National PBM Drug Monograph
Rifaximin (Xifaxan™)
VHA Pharmacy Benefits Management Strategic Healthcare Group and Medical Advisory Panel

EXECUTIVE SUMMARY

- Rifaximin is a non-absorbed (<0.4%) antibiotic in the rifamycin family indicated for the treatment of travelers' diarrhea caused by noninvasive strains of *Escherichia coli* in patients ≥ 12 years of age. Rifaximin should NOT be used for diarrhea complicated by fever, bloody stools, or pathogens other than *E coli.*

- Enterotoxigenic *E. coli* is the most commonly isolated pathogen responsible for travelers' diarrhea in all geographic locations.

- Due to issues with resistance, agents such as co-trimoxazole and ampicillin are no longer used for treatment of travelers' diarrhea. The quinolones, and more recently azithromycin, are treatment options.

- Because rifaximin is not absorbed, it has a lower potential for drug interactions and systemic side effects.

- There are 4 randomized clinical trials. A dose-finding trial compared rifaximin 200mg or 400mg three times daily to trimethoprim/sulfamethoxazole 160/800mg twice daily for 5 days. A second trial compared rifaximin 200mg or 400mg three times daily to placebo. There are 2 trials comparing rifaximin to ciprofloxacin. The first compared rifaximin 400mg twice daily to ciprofloxacin 500mg twice daily for 3 days. A second unpublished study compared rifaximin 200mg three times daily to ciprofloxacin 500mg twice daily or placebo for 3 days.

- Compared to placebo, rifaximin reduced the time to last unformed stool (TLUS) from 60-65 hours to 32hours. The TLUS was similar between rifaximin and ciprofloxacin. This improvement was also seen in patients whose stool samples were negative for bacterial pathogens.

- Clinical cure was achieved in 77 – 87% of patients receiving rifaximin, 78-88% receiving ciprofloxacin and in approximately 61% receiving placebo.

- The microbiological cure rate for enterotoxigenic *Escherichia coli* (ETEC) ranged from 65-75% compared to 70-74% for placebo and 87-96% for ciprofloxacin. Eradication of or failure to eradicate did not always correlate with clinical improvement.

- Rifaximin also has an orphan designation for use in hepatic encephalopathy. The manufacturer will be submitting data to the FDA in December 2004 for approval for this indication. An improvement from baseline was seen in the portal systemic encephalopathy score or index in patients taking rifaximin or the active comparators (lactulose, lactitol, and neomycin). Two studies showed a statistically significantly greater improvement with rifaximin compared to lactulose or lactitol.

- The dose of rifaximin for the treatment of travelers' diarrhea is 200mg three times daily for 3 days. The cost of therapy for rifaximin for the treatment of travelers' diarrhea is $18.81. In comparison, the cost of ciprofloxacin ranges from $0.12 -1.50 and levofloxacin from $2.46 – 6.05 depending on the regimen used. The cost of rifaximin compares favorable to azithromycin. In the treatment of hepatic encephalopathy the dose of rifaximin used in the clinical trials was 400mg three times daily. Based on commonly used doses of lactulose and neomycin, the daily cost is $0.28-0.78 and $4.41 respectively compared to $12.54 per day for rifaximin.

- Rifaximin is an alternative for the treatment of travelers' diarrhea for patients in whom the use of fluoroquinolones are undesirable or contraindicated (e.g. at risk for phototoxicity, risk for QTc prolongation, etc.). Rifaximin is an alternative agent for hepatic encephalopathy in patients unable to tolerate lactulose or in patients who are at high risk of ototoxicity or nephrotoxicity with neomycin. Rifaximin may also be an alternative in patients who have not responded to lactulose or neomycin.

Introduction

Bacteria are responsible for approximately 80% of enteric pathogens responsible for travelers' diarrhea. The most common bacteria are enterotoxigenic *Escherichia coli* (ETEC), enteroaggregative *E. coli*, *Shigella species, Campylobacter jejuni,* and *Salmonella species*. Among these bacteria, ETEC is the most common bacteria associated with travelers' diarrhea. High-risk destinations include most of the low-income countries of Latin America, Africa, the Middle East, and Asia. Intermediate-risk destinations include most of the southern European countries and a few Caribbean islands. Low-risk destinations include Canada, northern Europe, Australia, New Zealand, the United States, and some of the Caribbean islands. Not all cases of travelers' diarrhea require antibiotic treatment. However, those who have diarrhea with three or more loose stools in an 8-hour period, especially if associated with nausea, vomiting, abdominal cramps, fever, or blood in the stools, might benefit from antimicrobial treatment. www.cdc.gov/travel/diarrhea/htm

Pharmacology/Pharmacokinetics

Rifaximin, a non-systemic antibiotic, is a structural analog of rifampin. Rifaximin inhibits bacterial RNA synthesis by binding to the beta-subunit of bacterial DNA-dependent RNA polymerase.

Less than 0.4% of an oral dose of rifaximin is absorbed. The following pharmacokinetics parameters were determined in 14 healthy subjects following a single oral dose of 400mg.

Table 1: Rifaximin pharmacokinetics

	Fasting	Fed
Cmax (ng/mL)	3.8 ± 1.32	9.63 ± 5.93
Tmax (h)	1.21 ± 0.47	1.90 ± 1.52
Half-life (h)	5.85 ± 4.34	5.95 ± 1.88
AUC (ng · h/mL)	18.35 ± 9.48	34.70 ± 9.23
Distribution	80-90% of orally administered drug is concentrated in the gut; < 0.2% in the liver and kidney; < 0.01% in other tissues	
Metabolism	Does not inhibit any of the CYP450 enzymes. Rifaximin induces CYP3A4 isoenzyme.	
Excretion	97% is excreted in the feces mostly as unchanged drug; 0.32% was recovered in the urine	

Data obtained from product package insert June 2004

The pharmacokinetics of rifaximin 200mg TID for 3 days was also evaluated in 13 patients with shigellosis. After the last dose, Cmax ranged from 0.68-2.26 ng/ml and $AUC_{0\text{-last}}$ was 7.83 ± 63.10 ng · h/mL.

FDA Approved Indication and Off-label Uses

Rifaximin was approved in May 2004 for the treatment of travelers' diarrhea caused by noninvasive strains of *Escherichia coli* in patients ≥ 12 years of age. Rifaximin should NOT be used for diarrhea complicated by fever, bloody stools, or pathogens other than *E. coli.*

Rifaximin has orphan designation for use in hepatic encephalopathy and the manufacturer will be submitting data to the FDA in December 2004 for approval for this indication. Other uses for which clinical data exist include Crohn's disease, small intestinal bacterial overgrowth, irritable bowel syndrome, traveler's diarrhea prophylaxis, diverticular disease, dysentery, pouchitis, *C. difficile*-associated diarrhea, peptic ulcer disease, and surgical prophylaxis.

Current VA National Formulary Alternatives

Ciprofloxacin and azithromycin

Dosage and Administration
For travelers' diarrhea, the dose is 200mg three times daily for 3 days. Rifaximin may be taken without regard to meals.

In vitro activity
Because rifaximin works locally in the GI tract, plasma levels cannot be used to determine the minimum inhibitory concentration (MICs). Although MIC values for rifaximin have been determined for various enteric organisms, fecal drug concentration may be a more appropriate measure when evaluating susceptibility. It has been assumed that fecal mass and water have equivalent densities; therefore, fecal concentration on a mcg/g basis would be equivalent to concentrations on a mcg/ml basis.

Fecal concentration of rifaximin was evaluated in 39 patients. This study was part of a larger clinical trial by DuPont that compared rifaximin 400mg BID and ciprofloxacin 500mg BID for 3 days. The fecal concentration exceeded the MIC of the bacterial isolates. [1]

Table 2: Fecal concentration of rifaximin[1]

Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
7961mcg/g	7425 mcg/g	4405mcg/g	2891mcg/g	3266mcg/g	154mcg/g

Table 3: Rifaximin MICs[1-3, 6, 7]

Organism	Reference	# isolates	MIC_{90}	MIC range
ETEC	DuPont 1998	18	-	0.098-25
	Jiang 2000*	120	-	<0.098-200
	DuPont 2001	36	32	0.5-128
	Gomi 2001	97	32	-
	Sierra 2001	38	16	-
EAEC	Gomi 2001	75	32	-
	Sierra 2001	28	16	-
Shigella spp	DuPont 1998	2	-	0.39-0.75
	Jiang 2000	17	-	1.25-200
	DuPont 2001	5	64	16-256
	Gomi 2001	36	64	-
	Sierra 2001	64	16	-
Salmonella spp	DuPont 1998	4	-	12.5-50
	DuPont 2001	3	16	16
	Gomi 2001	46	64	-
	Sierra 2001	14	4	-

ETEC= enterotoxigenic *E. coli*; EAEC = enteroaggregative *E.coli*
*Combined values given for 112 ETEC and 8 Salmonella isolates

Gomi et al. tested several other antibiotics and found that over 97% of all isolates were susceptible to ciprofloxacin and levofloxacin. The MIC_{90} for aztreonam was 0.0625mcg/ml (range $\leq$ 0.0156-16). At the time, NCCLS breakpoints for aztreonam for enteropathogens were not available.[2] In Sierra et al., 3.5% of EAEC were resistant to ciprofloxacin.[3]

Resistance
In vitro
Spontaneous emergence of resistant bacteria to rifaximin was evaluated using broth and agar dilution. Forty-six aerobic and anaerobic bacteria were tested. Bacteria were preincubated in the presence of subinhibitory concentrations of rifaximin (0.5 x MIC). With the broth method, the experiment ended when the bacteria were able to grow in 100mcg/ml of rifaximin. With the agar method, resistance was defined as the MIC increasing by $\geq$ 8-fold of the original MIC.

- **Anaerobic bacteria:** With the broth method, bacteria were able to grow in 100mcg/ml of rifaximin after 4-5 transfers for *Bacteroides spp.* and *C. perfringens* and after 2 transfers for *F. nucleatum. C. difficile* and *Peptostreptococcus spp*. did not grow in media containing rifaximin at concentrations above the sub-MIC. With the agar dilution method, resistant clones of *C. perfringens, B. fragilis,* and *F. nucleatum* were selected on plates containing rifaximin at concentration corresponding to 2, 4, and 8 x their MIC. There were no spontaneously resistant mutants among the *Peptostreptococcus spp.* and *B.*

distasonis. Resistant mutants for *C. difficile* were detected at 2x MIC for 1 of the isolates; no resistant mutants were detected at 4 and 8x MIC.

- **Aerobic bacteria:** When incubated under aerobic conditions using the broth method, *methicillin-sensitive Staphylococcus aureus* (MSSA) and *methicillin-resistant Staphylococcus aureus* (MRSA) acquired resistance after 5 transfers and *E. faecalis* and *E. faecium* after 2-3 transfers. The gram-negative organisms tested (*C. freundii, P. rettgeri, M. morganii, P. mirabilis, P. vulgaris, E.coli* [EPEC, EHEC, ETEC, EIEC], and *S. enteritidis*) acquired resistance after 2-3 transfers. When incubated under anaerobic conditions, the gram-negative organisms acquired resistance after 1-3 transfers, MSSA after 5 transfers, MRSA after 4-5 transfers, and *E. faecalis* and *E. faecium* after 1-2 transfers. Using the agar dilution method, spontaneously resistant mutants emerged at various rates for the gram-positive and gram-negative organisms (under both anaerobic and aerobic conditions) on plates containing rifaximin at concentration corresponding to 2, 4, and 8 x their MIC.

Clinical

In the 2 studies by DuPont and the study by Steffan, 50 patients had the same pathogen identified pre-treatment and post-treatment. In 9 cases, the MIC increased by 2 or 4-fold and in 7 cases, the MIC decreased by 2- >4-fold.[9]

In the clinical trial by Steffan et al., enterococci were recovered at baseline and/or post-treatment in stool samples from 71 patients.[4] Among these 71 patients, enterococci were isolated both pre- and post-treatment (paired-samples) in 27 patients. Samples were tested for the development of resistance to rifaximin and cross-resistance to rifampin. The MIC_{90} and MIC range for rifaximin and rifampin were similar both pre- and post-treatment and between treatment groups. However, the number of patients positive for enterococci in the stool doubled post-treatment in all 3 groups (table 4).

Table 4: Rifaximin and rifampin MICs for enterococci

	Rifaximin 600mg/d	Rifaximin 1200mg/d	Placebo
# of patients + for enterococci	23	24	24
# of patients + for enterococci pre- and post-tx (paired samples)	9/23 (39%)	10/24 (42%)	8/24 (33%)
Rifaximin MIC_{90} days 0 and 3 (from paired samples)	64 / 64	64 / 64	64 / 64
Rifaximin MIC range days 0 and 3 (from paired samples)	8-64 / 8-64	8-64 / 8-64	8-64 / 4-64
Rifampin MIC_{90} days 0 and 3 (from paired samples)	16 / 16	2 / 2	8 / 8
Rifampin MIC range days 0 and 3 (from paired samples)	1-16 / 1-16	0.25-8 / 0.5-8	0.25-8 / 0.25-8
# of patients + for enterococci post-tx	18	20	17

The number of fecal (CFU/g) rifaximin and rifampin resistant gram-negative coliforms were compared between samples obtained pre-treatment and on days 3 and 5. There were a low number of resistant organisms isolated, and while the number of resistant organisms increased with treatment, the authors concluded that these increases were not significant (table 5).[4]

Table 5: Rifaximin and rifampin resistant gram negative coliforms

	Rifaximin 600mg/d	Rifaximin 1200mg/d	Placebo
# of fecal rifaximin resistant GNB (CFU/g) isolated on days 0, 3, and 5*	200 / 500 / 600	600 / 950 / 1200	0 / 0 / 0
# of fecal rifampin resistant GNB (CFU/g) isolated on days 0, 3, and 5*	500 / 1100 / 1300	800 / 1700 / 3000	0 / 0 / 0

*Values estimated from graph
GNB = gram negative coliforms, CFU= colony-forming units

Another concern is whether low concentrations of rifaximin leads to selection of rifampin-resistant *Mycobacterium tuberculosis*. The MICs of rifaximin and rifampin for 5 *M. tuberculosis* isolates were determined before and after exposure to different concentrations of rifaximin. The MICs of rifampin and rifaximin were unchanged after exposure to rifaximin.[5] This was also shown to be the case in an animal study. Groups of 20 guinea pigs were infected with *M. tuberculosis* and treated with either 60mg/kg of rifaximin, 30mg/kg of rifampin, or served as a control. Animals were sacrificed after 90 days, and MIC values for samples from the liver, spleen, and lung remained 0.5mcg/mL after treatment with either drug.[12]

Efficacy

There are 4 clinical trials evaluating rifaximin in the treatment of travelers' diarrhea.[6-9] In a dose-finding study, DuPont compared rifaximin 200mg TID, 400mg TID, and TMP/SMX 160mg/800mg BID x 5 days (this study was not powered to compare outcomes versus TMP/SMX).[6] Steffan compared rifaximin 200mg TID, 400mg TID, and placebo x 3 days.[8] DuPont also compared rifaximin 400mg BID to ciprofloxacin 500mg BID x 3 days (this study was not considered to be pivotal by the FDA because of the rifaximin dose used).[7] There is also an unpublished study comparing rifaximin 200mg TID to ciprofloxacin 500mg BID x 3 days.[9]

The following definitions were used in the clinical trials:

Wellness (cure)	passage of no unformed stools in a 48h interval and no fever with or without other clinical symptoms or passage of no watery stools and no more than 2 soft stools in a 24h interval and no fever or other clinical symptoms of enteric infection
Improvement	≥ 50% reduction in the number of unformed stools passed during a 24h period in comparison with the number of unformed stools passed during the 24h immediately before enrollment in the study.
Failure	clinical deterioration or worsening of clinical symptoms after at least 24h of treatment in comparison to pretreatment symptoms and number of stools passed, failure of clinical symptoms to abate after at least 24h of therapy, illness continuing for > 120 hours
Bacteriologic cure	negative post-treatment stool examination for the etiologic organism identified before treatment

The primary endpoint in all trials was time to last unformed stool (TLUS) which was defined as the interval from initiation of therapy until passage of the last unformed stool after which patients were declared healthy.

To qualify for enrollment, patients had to be ≥ 18y/o, have ≥ 3 unformed stools in 24h, ill for ≤ 72h **AND ≥ 1 of the following:** nausea, vomiting, abdominal cramps/pain, tenesmus, fever ≥ 100°F, macroscopic blood in stools, fecal urgency, excessive gas/flatulence.[8, 9] Fever and excessive gas/flatulence were not part of the inclusion criteria in both DuPont studies; additionally bloody stool was not an inclusion criterion in the first DuPont study.[6, 7]

Exclusions included pregnancy, breast feeding, unstable or clinically significant medical condition, > 2 doses of antidiarrheal medication within 8 hours of randomization (24hours in DuPont 2001), use of any symptomatic drug within 2 hours of randomization, and any antimicrobial with activity against enteric bacterial pathogens 1 week prior to randomization. Additionally, moderate-severe dehydration was an exclusion in Steffan et al, and study 3001.

Rifaximin shortened the mean TLUS compared to placebo and TMP/SMX in the intent-to-treat groups. Both rifaximin and ciprofloxacin had a similar TLUS. Results of the TLUS broken down by country, pathogen +/-, fecal leukocyte +/-, etc. are provided in Appendix 1.

Table 6: Median TLUS for the intent-to-treat population

DuPont 1998				DuPont 2001		Steffen			Study 3001		
RFX 600	**RFX 1200**	**RFX 1800**	**TMP/ SMX**	**RFX**	**CIPRO**	**RFX 600**	**RFX 1200**	**PL**	**RFX**	**CIPRO**	**PL**
36.9h	38.6h	53	55.7h	25.7h	25h	32.5h	32.9h	60h	32h	28.8h	65.5h

Enteroaggregative *E.coli* (EAEC) is being recognized as a pathogen that can cause travelers' diarrhea. EAEC has been identified in fecal samples that were previously determined to be pathogen- negative. In order to detect EAEC, a Hep-2 cell assay is used. In the study by Steffen, 137 stool samples that were negative for pathogens were evaluated for the presence of EAEC. Of the 137 samples, 44 were found to have EAEC. The median TLUS for patients with EAEC-positive stools receiving rifaximin was 22h [95%CI 15-25] compared to 72h [20-72] with placebo.[10] In study 3001, the median TLUS for 29 EAEC isolates were 24h (range 0-120h), 27.3h, and 42.4h for rifaximin, ciprofloxacin, and placebo respectively.[9]

Clinical cure was achieved in 77 – 87% of patients receiving rifaximin, 78-88% receiving ciprofloxacin and in approximately 61% receiving placebo.[7-9]

Bacterial eradication rate was assessed in stool samples obtained 24-48 hours after last dose. Results broken down by pathogen are presented in table 7. When compared to placebo, the eradication rate for rifaximin was not significant; however, the eradication rate for ciprofloxacin versus placebo was statistically significant. Eradication of or failure to eradicate did not always correlate with clinical improvement.

Table 7: Microbiological eradication rate by pathogen (mITT population)

	DuPont 2001		Steffen			Study 3001		
	RFX	CIPRO	RFX 200	RFX 400	PL	RFX	CIPRO	PL
n	93	94	125	126	129	197	101	101
Microbiological population	87/187 (47%)		65	98	55	128	58	62
ETEC	20/30 (67%)	27/31 (87%)	45/60 (75%)	32/49 (65%)	40/54 (74%)	62/83 (74%)	43/45 (96%)	30/43 (70%)
Salmonella spp	2/2 (100%)	3/3 (100%)	2/3 (67%)	5/8 (63%)	2/2 (100%)	2/4 (50%)	2/2 (100%)	1/1 (100%)
Shigella spp	3/3 (100%)	5/5 (100%)	4/5 (80%)	½ (50%)	2/2 (100%)	10/11 (91%)	2/2 (100%)	3/5 (60%)
Campylobacter	1/1 (100%)	0	¾ (75%)	0	0/1	9/25 (36%)	6/9 (67%)	4/10 (40%)
Cryptosporidium	0	1/1 (100%)	12/18 (67%)	5/15 (33%)	1/1 (100%)	2/6 (33%)	2/6 (33%)	¼ (25%)
Giardia						6/15 (40%)	3/5 (60%)	2/8 (25%)

In study 3001, bacterial eradication rates with rifaximin according to *E.coli* subtypes, were 69.3%, 79.5%, and 67.2% for heat-labile ETEC, heat-labile/heat-stable ETEC, and heat-stable ETEC respectively.[9]

In study 3001, 14.1%, 15.5%, and 17.7% of the rifaximin, ciprofloxacin, and placebo-treated groups had a newly isolated pathogen 24-48 hours post-treatment.[9] In Steffan et al, less than 20% of the patients in each group had pathogens detected in their stool that had not been there pretreatment.[8] The most common newly isolated pathogens were heat-labile ETEC, heat-stable ETEC, heat-labile/heat-stable ETEC, and *Cryptosporidia.*

A study in the prevention of *Shigella* induced diarrhea is underway as well as a research study evaluating the use of rifaximin with loperamide HCl in the treatment of acute infectious diarrhea in travelers.

Hepatic encephalopathy

There are several small trials evaluating rifaximin in the treatment of hepatic encephalopathy. Open-label trials and small trials with ≤ 30 patients were excluded from the review. Six trials were reviewed (see appendix 2). Of these, 4 compared rifaximin 400mg TID to lactulose or lactitol, [14-17] 1 was a comparison with neomycin, [18] and 1 was a dose-finding study[13]. See Appendix 2 for study details.

The portal systemic encephalopathy (PSE) score or index was used to assess severity of disease and outcomes. The Parsons-Smith (modified by Conn) classification was used to assess mental status (Massa et al. used the West-Haven classification). The PSE score was determined by summing the score of the 6 individual components (see table 8). Although arbitrarily determined, a total score of 0-4 = no PSE, 5-10 = mild PSE, 11-20 = moderate PSE, and >20 = severe PSE. In lieu of the PSE score, Williams and Mas calculated the PSE index (excludes the cancellation test) which is the PSE score divided by the total number of possible points of 28. The grade for each of the remaining 5 components was weighted in proportion to its importance. Mental status was weighted by a factor of 3 and the others a factor of 1.

Table 8: Components of the portal systemic encephalopathy score or index

Mental state	Grade 0= no abnormality; Grade 1= trivial loss of awareness, euphoria or anxiety, shortened attention span, difficulty performing addition and subtraction; Grade 2= lethargy, disorientation to time, obvious personality change, inappropriate behavior; Grade 3= somnolence to semi-stupor, responsive to stimuli, confusion, gross disorientation, bizarre behavior; Grade 4= coma, mental function test not possible
Severity of asterixis	Grade 0= no flapping; grade 1= rare flapping motions; grade 2= occasional, irregular flaps;

	Grade 3= frequent flaps; Grade 4= almost continual flapping motions
Time to connect 25 progressive numbers (Reitan test)	Grade 0= <30s; Grade 1= 31-50s; Grade 2= 51-80s; Grade 3= 81-120s; Grade 4= >120s
EEG mean cycle frequency	Grade 0= 8-12 counts per second (cps); Grade 1= 7-8 cps; Grade 2= 5-7 cps; Grade 3= 3-5 cps; Grade 4= < 3 cps
Blood ammonia concentration	Breakdown of grade varies according to lab assay used
Cancellation test - cross out 28 letter A's in a grid containing 100 letters	Number of letter A's remaining Grade 0= none remaining; Grade 1= 1-3 remaining; Grade 2= 4-8 remaining; stage 3= 9-16 remaining; stage 4= > 16 or inability to perform test

In a dose finding study by Williams, 400mg every 8 hours was found to be the most effective dose and increasing to 800mg every 8 hours offered no additional benefit; therefore, 400mg was the dose used in subsequent studies with the duration of therapy varying from 5-15 days.

Compared to baseline, the PSE score or index improved for all patients receiving rifaximin, lactulose, or neomycin. Two studies showed a statistically significantly greater improvement with rifaximin compared to lactulose or lactitol.[13, 17]

Other uses
Several small studies have evaluated rifaximin for other uses including Crohn's disease, small intestinal bacterial overgrowth, irritable bowel syndrome, traveler's diarrhea prophylaxis, diverticular disease, dysentery, pouchitis, *C. difficile*-associated diarrhea, peptic ulcer disease, and surgical prophylaxis. These studies have not been reviewed; however, a brief description (Appendix 3) and references are provided.

Adverse Events (Safety Data)
The following adverse event data are derived from the pivotal trials (Steffen et al. and study 3001).

Table 9: Most commonly reported drug-related adverse events

	Rifaximin 600mg/d (n=320)	Ciprofloxacin (n=100)	Placebo (n=228)
Flatulence	9.7%	0	19.3%
Abdominal pain NOS	5.9%	0	9.2%
Nausea	4.7%	1%	8.3%
Rectal tenesmus	4.1%	0	6.1%
Defecation urgency	3.8%	0	6.6%
Constipation	3.4%	7%	2.6%
Headache	5.3%	2%	5.7%

Events occurring more frequently in the rifaximin than the placebo groups:
Lymphocytosis (0.6%), monocytosis (0.3%), neutropenia (0.6%), dry throat (0.3%), fecal abnormality (0.6%), dry lips (0.3%), chest pain (0.6%), malaise (0.3%), sunburn (0.3%), abnormal dreams (0.3%), taste loss (0.3%), hematuria (0.9%), polyuria (0.3%), increased urinary frequency (0.3%), hot flushes (0.3%), myalgia (0.3%), anorexia (0.3%).

Post-marketing events reported with use in foreign countries: hypersensitivity reactions, allergic dermatitis, angioneurotic edema, pruritus, rash and urticaria.

Precautions/Contraindications
Rifaximin is contraindicated in patients with hypersensitivity to any of the rifamycin antimicrobial agents (eg. rifampin), or any of the components in rifaximin.

Rifaximin should not be used for diarrhea complicated by fever, bloody stools, or pathogens other than *E. coli.*

Look-alike/ Sound-alike Error Risk Potential
As part of a pilot program, the VA PBM and Center for Medication Safety queried a multi-attribute drug product search engine for similar sounding and appearing drug names based on orthographic and phonological similarities, as well as similarities in dosage form, strength and route of administration. By

incorporating similarity scores as well as clinical judgment, it was determined that the following drug names may pose as potential sources of drug name confusion.

Rifaximin (generic name) Potential name confusion: rifampin, rifapentine, rifabutin, Rifater®
Potential Severity: can be severe if rifaximin is accidentally given for any of the systemic rifamycins.
Probability: Occasional – both the strength and dosing for rifaximin differs from the systemic rifamycins.

Xifaxan (brand name) Potential name confusion: Xanax, Biaxin
Potential Severity: can be severe if rifaximin is accidentally given for Biaxin
Probability: Uncommon for Xanax- strength of rifaximin and Xanax differ, but both are dosed three times daily. Uncommon for Biaxin – both the strength and dosing of rifaximin differs from Biaxin

Drug Interactions

Because rifaximin is a non-systemic agent, the potential for drug interactions is low. In an in vitro model, rifaximin was found to induce the CYP3A4 isoenzyme; therefore, pharmacokinetic studies were carried out using drugs known to be metabolized by CYP3A4. In one study, rifaximin 200mg every 8 hours for 3 days and 7 days was administered with a single dose of midazolam 2mg IV or 6mg orally. There was no difference in the elimination of midazolam or its major metabolite when midazolam + rifaximin were co-adminstered versus when midazolam administered alone. In another study, there were no pharmacokinetic interactions between rifaximin 200mg every 8 hours for 3 days and a single dose of ethinyl estradiol 0.07mg/norgestimate0.5mg.

Thera are no drug interaction studies looking at the combination of rifaximin and other drugs that might be used during an episode of travelers' diarrhea (e.g. antacids, bismuth subsalicylate, etc.). In the clinical trials, antimalarials were continued; however, there were no formal studies evaluating their combined use.

Pharmacoeconomics

There are presently no pharmacoeconomics or budget impact model studies.

Acquisition Costs

Available as 200mg tablets in bottles of 30.

Table 10: Comparative costs of antibiotics used to treat travelers' diarrhea

Drug, dosage, duration of treatment	FSS cost per unit	Cost of therapy
Rifaximin 200mg TID x 3 days	$2.09	$18.81
Ciprofloxacin 750mg x 1 dose	$0.12-0.25	$0.12-0.25
Ciprofloxacin 500mg BID x 3 days	$0.10-0.25	$0.60 – 1.50
Levofloxacin 500mg x1dose	$2.46	$2.46
Levofloxacin 500mg x 3 days		$6.05
Norfloxacin 400mg BID x 3 days	$2.39	$14.34
Ofloxacin 400mg x1 dose	$3.72	$3.72
Ofloxacin 300mg BID x 3 days	$3.52	$21.12
Azithromycin 500mg once daily then 250mg QD days 2-5	$4.20	$25.20
Azithromycin 1000mg (2 x500mg) x 1 dose	$8.40 (500mg)	$16.80

Recommendations for the quinolones and azithromycin from NEJM 2000; 342(23):1716-25.
Gatifloxacin or moxifloxacin 400mg QD x3 days ($4.05 and $4.65 respectively) would probably work, but not FDA approved indication (CDC)

Comparative costs for management of hepatic encephalopathy

Drug and dosage	FSS cost per unit	FSS cost per day
Rifaximin 400mg (2 x 200mg) tid	$2.09 / 200mg	$12.54
Lactulose 10gm/15ml tid*	$0.093 – $ 0.26 / 15ml	$0.28 – $0.78
Neomycin 1gm (2 x 500mg) tid	$0.74 / 500mg	$4.41

*Dose of lactulose is adjusted to maintain 2-3 soft stools per day

References (Travelers' diarrhea)

1. Jiang ZD, Ke S, Palazzini E, et al. In vitro activity and fecal concentration of rifaximin after oral administration. Antimicrob Agents Chemother 2000; 44: 2205-2206.

2. Gomi H, Jiang ZD, Adachi JA, et al. In vitro susceptibility testing of bacterial enteropathogens causing travelers' diarrhea in four geographic regions. Antimicrob Agents Chemother 2001; 45: 212-216.

3. Sierra JM, Ruiz J, Navia MM, et al. In vitro activity of rifaximin against enteropathogens producing travelers' diarrhea. Antimicrob Agents Chemother 2001; 45: 643-644. (letter to the editor)

4. DuPont HL, Jiang ZD. Influence of rifaximin treatment on the susceptibility of intestinal gram-negative flora and enterococci. Clin Micobiol Infect 2004; 10: 1009-1011.

5. Soro, O, Pesce A, Raggi M, et al. Selection of rifampicin-resistant Mycobacterium tuberculosis does not occur in the presence of low concentrations of rifaximin. Clin Micobiol Infect 1997; 3: 147-151.

6. DuPont HL, Ericsson CS, Mathewson JJ, et al. Rifaximin: a nonabsorbed antimicrobial in the therapy of travelers' diarrhea. Digestion 1998; 59: 708-714.

7. DuPont HL, Jiang ZD, Ericsson CD, et al. Rifaximin versus ciprofloxacin for the treatment of travelers' diarrhea: a randomized, double-blind clinical trial. Clin Infec Dis 2001; 33: 1807-1815.

8. Steffen R, Sack DA, Riopel L, et al. Therapy of travelers' diarrhea with rifaximin on various continents. Am J Gastroenterol 2003; 98: 1073-1078.

9. FDA review of rifaximin http://www.fda.gov/cder/foi/nda/2004/21-361_Xifaxan.htm (accessed November 2004)

10. Infante RM, Ericsson CD, Jiang ZD, et al. Enteroaggregative *Escherichia coli* diarrhea in travelers: response to rifaximin therapy. Clin Gastroenterol and Hepatol 2004; 2: 135-138.

11. Marchese A, Salerno A, Pesce A., et al. In vitro activity of rifaximin, metronidazole and vancomycin against Clostridium difficile and the rate of selection of spontaneously resistant mutants against representative anaerobic and aerobic bacteria, including ammonia-producing species. Chemotherapy 2000; 46 (4): 253-256.

12. Malvisi Stracciari J, Venturini AP, Anfossi P, et al. Sensitivity to rifaximin and rifampicin of Mycobacterium tuberculosis isolated from guinea pigs treated orally with rifaximin. Chemioterapia 1987; 6 (2): 82-84.

Hepatic encephalopathy

13. Mas A, Rodes J, Sunyer L, et al. Comparison of rifaximin and lactitol in the treatment of acute hepatic encephalopathy: results of a randomized, double-blind, double-dummy, controlled clinical trial. J Hepatol 2003; 38: 51-58.

14. Williams R, James OFW, Warnes TW, et al. Evaluation of the efficacy and safety of rifaximin in the treatment of hepatic encephalopathy: a double-blind, randomized, dose-finding multi-center study. Eur J Gastroenterol Hepatol 2000; 12: 203-208.

15. Bucci L, Palmieri GC. Double-blind, double-dummy comparison between treatment with rifaximin and lactulose in patients with medium to sever degree hepatic encephalopathy. Curr Med Res Opin 1993; 13: 109-118.

16. Fera, G, Agostinacchio F, Nigro M, et al. Rifaximin in the treatment of hepatic encephalopathy. Eur J Clin Res 1993; 4: 57-66.

17. Massa P, Vallerino E, Dodero M, et al. Treatment of hepatic encephalopathy with rifaximin: double blind, double dummy study versus lactulose. Eur J Clin Res 1993; 4: 7-18.

18. Miglio F, Valpiani D, Rossellini S, et al. Rifaximin, a non-absorbable rifamycin, for the treatment of hepatic encephalopathy. A double-blind, randomized trial. Curr Med Res Opin 1997; 13: 593-601.

Small intestinal bacteria overgrowth and irritable bowel disease

19. Corazza GR, Ventrucci M, Strocchi A, et al. Treatment of small intestine bacteria overgrowth with rifaximin, a non-absorbable rifamycin. J Int Med Res 1998; 16: 312-316.

20. Cuoco L, Montalto M, Jorizzo RA, et al. Eradication of small intestinal bacterial overgrowth and oro-cecal transit in diabetics. Hepato-gastroenterol 2002; 49: 1582-1586.

21. Trespi, E, Ferrieri A. Intestinal overgrowth during chronic pancreatitis. Curr Med Res Opin 1000; 15: 47-52.

22. Certo M, Cuoco L, Papa A, et al. Small intestine bacterial contamination syndrome in subjects without primary intestinal pathologies: a frequent cause of chronic diarrhea. New Prospects in Therapy 1996; 1-12.

23. Di Stefano M , Malservisi S, Veneto G, et al. Rifaximin versus chlortetracycline in the short-term treatment of small intestinal bacterial overgrowth. Aliment Pharmacol Ther 2000; 14: 551-556.

24. Di Stefano M, Strocchi A, Malservisi S, et al. Non-absorbable antibiotics for managing intestinal gas production and gas-related symptoms. Aliment Pharmacol Ther 2000; 14: 1001-1008.

25. Nucera G, Lupascu A, Gabrielli M, et al. Sugar intolerance in irritable bowel syndrome: the role of small bowel bacterial overgrowth. 2004 DDW meeting; May 15-20; New Orleans, Louisiana [Poster #T1783].

26. Tursi A, Brandimarte G, Giorgetti G. High prevalence of small intestinal bacterial overgrowth in celiac patients with persistence of gastrointestinal symptoms after gluten withdrawal. Am J Gastroenterol 2003; 98:839-843.

Crohn's Disease and Ulcerative Colitis

27. Shafran I, Johnson LK, Hamm L, et al. Efficacy and tolerability of rifaximin, a nonabsorbed oral antibiotic, in the treatment of active Crohn's disease: results of an open-label study. 68th Annual ACG Scientific Meeting; October 13-15, 2003; Baltimore, Maryland [poster #281].

28. Biancone L, Ferrieri A, Silvestri M, et al. Rifaximin in inactive Crohn's disease: effect on the intestinal protein loss as assessed by the fecal α1-anitrypsin clearance. J Clin Res 1998; 1: 289-304.

29. Brigidi P, Swennen E, Rizzello F, et al. Effects of rifaximin administration on the intestinal microbiota in patients with ulcerative colitis. J Chemother 2002; 14: 290-295.

30. Lukas M, Konecny M, Zboril V. Rifaximin in patients with mild to moderate activity of ulcerative colitis: open label study. Abstract presented at Digestive Disease Week conference May 19-22, 2002; San Francisco.

31. Gionchetti P, Rizzello F, Ferrieri A, et al. Rifaximin in patients with moderate or severe ulcerative colitis refractory to steroid-treatment: a double-blind s, placebo-controlled trial [Letter}. Dig Dis Sci 1999; 44: 1220-1221.

32. Pinto A, Borruto G, Dell'Anna A, et al. An open, uncontrolled trial of oral rifaximin, a non-absorbable antibiotic, in inflammatory bowel disease refractory to conventional therapy. Eur J Clin Res 1997; 9: 217-224.

33. Riegler G, Russo MI, Carratu R, et al. Clinical and therapeutic considerations in the treatment of non-specific abdominal disorders in patients with quiescent ulcerative colitis: preliminary notes on therapy with rifaximin. Eur Rev Med Pharmacol Sci 1992; 14: 9-14. [In Italian]

Pouchitis

34. Abdelrazeq AS, Lund JN, Kelley SM, et al. Rifaximin-ciprofloxacin combination therapy is effective in patients with chronic, active, refractory pouchitis. 2004 DDW meeting; May 15-20; New Orleans, Louisiana.

35. Gionchetti P, Rizzello F, Venturi A, et al. Antibiotic combination therapy in patients with chronic, treatment resistant pouchitis. Aliment Pharnacol Ther 1999; 13: 713-718.

Travelers' diarrhea prophylaxis

36. DuPont HL, Jiang Z-D, Okhuysen PC, et al. Rifaximin, a nonabsorbed (0.4%) antibiotic, prevents bacterial diarrhea. Presented at the 7th Annual Force Health Protection Conference; Aug. 9-12, 2004; Albuquerque, New Mexico and at the 2004 DDW meeting; May 15-20, 2004; New Orleans, Louisiana.

***Clostridium difficile* colitis**

37. Boero M, Berti E, Morgando A, et al. Treatment for colitis caused by *Clostridium difficile*: results of a randomized open study of rifaximin vs. vancomycin. Microbiologia Medica 1990: 5:74-77.

Pre-op bowel surgery

38. Bresadola F, Intini S, Anania G, et al. Chemotherapeutic prophylaxis in the preparation of the large intestine for surgical interventions: rifaximin p.o. vs cephalosporin i.v. Ann Ital Chir 1992; 63: 201-207. [In Italian]

39. Porta E, Berta V. A new prophylaxis program for colorectal surgery. Chir Gastroenterol 1992; 26. [In Italian].

40. Gruttadauria G, La Barbera F, Cutaia G, et al. Prevention of infection in colonic surgery by rifaximin. A controlled, prospective, randomized trial. Eur Rev Med Pharmacol Sci 1987; 9: 101-105.

41. Scalco et al. Rifaximin: a new rifamycin for the prophylaxis of the septic complications in the larger bowel surgery. Policlinico Sez Chir 1987; 94: 41-45

42. Verardi S, Varardi V, Fusillo M. Rifaximin effectiveness evaluation in the preparation of large intestine to surgery. Eur Rev Med Pharmacol Sci. 1986; 8: 267-270.

Helicobacter pylori eradication

43. Dell'Anna A, Azzarone P, Ferrieri A. A randomized openly comparative study between rifaximin suspension versus rifaximin pills for eradication of *Helicobacter pylori*. Eur Rev Med Pharamacol Sci 1999; 3: 105-110.

44. DeGiorgio R, Stanghellini V, Barabara G, et al. Rifaximin and Helicobacter pylori eradication. Eur Rev Med Pharmacol Sci 1997; 1: 105-110.

Uncomplicated diverticular disease

45. Aragona G, Leandro G, Fanigliulo L, et al. Efficacy of mesalazine in the treatment of symptomatic diverticular disease. [poster] DDW meeting May 15-20, 2004 New Orleans, Louisiana.

46. Latella G, Pimpo MT, Sottili S, et al. Rifaximin improves symptoms of acquired uncomplicated diverticular disease of the colon. Int J Colorectal Dis 2003; 18: 55-62.

47. Tursi A, Brandimarte G, Daffina R. Long-term treatment with mesalazine and rifaximin versus rifaximin alone for patients with recurrent attacks of acute diverticulitis of colon. Dig Liver Dis 2002; 34: 510-515.

48. Dal Monte PR, Dal Monte P, Cennamo V, et al. Rifaximin in patients with diverticulitis or hepatic encephalopathy. G Ital Ric Clin Ter 1995; 16. [In Italian]

49. Papi C, Ciaco A, Koch M et al. Efficacy of rifaximin in the treatment of symptomatic diverticular disease of the colon. A multicenter double-blind placebo-controlled trial. Aliment Pharamcol Ther 1995; 9: 33-39.

50. Porta E, Germano A, Ferrieri A, et al. the natural history of diverticular disease of the colon: a role for antibiotics in preventing complications? A retrospective study. Riv Eur Sci Med Farmacol 1994; 16: 33-39.

51. Ventrucci M, Ferrieri A, Bergami R, et al. Evaluation of the effect of rifaximin in colon diverticular disease by means of lactulose hydrogen breath test. Curr Med Res Opin 1994; 13: 202-206.

52. Giaccari S, Tronci S, Falconieri M, et al. Long-term treatment with rifaximin and lactobacilli in post-diverticulitic stenoses of the colon. Riv Eur Sci Med Farmacol 1993; 15: 29-34. [In Italian]

53. Ciaco A, Papi C, Koch M, et al. Rifaximin in the treatment of diverticular disease of the colon: a multcentric study. Presented at the 5th Italian Digestive Disease Congress, 5/31-6/4, 1992; Bologna, Italy.

54. Papi C, Ciaco A, Koch M, et al. Efficacy of rifaximin on symptoms of uncomplicated diverticular disease of the colon. A pilot multicenter open trial. Ital J Gastroenterol 1992; 24: 452-456.

55. Lombardo L, Lapertosa G. The ambulatory medical treatment of colonic diverticulitis. An open clinical-endoscopic-histological study with rifaximin, a nonaminoglycoside enteric antibiotic. Rec Prog Med 1991; 82: 300-304. [In Italian].

Prepared by Deborah Khachikian, Pharm.D.
November 2004

Appendix 1: Clinical trials in travelers' diarrhea

<table>
<tr><th>Study</th><th>Baseline data</th><th>Results</th><th>Comments</th></tr>
<tr>
<td>DuPont 1998[6]
R, DB, DD, PR

Study conducted July and August 1996

U.S. students attending school in Guadalajara and Morelia, Mexico

<u>Treatment arms</u>
•Rifaximin 200mg TID x 5 days (n=18)
•Rifaximin 400mg TID x 5 days (n=18)
•Rifaximin 600mg TID x 5 days (n=19)
•TMP/SMX 160mg /800mg BID x 5 days (n=17)

Antidiarrheal compounds, ASA, NSAIDs, antiperistaltic agents were prohibited</td>
<td>% male 47.2%
Mean age – 24.5 years
% white – 83%
Mean duration of illness prior to enrollment (h)- RFX200 25.3; RFX400 30.5; RFX600 30.9; TMP/SMX 32.8
Pre-tx # unformed stools (mean)- RFX200 5.7; RFX400 5.9; RFX600 6.1; TMP/SMX 6.5</td>
<td>
<table>
<tr><th></th><th>RFX 200</th><th>RFX 400</th><th>RFX 600</th><th>TMP/SMX</th></tr>
<tr><td>Dropouts (n)</td><td>1</td><td>1</td><td>0</td><td>2</td></tr>
<tr><td>TLUS (mean)</td><td>36.9h</td><td>38.6h</td><td>53h</td><td>55.7h</td></tr>
<tr><td>%pts/w improvement by 24 h</td><td>56%</td><td>44%</td><td>53%</td><td>65%</td></tr>
<tr><td>%pts/w improvement by 48 h</td><td>83%</td><td>78%</td><td>89%</td><td>76%</td></tr>
<tr><td>% failure</td><td colspan="3">6/55 (11%); 4/6 occurred in the RFX 600 group</td><td>5/17 (29%)</td></tr>
</table>
Sample size too small to show statistical differences
</td>
<td>Dose-finding study

Small number of patients per treatment arm; intended as a preliminary study

5-day duration of tx used

TMP/SMX no longer considered to be appropriate due to high rate of resistance</td>
</tr>
<tr>
<td>DuPont 2001[7]
R, DB, DD, PR

Study conducted June 1997-Sept. 1998

•U.S students attending summer school in Guadalajara, Mexico (n=163)
•International tourists staying in resort hotels in Ocho Rios, Jamaica (n=24)

<u>Treatment arms</u>
•Rifaximin 400mg BID x 3 days (n=93)
•Ciprofloxacin 500mg BID x 3 days (n=94)

Antidiarrheal compounds, ASA, NSAIDs, antiperistaltic agents were prohibited</td>
<td>% male -RFX 42%; CIP 46%
% white- RFX 82%; CIP 79%
Mean age ± SD (years)- RFX 26.3 ± 9.5; CIP 25.6 ± 9.2
Mean weight ± SD (kg)- RFX 69.1 ± 15.5; CIP 69.9 ± 20.3
Pre-tx nausea – RFX 57%; CIP 67%
Pre-tx vomiting – RFX 19%; CIP 17%
Pre-tx abdominal pain/cramps- RFX 91%; CIP 89%
Pre-tx fever - RFX 9%, CIP 9%
Total # unformed stools – RFX 6 ± 3.1; CIP 6.1 ± 3.7
Duration of illness (h)- RFX 30.4 ± 21.2; CIP 27.2 ± 18.3
Pathogen negative (#)- RFX 47; CIP 46</td>
<td>
<table>
<tr><th></th><th>Rifaximin</th><th>Ciprofloxacin</th></tr>
<tr><td>Completed study</td><td>92/93</td><td>90/94</td></tr>
<tr><td>TLUS [95% CI]</td><td>25.7h
[20.9, 38]</td><td>25h
[18.5, 35.2]</td></tr>
<tr><td>TLUS pathogen negative</td><td>25.5h</td><td>30.0h</td></tr>
<tr><td>TLUS pathogen specific</td><td>25.7h</td><td>25.0h</td></tr>
<tr><td>Improvement w/i 24h of enrollment</td><td>58%</td><td>64%</td></tr>
<tr><td>Improvement w/i 48h of enrollment</td><td>83%</td><td>85%</td></tr>
<tr><td>Clinical cure</td><td>87%</td><td>88%</td></tr>
<tr><td>Treatment failure</td><td>10%</td><td>6%</td></tr>
<tr><td>Microbiological cure/failure for ETEC</td><td>20/30 (67%)
10/30 (33%)</td><td>27/ 31 (87%)
3/31 (10%)</td></tr>
<tr><td>TLUS for those who failed to eradicate ETEC</td><td>35.6h
(n=10)</td><td>10.9h
(n=4)</td></tr>
</table>
Median values
</td>
<td>Not considered to be a pivotal trial by the FDA because of the dose of rifaximin used. Considered to be a supportive trial

Study designed to demonstrate non-inferiority between treatments</td>
</tr>
</table>

BID= twice daily; DB= double-blind; DD= double-dummy; PR= parallel; R= randomized; TID= three times daily; TMP/SMX= trimethoprim-sulfamethoxazole; RFX= rifaximin; TLUS= time to last unformed stool

Steffen 2003[8]
R, DB, PC, PR

Study conducted May 1999- June 2000

•Antigua, Guatemala (n=100)
•Guadalajara and Morelia, Mexico (n=195)
•coast of Kenya north and south of Mombasa (n=85)

Treatment arms
•Rifaximin 200mg TID x 3 days(n=125)
•Rifaximin 400mg TID x 3 days (n=126)
•Placebo x 3 days (n=129)

% male – 48-54%
Mean age ± SD (years)- RFX600 29 ± 1.1; RFX1200 29.9 ± 1.0; PL 28.3 ± 0.9
Pre-tx nausea – 53.2%-59.2%
Pre-tx vomiting – 9.3%-16%
Pre-tx abdominal pain/cramps- 86.4%-91.5%
Pre-tx fever – 20.6%- 24.8%
Total # unformed stools – median 5 (range 3-25)
Duration of illness (h)- 30-31.8
Fecal leukocyte + RFX600 16.2%; RFX1200 15%; PL 18.7%
Pathogen + RFX600 56%; RFX1200 47.6%; PL 47.3%

	Rifaximin 600mg/d	**Rifaximin 1200mg/d**	**Placebo**
Completed study	92%	90.5%	85.3%
d/c 2° LOE	3.2%		7.8%
d/c 2° AE	0.8%		0
TLUS (all) [95%CI]	32.5h* [28.4, 43.4]	32.9h* [22.7, 41.8]	60.0h [45.5, 79.5]
TLUS Mexico	32.5h	46.1h	59.1h
TLUS Guatemala	28.9h	23.3h	49.0h
TLUS Kenya	42.7h	30.3h	74.3h
TLUS Fecal leukocyte +	45.1h	36.7h	Not available
TLUS Fecal leukocyte -	32.5h*	30.1h*	57.0h
TLUS ETEC	28.4h*	26.8h*	57.8h
TLUS Bacterial infec +	28.4h*	30.3h	58.6h
TLUS Bacterial infec -	43.4h*	36.8h*	64.4h
TLUS Parasitic infec +	37.3h*	43.8h	60.8h
TLUS Parasitic infec -	32.2h*	28.5h*	60.0h
% Clinical cure	79.2%*	81%*	60.5%
% tx failure	16%*	16.7%*	34.9%
% clinical cure (leukocyte + pts.)	14/20 (70%)	15/17 (88%)	11/23 (48%)
% pts with improvement at 24-48h	87%*		72%
% pts with improvement at 48-72h	91%*		78%

*significant vs. placebo
Significance not determined for subgroups by country

AE= adverse event; DB= double-blind; LOE= lack of efficacy; PC= placebo-controlled; PR= parallel; TID= three times daily; R= randomized; TLUS= time to last unformed stool

Study RFDI3001[9]
R, DB, PC, PR

Study conducted July 2003-May 2003

•Mexico (n=87)
•Guatemala (n=103)
•Calcutta, India (n=89)
•Goa, India (n=117)
•Peru (n=3)

Treatment arms
•Rifaximin 200mg TID x 3 days (n=197)
•Ciprofloxacin 500mg BID x 3 days (n=101)
•Placebo x 3 days (n=101)

Antimotility agents other antidiarrheals, acetaminophen, NSAIDs, antacids, probiotics, other antibiotics, and theophylline were not allowed

% male – 52.4%
% white- 82%
Mean age ± SD (years)- RFX 32.5 ± 13.33; CIP 34.2 ± 14.36; PL33.4 ± 14.09
Pre-tx nausea – RFX 60.4%; CIP 58.4%; PL 58.4%
Pre-tx vomiting – RFX 19.3%; CIP 16.8%; PL 18.8%
Pre-tx abdominal pain/cramps- RFX 94.4%; CIP 95%; PL 91.1%
Pre-tx fever – RFX 19.8%; CIP 19.8%; PL 15.8%
Pre-tx blood/mucus in stool- RFX 32.5%; CIP 24.8%; PL 33.7%
Mean # unformed stools 24h pre-enrollment– RFX 7.3 ±4.61; CIP6.9 ± 3.88; PL 6.9 ± 4.58
Duration of illness (h) - RFX 30.4 ± 21.2; CIP 27.2 ± 18.3; PL ??
Fecal leukocyte + RIFX 46.2%; CIP 37.6%; PL 44.6%
% w/ diarrheagenic *E.coli*- RFX 37.6%; CIP 45.5%; PL 37.6%
% w/ inflammatory/invasive pathogens- RFX 23.4%; CIP 12.9%; PL 18.8%

	Rifaximin	**Ciprofloxacin**	**Placebo**
Completed study	89.8%	93.1%	83.2%
d/c 2° LOE	8.6%	2.0%	11.9%
d/c 2° AE	1.0%	3.0%	1.0%
All patients	32.0h*	28.8 *	65.5
TLUS [95% CI]	[24.3, 44.9]	23.6, 48.0]	[40.2, 83.5]
All patients			
% clinical cure	76.6%	78.2%	61.4%
% bacterial eradication	61.6%	80.7%*	51.7%
% tx failure	14.7%	6.9%	Not shown
Any pathogen positive			
TLUS	40.3h	28.3h	48.3h
% clinical cure	73.4%	74.1%	64.5%
% bacterial eradication	60.2%	79.3%	50%
***E.coli* positive**			
TLUS	23.9h*	23.4h	38h
% clinical cure	84%	82.5%	73.7%
% bacterial eradication	76.7%	92.5%	63.2%
Pathogen negative			
TLUS	23.5h*	29.7h	71.6h
% clinical cure	82.6%	83.7%	56.4%
Mexico			
TLUS	33.0h	15.5h	26.7h
% clinical cure	83.7%	76.2%	65.2%
Guatemala & Peru			
TLUS	23.5h	20.8h	41.4h
% clinical cure	88.7%	96.3%	80.8%
Calcutta			
TLUS	24.5h	24.1h	NC
% clinical cure	88.4%	91.3%	47.8%
Goa			
TLUS	72h	70.5h	69.7h
% clinical cure	51.7%	53.3%	51.7%
Fever at baseline			
TLUS	NC	23.4h	51.1h
% clinical cure	48%	85.7%	66.7%
% bacterial eradication	56%	85.7%	50%
Blood at baseline			
TLUS	63.5h	55.5h	69.7h
% clinical cure	57.1%	72.2%	56%
% bacterial eradication	61.9%	72.2%	48%
TLUS Fecal leukocyte +	29.0h*	23.4h	72h
TLUS Fecal leukocyte -	35.8h	44.1h	48.3h

Median values for TLUS
NC – not calculable
*significant vs. placebo; Significance not calculated for TLUS by country, % clinical cure and the subgroups for cipro vs. placebo, and bacterial eradication by subgroup

1° analysis superiority of rifaximin vs. placebo; non-inferiority vs. cipro (2° endpoint)

There were problems with the data from the Goa and Mexico sites; therefore, data for each site is presented separately. The TLUS when Goa and Mexico are excluded is:
Rifaximin 23.8h
Cipro 23.6h
Placebo 65.5h

Appendix 2: Hepatic encephalopathy

Trial	Cirrhosis history	Dosage	Duration of tx	Distribution of severity	Baseline PSE	Improvement in PSE	Other assessments
Williams 2000[14] R, DB, dose-finding	Bx proven cirrhosis History of HE Recent deterioration in their neuropsychiatric status	Rifaximin 200mg q 8h (n=18) Rifaximin 400mg q 8h (n=19) Rifaximin 800mg q 8h (n=17) *No protein restriction*	7 days	Mental status grade Grade I (n=39) Grade II (n=12) Grade III (n=1) Subclinical (n=2)	Baseline PSE index (%) Mean ± SD 37.8 ± 11.4 (600mg/d) 38.4 ± 13.8 (1200mg/d) 41.7 ± 8.5 (2400mg/d)	Δ PSE index Mean ± SD [95%CI] -6.4 ± 13.7 [-14, 1.2] -10.3 ± 13.7 [-17.4, -3.1] -10.7 [-17.8, -3.6]	Ammonia (mean) 600mg: 132.8 →107.1 µmol/l 1200mg: 143.5 →143 µmol/l 2400mg: 183.3→188.6 µmol/l
Mas 2003[13] R, DB, DD, PR	Cirrhosis with an acute HE episode	Rifaximin 400mg q 8h (n=50) Lactitol 20g q 8h (adjusted to obtain 2 soft stools/d) (n=53) *Protein initially restricted to 20g/d and gradually increased to 0.5g/kg/d*	5-10 days Mean length of tx 5.65d (rifaximin) 5.75d (lactitol)	HE Stage Stage I (n=31) Stage II (n=50) Stage III (n=22)	Baseline PSE index (%) Rifaximin 61 (32 - 85) Lactitol 55 (25 - 89) Baseline PSE score Rifaximin 17 (19-21) Lactitol 15 (7-25) Median (range)	PSE index at end Rifaximin 14 (0-61)* Lactitol 21 (7-68) PSE score at end Rifaximin 4.0 (0-17)* Lactitol 6.0 (2-19) Both groups had significant improvement versus baseline for the individual components of the PSE score. Median (range) *significant vs. lactitol	Ammonia (median) 120.5 →69.5 g/dl* 124.1 →109 g/dl Resolution/improvement 81.5% rifaximin 80.4% lactitol Complete resolution 53.1% rifaximin* 37.2% lactitol *significant vs. lactitol
Massa 1993[17] R, DB, DD, PR	Cirrhosis diagnosed by clinical and laboratory data Patients presented with 1st to 3rd degree HE according to West Haven Criteria	Rifaximin 400mg q 8h (n=20) Lactulose 10g q 8h (n=20) *Protein restriction for HE stage I- <0.5g/kg/d HE stages II-III – no protein initially then 20g/d qod was started as pt. improved*	15 days	HE Stage Stage II (n=37) Stage III (n=3)	PSE score (mean ± SEM) 16.4 ± 0.6 16.6 ± 0.7	Mean PSE score (estimated from graph) Rifaximin 3* Lactulose 5 • Both groups had significant improvement versus baseline for the individual components of the PSE score. • Mental status score, Reitan test, and EEG (days 6, 9) showed significantly greater improvement with rifaximin *significant vs. lactulose	Ammonia (mean ± SEM) Rifaximin: 117.3 ± 8.5 → 62.4 ± 4.4mcg/100ml* lactulose: 124.1 ± 7.7 → 73.5 ± 2.8mcg/100ml *significant vs. lactulose

DB=double-blind; DD= double-dummy; HE= hepatic encephalopathy; PR= parallel; PSE= portal systemic encephalopathy; R= randomized

Bucci 1993[15] R, DB, DD, PR	Bx proven cirrhosis Signs and symptoms of PSE	Rifaximin 400mg tid (n=30) Lactulose 10g tid (n=28) *Protein restricted to < 50g/d*	15 days	PSE severity Mild (n=9) Moderate (n=38) Severe (n=11)	PSE score (mean ± SD) 16 ± 12 (rifaximin) 18 ± 24 (lactulose)	PSE score at day 15 (estimated from graph) 10 (rifaximin) 11.4 (lactulose) • Both groups had significant improvement versus baseline for the individual components of the PSE score. • Mental status score, cancellation test, and EEG showed significantly greater improvement with rifaximin	<u>Ammonia (mean)</u> 119 → 74mcg/100ml 121→ 78mcg/100ml
Fera 1993[16] R, DB, DD, PR	Cirrhosis of liver with signs and/or symptoms of HE (ammonia >115mg/100ml)	Rifaximin 400mg q 8h (n=20) Lactulose 40mg q 8h (n=20) *Protein restriction < 0.5g/kg/d*	For the first 2 weeks of each month x 90 days	PSE Severity Mild (n=38) Moderate (n=2)	PSE score 8.2 (rifaximin) 8.1 (lactulose)	<u>PSE score at 2 weeks</u> 4.75 ± 0.34 (rifaximin) 5.8 ± 0.32 (lactulose) <u>PSE score at 90d</u> 1.4 (rifaximin) 3.0 (lactulose) • Both groups had significant improvement versus baseline for the individual components of the PSE score. • Mental status score, Reitan test, and EEG showed significantly better improvement with rifaximin	<u>Ammonia (estimated from graph)</u> Rifaximin: 120 → 68mcg/100ml Lactulose: 125 → 80mcg/100ml
Miglio 1997[18] R, DB, PR	Dx cirrhosis (liver bx, laparoscopy with bx, US, or clinical and lab data) Patients had chronic HE of grade 1 or 2	Rifaximin 400mg tid (n=30) Neomycin 1g tid (n=30) *Maximum protein intake 40g/d*	14 consecutive days each month x 6 months	HE grade§ Grade I (n=37) Grade II (n=23)	Not determined	In all patients reduction in HE grade seen. There were no difference between groups Improvement in the Reitan test was statistically greater with rifaximin.	<u>Ammonia (mean ± SD)</u> Rifaximin: 210 ± 65.6 → 88.9 ± 39.6mcg/100ml Neomycin: 202.1 ± 60.1 → 86.2 ± 42.9mcg/100ml

§In Miglio et al., Grade I HE was defined as the presence of ≥ 3 of the following: slow or slurred speech, disturbance of memory, abnormalities of behavior and/or mood, disturbance of gait, asterixis, writing abnormalities, abnormal performance of serial subtraction of 7's, abnormalities of 5-pointed star, Reitan trail-making test, EEG changes according to Romer and Kurtz classification, fasting ammonia > 100mcg/100ml.. Grade 2 included patients with major mental status and behavioral changes, somnolence and disorientation.

DB=double-blind; DD= double-dummy; HE= hepatic encephalopathy; PR= parallel; PSE= portal systemic encephalopathy; R= randomized

Appendix 3: Other GI-related studies

	Randomized double-blind	Randomized open label	Open label	Retrospective
Small intestinal bacterial overgrowth/ irritable bowel syndrome	• RFX 400mg TID x 7d ays vs. chlortetracycline 333mg TID x 7 days (n=21)[23] • RFX 400mg BID x 7days vs. activated charcoal 400mg BID x 7 days (n=34)[24]		• RFX 750mg/d + paromomycin 750mg/d for 1 week per month for 4 months (n=150)[25] • RFX 800mg/d x 7 days (n=10)[26] • RFX 400mg TID x 10 days (n=21)[20] • RFX 400mg TID x 7 days for 3 months (n=12)[21] • RFX 800-1200mg/ d for 5 days (n=16)[22] • RFX 400mg BID or TID for 5 days (n=12)[19]	
Crohn's Disease	RFX 400mg BID x 7days vs. placebo (n=26) [28] RFX 400mg BID x 7 days/month for 12 months vs. placebo (n=10)[28]		RFX 200mg TID x 16 weeks (n=29)[27]	
Ulcerative colitis	RFX 400mg BID x 10 days vs. placebo (n=28)[31]		• RFX 1800mg/d for three 10-d treatment periods (n=12)[29] • RFX 400mg BID x 10 days (n= 31)[30] • RFX 400mg BID x 5 days (n=12)[32] • RFX 200mg TID x 10 days (n=12)[33]	
Pouchitis			• RFX 1000mg + cipro 500mg BID x 2 weeks (n=8)[34] • RFX 1000mg BID + cipro 500mg BID x 15 days (n=18)[35]	
Travelers' diarrhea prophylaxis	RFX 200mg QD, BID, TID vs. placebo x 2 weeks (n=209)[36]			
Clostridium difficile		RFX 200mg TID x 10 days vs. vancomycin		

colitis		500mg BID x 10 days (n=20)[37]		
Pre-operative bowel preparation	RFX 200mg TID x 3 days vs. perioperative gentamicin vs. RFX 200mg TID + perioperative gentamicin (n=128)[40]	• Cefotaxime 3g/day IV + RFX 400mg tid x 5 days vs. cefotaxime 3g/day IV x 5 days (n=30)[38] • RFX 200mg tid vs. RFX 400mg tid x 3 days (n=36)[41] • RFX 400mg bid x 3 days vs. paromomycin 500mg bid x 3 days (n=38)[42]		Tobramycin + clindamycin compared to aztreonam + RFX 200mg TID x 2 days (n=535)[39]
H. pylori eradication		• RFX suspension 1800mg TID + omeprazole 20mg BID x 14 days vs. RFX tablets 1800mg TID + omeprazole 20mg BID x 14 days (n=20)[43] • RFX suspension 200mg TID + amoxicillin 1000mg BID + omeprazole 40mg qd x 14 days vs. RFX suspension 200mg TID + erythromycin 600mg TID + omeprazole 40mg QD x 14 days (n=20)[44]		
Uncomplicated diverticular disease	Glucomannan 2g/day for 7 days/month x 12 months vs. glucomannan 2g/d + RFX 400mg BID x 7 days/month x 12 months (n=168)[47]	• RFX 200mg BID vs. RFX 400mg BID vs. mesalazine 400mg BID vs. mesalazine 800mg BID for 10 days/month x 12 months (n=248)[45] • Glucomannan 4g/d + RFX 400mg BID x 7 days /month x 12 months vs. Glucomannan 4g/d x 12 months (n=968)[46] • RFX 400mg BID + mesalazine 800mg TID x 7 days followed by RFX 400mg BID + mesalazine 800mg BID for 7 dys/months x 12 months vs. RFX 400mg BID x 7 days then RFX 400mg BID for 7 days/months x 12 months (n=218)[47] • Fiber 20g/d x 12 months vs. fiber 20g/d + RFX 400mg BID x 7 days/ month x 12 months (n=217)[53] • Glucomannan 2g/day x 12 months vs. glucomannan 2g/day + RFX 400mg BID x 7 days/month x 12 months (n=217)[54]	• RFX 400mg TID x 14 days (n=56)[48] • RFX 400mg BID x 10 days (n=33)[51] • RFX 400mg BID x 7 days followed by lactobacilli recolonization x 7 days for 12 months (n=45)[52] • RFX 400mg BID x 10 days (n=20)[55]	Neomycin + bacitracin, paromomycin, or rifaximin administered at monthly cycles of 7-day courses vs. no antibiotics (n=505)[50]

BID= twice daily; cipro= ciprofloxacin; QD= once daily; RFX= rifaximin; TID= three times daily