



# Medicaid Drug Use Criteria

## *Rifaximin (Xifaxan®)*

- Developed September 2006.
- Revised June 2020; May 2018; June 2017; June 2015; October 2013; December 2011; April 2010; December 2006.

Information on indications for use or diagnosis is assumed to be unavailable. All criteria may be applied retrospectively; prospective application is indicated with an asterisk [\*]. The information contained is for the convenience of the public. The Texas Health and Human Services Commission is not responsible for any errors in transmission or any errors or omissions in the document.

Medications listed in the tables and non-FDA approved indications included in these retrospective criteria are not indicative of Vendor Drug Program formulary coverage.

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## 1 Dosage

### 1.1 Adults

Rifaximin is not indicated for treatment of systemic infections as less than 0.4% of drug is absorbed after oral administration.<sup>1</sup>

Rifaximin, a derivative of rifampin, is a non-systemically absorbed antibiotic with bactericidal activity against aerobic and anaerobic gram-positive and gram-negative

microorganisms. Rifaximin is FDA-approved for use in managing travelers' diarrhea due to noninvasive strains of *Escherichia coli* (*E. coli*) in adults and children 12 years of age and older and should not be used in diarrhea due to pathogens other than *E. coli* or complicated by fever or blood in the stool.<sup>1-12</sup>

Rifaximin is also FDA-approved for reducing risk of overt hepatic encephalopathy (HE) recurrence in patients 18 years of age and older.<sup>1, 2, 6-8</sup> In a randomized, double-blind, placebo-controlled trial over a six-month time period, Bass and cohorts evaluated rifaximin safety and efficacy to maintain remission from HE episodes in 299 adult outpatients receiving concurrent lactulose therapy with a recent history of recurrent, overt HE. Results showed that the risk of a breakthrough HE episode was significantly lower with rifaximin therapy compared to placebo [hazard ratio (HR), 0.42; 95% confidence interval (CI), 0.28 to 0.64; P less than 0.001]. The risk of hospitalization was also significantly lower in rifaximin-treated patients compared to those receiving placebo (HR, 0.50; 95% CI, 0.29 to 0.87; P = 0.01).<sup>13</sup>

In May 2015, rifaximin gained FDA approval for treating irritable bowel syndrome with diarrhea (IBS-D) in adults.<sup>1, 2</sup> Pimentel and cohorts compared rifaximin efficacy to placebo in two separate trials involving 1260 patients with IBS without constipation. Patients were randomly administered rifaximin 550 mg three times daily or placebo for 14 days, and then followed for 10 weeks. Results showed that rifaximin was significantly better than placebo in relieving IBS symptoms (e.g., bloating; abdominal pain; loose, watery stools).<sup>14</sup> Data have also shown that rifaximin-treated patients respond better than those receiving placebo with a first recurrence of IBS-D.<sup>1</sup> A few small studies have evaluated rifaximin use in irritable bowel syndrome/Crohn's disease. Gionchetti and cohorts assessed rifaximin efficacy compared to placebo in 26 ulcerative colitis patients unresponsive to steroid therapy and found that while overall clinical response was not significantly better than placebo, rifaximin-treated patients showed a significant reduction in stool frequency and rectal bleeding.<sup>15</sup> Prantera and colleagues evaluated rifaximin dosing and efficacy compared to placebo in 83 Crohn's disease patients and found no statistical difference in clinical response or clinical remission but observed a significantly reduced number of treatment failures in rifaximin-treated patients.<sup>16</sup>

Although not FDA-approved, rifaximin has shown some efficacy in hepatic encephalopathy treatment and infectious diarrhea due to *Salmonella*, noninvasive *Shigella* and *Campylobacter*.<sup>17-27</sup> One small, open-label, randomized trial in 54 Korean patients with liver cirrhosis evaluated rifaximin therapy in hepatic encephalopathy and found rifaximin comparable to lactulose in improving blood

ammonia, flapping tremor and mental status.<sup>23</sup> Similarly, Mas et al, in a randomized, double-blind, double-dummy trial, compared rifaximin to lactitol in 103 acute hepatic encephalopathy patients and found rifaximin as effective as lactitol in managing hepatic encephalopathy episodes. Investigators found rifaximin significantly better than lactitol in improving ammonia levels and EEG grade, which led to better portal-systemic encephalopathy scores in rifaximin-treated patients.<sup>24</sup> Miglio and cohorts assessed rifaximin benefit and tolerability when compared to neomycin in 49 cirrhosis patients with hepatic encephalopathy and found rifaximin as effective as neomycin in improving neuropsychiatric signs and blood ammonia levels.<sup>25</sup>

Table 1 summarizes adult oral recommended maximum rifaximin dosages for FDA-approved uses. Dosages exceeding these recommendations will be reviewed.

**Table 1. Adult Maximum Recommended Oral Rifaximin Dosages**

Treatment Indication	Drug Name	Dosage Form/Strength	Maximum Recommended Dosage
travelers' diarrhea (due to noninvasive <i>E. coli</i> strains)	rifaximin (Xifaxan®)	200 mg tablets	200 mg three times daily (600 mg/day) x 3 days <sup>1-9</sup>
reduce the risk of HE recurrence	rifaximin	550 mg tablets	550 mg twice daily (1100 mg/day) 1, 2, 6-8, 13
IBS-D	rifaximin		550 mg 3 times daily for 14 days; retreatment for patients with symptom recurrence may occur up to 2 times with same dosage regimen <sup>1, 2, 6-8</sup>

- HE = hepatic encephalopathy
- IBS-D = irritable bowel syndrome with diarrhea

## 1.2 Pediatrics

Rifaximin is FDA-approved in children 12 years of age and older for use in managing travelers' diarrhea due to noninvasive strains of *E. coli*. The recommended oral rifaximin dose for pediatric patients is 200 mg three times daily for three days. Rifaximin should not be prescribed for use in diarrhea caused by pathogens other than *E. coli* or complicated by fever or blood in the stool.<sup>1, 6-8</sup>

The safety and efficacy of rifaximin 200 mg for travelers' diarrhea in pediatric patients younger than 12 years of age or rifaximin 550 mg for HE or IBS-D in pediatric patients younger than 18 years of age have not been established.<sup>1, 6-8</sup>

## 2 Duration of Therapy

The recommended treatment duration for rifaximin use in *E. coli*-mediated travelers' diarrhea is a maximum of three days.<sup>1, 9-11</sup> Treatment regimens lasting greater than three days will be reviewed.

Rifaximin 550 mg tablets may be prescribed on a chronic basis (i.e., for at least 6 months) to reduce the risk of HE recurrence, based on results from the Bass and colleagues study.<sup>13</sup>

Rifaximin 500 mg tablets may be administered for 14 days to treat acute IBS-D episodes and may be repeated for up to two IBS-D recurrences per treatment course. IBS-D is a chronic condition, however, and rifaximin may be prescribed on a chronic basis to manage this disease state.<sup>1, 2</sup>

## 3 Duplicative Therapy

Concurrent administration of rifaximin with other approved antibiotic therapies for travelers' diarrhea (i.e., azithromycin, fluoroquinolones, and trimethoprim-sulfamethoxazole) is not recommended as these combinations do not provide additional therapeutic benefit and may result in enhanced adverse events. Patient profiles containing concurrent prescriptions for rifaximin and additional travelers' diarrhea antibiotic therapy will be reviewed.

## 4 Drug-Drug Interactions

Patient profiles will be assessed to identify those drug regimens which may result in clinically significant drug-drug interactions. Drug-drug interactions considered clinically relevant for rifaximin are summarized in Table 2. Only those drug-drug

interactions classified as clinical significance level 1 or those considered life-threatening which have not yet been classified will be reviewed.

**Table 2. Select Rifaximin Drug-Drug Interactions<sup>1, 6-8</sup>**

Interacting Drug	Interaction	Recommendation	Clinical Significance Level <sup>#</sup>
cyclosporine	adjunctive use markedly increases systemic rifaximin concentrations, as rifaximin is P-glycoprotein and OATP1B1/3 substrate, and cyclosporine is P-glycoprotein and OATP1B1/3 inhibitor	clinical significance of increased exposure unknown; observe for increased adverse effects if combined therapy necessary	3-moderate (CP)
eliglustat (Cerdelga®)	adjunctive use may increase systemic rifaximin concentrations, as rifaximin is P-glycoprotein substrate, and eliglustat is P-glycoprotein inhibitor	clinical significance of increased exposure unknown; observe for increased adverse effects if combined therapy necessary	major (DrugReax)
warfarin	concurrent use may result in changes in INR levels due to an undetermined mechanism	monitor INR values and adjust warfarin doses as needed	3-moderate (CP)

- #CP = Clinical Pharmacology
- INR = international normalized ratio

## 5 References