1 INDICATIONS AND USAGE

MYTESI™ (crofelemer) delayed-release tablets for oral use
MYTESI™ (crofelemer) delayed-release tablets are indicated for the symptomatic relief of non-infectious diarrhea in adult patients with HIV/AIDS on anti-retroviral therapy.

2 DOSAGE AND ADMINISTRATION

The recommended dose of MYTESI is one 125 mg delayed-release tablet taken orally twice a day, with or without food.

3 DOSAGE FORMS AND STRENGTHS

MYTESI™ (crofelemer) delayed-release tablets are available as 125 mg delayed-release tablets.

4 CONTRAINDICATIONS

MYTESI™ (crofelemer) is contraindicated in patients with known hypersensitivity to MYTESI™ (crofelemer) or any of its excipients.

5 WARNINGS AND PRECAUTIONS

5.1 Risks of Treatments in Patients with Infectious Diarrhea

Rule out infectious etiologies of diarrhea before starting crofelemer. If infectious etiologies are not considered, there is a risk that patients with infectious etiologies will not receive the appropriate therapy and their disease may worsen.

5.2 Pregnancy

Pregnancy Category C

Reproduction studies performed with crofelemer in rats at oral doses up to 177 times the recommended daily human dose of 4.2 mg/kg revealed no evidence of impaired fertility or harm to the fetus. In pregnant rabbits, crofelemer at an oral dose of about 96 times the recommended daily human dose of 4.2 mg/kg, caused abortions and resorptions of fetuses. However, it is not clear whether these effects are related to the maternal toxicity observed. A pre- and postnatal development study performed with crofelemer in rats at oral doses of up to 177 times the recommended daily human dose of 4.2 mg/kg revealed no evidence of adverse pre- and postnatal effects in offspring. There are, however, no adequate, well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

5.3 Nursing Mothers

It is not known whether crofelemer is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for adverse reactions in nursing infants from MYTESI, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

5.4 Pediatric Use

Clinical studies with crofelemer did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently than younger patients.

5.5 Use in Patients with Low CD4 Counts and High Viral Loads

No dose modifications are recommended with respect to CD4 cell count and HIV viral load, based on the findings in subgroups of patients defined by CD4 cell count and HIV viral load.

5.6 Use in Patients with Low CD4 Counts and High Viral Loads

The safety profile of crofelemer was similar in patients with baseline CD4 cell count less than 400 cells/µL (lower limit of normal range) (N=366) and patients with baseline CD4 cell counts greater than or equal to 400 cells/µL (N=299).

5.7 7.2 Nelfinavir, Zidovudine, and Lamivudine

MYTESI administration did not have a clinically relevant interaction with nelfinavir, zidovudine, or lamivudine in a drug-drug interaction trial.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

8.2 Use in Patients with Low CD4 Counts and High Viral Loads

No dose modifications are recommended with respect to CD4 cell count and HIV viral load, based on the findings in subgroups of patients defined by CD4 cell count and HIV viral load.

The safety profile of crofelemer was similar in patients with baseline CD4 cell count less than 400 cells/µL (lower limit of normal range) (N=366) and patients with baseline CD4 cell counts greater than or equal to 400 cells/µL (N=299).

9 ADVERSE REACTIONS

The most common adverse reaction is abdominal pain, occurring in 5.7% of patients with the 125 mg twice daily dose of MYTESI and in 8.1% of patients with the 250 mg twice daily dose. Adverse reactions were similar in patients who received doses greater than 250 mg daily.

10 OVERDOSAGE

There has been no reported experience with overdosage of crofelemer.

11 DESCRIPTION

MYTESI™ (crofelemer) delayed-release tablets is an anti-diarrheal, enteric-coated drug product for oral administration. It contains 125 mg of crofelemer, a botanical drug substance that is derived from the red latex of Croton lechleri Willd., a plant native to the Amazon basin of South America. Crofelemer is a white, oval, enteric-coated 125 mg delayed-release tablet printed on one side with 125SL10®.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Crofelemer is a synthetic, low molecular weight, trimethylated tannin that is isolated from Croton lechleri Willd. Crofelemer is a mixture primarily composed of (+)-catechin, (+)-epicatechin, (+)-galloic acid, and (+)-epigallocatechin monomer units linked in random sequence, as represented below. The average degree of polymerization for the oligomers ranges between 5 and 7.5, as determined by phloroglucinol-phenol degradation.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 2-year carcinogenicity study in Sprague-Dawley rats, MYTESI revealed no evidence of impaired fertility or harm to the fetus. In a rat reproduction study, MYTESI (at a daily human dose of 4.2 mg/kg) revealed no evidence of impaired fertility or harm to the fetus. In a mouse reproduction study, MYTESI (at a daily human dose of 4.2 mg/kg) revealed no evidence of impaired fertility or harm to the fetus. In a rabbit reproduction study, MYTESI (at a daily human dose of 4.2 mg/kg) revealed no evidence of impaired fertility or harm to the fetus.

14 CLINICAL STUDIES

14.1 How Supplied/Storage and Handling

MYTESI™ (crofelemer) delayed-release tablets are supplied as 125 mg delayed-release tablets. Each white, oval, enteric-coated 125 mg delayed-release tablet contains 125 mg of MYTESI™ (crofelemer) for oral use. Store at 25°C (77°F), excursions permitted between 15° and 30°C (59° and 86°F).

15 PATIENT COUNSELING INFORMATION

15.1 Take as directed

15.2 Avoid ingestion of foods high in fiber

15.3 Avoid ingestion of foods high in calcium

15.4 Avoid ingestion of alcohol

15.5 Avoid ingestion of caffeine

15.6 Avoid ingestion of milk

15.7 Avoid ingestion of dairy products

15.8 Avoid ingestion of soy products

15.9 Avoid ingestion of nuts

15.10 Avoid ingestion of seeds

15.11 Avoid ingestion of beans

15.12 Avoid ingestion of legumes

15.13 Avoid ingestion of lentils

15.14 Avoid ingestion of chickpeas

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16 USE IN SPECIFIC POPULATIONS

17 PATIENT COUNSELING INFORMATION

Revised 06/2016
Inactive ingredients: microcrystalline cellulose, croscarmellose sodium, colloidal silicon dioxide, and magnesium stearate.

Coating ingredients: ethylcellulose and methylcellulose copolymer dispersion, talc, triethyl citrate, and white dispersion which contains xanthan gum, titanium dioxide, propyl paraben, and methyl paraben.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Crofelemer is an inhibitor of both the cyclical adenosine monophosphate (cAMP)-stimulated cytosolic PfEMP1 transmembrane conductance regulator (CFTR) chloride ion (Cl−) channel, and the calcium-activated Cl− channels (CaCC) at the luminal membrane of enterocytes. The CFTR Cl− channel and CaCC regulator Cl− and fluid secretion by intestinal epithelial cells. Crofelemer acts by blocking Cl− secretion and accompanying high volume water loss in diarrhea, normalizing the flow of Cl− and water in the GI tract.

12.2 Pharmacodynamics

Consistent with the mechanism of action of crofelemer (i.e., inhibition of CFTR and CaCC in the GI lumen), data suggest chloride concentrations decreased in patients treated with MYTESI (500 mg four times daily) (n=25) for four days relative to placebo (n=24); stool chloride concentrations decreased in both African American patients treated with MYTESI (n=3) relative to placebo (n=5) and non-African American patients treated with MYTESI (n=22) relative to placebo (n=19).

At a dose 10 times the maximum recommended dose, crofelemer does not prolong the QTc interval to any clinically relevant extent.

12.3 Pharmacokinetics

Absorption

The absorption of crofelemer is minimal following oral dosing in healthy adults and HIV-positive patients and concentrations of crofelemer in plasma are below the level of quantification (50 ng/ml). Therefore, standard pharmacokinetic parameters such as area under the curve, maximum concentration, and half-life cannot be estimated.

Distribution

The distribution of crofelemer has not been determined.

Metabolism

No metabolites of crofelemer have been identified in healthy subjects or patients in clinical trials.

Elimination

The elimination route has not been identified in humans.

Food Effect

Administration of crofelemer with a high-fat meal was not associated with an increase in systemic exposure of crofelemer in healthy volunteers. In the clinical trial, a single 500 mg dose of crofelemer was administered one-half hour before the morning and evening meals. Therefore, crofelemer may be administered with or without a meal.

Drug–Drug Interactions

Results of a crossover study in healthy volunteers showed crofelemer 500 mg administered four times daily for five days had no effect on the exposure of zidovudine and nelfinavir when administered as the double-blind period. Each stage enrolled patients separately; the dose for the second stage was selected based on an interim analysis of data from the first stage. In the first stage, patients were randomized 1:1:1:1 to one of three crofelemer dose regimens (125, 250, or 500 mg twice daily) or placebo. In the second stage, patients were randomized 1:1:1 to crofelemer 125 mg twice daily or placebo. The efficacy analysis was based on results from the double-blind portion of both stages.

Each study stage also had a five month period (placebo-free period) that followed the double-blind period. Patients treated with crofelemer continued the same dose in the placebo-free period. In the first stage, patients that received placebo were re-randomized 1:1:1 to one of the three crofelemer dose regimens (125, 250, or 500 mg twice daily) in the placebo-free period. In the second stage, patients that received placebo were treated with crofelemer 125 mg twice daily in the placebo-free period.

The median time since diagnosis of HIV was 12 years. The percentage of patients with a CD4 cell count of less than 404 was 39%. The percentage of patients with a HIV viral load greater than or equal to 100 to 400 400 to 999, and less than 400 HIV copies/mL was 7%, 3%, and 9%, respectively, the remainder had a viral load that was not detectable. The median time since diarrhea started was 4 years. The median number of daily watery bowel movements was 2.5 per day.

Most patients were male (85%). The percentage of patients that were Caucasian was 46%; the percentage of patients that were African-American was 32%. The median age was 45 years with a range of 21 to 68 years.

In the double-blind period of the study, 136 patients received crofelemer 125 mg twice daily, 54 patients received 250 mg twice daily, 47 patients received 500 mg twice daily, and 138 patients received placebo. The percentages of patients that completed the double-blind period were 92%, 100%, 85%, and 94% in the 125 mg, 250 mg, 500 mg, and placebo arms, respectively.

Most patients received concomitant protease inhibitors (PI) during the double-blind period (Table 2). The most frequently used ARTs in each group were tenofovir/emtricitabine, ritonavir, and lopinavir/ritonavir.

The primary efficacy endpoint was the proportion of patients with a clinical response, defined as less than or equal to 2 water bowel movements per week during at least 2 of the 4 weeks of the placebo-controlled phase. Patients who received concomitant AIDs or opiates were counted as clinical non-responders.

A significantly larger proportion of patients in the crofelemer 125 mg twice daily group experienced clinical response compared with patients in the placebo group (17.6% vs. 8.0%, 1-sided p < 0.01).

In the randomized clinical study, examination of duration of diarrhea, baseline number of daily watery bowel movements, use of protease inhibitors, CD4 cell count and age subgroups did not identify differences in the consistency of the crofelemer treatment effect among these subgroups. There were too few female subjects and subjects with an HIV viral load > 400 copies/mL to adequately assess differences in effects in these populations. Among race subgroups, there were no differences in the consistency of the crofelemer treatment effect except for the subgroup of African-Americans; crofelemer was less effective in African-Americans than non-African-Americans.

Although the CD4 cell count and HIV viral load did not appear to change over the one month placebo-controlled period, the clinical significance of this finding is unknown because of the short duration of the placebo-controlled period.

Of the 24 clinical responders to crofelemer (125 mg twice daily), 22 entered the placebo-free period; 16 were responding at the end of month 3, and 14 were responding at the end of month 5.

16 HOW SUPPLIED/STORAGE AND HANDLING

Crofelemer delayed-release tablets, 125 mg, are white, oval enteric-coated tablets printed on one side with 125SLXP. They are available in the following package size: Bottles of 60: NDC 70664-802-60

Store at 20°C-25°C (68°F-77°F); excursions permitted between 15°C-30°C (59°F-86°F). See USP Controlled Room Temperature.

17 PATIENT COUNSELING INFORMATION

• Instruct patients that MYTESI tablets may be taken with or without food.

• Instruct patients that MYTESI tablets should not be crushed or chewed. Tablets should be swallowed whole.

Rx Only

Manufactured by Patheon, Inc. for Napo Pharmaceuticals, Inc.

Napo Pharmaceuticals, Inc., 14960 S. Olympic Blvd., Los Angeles, CA 90058

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The botanical drug substance of MYTESI is extracted from Croton lechleri (the botanical raw material) that is harvested in the wild in South America.