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New Drug Evaluation: Aemcolo™ (rifamycin) delayed release tablet, oral

Date of Review: November 2019
Generic Name: rifamycin

End Date of Literature Search: December 2018
Brand Name (Manufacturer): Aemcolo™ (Cosmo Technologies, Ltd)
Dossier Received: no

Research Questions:

1. What is the efficacy of rifamycin compared to placebo or currently available therapy for the treatment of adults with travelers' diarrhea (TD)?
2. Is rifamycin safer than alternative treatments for TD?
3. Are there any subgroups (based on age, ethnicity, comorbidities, disease duration or severity) that would particularly benefit or be harmed from treatment with rifamycin?

Conclusions:

- Low strength of evidence from one poor quality randomized controlled trial (RCT) demonstrated that rifamycin is more effective compared to placebo in reducing the duration of TD caused by *E.Coli* (46 hours vs. 68 hours; p=0.0008).[1] In addition, low strength of evidence shows that a larger percentage of rifamycin-treated patients (81.4%) achieved clinical cure compared with placebo-treated patients (56.9%; difference=24.5%; p=0.0001; 95% Confidence Interval (CI) 11.3 to 37.7; Number Needed to Treat (NNT) 5).[1] Clinical cure was defined by the investigators as two or fewer soft stools and minimal enteric symptoms at the beginning of a 24-hour period or no unformed stools at the beginning of a 48-hour period.[1]
- A non-inferiority study at high risk of bias provides insufficient evidence that rifamycin was non-inferior to ciprofloxacin in treating non-dysenteric TD.[2] In this trial investigators reported the median time to last unformed stool (TLUS) in Per Protocol (PP) analysis of the rifamycin-treated group was 42.8 hours versus 36.8 hours in the ciprofloxacin group (p=0.0035 for non-inferiority).[2] There was no statistically significant difference in clinical cure rates between rifamycin (85%) compared to ciprofloxacin (84.8%; p=0.942).[2]
- There is low-quality evidence that the tolerability of rifamycin is comparable to placebo or ciprofloxacin. In the 2 low quality studies, constipation (3.5% rifamycin, 1.5% placebo) and headache (3.3% rifamycin, 1.9% ciprofloxacin) were the only reported treatment-emergent adverse events (TEAEs) that occurred with rifamycin at a rate greater than placebo or ciprofloxacin.[3] No severe adverse effects were reported during either RCT. Only 1% (n=6) of patients from both trials were reported to have discontinued the trials due to an adverse effect.[1,2]
- The safety of rifamycin has not been evaluated in pediatric patients, pregnant women, breast feeding women, or adults aged 65 years and older.
- The efficacy of rifamycin has not been demonstrated in infectious diarrhea or in TD due to pathogens other than *E.coli* or TD complicated by fever and bloody diarrhea. The safety of rifamycin has not been evaluated in pediatric patients.
- Evidence is insufficient to determine the comparative safety of rifamycin and rifaximin or azithromycin.

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Recommendations:

- Designate rifamycin as non-preferred on the preferred drug list (PDL).
- Add rifamycin to PA criteria for rifaximin to ensure appropriate utilization of both medications. (**Appendix 2**).

Summary of Prior Reviews and Current Policy

Previous P and T Committee recommendations for drugs used to manage infectious diarrhea were addressed at the May 2015 meeting when PA criteria for the use of rifaximin in hepatic encephalopathy (HE) were presented. Use of rifaximin is restricted to Oregon Health Plan (OHP)-funded conditions such as prevention or treatment of HE. Rifaximin also has an FDA-approved indication for treatment of traveler's diarrhea caused by noninvasive strains of Escherichia coli. Both HE and infectious diarrhea are funded conditions under the OHP.

Background:

Travelers' diarrhea is defined as passage of 3 or more unformed stools plus at least 1 accompanying symptom in a 24 hour period that develops during or within 14 days of returning from travel to a resource-limited location.[4] Travelers' diarrhea is the most common illness afflicting travelers, and several observational studies report an incidence of 10-40% after a 2-week travel period depending on destination and traveler characteristics.[5] As a large number of individuals experiencing symptoms self-treat, the actual magnitude of the disease burden is uncertain.[3] Travel destination has a major impact on the risk for TD. According to the Centers for Disease Control and Prevention (CDC), the world is divided into 3 grades of TD risk: low, intermediate and high.[4]

- Low-risk countries include the United States, Canada, Australia, New Zealand, Japan, and countries in Northern and Western Europe.[4]
- Intermediate-risk countries include those in Eastern Europe, South Africa, and some Caribbean islands.[4]
- High-risk areas include most of Asia, the Middle East, Africa, Mexico, and Central and South America.[4]

Travelers' diarrhea is usually infectious and is caused by microbial pathogens endemic at the travel destination.[6] Most TD cases are contracted from contaminated food and less commonly from water.[1] Bacteria account for up to 90% of identified infectious etiologies for acute TD, predominately enterotoxigenic *E. coli* (ETEC), and enteroaggregative *E. coli* (EAEC), although there is regional variability.[7] Other bacterial pathogens that can cause TD include *Campylobacter jejuni*, *Shigella* species, and *Salmonella* species.[8] There is increasing recognition of *Aeromonas* species, *Plesiomonas* species, and newly identified pathogens (*Acrobacter, Larobacter*, enterotoxigenic *Bacteroides fragilis*) as potential causes of TD as well.[4] Regardless of cause, most cases of TD have a similar clinical appearance, with patients complaining of watery diarrhea with abdominal pain or cramps of variable severity.[8] The disease is present if travelers develop at their destination 3 or more unformed stools per 24 hours plus at least 1 additional symptom, such as abdominal cramps, tenesmus, nausea, vomiting, fever, or fecal urgency.[5] Travelers are recognized as an important vector for transmission of emerging and multi-drug resistant (MDR) enteropathogens globally.[9]

Rates of TD can be reduced if travelers are educated how to select safe food and beverages items.[8] Safe foods include those served steaming hot (≥ 59°C), dry items such as bread, and fruit that can be peeled.[8] Travelers should remember to use only beverages that are sealed, treated with chlorine, boiled, or are otherwise known to be purified.[4] When otherwise healthy travelers develop diarrhea they should be encouraged to consume fluids and salty foods.[8] Bismuth subsalicylate has antibacterial properties and prevents 65% of expected TD cases when taken at recommended doses (2.1 gm per day divided into 4 doses).[8] Probiotics are not recommended due insufficient evidence demonstrating their efficacy.[4] Antimotility agents provide symptomatic relief and are useful therapy in TD.[4] Loperamide or diphenoxylate can reduce frequency of bowel movements and therefore enable travelers to ride on public transportation.[4] Antimotility agents alone are not recommended for patients with bloody diarrhea or those who have diarrhea and fever.[4] Loperamide can be used in children, and liquid formulations are available.[4]

Antimicrobial therapy is not routinely recommended for mild TD, but should be considered for people with suspected *Shigella* or *Campylobacter* species and certain *E. coli* infections and moderate to severe TD symptoms.[8] Knowledge of global resistance patterns can help inform the choice of empiric antibiotics in returning travelers.[10] Increasing microbial resistance to the fluoroquinolones, especially among *Campylobacter* isolates, may limit their usefulness in many destinations, particularly South and Southeast Asia, where both *Campylobacter* infection and fluoroquinolone resistance is prevalent.[4] Increasing fluoroquinolone resistance has been reported from other destinations and in other bacterial pathogens, including in *Shigella* and *Salmonella*.[4] In general, azithromycin or a fluoroquinolone are recommended.[5] In particular, azithromycin is the preferred option for patients with fever or dysentery (bloody or mucoid diarrhea), pregnant women, children, and for travelers to locations (such as Southeast Asia) where fluoroquinolone-resistant pathogens are prevalent.[5] Fluoroquinolones had long been the first choice for treatment of travelers' diarrhea, but the emergence of resistance to this drug class and increased awareness of adverse events make the risk-benefit assessment less clear.[5] Rifaximin is an alternative for travelers' diarrhea suspected to be caused by noninvasive strains of *E. coli*, but its effectiveness against invasive pathogens is unknown, and it should not be used in patients with fever or bloody diarrhea.[5] Due to widespread resistance, sulfamethoxazole/trimethoprim is no longer recommended to treat TD.[3] A 2000 Cochrane review concluded that antibiotics shorten the overall duration of moderate to severe traveler's diarrhea to about a day and a half.[11] The mean duration of travelers' diarrhea, even if untreated, is 4 to 5 days.[12]

Guidelines:

American College of Gastroenterology

In 2016, the American College of Gastroenterology (ACG) published a clinical guideline focused on diagnosis, treatment, and prevention of acute diarrheal infections in adults.[13] No financial support was received by any of the authors for development of the recommendations. Potential conflicts of interest due to research support or participation on advisory boards was clearly stated in the publication. All 3 primary authors serve on the advisory boards of several pharmaceutical manufacturers including the manufacturer of rifaximin. One of the authors is an employee of the U.S. government and completed this work as part of his official duties. The evidence was evaluated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach.[14] Treatment recommendations based on moderate to high quality evidence are highlighted below. **Table 1** includes a summary of antibiotics recommended by the ACG to treat acute diarrhea symptoms in adults.

- The evidence does not support empiric anti-microbial therapy for routine acute diarrheal infection, except in cases of TD where the likelihood of bacterial pathogens is high enough to justify the potential side effects of antibiotics (Strong recommendation, high level of evidence).[13]
- Bismuth subsalicylates can be administered to control rates of passage of stool and may help travelers function better during bouts of mild to moderate illness (Strong recommendation, high level of evidence).[13]
- In patients receiving antibiotics for TD, adjunctive loperamide therapy can be administered to decrease duration of diarrhea and increase chance for a cure (Strong recommendation, moderate level of evidence).[13]

Table 1. Acute diarrhea treatment recommendations for adults[13]

Antibiotic	Dose	Treatment Duration
Levofloxacin	500 mg orally	Single dose - If symptoms not resolved after 24 hours, complete a 3 day course
Ciprofloxacin	750 mg orally **OR** 500 mg orally once a day	Single dose - If symptoms not resolved after 24 hours, complete a 3 day course 3-day course
Ofloxacin	400 mg orally	Single dose - If symptoms not resolved after 24 hours, complete a 3 day course
Azithromycin[a,b]	1000 mg orally	Single dose - If symptoms not resolved after 24 hours, complete a 3 day course

	OR 500 mg once a day	3-day course[b]
Rifaximin[c]	200 mg orally three times a day	3-days (in patients > 12 years old)

a. Use empirically as first-line in Southeast Asia and India to cover fluoroquinolone resistant *Campylobacter* or in other geographic areas if *Campylobacter* or resistant ETEC are suspected.
b. Preferred regimen for dysentery or febrile diarrhea.
c. Do not use if clinical suspicion for *Campylobacter, Salmonella, Shigella*, or other causes of invasive diarrhea.

See **Appendix 1** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:

Rifamycin, an antibiotic closely related to rifaximin, binds to bacterial DNA-dependent RNA polymerase, blocking one of the steps in DNA transcription.[15] This results in inhibition of bacterial synthesis and growth. The FDA approved indication for rifamycin is treatment of TD caused by non-invasive species of *E.Coli* in adults.[15] Rifamycin is poorly absorbed into the systemic circulation after oral administration.[15] It is manufactured with an enteric coating which allows the delivery of the active ingredient to the distal small bowel and colon.[15] Administration of rifamycin directly to the colonic lumen minimizes activity on the beneficial flora of the upper intestinal tract.[15] The Food and Drug Administration (FDA) approval of rifamycin was based on data from two randomized, multi-center, controlled Phase 3 clinical trials which were conducted entirely outside of American research sites. Trial 1 (NCT01142089), a placebo-controlled superiority study, was conducted at sites in Guatemala and Mexico. This trial was the primary basis for assessment of efficacy by the FDA.[3] The data from Trial 2 (NCT01208922), a non-inferiority comparison of rifamycin to ciprofloxacin, was considered supportive for efficacy in the FDA review.[3] Trial 2 was conducted at clinical sites in India, Guatemala and Ecuador.[2] This trial was funded by a different manufacturer than Trial 1 and was not conducted under an American Investigational New Drug (IND) application.[3]

Trial 1 enrolled 264 adults traveling to Mexico or Guatemala experiencing acute diarrhea.[1] Subjects were randomized 3:1 to rifamycin (400 mg orally twice daily for 3 days) or placebo. Patients with fever and/or bloody stools were excluded from the trial. Patients recorded in diaries the date, time, and consistency of stools (formed, soft, or watery), study drug administration, symptoms of enteric infection, and adverse events.[1] Safety and efficacy were assessed at visit 2 (day 2), visit 3 (day 4 or 5), and visit 4 (days 6–10).[1] Drug compliance was verified by review of diaries and by counting remaining tablets when medicine containers were returned.[1] Stool samples were collected at visit 1 and visit 3 and sent to a central laboratory (Center for Infectious Diseases at University of Texas School of Public Health) for pathogen identification and antibiotic susceptibility testing.[1] Patients were eligible to receive rescue therapy if diarrhea and/or symptoms of enteric infection worsened or failed to improve. Patients receiving rescue therapy were withdrawn from the study and given the maximum TLUS (time to last unformed stool) value of 120 hours.[1] The most common reason for not completing the trial was that the patient required rescue medication, seen in 12.3% of placebo patients and 8.5% of rifamycin patients.[1]

The primary endpoint was the length of time between administration of the first medication dose to last unformed (watery or soft) stool (TLUS) before achieving clinical cure.[1] Clinical cure was defined as two or fewer soft stools and minimal enteric symptoms at the beginning of a 24-hour period or no unformed stools at the beginning of a 48-hour period.[1] The investigators reported TLUS was significantly shorter in the rifamycin group (median: 46.0 hours) compared with placebo (median: 68.0 hours; p=0.0008, due to the distribution of placebo TLUS values, it was not possible to compute a 95% confidence interval for this difference).[1] In

addition, a larger percentage of rifamycin-treated patients (81.4%) achieved clinical cure compared with placebo-treated patients (56.9%) [Difference=24.5%; p=0.0001; 95% CI 11.3 to 37.7; NNT 5].[1] The predominant pathogen identified from collected stool samples was *E. coli*.[1]

Trial 2 was a randomized, double-blind, multi-center, non-inferiority trial in which subjects were randomized 1:1 to a 3-day course of rifamycin (400 mg orally twice daily) or ciprofloxacin (500 mg orally twice daily).[2] A total of 835 subjects traveling to India, Guatemala, or Ecuador were enrolled in the trial. Most of the study centers (89%) were located in India.[2] Inclusion and exclusion criteria were similar to Trial 1, although Trial 2 excluded subjects traveling from the United States, Canada and Australia for reasons that were not clearly stated in the FDA summary report.[3] Most to the travelers in Trial 2 originated in Europe.[3] Safety and efficacy were evaluated at Visit 2 (day 2), Visit 3 (day 4 or 5), and the final visit (day 6). Stool samples were collected at the baseline visit and the end of treatment visit and sent to a central laboratory for pathogen identification and antibiotic susceptibility testing. If a patient received rescue therapy within 120 hours after ingestion of the first dose of the study drug, the patient was considered a treatment failure.[2]

The primary endpoint for Trial 2 was TLUS as documented by subjects in a daily diary over 5 days, which was similar to Trial 1.[2] The median TLUS for ciprofloxacin-treated patients was assumed as 27.5 hours and 28.5 hours for rifamycin.[2] The non-inferiority margin was defined by a maximally acceptable difference in the median TLUS of 8.5 hours (with a corresponding delta = 0.764 for the hazard ratio) between rifamycin and ciprofloxacin.[2] The confirmatory non-inferiority test was performed on the per-protocol (PP) analysis set and confirmed with a sensitivity test of the intention-to-treat (ITT) population.[2] Patients with lack of compliance, intake of forbidden concomitant medication, violation of eligibility criteria or early discontinuation due to adverse effects without causal relationship with study drug, were excluded from the PP population.[2] In total, 835 patients were randomized and received at least one dose of study medication.[2] The PP population consisted of 767 subjects (8.1% attrition).[2]

The median TLUS in the PP analysis of the rifamycin-treated group was 42.8 hours versus 36.8 hours in the ciprofloxacin group (p=0.0035), indicating non-inferiority of rifamycin to ciprofloxacin.[2] In the ITT analysis, median TLUS in the rifamycin-treated group was 44.3 hours versus 40.3 hours in the ciprofloxacin-treated group (p=0.0011 for non-inferiority).[2] Clinical cure was defined as 24 hours with no clinical symptoms and no more than 2 soft stools or 48 hours without symptoms or any unformed stools.[2] There was no statistically significant difference in clinical cure rates between rifamycin (85%) compared to ciprofloxacin (84.8%; p=0.942).[2] In addition, the percentage of patients requiring rescue therapy was similar in both groups (rifamycin 2.6% vs. ciprofloxacin 1%; p =0.072).[2] The most common pathogen identified from collected stool samples was *E. coli*, although in 37.1% of patients no pathogen could be isolated.[2] Additional information about Trial 1 and Trial 2 is summarized in **Table 3.**

Trial Limitations:

According to the FDA summary, data for both Phase 3 trials of rifamycin were of adequate quality.[3] For Trial 1, the investigators' analysis of the primacy efficacy endpoint was accurate, but the analyses for a number of secondary endpoints (e.g. treatment failure, microbiological cure points) were inaccurate.[3] The FDA reviewer noted that the "time to unformed stool" is a misnomer.[3] For example, if a participant had a watery stool at 12 hours, soft stools at 30 and 35 hours, with no additional unformed stools, fever, or enteric symptoms, then the participant achieved clinical cure prior to the unformed stools at 30 and 35 hours.[3] Therefore, the TLUS value is 12 hours, even though there were two subsequent unformed stools.[3] In addition, the FDA reviewer noted the definition of clinical cure seems inadequate, as it accounts for rescue medication administered by study physicians but ignores prohibited medications self-administered (e.g., loperamide) or prescribed or administered by non-study physicians (e.g., antibacterial drugs).[3] Since use of such prohibited medications prior to the achievement of clinical cure (as defined by the investigators) could have contributed to that achievement, ignoring the use of prohibited medications when assessing clinical cure confounds the attribution of cure to the study medication.[3] The FDA reviewer noted in Trial 1 that 2% of patients (n=4) took prohibited medications and 5% of subjects (n=10) took an additional 2 doses of medication (or 1 extra treatment day) in the rifamycin-treated arm of the ITT population.[3] The extra doses were

supplied as a contingency reserve in case of loss or mishap. However, one primary investigator prescribed additional doses to 4 subjects due to continued symptoms. It is not clear why the other subjects took the extra doses.[3] In Trial 2, 2% of patients in both arms (rifamycin and ciprofloxacin) took prohibited medications in the PP population set.[3] Nineteen subjects (4.5%) in the rifamycin arm and 13 subjects (3.1%) in the ciprofloxacin did not submit complete diary cards.[3]

An additional concern was the incorrect handling of missing TLUS observations due to incomplete diary recordings. For example, one subject in the rifamycin arm maintained the daily diary for only 24 hours and recorded no stools during that period, the investigator assigned that subject a censored TLUS of 24 hours, meaning that the true (but unobserved) TLUS value is larger than 24 hours.[3] However, it is possible that the participant's true TLUS value is 0.[3] This would be the case if the participant also had no unformed stools during hours 24-48, as then hours 0-48 would constitute a 48-hour qualifying period for clinical cure and clinical cure would be achieved at hour 0.[3] Hence, this participant's TLUS value should be censored at 0 hours rather than 24 hours.[3] Instances of censoring due to incomplete diaries could be cases of informative censoring.[3] Four subjects submitted incomplete symptom diaries in Trial 1.

Since the non-inferiority design of Trial 2 did not include a placebo arm, the investigators had to rely on the use of historical information to determine efficacy, which means the results should be interpreted with caution.[3] The FDA reviewers also noted the establishment of the non-inferiority margin using the hazard ratio was flawed.[3] In order to determine a hazard ratio corresponding to a median TLUS margin of 8.5 hours, the investigators made strong assumptions about the true value of the ciprofloxacin median TLUS value and about the distribution of the rifamycin and ciprofloxacin TLUS values.[3] It is highly implausible that a hazard ratio of 0.764 corresponds to a median margin of 8.5 hours, given the true but unknown ciprofloxacin median TLUS and the true but a priori unknown distributions of the rifamycin and ciprofloxacin TLUS values.[3] The specification of a hazard ratio does not accurately specify a non-inferiority margin.[3]

In summary, Trial 1 provides moderate quality evidence of the effectiveness of rifamycin in treating TD caused by non-invasive E.coli in adults who were not experiencing fever or bloody stools compared to placebo.[1] Trial 2 provides low quality evidence that rifamycin is non-inferior to ciprofloxacin in treating non-dysenteric TD.[2] Rifamycin has a similar spectrum of activity as rifaximin. Both antibiotics have low systemic absorption and duration of therapy (3-day course of treatment). Similar to rifaximin, rifamycin shortens the course of TD by approximately 1 day.[3] The efficacy of rifamycin has not been demonstrated in infectious diarrhea or in TD due to pathogens other than E.coli or complicated by fever and bloody diarrhea. The efficacy or safety of rifamycin has not been evaluated in pediatric patients.

Clinical Safety:
In phase 3 studies, headache and constipation were the only reported treatment-emergent adverse events (TEAEs) that occurred with rifamycin at a rate greater or equal to 2% and higher than placebo or ciprofloxacin.[3] Discontinuation of rifamycin due to adverse reactions occurred in 1% of patients during the 2 clinical trials (n=619 total enrollment).[16] The most frequent adverse reactions leading to discontinuation of rifamycin were abdominal pain (0.5%) and pyrexia (0.3%).[15] In Trial 1 (placebo-controlled), the adverse reaction that occurred in at least 2% of rifamycin-treated patients (n=199) and with an incidence higher than in the placebo group was constipation (3.5% rifamycin, 1.5% placebo).[15] In Trial 2 (active comparator: ciprofloxacin), the adverse reaction that occurred in at least 2% of rifamycin-treated patients (n=420) and with an incidence higher than in the ciprofloxacin group was headache (3.3% rifamycin, 1.9% ciprofloxacin).[15] No deaths occurred in either clinical trial.

Look-alike / Sound-alike Error Risk Potential: Rifaximin

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Reduction in symptoms (diarrhea, abdominal pain, nausea)
2) Resolution of symptoms (clinical cure)
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:

1) Time to last unformed stool (TLUS)
2) Percentage of patients with a clinical cure (two or fewer soft stools and minimal enteric symptoms at the beginning of a 24-hour period or no unformed stools at the beginning of a 48-hour period)

Table 2. Pharmacology and Pharmacokinetic Properties.

Parameter	
Mechanism of Action	Binds to bacterial DNA-dependent RNA polymerase, blocking one of the steps in DNA transcription. This results in inhibition of bacterial synthesis and growth of bacteria.
Oral Bioavailability	Minimal systemic absorption: less than 0.1% oral bioavailability
Distribution and Protein Binding	Protein Binding: 80%
Elimination	Fecal: 86%
Half-Life	Unknown
Metabolism	Not applicable

Table 3. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Dupont, et al.[1] Phase 3 RCT, DB, MC, PC N=264	1. Rifamycin 400 mg orally twice daily for 3 days 2. Placebo orally twice daily for 3 days	Demographics: 1. Median age: 24 yo 2. 50% female 3. Duration of diarrhea: 33 hrs. 4. Country visited: Mexico - 66% Guatemala - 34% Key Inclusion Criteria: 1. ≥ 18 years of age 2. Travel from industrialized country within 30 days before randomization 3. ≥ 3 unformed stools within 24 hrs. 4. Duration of illness < 72 hrs. 5. At least one symptom of enteric infection (nausea, vomiting, abdominal pain, defecation urgency) Key Exclusion Criteria: 1. Fever > 38°C 2. Symptom of systemic infection 3. Infection with non-bacterial pathogen 4. Grossly bloody stool 5. Severe dehydration 6. Taking more than 2 doses of AD medicine within 24 hrs. 7. Taking an antibiotic against gram negative bacteria within 7 days	ITT: (all subjects who received 1 dose of medication) 1. 199 2. 65 PP: (all subjects that completed the trial) 1. 179 2. 53 Attrition: 1. 21 (10.6%) 2. 12 (18.5%)	Primary Endpoint: Length of time to TLUS 1. 46 hrs. 2. 68 hrs. Difference = 22 hours; p=0.0008 95% CI not able to be calculated Secondary Endpoint: Clinical Cure (≤2 stools/24 hrs. or 0 stools/48 hrs.) 1. 163 (81.4%) 2. 37 (56.9%) Difference = 24.5% p=0.0001 95% CI 11.3 to 37.7	NA 24.5%/ 5	Study withdrawal due to AE 1. 1 (0.5%) 2. 9 (13.5%) Diarrhea 1. 20 (10%) 2. 11 (16.9%) Headache 1. 17 (8.5%) 2. 6 (9.2%) Constipation 1. 7 (3.5%) 2. 1 (1.5%) p value and 95% CI NR for all	NA NA NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Randomized 3:1 via blocks of 4 developed by an independent statistician. Stratified by site. Baseline characteristics similar in both arms. Performance Bias: Unclear. Protocol deviations varied from site to site as reported in FDA summary. Blinding was not clearly described. Detection Bias: Unclear. Investigators and patients blinded to study medication via the blister packet in which medication was dispensed. Patients reported symptoms in a daily diary and interpretation of results may be subject to bias. Attrition Bias: Low. Higher withdrawal in placebo group due to the need for rescue therapy which may lead to a more conservative estimate of effect. Reporting Bias: Unclear. Protocol unavailable. Other Bias: Unclear. Trial funded by Santarus. Several investigators received consulting fees from Santarus or were employed by Santarus. **Applicability**: Patient: Primarily applies to travelers in Mexico and Central America. Patients with fever or bloody diarrhea were excluded. Intervention: Appropriate dosing based on Phase 2 trials of rifamycin. Comparator: Compared to placebo to demonstrate superiority. Active comparator could have been rifaximin or azithromycin to provide comparative safety/efficacy data to standard of care. Outcomes: TLUS reported by patients in a daily diary, subject to misinterpretation by investigators. Definition of clinical cure was ambiguous. Setting: 8 centers in Mexico (n=175) and 2 in Guatemala (n=89).

2. Steffen, et al.[2] Phase 3 RCT, DB, MC N=835	1.Rifamycin 400 mg orally twice daily for 3 days 2.Ciprofloxacin 500 mg orally twice daily for 3 days	Demographics: 1. Median age: 35 yo 2. 50% female 3. Country visited: India - 96% Guatemala - 2% Ecuador – 2% Key Inclusion Criteria: 1. ≥ 18 years of age 2. Travel from industrialized country within 30 days before randomization 3. ≥ 3 unformed stools within 24 hrs. 4. Duration of illness < 72 hrs. 5. At least one symptom of enteric infection (nausea, vomiting, abdominal pain, defecation urgency) Key Exclusion Criteria: 1. Fever > 38°C 2. Symptom of systemic infection 3. Infection with non-bacterial pathogen 4. Grossly bloody stool 5. Severe dehydration 6. Taking more than 2 doses of AD medicine within 24 hrs. 7. Resident of any country with high incidence rates of diarrhea 8. Travelers from the US, Canada, and Australia	ITT: (all subjects who received 1 dose of medication) 1. 420 2. 415 PP: (all subjects who completed at least 2 days of diary recordings) 1. 384 2. 383 Attrition: 1. 36 (8.5%) 2. 42 (10%)	Primary Endpoint: Noninferiority assessment of median length of time to TLUS in PP population 1. 42.8 hrs. 2. 36.8 hrs. p=0.0035 for noninferiority HR = 0.943 95% CI 0.804 to 1.100 Noninferiority assessment of median length of time to TLUS in ITT population 1. 44.3 hrs. 2. 40.3 hrs. P=0.0011 for noninferiority HR = 0.962 95% CI = 0.826 to 1.119 Secondary Endpoint: Clinical Cure (≤2 stools/24 hrs. or 0 stools/48 hrs.) 1. 357 (85.0%) 2. 352 (84.8%) Difference = 0.2% p=0.942 Requirement of Rescue Therapy 1. 11 (2.6%) 2. 4 (1%) Difference = 1.6% p=0.072	NA NA NS NS	Incidence of AEs 1. 62(14.8%) 2. 62 (14.9%) Incidence of ADRs 1. 34 (8.1%) 2. 31 (7.5%) Study withdrawal due to AE 1. 1 (<1%) 2. 0 p value and 95% CI NR for all	NA NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: Unclear. Randomized 1:1 via blocks of 4 using a computer-generated list of numbers. Baseline characteristics similar in both arms. Performance Bias: Unclear. Protocol deviations varied from site to site as reported in FDA summary. Investigators dispensed blinded study medication according to randomization schedule. Detection Bias: Unclear. Investigators and patients blinded to study medication via the package medication was dispensed in. Patients reported symptoms in a daily diary and interpretation of results may be subject to bias. Attrition Bias: Low. 3% of patient withdrew due to lack of efficacy, or follow-up. 7-8% withdrew due to protocol deviations. Reporting Bias: Unclear. Protocol unavailable. Other Bias: Unclear. Trial funded by Dr. Falk Pharma GmBH. Several investigators received honoraria from Dr. Falk Pharma GmBH or were employed by Dr. Falk Pharma GmBH. **Applicability**: Patient: Primarily applies to travelers to India. Patients with fever or bloody diarrhea were excluded. Excluded U.S. travelers, which limits generalizability to U.S. subjects. Patients in this trial were on average 10 years older than Trial 1. Intervention: Appropriate dosing based on Phase 2 trials of rifamycin. Comparator: Compared to ciprofloxacin to establish non-inferiority. No placebo armed included to assess efficacy of rifamycin. Active comparator could have been rifaximin to provide comparative safety/efficacy data with a similar antibiotic. Outcomes: TLUS reported by patients in a daily diary, subject to misinterpretation by investigators. Definition of clinical cure was ambiguous. Setting: 17 centers in India (n=805), 1 in Guatemala (n=15) and 1 in Ecuador (n=15).

Abbreviations : AD = antidiarrheal; ADR = adverse drug event; AE = adverse effect; ARR = absolute risk reduction; CI = confidence interval; DB = double-blinded; Hrs. = hours; ITT = intention to treat; MC = multi-center; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; PC = placebo-controlled; PP = per protocol; RCT = randomized controlled trial; TLUS = time to last unformed stool; US = United States; YO = years old

References:

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Appendix 1: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use AEMCOLO safely and effectively. See full prescribing information for AEMCOLO.

AEMCOLO (rifamycin) delayed-release tablets, for oral use.
Initial U.S. Approval: 2018

----------INDICATIONS AND USAGE----------
AEMCOLO is a rifamycin antibacterial indicated for the treatment of travelers' diarrhea caused by noninvasive strains of *Escherichia coli* in adults. (1.1)

Limitations of Use:
AEMCOLO is not recommended for use in patients with diarrhea complicated by fever and/or bloody stool or due to pathogens other than noninvasive strains of *E. coli*. (1, 5.1, 14)

To reduce the development of drug-resistant bacteria and maintain the effectiveness of AEMCOLO and other antibacterial drugs, AEMCOLO should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria (1.2).

----------DOSAGE AND ADMINISTRATION----------
- The recommended dosage of AEMCOLO is 388 mg (two tablets) orally twice daily for three days. (2.1)
- Take each dose with a glass of liquid. Do **NOT** take AEMCOLO concomitantly with alcohol. (2.1)
- AEMCOLO can be taken with or without food. (2.1)
- Swallow AEMCOLO tablets whole. Do NOT crush, break or chew the tablets. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------
Delayed-Release Tablets: 194 mg rifamycin. (3)

----------CONTRAINDICATIONS----------
AEMCOLO is contraindicated in patients with a known hypersensitivity to rifamycin, any of the other rifamycin class antimicrobial agents (e.g. rifaximin), or any of the components in AEMCOLO (4)

----------WARNINGS AND PRECAUTIONS----------
- Risk of Persistent or Worsening Diarrhea Complicated by Fever and/or Bloody Stool: AEMCOLO was not shown to be effective in patients with diarrhea complicated by fever and/or bloody stool or diarrhea due to pathogens other than noninvasive strains of *E. coli* and is not recommended for use in such patients. Discontinue use if diarrhea gets worse or persists more than 48 hours, and consider alternative antibacterial therapy. (1. 5.1)
- *Clostridium difficile*-associated Diarrhea: Evaluate if diarrhea occurs after therapy or does not improve or worsens during therapy. (5.2)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > 2%) are headache and constipation. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Aries Pharmaceuticals Inc. at 888-ARIES-08 (888-274-3708) option 1 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised:11/2018

Appendix 2: Proposed Prior Authorization Criteria

Rifaximin (Xifaxan®) and Rifamycin (Aemcolo®)

Goal(s):

- Promote use that is consistent with medical evidence and product labeling.

Length of Authorization:

- 3 days for traveler's diarrhea caused by non-invasive strains of *E.Coli* for rifaximin or rifamycin.
- Up to 12 months for hepatic encephalopathy for rifaximin.

Requires PA:

- Rifaximin and Rifamycin

Covered Alternatives:

- Preferred alternatives listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this an FDA approved indication and is the indication funded by OHP?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the diagnosis traveler's diarrhea caused by non-invasive strains of E.Coli?	**Yes:** Go to #4	**No:** Go to # 5

Approval Criteria		
4. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require a PA. • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics Committee. • Preferred products for traveler's diarrhea are dependent on traveler's destination and resistance patterns in that area. Refer to **Table 1** for adult treatment recommendations.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Approve for 3 days.
5. Is the request for rifaximin to prevent or treat hepatic encephalopathy?	**Yes**: Go to #6	**No**: Pass to RPh. Deny; not funded by OHP or for medical appropriateness
6. Is the patient currently managed with a regularly scheduled daily regimen of lactulose?	**Yes**: Go to #8	**No**: Go to #7
7. Does the patient have a contraindication to lactulose?	**Yes**: Go to #8	**No**: Pass to RPh Deny; medical appropriateness Note: studies demonstrate effectiveness of rifaximin as add-on therapy to lactulose.
8. Is the patient currently prescribed a benzodiazepine drug?	**Yes**: Go to #9	**No**: Approve for up to 12 months

Approval Criteria		
9. Is the patient tapering off the benzodiazepine? Note: tapering process may be several months	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness Note: studies explicitly excluded use of benzodiazepines and benzodiazepine-like drugs because of their risk for precipitating an episode of hepatic encephalopathy**.**

Table 1. Acute diarrhea treatment recommendations for adults[1]

Antibiotic	Dose	Treatment Duration
Levofloxacin	500 mg orally	Single dose - If symptoms not resolved after 24 hours, complete a 3 day course
Ciprofloxacin	750 mg orally **OR** 500 mg orally once a day	Single dose - If symptoms not resolved after 24 hours, complete a 3 day course 3-day course
Ofloxacin	400 mg orally	Single dose - If symptoms not resolved after 24 hours, complete a 3 day course
Azithromycin[a,b]	1000 mg orally **OR** 500 mg once a day	Single dose - If symptoms not resolved after 24 hours, complete a 3 day course 3-day course[b]
Rifaximin[c]	200 mg orally three times a day	3-days (in patients > 12 years old)

a. Use empirically as first-line in Southeast Asia and India to cover fluoroquinolone resistant *Campylobacter* or in other geographic areas if *Campylobacter* or resistant enterotoxigenic *E. coli* are suspected.

b. Preferred regimen for dysentery or febrile diarrhea.

c. Do not use if clinical suspicion for *Campylobacter, Salmonella, Shigella*, or other causes of invasive diarrhea.

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