOS, inguinal hernia NOS, dry lips, stomach discomfort
- 161 *General Disorders and Administration Site Conditions:* chest pain, fatigue, malaise, pain  
 162 NOS, weakness
- 163 *Infections and Infestations:* dysentery NOS, respiratory tract infection NOS, upper  
 164 respiratory tract infection NOS
- 165 *Injury and Poisoning:* sunburn
- 166 *Investigations:* aspartate aminotransferase increased, blood in stool, blood in urine, weight  
 167 decreased
- 168 *Metabolic and Nutritional Disorders:* anorexia, dehydration
- 169 *Musculoskeletal, Connective Tissue, and Bone Disorders:* arthralgia, muscle spasms,  
 170 myalgia, neck pain
- 171 *Nervous System Disorders:* abnormal dreams, dizziness, migraine NOS, syncope, loss of  
 172 taste
- 173 *Psychiatric Disorders:* insomnia
- 174 *Renal and Urinary Disorders:* choluria, dysuria, hematuria, polyuria, proteinuria, urinary  
 175 frequency
- 176 *Respiratory, Thoracic, and Mediastinal Disorders:* dyspnea NOS, nasal passage irritation,  
 177 nasopharyngitis, pharyngitis, pharyngolaryngeal pain, rhinitis NOS, rhinorrhea
- 178 *Skin and Subcutaneous Tissue Disorders:* clamminess, rash NOS, sweating increased
- 179 *Vascular Disorders:* hot flashes NOS
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## 6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of XIFAXAN Tablets. 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 XIFAXAN.

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

## 7 DRUG INTERACTIONS

Based on the results of these studies in healthy volunteers and *in vitro* induction and inhibition studies using human liver fractions, no clinically relevant drug interactions are anticipated with XIFAXAN Tablets [see *Clinical Pharmacology (12.3)*].

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

Pregnancy Category C:

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. Rifaximin was teratogenic in rats at doses of 150 to 300 mg/kg (approximately 2.5 to 5 times the clinical dose for travelers' diarrhea [600 mg/day], 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 for travelers' diarrhea [600 mg/day], 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.

### 8.3 Nursing Mothers

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.

### 8.4 Pediatric Use

The safety and effectiveness of XIFAXAN Tablets in pediatric patients with Travelers' Diarrhea less than 12 years of age have not been established.

### 8.5 Geriatric Use

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

230 **8.6 Renal Insufficiency**

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

233  
234 **8.7 Hepatic Insufficiency**

235 The pharmacokinetics of rifaximin were evaluated in patients with hepatic encephalopathy  
236 or mild to moderate hepatic impairment (Child Pugh A and B). An increase in systemic  
237 exposure to rifaximin in patients with hepatic impairment was seen in these studies, but no  
238 dosing adjustment with XIFAXAN Tablets is necessary due to its limited systemic absorption  
239 [see *Clinical Pharmacology* (12.3)].

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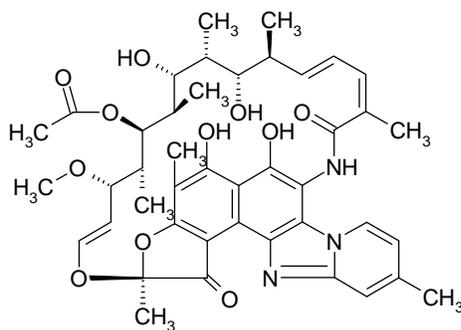
242 **10 OVERDOSAGE**

243 No specific information is available on the treatment of overdose with XIFAXAN  
244 Tablets. In clinical studies at doses higher than the recommended dose (> 600 mg/day for  
245 travelers' diarrhea), adverse reactions were similar in subjects who received doses higher than  
246 the recommended dose and placebo. In the case of overdose, discontinue XIFAXAN  
247 Tablets, treat symptomatically, and institute supportive measures as required.

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250 **11 DESCRIPTION**

251 XIFAXAN Tablets contain rifaximin, a non-aminoglycoside semi-synthetic, nonsystemic  
252 antibiotic derived from rifamycin SV. Rifaximin is a structural analog of rifampin. The  
253 chemical name for rifaximin is (2*S*,16*Z*,18*E*,20*S*,21*S*,22*R*,23*R*,24*R*,25*S*,26*S*,27*S*,28*E*)-  
254 5,6,21,23,25-pentahydroxy-27-methoxy-2,4,11,16,20,22,24,26-octamethyl-2,7-  
255 (epoxypentadeca-[1,11,13]trienimino)benzofuro[4,5-*e*]pyrido[1,2-*á*]benzimidazole-1,15(2*H*)-  
256 dione,25-acetate. The empirical formula is C<sub>43</sub>H<sub>51</sub>N<sub>3</sub>O<sub>11</sub> and its molecular weight is 785.9. The  
257 chemical structure is represented below:  
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262 XIFAXAN Tablets for oral administration are film-coated and contain 200 mg of  
263 rifaximin.

264 Inactive ingredients: Each tablet contains colloidal silicon dioxide, disodium edetate,  
265 glycerol palmitostearate, hypromellose, microcrystalline cellulose, propylene glycol, red iron  
266 oxide, sodium starch glycolate, talc, and titanium dioxide.

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268 **12 CLINICAL PHARMACOLOGY**

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270 **12.1 Mechanism of Action**

271 Rifaximin is a rifamycin antibacterial drug [see *Clinical Pharmacology (12.4)*].

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### 273 12.3 Pharmacokinetics

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#### 275 *Absorption*

276 The mean plasma pharmacokinetic parameters of rifaximin in 14 healthy subjects  
277 after a single oral 400 mg dose given as 2 x 200 mg doses and a single 550 mg dose in 12  
278 healthy subjects under fed and fasting conditions are summarized in Table 2.

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**Table 2. Effect of Food on the Mean ± S.D. Pharmacokinetic Parameters**

Parameter	Single 400 mg Dose of Rifaximin (N = 14)		Single 550 mg Dose of Rifaximin (N= 12)	
	Fasting	Fed	Fasting	Fed
C <sub>max</sub> (ng/mL)	3.80 ± 1.32	9.63 ± 5.93	4.04 ± 1.51	4.76 ± 4.25
T <sub>max</sub> (h)	1.21 ± 0.47	1.90 ± 1.52	0.75 (0.50-2.05)*	1.50 (0.50-4.08)*
Half-Life (h)	5.85 ± 4.34	5.95 ± 1.88	1.83 ± 1.38	4.84 ± 1.34
AUC (ng·h/mL)	18.35 ± 9.48	34.70 ± 9.23	11.1 ± 4.15	22.5 ± 12.0

281 \*Median (range)

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Because systemic absorption of rifaximin was minimal in both the fasting state and when administered within 30 minutes of a high-fat breakfast, XIFAXAN Tablets can be administered with or without food [see *Dosage and Administration (2.2)*].

Systemic absorption of rifaximin (XIFAXAN Tablets 200 mg three times daily) was also 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<sub>0-last</sub> estimates were 6.95 ± 5.15 ng·h/mL on Day 1 and 7.83 ± 4.94 ng·h/mL on Day 3. XIFAXAN Tablets are not suitable for treating systemic bacterial infections because less than 0.4% of the drug is absorbed after oral administration [see *Warnings and Precautions (5.1)*].

#### 308 *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.

#### 309 *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 [see *Drug Interactions (7)*].

*In vitro* study data suggest that rifaximin is a substrate for P-glycoprotein. Rifaximin is a weak inhibitor of P-gp; at concentrations (50 µM) significantly higher than those

314 anticipated in plasma following oral dose administration, rifaximin only partially  
315 inhibited transport of a model P-gp substrate. Therefore, no clinically significant  
316 interactions with other drugs affected by P-glycoprotein are anticipated.

#### 317 318 *Excretion*

319 400 mg <sup>14</sup>C-Rifaximin was administered as a single dose to 4 healthy male subjects.  
320 The mean overall recovery of radioactivity in the urine and feces of 3 subjects during the  
321 168 hours after administration was 96.94 ± 5.64% of the dose. Radioactivity was excreted  
322 almost exclusively in the feces (96.62 ± 5.67% of the dose), with only a small proportion  
323 of the dose (mean 0.32% of the dose) excreted in urine. Analysis of fecal extracts  
324 indicated that rifaximin was being excreted as unchanged drug. The amount of  
325 radioactivity in urine (<0.4% of the dose) suggests that rifaximin is poorly absorbed from  
326 the gastrointestinal tract and is almost exclusively and completely excreted in feces as  
327 unchanged drug. Mean rifaximin pharmacokinetic parameters were C<sub>max</sub> 4.3 ± 2.8 ng/mL  
328 and AUC<sub>t</sub> 19.5 ± 16.5 ng•h/mL with a median T<sub>max</sub> of 1.25 hours.

#### 329 330 *Drug Interactions*

331 Since rifaximin was shown to induce CYP3A4 *in vitro*, drug interaction studies in healthy  
332 volunteers were conducted with midazolam and an oral contraceptive containing ethinyl  
333 estradiol and norgestimate to assess the effect of rifaximin on these CYP3A4 substrates.

334  
335 Two clinical drug-drug interaction studies were conducted with the rifaximin 200 mg  
336 tablet.

#### 337 338 *Midazolam*

339 An open-label, randomized, crossover, drug-interaction trial designed to assess the effect  
340 of rifaximin 200 mg administered orally (PO) every 8 hours (Q8H) for 3 days and Q8H for 7  
341 days, on the pharmacokinetics of a single dose of either midazolam 2 mg intravenous (IV) or  
342 midazolam 6 mg PO. No significant difference was observed in the metrics of systemic  
343 exposure or elimination of IV or PO midazolam or its major metabolite, 1'-  
344 hydroxymidazolam, between midazolam alone or together with rifaximin. Therefore,  
345 rifaximin was not shown to significantly affect intestinal or hepatic CYP3A4 activity.

#### 346 347 *Oral Contraceptives*

348 The oral contraceptive study utilized an open-label, crossover design in 28 healthy female  
349 subjects to determine if rifaximin 200 mg PO administered Q8H for 3 days altered the  
350 pharmacokinetics of a single dose of an oral contraceptive containing 0.07 mg ethinyl estradiol  
351 and 0.50 mg norgestimate. Results showed that the pharmacokinetics of single doses of  
352 ethinyl estradiol and norgestimate were not altered by rifaximin [see *Drug Interactions* (7)].

353  
354 Based on the results of the interaction studies in healthy volunteers and *in vitro*  
355 induction and inhibition studies using human liver fractions, no clinically relevant drug  
356 interactions are anticipated with XIFAXAN Tablets [see *Drug Interactions* (7)].

## 357 358 **12.4 Microbiology**

### 359 *Mechanism of Action*

360 Rifaximin is a non-aminoglycoside semi-synthetic antibacterial derived from  
361 rifamycin SV. Rifaximin acts by binding to the beta-subunit of bacterial DNA-dependent  
362 RNA polymerase resulting in inhibition of bacterial RNA synthesis.

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364 *Escherichia coli* has been shown to develop resistance to rifaximin *in vitro*.  
365 However, the clinical significance of such an effect has not been studied.

366

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

371

372 Rifaximin has been shown to be active against the following pathogen in clinical  
373 studies of infectious diarrhea as described in the *Indications and Usage (1)* section:  
374 *Escherichia coli* (enterotoxigenic and enteroaggregative strains).

375

#### 376 *Susceptibility Tests*

377 *In vitro* susceptibility testing was performed according to the National Committee for  
378 Clinical Laboratory Standards (NCCLS) agar dilution method M7-A6 [see *References*  
379 (15)]. However, the correlation between susceptibility testing and clinical outcome has  
380 not been determined.

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## 383 **13 NONCLINICAL TOXICOLOGY**

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### 385 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

386 Malignant schwannomas in the heart were significantly increased in male Crl:CD®  
387 (SD) rats that received rifaximin by oral gavage for two years at 150 to 250 mg/kg/day  
388 (doses equivalent to 2.4 to 4 times the recommended daily dose of 200 mg TID, based on  
389 relative body surface area comparisons). There was no increase in tumors in Tg.rasH2  
390 mice dosed orally with rifaximin for 26 weeks at 150 to 2000 mg/kg/day (doses  
391 equivalent to 1.2 to 16 times the recommended daily dose, based on relative body surface  
392 area comparisons).

393

394 Rifaximin was not genotoxic in the bacterial reverse mutation assay, chromosomal  
395 aberration assay, rat bone marrow micronucleus assay, rat hepatocyte unscheduled DNA  
396 synthesis assay, or the CHO/HGPRT mutation assay. There was no effect on fertility in  
397 male or female rats following the administration of rifaximin at doses up to 300 mg/kg  
398 (approximately 5 times the clinical dose of 600 mg/day, adjusted for body surface area).

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## 401 **14 CLINICAL STUDIES**

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### 403 **14.1 Travelers' Diarrhea**

404 The efficacy of XIFAXAN Tablets given as 200 mg orally taken three times a day for  
405 3 days was evaluated in 2 randomized, multi-center, double-blind, placebo-controlled  
406 studies in adult subjects with travelers' diarrhea. One study was conducted at clinical  
407 sites in Mexico, Guatemala, and Kenya (Study 1). The other study was conducted in  
408 Mexico, Guatemala, Peru, and India (Study 2). Stool specimens were collected before

409 treatment and 1 to 3 days following the end of treatment to identify enteric pathogens.  
410 The predominant pathogen in both studies was *Escherichia coli*.

411

412 The clinical efficacy of XIFAXAN Tablets was assessed by the time to return to  
413 normal, formed stools and resolution of symptoms. The primary efficacy endpoint was  
414 time to last unformed stool (TLUS) which was defined as the time to the last unformed  
415 stool passed, after which clinical cure was declared. Table 3 displays the median TLUS  
416 and the number of patients who achieved clinical cure for the intent to treat population  
417 (ITT) of Study 1. The duration of diarrhea was significantly shorter in patients treated  
418 with XIFAXAN Tablets than in the placebo group. More patients treated with XIFAXAN  
419 Tablets were classified as clinical cures than were those in the placebo group.

420

421 **Table 3. Clinical Response in Study 1 (ITT population)**

	<b>XIFAXAN (n=125)</b>	<b>Placebo (n=129)</b>	<b>Estimate (97.5% CI)</b>	<b>P-Value</b>
Median TLUS (hours)	32.5	58.6	1.78 <sup>a</sup> (1.26, 2.50)	0.0002
Clinical cure, n (%)	99 (79.2)	78 (60.5)	18.7 <sup>b</sup> (5.3, 32.1)	0.001

<sup>a</sup> Hazard Ratio

<sup>b</sup> Difference in rates

422

423 Microbiological eradication (defined as the absence of a baseline pathogen in culture  
424 of stool after 72 hours of therapy) rates for Study 1 are presented in Table 4 for patients  
425 with any pathogen at baseline and for the subset of patients with *Escherichia coli* at  
426 baseline. *Escherichia coli* was the only pathogen with sufficient numbers to allow  
427 comparisons between treatment groups.

428

429 Even though XIFAXAN Tablets had microbiologic activity similar to placebo, it  
430 demonstrated a clinically significant reduction in duration of diarrhea and a higher  
431 clinical cure rate than placebo. Therefore, patients should be managed based on clinical  
432 response to therapy rather than microbiologic response.

433

434 **Table 4. Microbiologic Eradication Rates in Study 1**  
435 **Subjects with a Baseline Pathogen**

	<b>XIFAXAN</b>	<b>Placebo</b>
Overall	48/70 (68.6)	41/61 (67.2)
<i>E. coli</i>	38/53 (71.7)	40/54 (74.1)

436

437 Study 2 provided additional information to support the results presented for Study 1.  
438 This study also provided evidence that subjects treated with XIFAXAN Tablets with  
439 fever and/or blood in the stool at baseline had prolonged TLUS. These subjects had  
440 lower clinical cure rates than those without fever or blood in the stool at baseline. Many  
441 of the patients with fever and/or blood in the stool (dysentery-like diarrheal syndromes)  
442 had invasive pathogens, primarily *Campylobacter jejuni*, isolated in the baseline stool.

443

444 Also in this study, the majority of the subjects treated with XIFAXAN Tablets who  
445 had *Campylobacter jejuni* isolated as a sole pathogen at baseline failed treatment and the  
446 resulting clinical cure rate for these patients was 23.5% (4/17). In addition to not being  
447 different from placebo, the microbiologic eradication rates for subjects with

448 *Campylobacter jejuni* isolated at baseline were much lower than the eradication rates  
449 seen for *Escherichia coli*.

450

451 In an unrelated phase 1, open-label, pharmacokinetic study of oral XIFAXAN  
452 Tablets 200 mg taken every 8 hours for 3 days, 15 adult subjects were challenged with  
453 *Shigella flexneri* 2a, of whom 13 developed diarrhea or dysentery and were treated with  
454 XIFAXAN. Although this open-label challenge trial was not adequate to assess the  
455 effectiveness of XIFAXAN in the treatment of shigellosis, the following observations  
456 were noted.

457

458 Eight subjects received rescue treatment with ciprofloxacin either because of lack of  
459 response to XIFAXAN treatment within 24 hours (2), or because they developed severe  
460 dysentery (5), or because of recurrence of *Shigella flexneri* in the stool (1). Five of the 13  
461 subjects received ciprofloxacin although they did not have evidence of severe disease or  
462 relapse.

463

464

## 465 **15 REFERENCES**

466 Methods for dilution antimicrobial susceptibility tests for bacteria that grow  
467 aerobically. National Committee for Clinical Laboratory Standards, Sixth Edition, Wayne  
468 PA. *Approved Standard NCCLS Document M7-A6* January 2003; 23 (2).

469

470

## 471 **16 HOW SUPPLIED/STORAGE AND HANDLING**

472 The 200 mg tablet is a pink-colored, round, biconvex tablet with “Sx” debossed on  
473 one side. It is available in the following presentations:

- 474 • NDC 65649-301-04, single blister unit (Professional Sample)
- 475 • NDC 65649-301-03, bottles of 30 tablets
- 476 • NDC 65649-301-41 bottles of 100 tablets
- 477 • NDC 65649-301-05 carton of 100 tablets, Unit Dose

478

### 479 **Storage**

480 Store XIFAXAN Tablets at 20–25°C (68–77°F); excursions permitted to 15–30°C  
481 (59–86°F). See USP Controlled Room Temperature.

482

483

## 484 **17 PATIENT COUNSELING INFORMATION**

485

### 486 **17.1 Persistent Diarrhea**

487 For those patients being treated for travelers’ diarrhea, XIFAXAN Tablets should be  
488 discontinued if diarrhea persists more than 24–48 hours or worsens, or if the patient has  
489 fever and/or blood in the stool the patient should seek medical care [see *Warnings and*  
490 *Precautions (5.1)*].

491

### 492 **17.2 *Clostridium difficile*-Associated Diarrhea**

493 *Clostridium difficile*-associated diarrhea (CDAD) has been reported with use of  
494 nearly all antibacterial agents, including XIFAXAN Tablets, and may range in severity  
495 from mild diarrhea to fatal colitis. Treatment with antibiotics alters the normal flora of  
496 the colon which may lead to *C. difficile*. Patients can develop watery and bloody stools  
497 (with or without stomach cramps and fever) even as late as two or more months after  
498 having taken the last dose of the antibiotic. If diarrhea occurs after therapy or does not

499 improve or worsens during therapy, patients should contact their physician as soon as  
500 possible [see *Warnings and Precautions* (5.2)].

501

### 502 **17.3 Administration with Food**

503 Patients should be informed that XIFAXAN Tablets may be taken with or without  
504 food.

505

### 506 **17.4 Antibacterial Resistance**

507 Patients should be counseled that antibacterial drugs including XIFAXAN Tablets should  
508 only be used to treat bacterial infections. They do not treat viral infections (e.g., the common  
509 cold). When XIFAXAN Tablets are prescribed to treat a bacterial infection, patients should be  
510 told that although it is common to feel better early in the course of therapy, the medication  
511 should be taken exactly as directed. Skipping doses or not completing the full course of  
512 therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the  
513 likelihood that bacteria will develop resistance and will not be treatable by XIFAXAN Tablets  
514 or other antibacterial drugs in the future.

515

516

517

518

519

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521 Alfa Wassermann S.p.A.

522

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528 XXX 2010

529 Product protected by US Patent Nos. 7,045,620 and 7,612,199 and other pending  
530 applications.

531

532

533

534 Web site: [www.Salix.com](http://www.Salix.com)

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NDA-21361

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SUPPL-11

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/s/  
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RENATA ALBRECHT

03/03/2010