

## 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 and other antibacterial drugs, XIFAXAN should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

### RECENT MAJOR CHANGES

Indications and Usage, Hepatic Encephalopathy (1.3) xx/xxxx  
Dosage and Administration, Hepatic Encephalopathy (2.2) xx/xxxx

### INDICATIONS AND USAGE

XIFAXAN is 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)
- Reduction in risk of overt hepatic encephalopathy (HE) recurrence in patients ≥ 18 years of age (1.2)

Limitations of Use

- TD: Do not use in patients with diarrhea complicated by fever or blood in the stool or diarrhea due to pathogens other than *Escherichia coli* (1.1)

### DOSAGE AND ADMINISTRATION

- Travelers' diarrhea: one 200 mg tablet taken orally three times a day for 3 days, with or without food (2.1)
- Hepatic encephalopathy: One 550 mg tablet taken orally two times a day, with or without food (2.2)

### DOSAGE FORMS AND STRENGTHS

- 200 mg and 550 mg tablets (3)

### CONTRAINDICATIONS

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

### WARNINGS AND PRECAUTIONS

- Travelers' Diarrhea Not Caused by *E. coli*: XIFAXAN was not effective in diarrhea complicated by fever and/or blood in the stool or diarrhea due to pathogens other than *E. coli*. If diarrhea symptoms get worse or persist for more than 24-48 hours, discontinue XIFAXAN and consider alternative antibiotics (5.1)
- *Clostridium difficile*-Associated Diarrhea: Evaluate if diarrhea occurs after therapy or does not improve or worsens during therapy (5.2)
- Hepatic Impairment: Use with caution in patients with severe (Child-Pugh C) hepatic impairment (5.4, 8.7)

### ADVERSE REACTIONS

- Most common adverse reactions in travelers' diarrhea (≥ 5%): Flatulence, headache, abdominal pain, rectal tenesmus, defecation urgency and nausea (6.1)
- Most common adverse reactions in HE (≥ 10%): Peripheral edema, nausea, dizziness, fatigue, ascites, flatulence, and headache (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)
- Nursing Mothers: Discontinue nursing or drug, taking into account the importance of the drug to the mother (8.3)

See 17 for PATIENT COUNSELING INFORMATION

Revised: xxx/2010

1	<b>FULL PRESCRIBING INFORMATION: CONTENTS*</b>
2	
3	<b>1 INDICATIONS AND USAGE</b>
4	1.1 Travelers' Diarrhea
5	1.2 Hepatic Encephalopathy
6	<b>2 DOSAGE AND ADMINISTRATION</b>
7	2.1 Dosage for Travelers' Diarrhea
8	2.2 Dosage for Hepatic Encephalopathy
9	<b>3 DOSAGE FORMS AND STRENGTHS</b>
10	<b>4 CONTRAINDICATIONS</b>
11	4.1 Hypersensitivity
12	<b>5 WARNINGS AND PRECAUTIONS</b>
13	5.1 Travelers' Diarrhea Not Caused by <i>Escherichia coli</i>
14	5.2 <i>Clostridium difficile</i> -Associated Diarrhea
15	5.3 Development of Drug Resistant Bacteria
16	5.4 Severe (Child-Pugh C) Hepatic Impairment
17	<b>6 ADVERSE REACTIONS</b>
18	6.1 Clinical Studies Experience
19	6.2 Postmarketing Experience
20	<b>7 DRUG INTERACTIONS</b>
21	<b>8 USE IN SPECIFIC POPULATIONS</b>
22	8.1 Pregnancy
23	8.3 Nursing Mothers
24	8.4 Pediatric Use
25	8.5 Geriatric Use
26	8.6 Renal Impairment
27	8.7 Hepatic Impairment
28	<b>10 OVERDOSAGE</b>
29	<b>11 DESCRIPTION</b>
30	<b>12 CLINICAL PHARMACOLOGY</b>
31	12.1 Mechanism of Action
32	12.3 Pharmacokinetics
33	12.4 Microbiology
34	<b>13 NONCLINICAL TOXICOLOGY</b>
35	13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
36	13.2 Animal Toxicology and/or Pharmacology
37	<b>14 CLINICAL STUDIES</b>
38	14.1 Travelers' Diarrhea
39	14.2 Hepatic Encephalopathy

40	<b>15 REFERENCES</b>
41	<b>16 HOW SUPPLIED/STORAGE AND HANDLING</b>
42	<b>17 PATIENT COUNSELING INFORMATION</b>
43	17.1 Persistent Diarrhea
44	17.2 <i>Clostridium difficile</i> -Associated Diarrhea
45	17.3 Administration with Food
46	17.4 Antibacterial Resistance
47	17.5 Severe Hepatic Impairment

52 \*Sections or subsections omitted from the full prescribing information are not listed

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## 72 FULL PRESCRIBING INFORMATION

### 75 1 INDICATIONS AND USAGE

76 To reduce the development of drug-resistant bacteria and maintain the  
77 effectiveness of XIFAXAN and other antibacterial drugs, XIFAXAN when used  
78 to treat infection should be used only to treat or prevent infections that are proven  
79 or strongly suspected to be caused by susceptible bacteria. When culture and  
80 susceptibility information are available, they should be considered in selecting or  
81 modifying antibacterial therapy. In the absence of such data, local epidemiology  
82 and susceptibility patterns may contribute to the empiric selection of therapy.

#### 84 1.1 Travelers' Diarrhea

85 XIFAXAN 200 mg is indicated for the treatment of patients ( $\geq$  12 years of  
86 age) with travelers' diarrhea caused by noninvasive strains of *Escherichia coli*  
87 [see *Warnings and Precautions* (5), *Clinical Pharmacology* (12.4) and *Clinical*  
88 *Studies* (14.1)].

#### 90 *Limitations of Use*

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

#### 93 1.2 Hepatic Encephalopathy

94  
95 XIFAXAN 550 mg is indicated for reduction in risk of overt hepatic  
96 encephalopathy (HE) recurrence in patients  $\geq$  18 years of age.

97 In the trials of XIFAXAN for HE, 91% of the patients were using lactulose  
98 concomitantly. Differences in the treatment effect of those patients not using  
99 lactulose concomitantly could not be assessed.

100 XIFAXAN has not been studied in patients with MELD (Model for End-  
101 Stage Liver Disease) scores > 25, and only 8.6% of patients in the controlled trial  
102 had MELD scores over 19. There is increased systemic exposure in patients with  
103 more severe hepatic dysfunction [see *Warnings and Precautions (5.4), Use in*  
104 *Specific Populations (8.7), Clinical Pharmacology (12.3)*].

105  
106

## 107 **2 DOSAGE AND ADMINISTRATION**

108

### 109 **2.1 Dosage for Travelers' Diarrhea:**

110 The recommended dose of XIFAXAN is one 200 mg tablet taken orally three  
111 times a day for 3 days. XIFAXAN can be administered orally, with or without  
112 food [see *Clinical Pharmacology (12.3)*].

113  
114

### 115 **2.2 Dosage for Hepatic Encephalopathy**

116 The recommended dose of XIFAXAN is one 550 mg tablet taken orally two  
117 times a day, with or without food [see *Clinical Pharmacology (12.3)*].

118  
119

## 120 **3 DOSAGE FORMS AND STRENGTHS**

121 XIFAXAN is pink-colored biconvex tablets and is available in the following  
122 strengths:

- 123 • 200 mg – a round tablet debossed with “Sx” on one side.
- 124 • 550 mg – an oval tablet debossed with “rfx” on one side.

125  
126

## 126 **4 CONTRAINDICATIONS**

### 127 **4.1 Hypersensitivity**

128 XIFAXAN is contraindicated in patients with a hypersensitivity to rifaximin,  
129 any of the rifamycin antimicrobial agents, or any of the components in  
130 XIFAXAN. Hypersensitivity reactions have included exfoliative dermatitis,  
131 angioneurotic edema, and anaphylaxis [see *Adverse Reactions (6.2)*].

132  
133

## 133 **5 WARNINGS AND PRECAUTIONS**

### 134 **5.1 Travelers' Diarrhea Not Caused by *Escherichia coli***

135 XIFAXAN was not found to be effective in patients with diarrhea complicated by fever  
136 and/or blood in the stool or diarrhea due to pathogens other than *Escherichia coli*.

137 Discontinue XIFAXAN if diarrhea symptoms get worse or persist more than 24-48 hours  
138 and alternative antibiotic therapy should be considered.

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

143  
144

### 144 **5.2 *Clostridium difficile*-Associated Diarrhea**

145

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

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

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

160

### 161 **5.3 Development of Drug Resistant Bacteria**

162 Prescribing XIFAXAN for travelers' diarrhea in the absence of a proven or strongly  
163 suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the  
164 patient and increases the risk of the development of drug-resistant bacteria.

165

### 166 **5.4 Severe (Child-Pugh C) Hepatic Impairment**

167 There is increased systemic exposure in patients with severe hepatic impairment. Animal  
168 toxicity studies did not achieve systemic exposures that were seen in patients with severe  
169 hepatic impairment. The clinical trials were limited to patients with MELD scores <25.  
170 Therefore, caution should be exercised when administering XIFAXAN to patients with severe  
171 hepatic impairment (Child-Pugh C) [see *Use in Specific Populations (8.7), Nonclinical*  
172 *Toxicology (13.2) and Clinical Studies (14.2)*].

173

## 174 **6 ADVERSE REACTIONS**

### 175 **6.1 Clinical Studies Experience**

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

179

#### 180 Travelers' Diarrhea

181 The safety of XIFAXAN 200 mg taken three times a day was evaluated in patients with  
182 travelers' diarrhea consisting of 320 patients in two placebo-controlled clinical trials with 95%  
183 of patients receiving three or four days of treatment with XIFAXAN. The population studied  
184 had a mean age of 31.3 (18-79) years of which approximately 3% were  $\geq 65$  years old, 53%  
185 were male and 84% were White, 11% were Hispanic.

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

189 All adverse reactions for XIFAXAN 200 mg three times daily that occurred at a frequency  
190  $\geq 2\%$  in the two placebo-controlled trials combined are provided in Table 1. (These include  
191 adverse reactions that may be attributable to the underlying disease.)

192

**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%)	45 (20%)
Headache	31 (10%)	21 (9%)
Abdominal Pain NOS*	23 (7%)	23 (10%)
Rectal Tenesmus	23 (7%)	20 (9%)
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 XIFAXAN 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:* Choloria, 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

*Hepatic Encephalopathy*

The data described below reflect exposure to XIFAXAN 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 XIFAXAN 550 mg taken two times a day for reducing the risk of overt hepatic encephalopathy recurrence in adult patients was evaluated in a 6-month placebo-

229 controlled clinical trial (n = 140) and in a long term follow-up study (n = 280). The population  
 230 studied had a mean age of 56.26 (range: 21-82) years; approximately 20% of the patients were  
 231  $\geq 65$  years old, 61% were male, 86% were White, and 4% were Black. Ninety-one percent of  
 232 patients in the trial were taking lactulose concomitantly. All adverse reactions that occurred at  
 233 an incidence  $\geq 5\%$  and at a higher incidence in XIFAXAN 550 mg-treated subjects than in the  
 234 placebo group in the 6-month trial are provided in Table 2. (These include adverse events that  
 235 may be attributable to the underlying disease).

236  
 237 **Table 2: Adverse Reactions Occurring in  $\geq 5\%$  of Patients Receiving XIFAXAN and**  
 238 **at a Higher Incidence Than Placebo**

MedDRA Preferred Term	Number (%) of Patients	
	XIFAXAN Tablets 550 mg TWICE DAILY N = 140	Placebo N = 159
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 (5%)
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%)

239  
 240 The following adverse reactions, presented by body system, have also been reported in the  
 241 placebo-controlled clinical trial in greater than 2% but less than 5% of patients taking  
 242 XIFAXAN 550 mg taken orally two times a day for hepatic encephalopathy. The following  
 243 includes adverse events occurring at a greater incidence than placebo, regardless of causal  
 244 relationship to drug exposure.

245  
 246 *Ear and Labyrinth Disorders:* Vertigo

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

249 *General Disorders and Administration Site Conditions:* Chest pain, generalized edema,  
 250 influenza like illness, pain NOS

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

253 *Injury, Poisoning and Procedural Complications:* Contusion, fall, procedural pain

254 *Investigations:* Weight increased

255 *Metabolic and Nutritional Disorders:* Anorexia, dehydration, hyperglycemia,  
256 hyperkalemia, hypoglycemia, hyponatremia  
257 *Musculoskeletal, Connective Tissue, and Bone Disorders:* Myalgia, pain in extremity  
258 *Nervous System Disorders:* Amnesia, disturbance in attention, hypoesthesia, memory  
259 impairment, tremor  
260 *Psychiatric Disorders:* Confusional state  
261 *Respiratory, Thoracic, and Mediastinal Disorders:* Epistaxis  
262 *Vascular Disorders:* Hypotension  
263  
264

## 265 **6.2 Postmarketing Experience**

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

### 270 *Infections and Infestations*

271 Cases of *C. difficile*-associated colitis have been reported [*see Warnings and Precautions*  
272 (5.2)].

#### 273 *General*

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

278

## 279 **7 DRUG INTERACTIONS**

280

281 *In vitro* studies have shown that rifaximin did not inhibit cytochrome P450 isoenzymes  
282 1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1 and CYP3A4 at concentrations ranging from 2 to 200  
283 ng/mL [*see Clinical Pharmacology (12.3)*]. Rifaximin is not expected to inhibit these enzymes  
284 in clinical use.

285

286 An *in vitro* study has suggested that rifaximin induces CYP3A4 [*see Clinical*  
287 *Pharmacology (12.3)*]. However, in patients with normal liver function, rifaximin at the  
288 recommended dosing regimen is not expected to induce CYP3A4. It is unknown whether  
289 rifaximin can have a significant effect on the pharmacokinetics of concomitant CYP3A4  
290 substrates in patients with reduced liver function who have elevated rifaximin concentrations.

291

292 An *in vitro* study suggested that rifaximin is a substrate of P-glycoprotein. It is unknown  
293 whether concomitant drugs that inhibit P-glycoprotein can increase the systemic exposure of  
294 rifaximin [*see Clinical Pharmacology (12.3)*].

295

296

297

## 298 **8 USE IN SPECIFIC POPULATIONS**

299

### 300 **8.1 Pregnancy**

301 *Pregnancy Category C*

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

305 Rifaximin was teratogenic in rats at doses of 150 to 300 mg/kg (approximately 2.5 to  
306 5 times the clinical dose for travelers' diarrhea [600 mg/day], and approximately 1.3 to  
307 2.6 times the clinical dose for hepatic encephalopathy [1100 mg/day], adjusted for body  
308 surface area). Rifaximin was teratogenic in rabbits at doses of 62.5 to 1000 mg/kg  
309 (approximately 2 to 33 times the clinical dose for travelers' diarrhea [600 mg/day], and  
310 approximately 1.1 to 18 times the clinical dose for hepatic encephalopathy [1100  
311 mg/day], adjusted for body surface area). These effects include cleft palate, agnatha, jaw  
312 shortening, hemorrhage, eye partially open, small eyes, brachygnathia, incomplete  
313 ossification, and increased thoracolumbar vertebrae.

314

315

### 316 **8.3 Nursing Mothers**

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

321

### 322 **8.4 Pediatric Use**

323 The safety and effectiveness of XIFAXAN 200 mg in pediatric patients with  
324 travelers' diarrhea less than 12 years of age have not been established.

325 The safety and effectiveness of XIFAXAN 550 mg for HE have not been established  
326 in patients < 18 years of age.

327

### 328 **8.5 Geriatric Use**

329 Clinical studies with rifaximin 200 mg for travelers' diarrhea did not include  
330 sufficient numbers of patients aged 65 and over to determine whether they respond  
331 differently than younger subjects.

332

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

339

### 340 **8.6 Renal Impairment**

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

343

### 344 **8.7 Hepatic Impairment**

345 Following administration of XIFAXAN 550 mg twice daily to patients with a history of  
346 hepatic encephalopathy, the systemic exposure (i.e.,  $AUC_{\tau}$ ) of rifaximin was about 10-, 13-,  
347 and 20-fold higher in those patients with mild (Child-Pugh A), moderate (Child-Pugh B) and  
348 severe (Child-Pugh C) hepatic impairment, respectively, compared to that in healthy  
349 volunteers. No dosage adjustment is recommended because rifaximin is presumably acting  
350 locally. Nonetheless, caution should be exercised when XIFAXAN is administered to patients

351 with severe hepatic impairment [see *Warnings and Precautions (5.4), Clinical Pharmacology*  
352 (12.3), *Nonclinical Toxicology (13.2), and Clinical Studies (14.2)*].

353

## 354 **10 OVERDOSAGE**

355 No specific information is available on the treatment of overdosage with XIFAXAN. In  
356 clinical studies at doses higher than the recommended dose (> 600 mg/day for travelers'  
357 diarrhea or > 1100 mg/day for hepatic encephalopathy), adverse reactions were similar in  
358 subjects who received doses higher than the recommended dose and placebo. In the case of  
359 overdosage, discontinue XIFAXAN, treat symptomatically, and institute supportive measures  
360 as required.

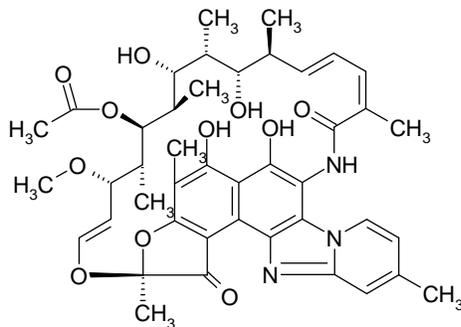
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362

## 363 **11 DESCRIPTION**

364 XIFAXAN tablets contain rifaximin, a non-aminoglycoside semi-synthetic, nonsystemic  
365 antibiotic derived from rifamycin SV. Rifaximin is a structural analog of rifampin. The  
366 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*)-  
367 5,6,21,23,25-pentahydroxy-27-methoxy-2,4,11,16,20,22,24,26-octamethyl-2,7-  
368 (epoxypentadeca-[1,11,13]trienimino)benzofuro[4,5-*e*]pyrido[1,2-*a*]-benzimidazole-1,15(2*H*)-  
369 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  
370 chemical structure is represented below:

371



372

373

374

375 XIFAXAN tablets for oral administration are film-coated and contain 200 mg or 550 mg  
376 of rifaximin.

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

380

## 381 **12 CLINICAL PHARMACOLOGY**

382

### 383 **12.1 Mechanism of Action**

384 Rifaximin is an antibacterial drug [see *Clinical Pharmacology (12.4)*].

385

### 386 **12.3 Pharmacokinetics**

387

#### 388 Absorption

##### 389 *Travelers' Diarrhea*

390 Systemic absorption of rifaximin (200 mg three times daily) was evaluated in 13  
391 subjects challenged with shigellosis on Days 1 and 3 of a three-day course of treatment.

392 Rifaximin plasma concentrations and exposures were low and variable. There was no  
 393 evidence of accumulation of rifaximin following repeated administration for 3 days (9  
 394 doses). Peak plasma rifaximin concentrations after 3 and 9 consecutive doses ranged  
 395 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>  
 396 estimates were 6.95 ± 5.15 ng•h/mL on Day 1 and 7.83 ± 4.94 ng•h/mL on Day 3.  
 397 XIFAXAN is not suitable for treating systemic bacterial infections because of limited  
 398 systemic exposure after oral administration [see Warnings and Precautions (5.1)].  
 399

#### 400 *Hepatic Encephalopathy*

401 After a single dose and multiple doses of rifaximin 550 mg in healthy subjects, the  
 402 mean time to reach peak plasma concentrations was about an hour. The pharmacokinetic  
 403 (PK) parameters were highly variable and the accumulation ratio based on AUC was  
 404 1.37.  
 405

406 The PK of rifaximin in patients with a history of HE was evaluated after  
 407 administration of XIFAXAN, 550 mg two times a day. The PK parameters were  
 408 associated with a high variability and mean rifaximin exposure (AUC<sub>τ</sub>) in patients with a  
 409 history of HE (147 ng•h/mL) was approximately 12-fold higher than that observed in  
 410 healthy subjects following the same dosing regimen (12.3 ng•h/mL). When PK  
 411 parameters were analyzed based on Child-Pugh Class A, B, and C, the mean AUC<sub>τ</sub> was  
 412 10-, 13-, and 20-fold higher, respectively, compared to that in healthy subjects (Table 3).  
 413

414 **Table 3. Mean (± SD) Pharmacokinetic Parameters of Rifaximin at Steady-State in**  
 415 **Patients with a History of Hepatic Encephalopathy by Child-Pugh Class<sup>1</sup>**

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

416 <sup>1</sup> Cross-study comparison with PK parameters in healthy subjects

417 <sup>2</sup> Median (range)

418

#### 419 *Food Effect in Healthy Subjects*

420 A high-fat meal consumed 30 minutes prior to XIFAXAN dosing in healthy subjects  
 421 delayed the mean time to peak plasma concentration from 0.75 to 1.5 hours and increased  
 422 the systemic exposure (AUC) of rifaximin by 2-fold (Table 4).  
 423

424 **Table 4. Mean (± SD) Pharmacokinetic Parameters After Single-Dose**  
 425 **Administration of XIFAXAN Tablets 550 mg in Healthy Subjects**  
 426 **Under Fasting and Fed Conditions (N = 12)**

Parameter	Fasting	Fed
C <sub>max</sub> (ng/mL)	4.1 ± 1.5	4.8 ± 4.3
T <sub>max</sub> <sup>1</sup> (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

427 <sup>1</sup>Median (range)

428

429 XIFAXAN can be administered with or without food [see Dosage and  
 430 Administration (2.1 and 2.2)].

431

432 Distribution

433 Rifaximin is moderately bound to human plasma proteins. *In vivo*, the mean protein  
434 binding ratio was 67.5% in healthy subjects and 62% in patients with hepatic impairment  
435 when XIFAXAN 550 mg was administered.

436

437 Metabolism and Excretion

438 In a mass balance study, after administration of 400 mg <sup>14</sup>C-rifaximin orally to  
439 healthy volunteers, of the 96.94% total recovery, 96.62% of the administered  
440 radioactivity was recovered in feces almost exclusively as the unchanged drug and 0.32%  
441 was recovered in urine mostly as metabolites with 0.03% as the unchanged drug.  
442 Rifaximin accounted for 18% of radioactivity in plasma. This suggests that the absorbed  
443 rifaximin undergoes metabolism with minimal renal excretion of the unchanged drug.  
444 The enzymes responsible for metabolizing rifaximin are unknown.

445

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

448

449 Specific Populations

450

451 Hepatic Impairment

452 The systemic exposure of rifaximin was markedly elevated in patients with hepatic  
453 impairment compared to healthy subjects. The mean AUC in patients with Child-Pugh  
454 Class C hepatic impairment was 2-fold higher than in patients with Child-Pugh Class A  
455 hepatic impairment (see Table 3), [see Warnings and Precautions (5.4) and Use in  
456 Specific Populations (8.7)].

457

458 Renal Impairment

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

461

462 Drug Interactions

463 *In vitro* drug interaction studies have shown that rifaximin, at concentrations ranging from  
464 2 to 200 ng/mL, did not inhibit human hepatic cytochrome P450 isoenzymes 1A2, 2A6, 2B6,  
465 2C9, 2C19, 2D6, 2E1, and 3A4.

466 In an *in vitro* study, rifaximin was shown to induce CYP3A4 at the concentration of 0.2  
467 μM.

468 An *in vitro* study suggests that rifaximin is a substrate of P-glycoprotein. In the presence  
469 of P-glycoprotein inhibitor verapamil, the efflux ratio of rifaximin was reduced greater than  
470 50% *in vitro*. The effect of P-glycoprotein inhibition on rifaximin was not evaluated *in vivo*.

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

473

474 Midazolam

475 The effect of rifaximin 200 mg administered orally every 8 hours for 3 days and for 7 days  
476 on the pharmacokinetics of a single dose of either midazolam 2 mg intravenous or midazolam  
477 6 mg orally was evaluated in healthy subjects. No significant difference was observed in the  
478 metrics of systemic exposure or elimination of intravenous or oral midazolam or its major  
479 metabolite, 1'-hydroxymidazolam, between midazolam alone or together with rifaximin.

480 Therefore, rifaximin was not shown to significantly affect intestinal or hepatic CYP3A4  
481 activity for the 200 mg three times a day dosing regimen.

482

483 After XIFAXAN 550 mg was administered three times a day for 7 days and 14 days to  
484 healthy subjects, the mean AUC of single midazolam 2 mg orally was 3.8% and 8.8% lower,  
485 respectively, than when midazolam was administered alone. The mean  $C_{max}$  of midazolam was  
486 also decreased by 4-5% when XIFAXAN was administered for 7-14 days prior to midazolam  
487 administration. This degree of interaction is not considered clinically meaningful.

488

489 The effect of rifaximin on CYP3A4 in patients with impaired liver function who have  
490 elevated systemic exposure is not known.

491

492 *Oral Contraceptives Containing 0.07 mg Ethinyl Estradiol and 0.5 mg Norgestimate*

493 The oral contraceptive study utilized an open-label, crossover design in 28 healthy female  
494 subjects to determine if rifaximin 200 mg orally administered three times a day for 3 days (the  
495 dosing regimen for travelers' diarrhea) altered the pharmacokinetics of a single dose of an oral  
496 contraceptive containing 0.07 mg ethinyl estradiol and 0.5 mg norgestimate. Results showed  
497 that the pharmacokinetics of single doses of ethinyl estradiol and norgestimate were not altered  
498 by rifaximin [*see Drug Interactions (7)*].

499

500 Effect of rifaximin on oral contraceptives was not studied for XIFAXAN 550 mg  
501 twice a day, the dosing regimen for hepatic encephalopathy.

502

## 503 **12.4 Microbiology**

### 504 Mechanism of Action

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

508

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

511

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

516

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

520

521 For HE, rifaximin is thought to have an effect on the gastrointestinal flora.

522

### 523 Susceptibility Tests

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

528

529

## 530 13 NONCLINICAL TOXICOLOGY

531

### 532 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

533 Malignant schwannomas in the heart were significantly increased in male Crl:CD®  
534 (SD) rats that received rifaximin by oral gavage for two years at 150 to 250 mg/kg/day  
535 (doses equivalent to 2.4 to 4 times the recommended dose of 200 mg three times daily for  
536 travelers' diarrhea, and equivalent to 1.3 to 2.2 times the recommended dose of 550 mg  
537 twice daily for hepatic encephalopathy, based on relative body surface area comparisons).  
538 There was no increase in tumors in Tg.rasH2 mice dosed orally with rifaximin for 26  
539 weeks at 150 to 2000 mg/kg/day (doses equivalent to 1.2 to 16 times the recommended  
540 daily dose for travelers' diarrhea and equivalent to 0.7 to 9 times the recommended daily  
541 dose for hepatic encephalopathy, based on relative body surface area comparisons).

542

543 Rifaximin was not genotoxic in the bacterial reverse mutation assay, chromosomal  
544 aberration assay, rat bone marrow micronucleus assay, rat hepatocyte unscheduled DNA  
545 synthesis assay, or the CHO/HGPRT mutation assay. There was no effect on fertility in  
546 male or female rats following the administration of rifaximin at doses up to 300 mg/kg  
547 (approximately 5 times the clinical dose of 600 mg/day, and approximately 2.6 times the  
548 clinical dose of 1100 mg/day, adjusted for body surface area).

549

### 550 13.2 Animal Toxicology and/or Pharmacology

551 Oral administration of rifaximin for 3-6 months produced hepatic proliferation of  
552 connective tissue in rats (50 mg/kg/day) and fatty degeneration of liver in dogs (100  
553 mg/kg/day). However, plasma drug levels were not measured in these studies.  
554 Subsequently, rifaximin was studied at doses as high as 300 mg/kg/day in rats for 6  
555 months and 1000 mg/kg/day in dogs for 9 months, and no signs of hepatotoxicity were  
556 observed. The maximum plasma AUC<sub>0-8 hr</sub> values from the 6 month rat and 9 month dog  
557 toxicity studies (range: 42-127 ng•h/mL) was lower than the maximum plasma AUC<sub>0-8 hr</sub>  
558 values in cirrhotic patients (range: 19-306 ng•h/mL).

559

560

## 561 14 CLINICAL STUDIES

562

### 563 14.1 Travelers' Diarrhea

564 The efficacy of XIFAXAN given as 200 mg orally taken three times a day for 3 days  
565 was evaluated in 2 randomized, multi-center, double-blind, placebo-controlled studies in  
566 adult subjects with travelers' diarrhea. One study was conducted at clinical sites in  
567 Mexico, Guatemala, and Kenya (Study 1). The other study was conducted in Mexico,  
568 Guatemala, Peru, and India (Study 2). Stool specimens were collected before treatment  
569 and 1 to 3 days following the end of treatment to identify enteric pathogens. The  
570 predominant pathogen in both studies was *Escherichia coli*.

571

572 The clinical efficacy of XIFAXAN was assessed by the time to return to normal,  
573 formed stools and resolution of symptoms. The primary efficacy endpoint was time to  
574 last unformed stool (TLUS) which was defined as the time to the last unformed stool  
575 passed, after which clinical cure was declared. Table 5 displays the median TLUS and  
576 the number of patients who achieved clinical cure for the intent to treat (ITT) population  
577 of Study 1. The duration of diarrhea was significantly shorter in patients treated with

578 XIFAXAN than in the placebo group. More patients treated with XIFAXAN was  
 579 classified as clinical cures than were those in the placebo group.

580  
 581

**Table 5. 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

582

583 Microbiological eradication (defined as the absence of a baseline pathogen in culture  
 584 of stool after 72 hours of therapy) rates for Study 1 are presented in Table 6 for patients  
 585 with any pathogen at baseline and for the subset of patients with *Escherichia coli* at  
 586 baseline. *Escherichia coli* was the only pathogen with sufficient numbers to allow  
 587 comparisons between treatment groups.

588

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

593

**Table 6. Microbiologic Eradication Rates in Study 1  
 Subjects with a Baseline Pathogen**

594  
 595

	<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)

596

597 The results of Study 2 supported the results presented for Study 1. In addition, this  
 598 study provided evidence that subjects treated with XIFAXAN with fever and/or blood in  
 599 the stool at baseline had prolonged TLUS. These subjects had lower clinical cure rates  
 600 than those without fever or blood in the stool at baseline. Many of the patients with fever  
 601 and/or blood in the stool (dysentery-like diarrheal syndromes) had invasive pathogens,  
 602 primarily *Campylobacter jejuni*, isolated in the baseline stool.

603

604 Also in this study, the majority of the subjects treated with XIFAXAN who had  
 605 *Campylobacter jejuni* isolated as a sole pathogen at baseline failed treatment and the  
 606 resulting clinical cure rate for these patients was 23.5% (4/17). In addition to not being  
 607 different from placebo, the microbiologic eradication rates for subjects with  
 608 *Campylobacter jejuni* isolated at baseline were much lower than the eradication rates  
 609 seen for *Escherichia coli*.

610

611 In an unrelated open-label, pharmacokinetic study of oral XIFAXAN 200 mg taken  
 612 every 8 hours for 3 days, 15 adult subjects were challenged with *Shigella flexneri* 2a, of  
 613 whom 13 developed diarrhea or dysentery and were treated with XIFAXAN. Although  
 614 this open-label challenge trial was not adequate to assess the effectiveness of XIFAXAN  
 615 in the treatment of shigellosis, the following observations were noted: eight subjects  
 616 received rescue treatment with ciprofloxacin either because of lack of response to  
 617 XIFAXAN treatment within 24 hours (2), or because they developed severe dysentery

618 (5), or because of recurrence of *Shigella flexneri* in the stool (1); five of the 13 subjects  
619 received ciprofloxacin although they did not have evidence of severe disease or relapse.

620

#### 621 **14.2 Hepatic Encephalopathy**

622 The efficacy of XIFAXAN 550 mg taken orally two times a day was evaluated in a  
623 randomized, placebo-controlled, double-blind, multi-center 6-month trial of adult  
624 subjects from the U.S., Canada and Russia who were defined as being in remission (Conn  
625 score of 0 or 1) from hepatic encephalopathy (HE). Eligible subjects had  $\geq 2$  episodes of  
626 HE associated with chronic liver disease in the previous 6 months.

627

628 A total of 299 subjects were randomized to receive either XIFAXAN (n=140) or  
629 placebo (n=159) in this study. Patients had a mean age of 56 years (range, 21-82 years),  
630 81% < 65 years of age, 61% were male and 86% White. At baseline, 67% of patients had  
631 a Conn score of 0 and 68% had an asterixis grade of 0. Patients had MELD scores of  
632 either  $\leq 10$  (27%) or 11 to 18 (64%) at baseline. No patients were enrolled with a MELD  
633 score of > 25. Nine percent of the patients were Child-Pugh Class C. Lactulose was  
634 concomitantly used by 91% of the patients in each treatment arm of the study. Per the  
635 study protocol, patients were withdrawn from the study after experiencing a breakthrough  
636 HE episode. Other reasons for early study discontinuation included: adverse reactions  
637 (XIFAXAN 6%; placebo 4%), patient request to withdraw (XIFAXAN 4%; placebo 6%)  
638 and other (XIFAXAN 7%; placebo 5%).

639

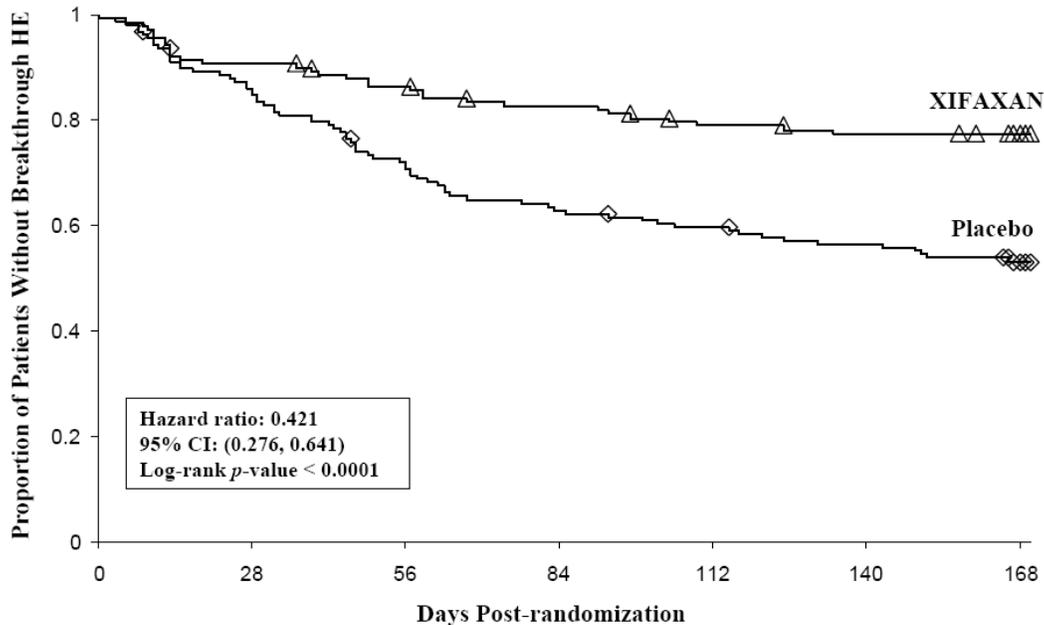
640 The primary endpoint was the time to first breakthrough overt HE episode. A  
641 breakthrough overt HE episode was defined as a marked deterioration in neurological  
642 function and an increase of Conn score to Grade  $\geq 2$ . In patients with a baseline Conn  
643 score of 0, a breakthrough overt HE episode was defined as an increase in Conn score of  
644 1 and asterixis grade of 1.

645

646 Breakthrough overt HE episodes were experienced by 31 of 140 subjects (22%) in  
647 the XIFAXAN group and by 73 of 159 subjects (46%) in the placebo group during the 6-  
648 month treatment period. Comparison of Kaplan-Meier estimates of event-free curves  
649 showed XIFAXAN significantly reduced the risk of HE breakthrough by 58% during the  
650 6-month treatment period. Presented below in Figure 1 is the Kaplan-Meier event-free  
651 curve for all subjects (n = 299) in the study.

652  
653  
654

**Figure 1: Kaplan-Meier Event-Free Curves<sup>1</sup> in HE Study (Time to First Breakthrough-HE Episode up to 6 Months of Treatment, Day 170) (ITT Population)**



655  
656  
657  
658  
659

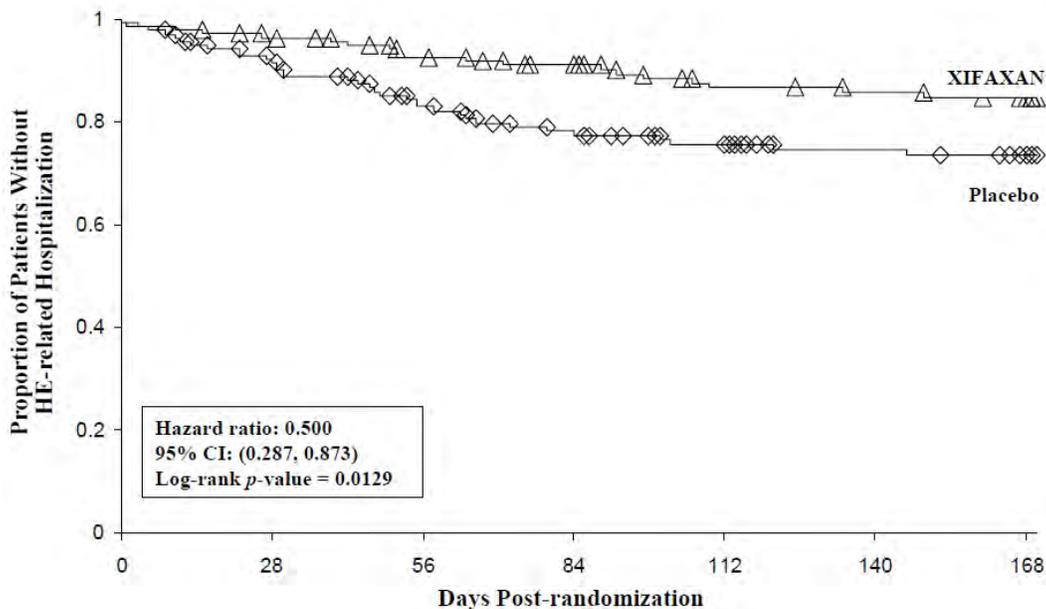
Note: Open diamonds and open triangles represent censored subjects.  
<sup>1</sup> Event-free refers to non-occurrence of breakthrough HE.

660 When the results were evaluated by the following demographic and baseline  
661 characteristics, the treatment effect of XIFAXAN 550 mg in reducing the risk of  
662 breakthrough overt HE recurrence was consistent for: sex, baseline Conn score, duration  
663 of current remission and diabetes. The differences in treatment effect could not be  
664 assessed in the following subpopulations due to small sample size: non-White (n=42),  
665 baseline MELD > 19 (n=26), Child-Pugh C (n=31), and those without concomitant  
666 lactulose use (n=26).

667  
668 HE-related hospitalizations (hospitalizations directly resulting from HE, or  
669 hospitalizations complicated by HE) were reported for 19 of 140 subjects (14%) and 36  
670 of 159 subjects (23%) in the XIFAXAN and placebo groups respectively. Comparison of  
671 Kaplan-Meier estimates of event-free curves showed XIFAXAN significantly reduced  
672 the risk of HE-related hospitalizations by 50% during the 6-month treatment period.  
673 Comparison of Kaplan-Meier estimates of event-free curves is shown in Figure 2.

674  
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676

**Figure 2: Kaplan-Meier Event-Free Curves<sup>1</sup> in Pivotal HE Study (Time to First HE-Related Hospitalization in HE Study up to 6 Months of Treatment, Day 170) (ITT Population)**



Note: Open diamonds and open triangles represent censored subjects.  
<sup>1</sup> Event-free refers to non-occurrence of HE-related hospitalization.

677  
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## 15 REFERENCES

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

687  
688

## 16 HOW SUPPLIED/STORAGE AND HANDLING

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

692  
693  
694

- NDC 65649-301-03, bottles of 30 tablets
- NDC 65649-301-41, bottles of 100 tablets
- NDC 65649-301-05, carton of 100 tablets, Unit Dose

695

The 550 mg tablet is a pink-colored, oval, biconvex tablet with “rfx” debossed on one side. It is available in the following presentations:

698  
699

- NDC 65649-303-02, bottles of 60 tablets
- NDC 65649-303-03, carton of 60 tablets, Unit Dose

700

### Storage

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

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706 **17 PATIENT COUNSELING INFORMATION**

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### **17.1 Persistent Diarrhea**

For those patients being treated for travelers' diarrhea, discontinue XIFAXAN if diarrhea persists more than 24-48 hours or worsens. Advise the patient to seek medical care for fever and/or blood in the stool [see *Warnings and Precautions (5.1)*].

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

*Clostridium difficile*-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including XIFAXAN, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibiotics alters the normal flora of the colon which may lead to *C. difficile*. Patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If diarrhea occurs after therapy or does not improve or worsens during therapy, advise patients to contact a physician as soon as possible [see *Warnings and Precautions (5.4)*].

### **17.3 Administration with Food**

Inform patients that XIFAXAN may be taken with or without food.

### **17.4 Antibacterial Resistance**

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

### **17.5 Severe Hepatic Impairment**

Patients should be informed that in patients with severe hepatic impairment (Child-Pugh C) there is an increase in systemic exposure to XIFAXAN [see *Warnings and Precautions (5.4)*].

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

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