PDL DRUG REVIEW

Proprietary Name: Aemcolo®
Common Name: rifamycin, delayed release
PDL Category: Antibiotics- Misc

Comparable Products	Preferred Drug List Status
Ciprofloxacin	Preferred
Xifaxan	Non-Preferred with Conditions

Summary

Pharmacology/Usage: Rifamycin, the active ingredient of Aemcolo®, is an antibacterial drug that belongs to the ansamycin class of antibacterial drugs. It acts by inhibiting the beta-subunit of the bacterial DNA-dependent RNA polymerase, blocking one of the steps in DNA transcription. This results in inhibition of bacterial synthesis and consequently growth of bacteria.

Indication: For the treatment of traveler's diarrhea (TD) caused by non-invasive strains of *Escherichia coli* in adults. It is not indicated in patients with diarrhea complicated by fever or bloody stool or due to pathogens other than noninvasive strains of *Escherichia coli*.

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 susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

There is no pregnancy category for this medication; however, the risk summary indicates that there are no available data on use in pregnant women to inform any drug associated risks for major birth defects, miscarriage, or adverse maternal or fetal outcomes. Systemic absorption of Aemcolo® in humans is negligible following oral administration of the recommended dose of Aemcolo®. Due to the negligible systemic exposure, it is not expected that maternal use of Aemcolo® will result in fetal exposure to the drug. The safety and efficacy of use have not been established in pediatric patients less than 18 years of age.

Dosage Form: Film-Coated, Delayed-Release Tablets: 194mg. Swallow tablets whole; do not crush, break, or chew.

These delayed-release tablets are enteric coated with a pH-resistant polymer film that breaks down above pH 7. The table core contains rifamycin.

Recommended Dosage: Take 388mg (two tablets) PO BID (in the morning and evening) for 3 days. Take each dose with a glass of liquid (6-8 ounces). Do not take Aemcolo® concomitantly with alcohol. Aemcolo® can be taken with or without food.

The pharmacokinetics of Aemcolo® in patients with impaired renal function or impaired hepatic function have not been studied. Given the minimal systemic exposure of rifamycin (taken as Aemcolo®) and minor role of renal

excretion in elimination of rifamycin, renal impairment, as well as hepatic impairment, are not expected to have a clinically meaningful effect on rifamycin systemic exposure necessitating a dose adjustment.

Drug Interactions: No clinical drug-drug interactions have been studied. Based on the minimal systemic rifamycin concentrations observed after the recommended dose of Aemcolo®, clinically relevant DDIs are not expected.

Box Warning: There is no box warning associated with this product.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Aemcolo®) minus reported % incidence for placebo in trial 1 that occurred in at least 2% of Aemcolo®-treated patients and with a higher incidence than placebo.* The most frequently reported adverse events included constipation (2%).

Listed % incidence for adverse drug reactions= reported % incidence for drug (Aemcolo®) minus reported % incidence for active comparator (ciprofloxacin) in trial 2 that occurred in at least 2% of Aemcolo®-treated patients and with a higher incidence than comparator. The most frequently reported adverse events included headache (1.4%).

Adverse reactions reported in <2% of patients receiving Aemcolo® with a higher incidence than the comparator group was dyspepsia.

Aemcolo® was not shown to be effective in patients with diarrhea complicated by fever and/or bloody stool. Patients with these conditions treated with Aemcolo® had prolonged time to last unformed stool (TLUS). The effectiveness of Aemcolo® in traveler's diarrhea caused by pathogens other than *E. coli* has not been demonstrated. Aemcolo® is not appropriate for patients with diarrhea accompanied by fever or bloody stools or due to pathogens other than noninvasive strains of *E. coli*. Discontinue Aemcolo® if diarrhea gets worse or persists more than 48 hours and consider alternative antibacterial therapy.

Clostridium difficile-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon which may lead to overgrowth of *C. difficile*. CDAD must be considered in all patients who present with diarrhea following antibacterial drug use. Careful medical history is necessary since CDAD has been reported to occur over 2 months after the administration of antibacterial agents. If CDAD is suspected or confirmed, antibacterial drug use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, specific antibacterial treatment of *C. difficile*, and/or surgical evaluation should be instituted as clinically indicated.

Contraindications: In patients with a known hypersensitivity to rifamycin, any of the other rifamycin class antimicrobial agents (e.g. rifaximin), or any of the components of the product

Manufacturer: RedHill Biopharma

Analysis: The safety and efficacy of Aemcolo® were assessed in a multicenter, randomized, double-blind, placebo-controlled study that included adults with traveler's diarrhea. This trial (Trial 1) was conducted at clinical sites in Guatemala and Mexico and provides the primary evidence for the efficacy of Aemcolo®. A second active-controlled trial (Trial 2) conducted in India, Guatemala, and Ecuador provided supportive evidence for the efficacy of Aemcolo®. While patients with fever and/or bloody stool at baseline were to be excluded from both trials, 18 subjects treated with Aemcolo® had fever and bloody diarrhea at enrollment in Trial 2. Stool specimens were collected before treatment and 1 to 2 days following the end of treatment to identify enteric pathogens, and the main pathogen in both trials was *E. coli.*

The clinical efficacy of Aemcolo® was assessed using an endpoint of time to last unformed (watery or soft) stool (TLUS) before achieving clinical cure. The endpoint of 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. Kaplan-Meier estimates of TLUS for the intent-to-treat population, which includes all randomized subjects, in Trial 1 demonstrate that Aemcolo® significantly reduced the TLUS compared to placebo (p=0.0008).

The table below, adapted from the prescribing information, includes the median TLUS and the number of patients who achieved clinical cure for the ITT population in Trial 1. The median duration of diarrhea was significantly shorter in patients treated with Aemcolo® than in the placebo group. In addition, more patients treated with Aemcolo® were classified as clinical cures than were those in the placebo group.

	Aemcolo® (N=199)	Placebo (N=65)	Difference	p-value
Median TLUS (hrs)	46.0	68.0	-22.0	p=0.0008
Clinical cure, n (%)	162 (81.4%)	37 (56.9%)	24.5%	p=0.0001

The results of Trial 2 supported the results presented in Trial 1. In addition, this trial provided evidence that Aemcolo®-treated subjects with fever and/or bloody diarrhea at baseline had prolonged TLUS. (These were the only results discussed in the prescribing information.)

Place in Therapy: Aemcolo®, a delayed-release rifamycin product, is indicated for the treatment of traveler's diarrhea (TD) caused by non-invasive strains of *Escherichia coli* in adults. It is not indicated in patients with diarrhea complicated by fever or bloody stool or due to pathogens other than noninvasive strains of *Escherichia coli*. 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 susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

In a multicenter, randomized, double-blind, placebo-controlled trial that included adults with TD, Aemcolo® significantly reduced the time to last unformed (watery or soft) stool (TLUS) compared to placebo (p=0.0008), with a difference of 22 hours. In addition, significantly more achieved clinical cure with Aemcolo® compared with placebo (NNT *calculated by CHC* of 5).

In the full-text study by Steffen et al[2] that compared rifamycin with ciprofloxacin 500mg BID for the treatment of TD in a randomized, double-blind, phase 3 study (ERASE), the primary outcome was TLUS, after which clinical cure was declared. The study was designed to prove non-inferiority of rifamycin to ciprofloxacin. Results of the per-protocol (PP) analysis suggest that the median TLUS was 42.8 hours in the rifamycin group as compared with 36.8 hours with ciprofloxacin, which indicated non-inferiority of rifamycin to ciprofloxacin (p=0.0035). Results from the ITT analysis confirmed the PP analysis (median TLUS was 44.3 hours with rifamycin vs 40.3 hours with ciprofloxacin, with p=0.0011 for non-inferiority in the ITT population). The incidence of adverse events and adverse drug reactions was similar in both treatment groups.

There is no evidence at this time to support that Aemcolo® is safer or more effective than the other currently preferred, more cost-effective medications. It is therefore recommended that Aemcolo® remain non-preferred and require prior authorization and be available to those who are unable to tolerate or who have failed on preferred medications.

PDL Placement: ☐ **Preferred**
☒ **Non-Preferred**

References

[1] Aemcolo [package insert]. Raleigh, NC: RedHill Biopharma; 2021.
[2] Steffen R, Jiang ZD, Gracias Garcia ML, et al. Rifamycin SV-MMX for treatment of traveler's diarrhea: equally effective as ciprofloxacin and not associated with the acquisition of multi-drug resistant bacteria. *J Travel Med*. 2018; 25(1):tay116.