AEMCOLO (rifampin) is a rifamycin antibacterial indicated for the treatment of travelers’ diarrhea caused by susceptible strains of Escherichia coli. (1.1)

Allergic reactions to rifamycin antibiotics have been reported. (1.5)

AEMCOLO is a rifamycin antibacterial indicated for the treatment of travelers’ diarrhea caused by susceptible strains of Escherichia coli. (1.1)

Adverse reactions to rifamycin antibiotics have been reported. (1.5)

AEMCOLO is available as 388 mg delayed-release tablets. (3)

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 whole tablets. Do NOT crush, break or chew the tablets. (2.2)

Risk of Persistent or Worsening Diarrhea Complicated by Fever and/or Bloody Stool: AEMCOLO is 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. (5.1)

In Trial 2 (placebo-controlled), the common adverse reaction that occurred in at least 2% of AEMCOLO-treated patients (n = 420) and with an incidence higher than in the ciprofloxacin group was constipation (3.5% AEMCOLO, 1.5% placebo). Adverse reactions reported in <2% of patients receiving AEMCOLO 388 mg twice daily with a higher incidence than in the placebo group was dry mouth. (6.1)

There are no specific animal data on AEMCOLO use in pregnant women to inform any associated risks for major birth defects, miscarriage, or adverse maternal or fetal outcome. Systemic absorption of AEMCOLO in humans is negligible following oral administration of the recommended dose of AEMCOLO (see Clinical Pharmacology (12.3)). Due to the negligible systemic exposure, it is not expected that AEMCOLO will result in fetal injury to the fetus. (8.4)

AEMCOLO produces toxins A and B which contribute to the development of CDAD. Hypertoxic strains of C. difficile produce toxins A and B which can cause increased morbidity and mortality, as these infections can be life-threatening. In the absence of local data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

AEMCOLO is indicated in patients with a known hypersensitivity to rifampin, any of the other rifamycin class antibacterial agents (e.g. rifabutin), or any of the components in AEMCOLO. (4)

AEMCOLO is a rifamycin antibacterial indicated for the treatment of travelers’ diarrhea caused by susceptible strains of Escherichia coli (<24 hours). (1.1)

AEMCOLO is contraindicated in patients with a known hypersensitivity to rifampin, any of the other rifamycin class antibacterial agents (e.g. rifabutin), or any of the components in AEMCOLO. (4)

AEMCOLO is contraindicated in patients with a known hypersensitivity to rifampin, any of the other rifamycin class antibacterial agents (e.g. rifabutin), or any of the components in AEMCOLO. (4)

AEMCOLO at more than 10 times the maximum human plasma concentration (Cmax) and 25,000 times the systemic exposure (AUC) due to decreased fetal weight, and variations in diaphragm formation. Similarity, treatment of pregnant rabbits with AEMCOLO at the mean human plasma concentrations (Cmax) of 25,000 times and slightly delayed fetal ossifications [See Data]. (14)

AEMCOLO is contraindicated in patients with a known hypersensitivity to rifampin, any of the other rifamycin class antibacterial agents (e.g. rifabutin), or any of the components in AEMCOLO. (4)

Full prescribing information for AEMCOLO. (10.1)

Most common adverse reactions (incidence ≥ 2%) are headache and constipation. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Aries Pharmaceuticals Inc. at 800-446-1370 or 1-800-332-1088 or www.fda.gov/medwatch.

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Concomitant use of rifabutin with rifampin is contraindicated. (4)

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Rifamycin is a fine or slightly granular powder, soluble in water, and freely soluble in anhydrous ethanol.

AEMCOLO, delayed-release tablets contain the following inactive ingredients: ammonium metavanadate/capsule (Type B), acacia acid, glyceraldehyde, butylated hydroxyanisole, magnesium stearate, mannitol, methocell with polyethylene glycol 6000, colloidal silicon dioxide, talc, titanium dioxide, triethylcitrate, yellow ferric oxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Rifamycin is an antibacterial drug [see Microbiology (12.2)].

12.2 Pharmacodynamics

AEMCOLO exposure-response relationships and time course of pharmacodynamic response are unknown.

12.3 Pharmacokinetics

Plasma Concentrations

In healthy adults receiving the recommended dose of 388 mg rifamycin taken as AEMCOLO twice daily for 5 days, the area under the observed concentration of rifamycin in plasma was 8.72 ng·h/mL, 16 hours after the last dose. A majority (67%) of rifamycin concentrations in plasma were below the level of quantification (≤ 2 ng/mL) at this time point.

Absorption

Rifamycin as AEMCOLO has limited systemic exposure after oral administration of the recommended dosage. Based on total urinary excretion data, bioavailability was < 0.1% under fasting conditions.

Food Effect

A food-effect study involving administration of AEMCOLO to healthy volunteers under a fasted state and with a meal (approximately 1,000 kcal including 500 kcal from fat) indicated that food decreased systemic exposure of rifamycin. The decrease in systemic exposure of rifamycin is not expected to be clinically relevant [see Dosage and Administration (2.3)].

Distribution

Plasma protein binding was approximately 80% in vitro. Binding was primarily to albumin and was inversely proportional to concentration.

Elimination

The apparent half-life of orally administered rifamycin (as AEMCOLO) in plasma is unknown.

Metabolism

Cytochrome P450 (CYP) based metabolism of rifamycin was not observed in vitro.

Excretion

After a single oral dose of 400 mg AEMCOLO (388 mg rifamycin base) in fasting healthy adults, fecal excretion of rifamycin was on average 86% of the nominal dose.

Specific Populations

The pharmacokinetics of rifamycin (as AEMCOLO) in patients with impaired renal or hepatic function have not been studied.

Drug Interaction Studies

Clinical Drug-Drug Interaction Studies of rifamycin (taken as AEMCOLO) have not been conducted.

In vitro Transporter Studies where Drug Interaction Potential Was Further Evaluated Clinically Rifamycin is a substrate of P-glycoprotein (P-gp) and anticipated to be an inhibitor of P-gp but breast cancer resistant protein (BCRP) does not interact with rifamycin.

Rifamycin is an inhibitor of renal transporters organic anion transporter (OAT) 3, multidrug and toxin extrusion (MATE) 1, and MATE 2-K transporters in vitro, however, based on systemic concentrations of rifamycin observed after administration of the recommended dose, clinically relevant inhibition of these transporters in vivo is unlikely.

In vitro Cytochrome P450 (CYP) Studies where Drug Interaction Potential Was Not Further Evaluated Clinically Rifamycin is an inhibitor of CYP1A2, 2B6, 2C19, 2D6, and 3A4 in vitro.

In vivo, rifamycin may be a moderate inducer of CYP3A4 and CYP2B6 but not CYP1A2 in vitro, however, based on systemic concentrations of rifamycin observed after administration of the recommended dose, clinically relevant induction of these enzymes in vivo is unlikely.

Rifamycin is not a substrate of CYP1A2, 2B6, 2C19, 2D6, and 3A4 in vitro.

12.4 Microbiological Tests

Mechanism of Action

Rifamycin belongs to the ansamycin class of antibacterial drugs and acts by inhibiting the β-subunit of the bacterial RNA-dependent RNA polymerase, blocking one of the steps in RNA transcription. This results in inhibition of bacterial synthesis and consequently growth of bacteria.

Resistance

Resistant to rifamycin is associated with mutations in the RNA polymerase beta subunit. Among E. coli strains, the spontaneous mutation frequency rate of rifamycin ranged from 10^{-10} to 10^{-12} at 10^{-9} M. In the minimum inhibitory concentrations were observed both in vitro and in vivo when administration follows an initial dose of rifamycin, cross-resistance between rifamycin and other ansamycins have been observed.

Antibacterial Activity

Rifamycin has been shown to be active against most isolates of the following pathogens both in vitro and in clinical studies of travelers’ diarrhea.

Enterococcus coli (enterotoxigenic and enteroaggregative isolates)

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity

No carcinogenicity studies have been conducted in animals with rifamycin.

Mutagenesis

Rifamycin was not genotoxic in the bacterial reverse mutation assays, mouse lymphoma cell mutagen assay, or mouse bone marrow micronucleus assay.

Impairment of Fertility

No fertility studies have been conducted in animals with rifamycin.

14 CLINICAL STUDIES

14.1 Travellers’ Diarrhea

The efficacy of AEMCOLO given as 388 mg orally, taken three times a day, for 3 days was evaluated in two multi-centre, randomized, double-blind, placebo-controlled trials in adults with travelers’ diarrhea. Trial 1 (NCT01142386) was conducted at clinical sites in Guatemala and Mexico, and provides the primary evidence for the efficacy of AEMCOLO. A second action-controlled trial (Trial 2 – NCT01136852) conducted in India, Guatemala and Ecuador, provided supportive evidence for the efficacy of AEMCOLO. Although 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 1. Stool samples were collected before treatment and 1 to 2 days following the end of treatment to identify enteric pathogens. The predominant pathogen in both trials was E. coli.

The clinical efficacy of AEMCOLO was assessed using an endpoint of time to last unformed (loose or soft stool) before achieving clinical cure. The endpoint of clinical cure was defined as two or fewer soft stools, accompanied by normal frequency of bowel movements at the beginning of a 24-hour period following the end of treatment at the 48-hour follow-up visit. Kaplan-Meier estimates of ITT for the intent-to-treat (ITT) Population, which includes all randomized subjects, in Trial 1 (figure 1) showed that AEMCOLO significantly reduced the placebo compared to placebo (p<0.0005).

Figure 1: Kaplan-Meier Estimates of Time to Last Unformed Stool (TLUS) (Trial 1) (ITT Population)

Table 1: displays the median TLUS and the number of patients who achieved clinical cure for the ITT population in Trial 1.

<table>
<thead>
<tr>
<th></th>
<th>Median TLUS (hrs)</th>
<th>Clinical cure, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEMCOLO (n=199)</td>
<td>46.5</td>
<td>67</td>
</tr>
<tr>
<td>Placebo (n=203)</td>
<td>65.8</td>
<td>55</td>
</tr>
<tr>
<td>Difference</td>
<td>13.3</td>
<td>12.0</td>
</tr>
<tr>
<td>P value</td>
<td>0.0005</td>
<td>0.005</td>
</tr>
</tbody>
</table>

ITT = intent-to-treat; TLUS = time to last unformed stool (in hours).

The results of Trial 2 supported the results presented for Trial 1. In addition, this trial provided evidence that AEMCOLO treated subjects with fever and/or bloody diarrhea at baseline had prolonged ITUS. [see Warnings and Precautions (5.7)].

15 REFERENCES


16 HOW SUPPLIED/STORAGE AND HANDLING

AEMCOLO, delayed-release tablets contain 154 mg of rifamycin (equivalent to 200 mg of rifamycin sodium), and are yellow brown, elliptical and film-coated. These are packaged in blister packs of 8 tablets. The tablets are supplied as follows:

NDC: 71068-001-01: child resistant box of 12 tablets.

NDC: 71068-001-11: box of 36 tablets.

Store at 20° to 25°C (68° to 77°F) excursions permitted to 15 to 30°C (59° to 86°F).

17 PATIENT COUNSELING INFORMATION

Persistent Diarrhea

Instruct the patient taking treated for travelers’ diarrhea to discontinue AEMCOLO if diarrhea persists more than 48 hours or worsens. Advise the patient to seek medical care for fever and/or blood in the stool. [see Warnings and Precautions (5.7)].

Fever and/or Bloody Stool

Instruct the patient that AEMCOLO is not recommended for use if they have fever and/or bloody stool [see Warnings and Precautions (5.7)].

Gastrointestinal Discomfort Associated Diarrhea

Advise patients that diarrhea is a common problem caused by antibacterial drugs, which usually ends when the antibacterial drug is discontinued. Sometimes after stopping treatment with antibacterial drugs, patients may develop watery or bloody stools (with or without stomach cramps and fever) even as late as two or more months after stopping therapy. In such cases, patients should contact their physician as soon as possible.

18 ADMINISTRATION INSTRUCTIONS

AEMCOLO tablets should be swallowed whole with a full glass of liquid (6-8 ounces).

AEMCOLO must not be taken with alcohol.

AEMCOLO tablets must not be chewed, broken or crushed.

AEMCOLO may be taken with or without food.

Antibacterial Resistance

Patients should be counseled that antibacterial drugs like AEMCOLO should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When AEMCOLO is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better during treatment, the drug will not treat viral infections and may need to be continued for an additional period to kill off these infections. Patients should be counseled that if diarrhea occurs after therapy or does not improve or worsens during therapy, patients should contact their doctor as soon as possible.

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Redhill Biopharma, Inc.
Raleigh, NC

Manufactured by:

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Laufen, Milan, Italy
Made in Italy

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