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Rifaximin: A Unique Gastrointestinal-Selective Antibiotic for Enteric Diseases

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Abstract

Purpose of review—Rifaximin is gaining attention for its potential activity in a multitude of gastrointestinal diseases. We review the unique pharmaceutical properties of this antibiotic and the published evidence in the literature regarding the use of rifaximin for different gastrointestinal disorders.

Recent findings—Rifaximin is a gastrointestinal-selective antibiotic with a broad spectrum of antimicrobial activity, an excellent safety profile, minimal drug interactions, and negligible impact on the intestinal microbiome. Rifaximin is currently approved in the United States for the treatment of travelers' diarrhea caused by noninvasive diarrheagenic *Escherichia coli* and is approved in more than 30 other countries for a variety of gastrointestinal disorders. Considerable research with this medication has been conducted for the treatment and prevention of travelers' diarrhea, the treatment of portal systemic encephalopathy, *Clostridium difficile* infection, small bowel intestinal overgrowth, irritable bowel syndrome, inflammatory bowel disease, pouchitis, and colonic diverticular disease.

Summary—Rifaximin is effective for the treatment of travelers' diarrhea and can be considered as the treatment of choice for uncomplicated travelers' diarrhea. When invasive travelers' diarrhea pathogens are suspected, an alternative antibiotic should be administered. Rifaximin appears promising as a chemoprophylaxis for travelers' diarrhea and as a treatment of portal systemic encephalopathy. This antibiotic may be effective for other gastrointestinal diseases, but more well-designed clinical studies are needed to confirm its efficacy for these off-label indications. Future studies will determine whether the development of significant bacterial resistance will limit rifaximin use.

Keywords

rifaximin; travelers' diarrhea; encephalopathy; gastrointestinal; bowel

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Introduction

Since its approval in Italy in 1987, rifaximin has been licensed in over 30 countries for the treatment of a variety of gastrointestinal diseases, particularly diarrhea and portal systemic encephalopathy (Table) (1). Rifaximin was approved in the United States in 2004 for the treatment of travelers' diarrhea secondary to noninvasive *Escherichia coli* (2). The unique properties of this medication, including its broad spectrum of antimicrobial activity, high fecal concentrations, and low systemic absorption, make this an ideal agent for the treatment of gastrointestinal diseases. In this review, we discuss the published studies that evaluate the effectiveness of rifaximin as a therapeutic agent for different gastrointestinal disorders.

Mechanism of Action

Rifaximin is a poorly absorbed bactericidal rifamycin derivative, which inhibits bacterial protein synthesis by irreversibly binding to RpoB, the beta-subunit of the bacterial DNA-dependent RNA polymerase (3).

Metabolism and Pharmacokinetics

The lack of absorption of rifaximin in the gastrointestinal tract enhances fecal concentrations of this drug and limits its systemic toxicity. Studies with radio-labeled rifaximin have demonstrated less than 0.4% of detectable rifaximin in the blood and urine, undetectable levels in the bile and breast milk, and 97% recovered unchanged in the stool after oral ingestion (2) (4). Fecal concentrations of approximately 8000 μg/g are attained after three days of rifaximin 800 mg per day administered to adults suffering travelers' diarrhea (5).

As a virtually nonabsorbable antibiotic, drug interactions with rifaximin are uncommon. While rifaximin is capable of inducing the cytochrome P450 3A4 (CYP3A4) isoenzyme in vitro studies, clinical studies with rifaximin have shown no significant effect on drug metabolism by cytochrome P450 isoenzymes (6, 7). No dosage adjustments are required for hepatic dysfunction, even with liver failure and hepatic encephalopathy because systemic absorption is minimal (2).

Antimicrobial Activity

Rifaximin is bactericidal against a broad array of enteric pathogens, including gram-positive, gram-negative, aerobic and anaerobic bacteria. An extensive microbiological survey performed by our research group demonstrated that the minimum inhibitory concentration for 90% of microorganism growth (MIC_{90}), ranged from 4 - 64 μg/ml for enteric pathogens isolated over three continents, including enterotoxigenic (ETEC) and enteroaggregative *Escherichia coli* (EAEC), *Salmonella, Shigella, Campylobacter, Plesiomonas,* and *Aeromonas* species (8). Similar bacterial susceptibility patterns have been confirmed by other studies (9, 10). With fecal concentrations approaching 8,000 μg/g in human hosts, rifaximin easily achieves concentrations effective against these bacterial pathogens (5).

Rifaximin appears to have some enteric anti-protozoal activity as well. Rifaximin has been shown to provide clinical resolution and intestinal microbiological eradication in a small

number of HIV (n = 15) and AIDS (n = 5) patients with *Cryptosporidium parvum* and *Blastocystis hominis* gastroenteritis (11, 12).

Despite high gut concentrations of rifaximin and its broad spectrum of activity, this medication produces minimal alterations in the intestinal microflora. After receiving two weeks of rifaximin, subjects experienced only a 1 log reduction in intestinal coliforms per gram of stool (13).

Rifaximin Safety Profile

With its lack of systemic absorption, rifaximin is a relatively safe medication and is associated a low incidence of adverse events. More than 1000 subjects who received rifaximin as participants in TD clinical trials, reported adverse events at a similar or lower frequency than subjects receiving placebo, ciprofloxacin, or TMP-SMX respectively (13-17). No serious adverse events or deaths were reported in these clinical trials. Clinical trials evaluating rifaximin for other gastrointestinal disease further support the safety and tolerability of this medication (18-21).

Treatment of Travelers' Diarrhea (TD)

The recommended dosage of rifaximin for the treatment of travelers' diarrhea caused by noninvasive strains of *Escherichia coli*, including ETEC and EAEC, in patients >12 years of age is 200 mg three times per day for 3 days (2, 22). The effectiveness of rifaximin as a therapeutic agent for travelers' diarrhea has been demonstrated in several pivotal randomized, double-blind clinical trials. The primary endpoint of these trials was the time to last unformed stool (TLUS), defined as the time from the first dose of medication to the passage of the last unformed stool after which subjects are declared well. Rifaximin has been shown to be more effective than placebo (15) and similar in efficacy to traditional TD antibiotics, trimethoprim-sulfamethoxazole (TMP-SMX) (17) and ciprofloxacin (14, 16), in shortening the duration of TD.

In a randomized, prospective, double-blind clinical trial including 72 US travelers to Mexico, no significant differences in the TLUS were observed comparing 5 day courses of rifaximin (200 mg, 400 mg, and 600 mg three times per day) and TMP-SMX (160/800 mg twice a day). There was a trend for shorter duration of diarrhea with the administration of rifaximin 200 mg three times a day (17).

Rifaximin 400 mg twice a day (n = 93) was compared to ciprofloxacin 500 mg twice a day (n = 94) as TD therapy for travelers to Mexico or Jamaica. The median TLUS (rifaximin 25.7 hours vs. ciprofloxacin 25.0 hours, p = 0.47), the clinical cure rates (87% vs. 88%, respectively, p = 0.80) and the microbiological cure rates (74% vs. 88%, respectively, p = 0.22) were similar for the two antibiotics (14).

Another clinical trial compared the efficacy of rifaximin to ciprofloxacin and placebo in 399 travelers to Mexico, Guatemala, or India. Subjects with TD received three days of either rifaximin 200 mg three times a day (n=197), ciprofloxacin 500 mg two times a day (n=101), or placebo (n = 101). The median TLUS was shorter for the rifaximin group compared to the

placebo group (32.0 hours vs. 65.5 hours, p = 0.001) and was similar to the ciprofloxacin group (28.8 hours, p = 0.35). More rifaximin patients experienced clinical cure (77%) compared to placebo subjects (61%, p=0.004), similar to the ciprofloxacin group (78%) (16).

The current recommended dose of rifaximin was confirmed by a clinical trial evaluating 380 subjects with TD acquired in Mexico, Guatemala, or Kenya. Study participants were randomized to receive either 3 days of rifaximin 200 mg three times a day (n=125) or rifaximin 400 mg three times a day (n = 126) or placebo (n = 129). For both rifaximin dosages, the median TLUS was significantly shorter compared to placebo (32.5 hours and 32.9 hours vs. 60.0 hours, respectively, p=0.0001). Both rifaximin groups experienced greater clinical cure than the placebo group (79.2% and 81.0% vs. 60.5%, p= 0.001) (15).

Prevention of Travelers' Diarrhea

Some experts consider antibiotic chemoprophylaxis for TD to be unnecessary and excessive because of their fears of antimicrobial resistance promotion and potential risk of adverse events for a self-limited disease in the majority of TD cases. However, the recognition of persistent and chronic complications, including post-infectious irritable bowel syndrome shown to occur in 5-10% of persons experiencing TD (23), has led to a re-evaluation of the need for TD chemoprophylaxis. As a gut-selective antibiotic with minimal systemic toxicity and a lack of drug interactions, rifaximin appears to be an ideal prophylactic drug for travelers' diarrhea (24).

Two large randomized, double-blind, placebo-controlled clinical trials support the efficacy of rifaximin as a chemoprophylactic agent for TD. In one dose-ranging clinical trial with 210 US travelers to Mexico, subjects were randomized to either two weeks of rifaximin 200 mg once daily (n = 50), 200 mg twice daily (n = 52), 200 mg three times daily (n = 54), or placebo (n = 54). Collectively, 15% of rifaximin subjects developed TD compared to 54% of the placebo group (p = 0.0001). The protection rate against travelers' diarrhea for rifaximin subjects was 72% (p < 0.001). All rifaximin doses were superior to placebo for the prevention of TD (13).

A second prophylaxis trial with 210 travelers to Mexico compared two weeks of rifaximin 600 mg daily dose (n = 106) to placebo (n = 104) for TD prevention. Rifaximin subjects were less likely to develop diarrhea compared to the placebo group (20% vs. 48%, respectively, p <0.0001) with a TD protection rate of 58% (25).

Travelers' Diarrhea and Invasive Enteric Pathogens

As a nonabsorbable antibiotic, rifaximin's bactericidal activity appears to be limited to the lumen of the gastrointestinal tract. As a result, rifaximin is less effective in treating invasive bacterial pathogens. In a clinical treatment trial for TD, rifaximin was less effective than ciprofloxacin in reducing the TLUS and in providing clinical resolution, when the etiologic agent was an invasive enteric pathogen, such as *Shigella* species, *Campylobacter jejuni*, and *Salmonella* species (16). In an experimental challenge trial with orally administered *Shigella flexneri*, rifaximin failed to adequately treat eight of 13 subjects who developed shigellosis.

These eight subjects required rescue treatment with ciprofloxacin to achieve clinical resolution (26). Rifaximin is not approved for the treatment of TD associated with invasive enteric pathogens such as *Shigella* species, *Campylobacter jejuni*, and *Salmonella* species and should be avoided when these invasive bacteria are suspected. An alternative antibiotic should be used for TD patients presenting with fever or dysentery.

In contrast, rifaximin's protective effect against travelers' diarrhea may extend to even TD cases associated with invasive enteric pathogens. It has been hypothesized that rifaximin may eradicate invasive diarrheagenic pathogens in the gastrointestinal tract prior to mucosal infiltration (27). In a randomized, double-blind, placebo-controlled prevention trial, 25 healthy adults were experimentally challenged with *S. flexneri*. Prior to their oral *S. flexneri* inoculation, subjects received either three days of rifaximin 200 mg three times a day or placebo. All 15 rifaximin subjects were protected and failed to develop diarrhea, while 6 of 10 placebo recipients developed shigellosis ($p = 0.001$) (28). The effectiveness of rifaximin as a prophylactic agent in southern Asia (Indian subcontinent) should be carried out to determine its value in preventing diarrhea due to invasive enteropathogens.

Portal Systemic Encephalopathy (PSE)

Clinical trials have demonstrated that rifaximin is effective for the treatment and prevention of portal systemic encephalopathy. Rifaximin is believed to reduce ammonia production by eliminating intestinal bacteria involved in the degradation of nitrogenous compounds (29). In a large randomized, double-blind, placebo-controlled trial (n=299), rifaximin at a dose of 1100 mg per day reduced the risk of developing breakthrough PSE by 58% and the risk of PSE-related hospitalizations by 48% compared to placebo in cirrhotic patients with a previous history of PSE (30). Rifaximin was compared to neomycin in a small randomized, double blind, clinical trial (n = 30). Similar efficacy in clinical resolution of the encephalopathy was shown between the two antibiotics, but rifaximin led to an earlier reduction in serum ammonia levels compared to neomycin (31). Rifaximin has been shown to be as or more effective in treating PSE as the non-absorbable disaccharides, lactulose (32, 33) and lactitol (21). Decreased hospitalizations and length of hospital stays have been associated with rifaximin compared to lactulose (20). Better tolerability is one of the key advantages of rifaximin compared to these other PSE therapies. With its minimal systemic absorption, rifaximin is associated with few adverse events. Neomycin use may be complicated by nephrotoxicity and ototoxicity (32). The disaccharides can cause significant diarrhea and gastrointestinal complaints such as flatulence, dyspepsia, anorexia (33). Rifaximin has been designated as an "orphan drug" for the treatment of PSE by the FDA.

Clostridium difficile infection (CDI)

Rifaximin has excellent in vitro activity for *Clostridium difficile* (34-36). The minimum inhibitory concentration ($MIC_{90} = 0.015$ mg/mL) was lower for rifaximin than for vancomycin, metronidazole, and other antibiotics active against *C. difficile* in one study (36). Clinical studies evaluating rifaximin treatment of CDI are limited to case reports and one small clinical trial (n = 20), in which 9 of 10 CDI patients responded to rifaximin compared to 10 of 10 patients receiving vancomycin. However, clinical resolution of CDI

occurred more rapidly with vancomycin than rifaximin (37). Two case series described rifaximin use for recurrent CDI (38, 39). Rifaximin was highly effective for both prevention and treatment of recurrent CDI with response rates of 88% (38) and 83% (39), respectively. One case report also described extended co-administration (7 weeks) of rifaximin with oral vancomycin and a probiotic for the successful treatment of refractory CDI (40). Larger prospective clinical trials are needed to confirm the efficacy of rifaximin for treatment of primary and recurrent CDI.

The development of *C. difficile* resistance to rifaximin during therapy needs to be monitored. Evidence for *C. difficile* resistance is primarily based on in vitro susceptibility testing for rifampin. Although agar dilution testing for *C. difficile* antibiotic susceptibility is considered as the most accurate test, most laboratories are not capable of performing this labor-intensive assay and rely on the episolometer test (E-test) to screen for antibiotic susceptibility. An E-test strip is currently not available for rifaximin. As a result, antibiotic susceptibility testing with the E-test rifampin strips has been used a surrogate assay, since both antibiotics belong to the rifamycin class (41). Significant rifampin resistance has been demonstrated among *C. difficile* isolates, particularly among epidemic BI/NAP1 *C. difficile* strains (41, 42). In one institution, approximately 81% of *C. difficile* isolates were found to be resistant to rifampin (42). Resistance to rifampin may be related to mutations in the *rpoB* gene, which encodes for the β-subunit of *C. difficile* RNA polymerase (41). In a preliminary study, we have shown that significant discordance between the susceptibility profiles of the two antibiotics for *C. difficile* may exist when the agar dilution method is used (34). Further evaluation of *C. difficile* susceptibility to rifaximin and the correlation between rifampin and rifaximin resistance is needed. It is also unknown whether these resistance mutations correlate with clinical failures.

Small Intestinal Bowel Overgrowth (SIBO) and Irritable Bowel Syndrome (IBS)

Small bowel bacterial overgrowth may be associated with a variety of bacteria, both aerobic and anaerobic microbes (43). As a result, an antimicrobial like rifaximin, with a broad spectrum of activity resulting in high luminal levels of drug, is ideal for the treatment of SIBO. Studies evaluating rifaximin as a treatment for SIBO are limited and involve a range of dosages. A clinical response of 59% in SIBO patients was shown in a small clinical trial (n=33), suggesting a potential role for rifaximin as a treatment for SIBO (44). Microbiological decontamination responses to rifaximin therapy, measured by hydrogen breath tests, range from 59% (44) to 70.4% (45, 46). However, SIBO may recur in up to 44% of patients, successfully treated with a one week course of rifaximin (1,200mg per day), particularly in those patients with predisposing conditions for SIBO, such as chronic proton-pump inhibitor use (47). Retreatment with rifaximin may be effective for these recurrences and for those recurrences failing to respond to other antibiotics (48).

Higher doses of rifaximin may be more effective for eradicating SIBO. Rifaximin 1200 mg per day led to 70% normalization of glucose breath tests compared to 27% with chlortetracycline 1g per day for SIBO patients (46). Higher doses of rifaximin (1600 mg per day vs. 1200mg per day) were more effective in normalizing breath tests (80% vs. 58%,

respectively) in another study (49). More accurate methods of detecting bacterial overgrowth than breath tests, which are influenced by gut transit, are needed.

Although the underlying pathogenesis of IBS is not well understood and the diagnosis is established by Rome II clinical criteria (50), it is hypothesized that SIBO contributes to this gastrointestinal disease. The clinical syndromes of IBS and SIBO overlap, and between 40 - 80% of IBS patients have abnormal hydrogen breath tests (51-53) or increased small bowel bacterial counts (54). In addition, clinical improvement of IBS symptoms appears to be associated with normalization of hydrogen breath tests following antibiotic treatment (53).

Symptomatic improvement in IBS symptoms has been demonstrated with tetracyclines and fluoroquinolones, with high relapse rates following antibiotic discontinuation (55). There are concerns about the development of antibiotic resistance with the widespread use of antimicrobial agents. Two randomized, double-blind, placebo-controlled trials evaluated the efficacy of rifaximin treatment for IBS. In the first trial, 87 patients diagnosed with IBS by Rome I criteria received either rifaximin 400 mg or placebo 3 times per day for 10 days. Throughout 10 weeks of follow-up, rifaximin patients experienced greater symptomatic improvement than the placebo group (18). In the second trial, 70 patients with IBS diagnosed by Rome II criteria were randomized to either 10 days of rifaximin 400 mg or placebo twice a day. Rifaximin patients experienced significantly greater symptomatic relief than the placebo group. Interestingly, none of these IBS subjects had an abnormal baseline hydrogen breath test (56).

Inflammatory Bowel Disease (IBD) and Pouchitis

An abnormal host immune response associated with a loss of tolerance to the commensal intestinal microbiome is believed to play an important role in the pathogenesis of inflammatory bowel diseases, including Crohn’s disease, ulcerative colitis (UC), and pouchitis (57). As a result, antibiotics such as metronidazole and ciprofloxacin have been used for the medical management of IBD, including refractory Crohn’s disease (58). However, despite the potential beneficial effect of prolonged antimicrobial therapy in IBD, side effects of these antibiotics including peripheral neuropathy with metronidazole and tendinitis or tendon rupture with ciprofloxacin and concern for antibiotic resistance limit their extended use. As a nonabsorable antibiotic, rifaximin is an attractive alternative.

Crohn’s Disease

Rifaximin appears promising as treatment for IBD, but a lack of well-designed clinical trials with sufficient power contribute to the difficulty in assessing the efficacy rifaximin for IBD. The optimal rifaximin dose also remains to be determined. In one multi-center, randomized, double-blind, placebo-controlled clinical trial, less treatment failures were seen with rifaximin, but there were no significant differences in clinical remission or improvement in active Crohn’s disease patients receiving rifaximin compared to placebo (19).

A small (n=29) open-label study of prolonged rifaximin therapy (200mg three times per day for 16 weeks) demonstrated clinical improvement of active Crohn’s disease (59). Rifaximin

800mg per day was effective as first line therapy for small intestinal Crohn's disease, with symptomatic and endoscopic healing, in a small case series of 3 patients (60).

Ulcerative colitis (UC)

Rifaximin may serve as a steroid-sparing treatment agent for some cases of UC. In one open-label study of 30 patients receiving maintenance mesalamine, rifaximin was used instead of steroids because these patients were poor candidates of steroid therapy due to their underlying conditions. Approximately 77% of these UC patients experienced clinical resolution with rifaximin 400mg twice daily for 4 weeks (61). In another trial, no significant clinical improvement with rifaximin compared to placebo was shown for patients with moderate-severe ulcerative colitis refractory to steroid therapy (62).

Pouchitis

Pouchitis is the most common complication of ileal pouch-anal anastomosis following restorative proctocolectomy, which is a surgical procedure performed for ulcerative colitis and familial adenomatous polyposis coli (FAP). Inflammation of the ileal pouch occurs in up to 50% of UC patients following this procedure (63, 64). It has been suggested that pouchitis may be related to fecal stasis with increased proliferation of anaerobic intestinal flora (65). Antibiotics such as metronidazole, ciprofloxacin, or a combination of these two are frequently empirically administered to treat pouchitis (66). The majority of patients respond to these antibiotics but 1-9% of pouchitis cases will be chronic and refractory to traditional antibiotics and other treatment modalities (67). Rifaximin as monotherapy (400mg TID for 4 weeks) for active acute and chronic pouchitis in a small randomized, double –blind, placebo-controlled trial failed to show any significant benefit compared to placebo (68). However, the combination of rifaximin 1 gram twice daily and ciprofloxacin 500 mg twice daily for 2 weeks was shown to be effective in providing clinical improvement or remission in up to 88% of chronic refractory pouchitis cases in several small open-label trials (69, 70). Rifaximin may also be effective as chronic maintenance therapy for chronic pouchitis patients, who require continuous or pulse-dosed antibiotic therapy to avoid relapsing. Among 51 patients with antibiotic-dependent pouchitis, 33 (65%) were successfully maintained on rifaximin suppressive therapy for at least 3 months in an open-label study (71).

Colonic Diverticular disease

Although the majority of individuals with diverticular disease are asymptomatic, approximately 20% of patients experience clinical illness and are at risk for complications such as diverticulitis and hemorrhage (72). Dietary fiber supplementation is considered the standard therapy for symptomatic diverticular disease and may prevent complications (73). Multiple randomized clinical studies involving over 1500 subjects have demonstrated that the addition of monthly rifaximin to fiber supplementation may further improve symptoms and prevent complications in patients with symptomatic, uncomplicated diverticular disease (74-77).

Conclusion

Rifaximin is a broad-spectrum nonabsorbed rifamycin antibiotic with an excellent safety profile, a lack of drug interactions, and minimal effect on the intestinal microbiome. This gut-selective antimicrobial is currently approved for the treatment of travelers' diarrhea caused with noninvasive *E. coli* strains. Rifaximin appears promising as a therapeutic and preventative agent for other gastrointestinal diseases as well. Published large, well-designed, controlled clinical trials best support the use of rifaximin for two additional gastrointestinal indications: prevention of travelers' diarrhea and treatment of portal systemic encephalopathy. Although there is a potential for rifaximin to be effective for other gastrointestinal diseases including small intestinal bowel overgrowth, irritable bowel syndrome, *C. difficile* infection, inflammatory bowel diseases, and diverticular disease, more studies are needed to confirm the beneficial role of rifaximin in these diseases.

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Table

Approved Indications for Rifaximin Use by Country

Country	Approved Indications
Argentina	• Treatment of acute and chronic intestinal infections caused by gram-positive and gram-negative bacteria • Treatment of summer diarrhea, travelers' diarrhea, and enterocolitis • Perioperative prophylaxis for gastrointestinal surgery • Treatment of portal systemic encephalopathy
Austria	• Treatment of gastrointestinal infections • Treatment of *Clostridium difficile* infection • Treatment of portal systemic encephalopathy • Treatment of small bowel intestinal overgrowth • Treatment of colonic diverticular disease • Perioperative intestinal decontamination
Bulgaria, Italy, Korea, Lebanon, Romania	• Treatment of acute and chronic diarrhea caused by gram-positive or gram-negative bacteria • Treatment of summer diarrhea, travelers' diarrhea, and enterocolitis • Perioperative prophylaxis for gastrointestinal surgery • Treatment of portal systemic encephalopathy
Colombia	• Treatment of acute and chronic intestinal infections caused by gram-positive or gram-negative bacteria • Perioperative prophylaxis for gastrointestinal surgery • Treatment of portal systemic encephalopathy
Czech Republic	• Treatment of acute and chronic intestinal infections caused by gram-positive or gram-negative bacteria • Treatment of summer diarrhea, travelers'diarrhea, and enterocolitis • Treatment of portal systemic encephalopathy • Perioperative prophylaxis for gastrointestinal surgery
Georgia, Kazakhstan, Moldavia, Russia, Tajikistan, Turkmenistan, Uzbekistan	• Treatment of acute gastrointestinal infections • Treatment of travelers' diarrhea • Treatment of small bowel intestinal overgrowth • Treatment of portal systemic encephalopathy • Treatment of symptomatic uncomplicated colonic diverticular disease • Treatment of inflammatory bowel disease • Perioperative prophylaxis for colorectal surgery
Germany	• Treatment of travelers' diarrhea caused by non-invasive enteric pathogens
Greece	• Treatment of portal systemic encephalopathy • Treatment of travelers' diarrhea • Treatment of severe gastrointestinal infections • Perioperative prophylaxis for gastrointestinal surgery
Hungary	• Treatment of portal systemic encephalopathy

Country	Approved Indications
	• Treatment of uncomplicated diverticulitis • Perioperative prophylaxis of colorectal surgery in combination with a third generation cephalosporin • Treatment of *Clostridium difficile* infection • Treatment of noninflammatory acute infectious gastroenteritis
Mexico	• Treatment of acute and chronic diarrhea caused by gram-positive or gram-negative bacteria • Treatment of traveler's diarrhea and enterocolitis • Perioperative prophylaxis for gastrointestinal surgery • Treatment of colonic diverticular disease • Treatment of portal systemic encephalopathy • Treatment of irritable bowel syndrome with bacterial overgrowth
Poland	• Treatment of the gastrointestinal infections • Treatment of travelers' diarrhea • Treatment of portal systemic encephalopathy
People's Republic of China	• Treatment of acute and chronic diarrhea • Treatment of summer diarrhea, travelers' diarrhea, and enterocolitis • Perioperative prophylaxis for gastrointestinal surgery • Treatment of portal systemic encephalopathy
Portugal	• Treatment of acute infectious non-invasive diarrhoea
Slovak Republic	• Treatment of acute and chronic intestinal infections caused by gram-positive or gram-negative bacteria • Treatment of summer diarrhea, travelers' diarrhea, and enterocolitis • Treatment of uncomplicated colonic diverticular disease. • Treatment of portal systemic encephalopathy • Perioperative prophylaxis for gastrointestinal surgery • Treatment of antibiotic-associated colitis resistant to vancomycin
Spain	• Treatment of bacterial enterocolitis resistant to the symptomatic treatment in patients with associated pathologies, immune depression or old age. • Treatment of antibiotic associated colitis in patients resistant to vancomycin • Treatment of acute diverticulitis. • Perioperative prophylaxis for gastrointestinal surgery • Treatment of portal systemic encephalopathy
Tunisia	• Treatment of acute and chronic diarrhea caused by gram-positive or gram-negative bacteria • Treatment of summer diarrhea, travelers' diarrhea, and enterocolitis • Perioperative prophylaxis for gastrointestinal surgery • Treatment of portal systemic encephalopathy
Turkey	• Treatment of acute gastrointestinal infections, • Treatment of travelers' diarrhea • Treatment of small bowel intestinal overgrowth • Treatment of portal systemic encephalopathy

Country	Approved Indications
	• Treatment of uncomplicated colonic diverticular disease • Treatment of inflammatory bowel disease • Perioperative prophylaxis for colorectal surgery
Ukraine	• Treatment of acute gastrointestinal infections • Treatment of travelers' diarrhea • Treatment of small bowel intestinal overgrowth • Treatment of portal systemic encephalopathy • Treatment of diverticulitis • Treatment of inflammatory bowel disease. • Perioperative prophylaxis for colorectal surgery
USA	• Treatment of travelers' diarrhea caused by non-invasive strains of *Escherichia coli*
Venezuela	• Treatment of intestinal infections • Perioperative prophylaxis for colonic surgery. • Treatment of portal systemic encephalopathy