napo pharmaceuticals | Mytesi (crofelemer) 125 mg

PRESCRIPTION INFORMATION AND NAPOCARES™ ENROLLMENT FORM

Please **complete and fax this form,** along with a cover letter, to (415) 963-9830

Or, **mail** to NapoCares at
P.O. Box 7613
Overland Park, KS 66207

For assistance, **call** (888) 527-NAPO (6276)

By enrolling in **NapoCares™**, patients will receive support and information to help access Mytesi, which may include the following depending on the program:

- Providing benefits investigations/verification and reimbursement support, including:
  - Assisting with prior authorization requirements from the patient's insurer
  - Assisting with appealing any denial from the patient's insurer
- Determining eligibility for and helping eligible patients access co-pay support
- Providing eligible patients with financial assistance resources and information
- Providing assistance to patient and specialty pharmacies where applicable

DISCLAIMER

Napo Pharmaceuticals, Inc.'s ("Napo's") third-party provider (the "Provider") provides patient insurance benefit verification under contract to Napo's patient support programs (collectively referred to as "NapoCares") to, among other things, assist patients in the determination of whether Mytesi® could be covered by the patient's third-party payer based on such payer's coverage guidelines and the patient information provided to the Provider by the patient's healthcare provider under appropriate authorization after the healthcare provider's exclusive determination of medical necessity.

Many factors affect a third-party payer's reimbursement determination. Napo and the Provider make no representations, warranties, or guarantees that insurance reimbursement or any other payment will be available for the patient's benefit. This information is provided as a service only. While the Provider tries to provide correct information, it and Napo make no representations, warranties, or guarantees, expressed or implied, as to the accuracy of such information. Neither the Provider, Napo, nor either of their respective employees or agents shall in any event be liable for any damages resulting from or relating to NapoCares.

P.O. BOX 7613 OVERLAND PARK, KS 66207
TELEPHONE: (888) 527-NAPO (6276) | **FAX:** (415) 963-9830
napocares@napopharma.com
napocares.com

NAPOCARES™ PATIENT SUPPORT ENROLLMENT

PATIENT INFORMATION

FIRST NAME / LAST NAME

DATE OF BIRTH

GENDER: ☐ Male ☐ Female ☐ Nonbinary

STREET ADDRESS

CITY, STATE

ZIP CODE

PHONE #

ALT PHONE #

EMAIL

PHONE # TYPE: ☐ Home ☐ Mobile ☐ Work

BEST TIME TO CALL: ☐ Morning ☐ Afternoon

OKAY TO LEAVE MESSAGE? ☐ Yes ☐ No

PREFERRED CONTACT METHOD: ☐ Phone ☐ Email

OPT OUT OF COMMUNICATIONS: ☐ Please check here if you do not wish to receive communications other than those related to the program.

PREFERRED LANGUAGE (IF OTHER THAN ENGLISH)

CAREGIVER NAME (OPTIONAL)

CAREGIVER PHONE # (OPTIONAL)

RELATIONSHIP TO PATIENT (OPTIONAL)

INSURANCE INFORMATION

CARDHOLDER FIRST NAME / LAST NAME

CARDHOLDER DATE OF BIRTH (OPTIONAL)

PATIENT RELATIONSHIP TO CARDHOLDER (OPTIONAL)

PHARMACY INSURANCE NAME

PHARMACY PLAN TYPE (OPTIONAL)

PHARMACY GROUP (OPTIONAL)

PHARMACY ID # (OPTIONAL)

PHARMACY BIN (OPT.)

PHARMACY PCN (OPT.)

PHARMACY INSURANCE PHONE # (OPTIONAL)

PATIENT AUTHORIZATION

By signing this Authorization, I authorize each of my healthcare providers, pharmacists, including any specialty pharmacy that receives my prescription for Mytesi (crofelemer), other healthcare providers (together "Healthcare Providers"), and any of my health insurers (together, "Insurers") to disclose my Protected Health Information to Napo Pharmaceuticals, Inc., its affiliated companies, vendors, agents, collaboration partners, and representatives (together, "Napo Pharmaceuticals, Inc."), including supporting NapoCares (the "Program") for Healthcare Providers and patients for the purposes described below. Protected Health Information may include, but is not limited to, medical records, information related to my medical condition and treatment, health insurance coverage, my name, address, telephone number, Social Security number, insurance plan, and/or group numbers (together, "Protected Health Information").

Specifically, I authorize disclosure of my Protected Health Information in order to:

I. Enroll me in and contact me about the Program, including online support, financial assistance services, co-pay assistance, and compliance and persistency services,
II. Communicate with my Healthcare Providers and Insurers about benefits, coverage, and medical care, including compliance with Product treatments,
III. Locate a specialty pharmacy that can fill my prescription and facilitate dispensing of my prescription by such pharmacy,
IV. Provide me with educational materials, information, and services related to my treatment experience with Mytesi and my condition,
V. Contact me and leave messages about my use of Mytesi and my medical care,
VI. Verify, investigate, assist with, and coordinate my coverage for Mytesi with my Insurers,
VII. Coordinate prescription fulfillment,
VIII. Conduct surveys, data analytics, market research, and other internal business activities related to the Program, Mytesi, and other Napo Pharmaceuticals, Inc. products and programs, and
IX. Contact me as otherwise required or permitted by law.

I understand that pharmacies that ship my medication may be paid to share this information with the Program to help provide the offerings requested for me. Once my Protected Health Information has been disclosed to Napo Pharmaceuticals, Inc., I understand that federal privacy laws no longer protect the information. However, Napo Pharmaceuticals, Inc. agrees to protect my Protected Health Information by using and disclosing it only for the purposes described in this authorization or as permitted by law. We do not sell de-identified personal health information to third parties.

I understand that I may refuse to sign this Authorization. My choice about whether to sign will not change the way my Healthcare Providers or Insurers treat me, but should I decline to sign, I will not have access to the Program and the services provided by Napo Pharmaceuticals, Inc. or others under the Program. If I refuse to sign the Authorization, or revoke my authorization later, I understand that this means I will not be able to participate or receive assistance from the Program.

This Authorization will last for a period of five (5) years (unless earlier termination is required by applicable state law). I understand that I may revoke this Authorization at any time in the future, except to the extent that actions have been taken in reliance on the Authorization, by mailing a request to P.O. Box 7613, Overland Park, KS 66207, via fax at (415) 963-9830, or by calling (888) 527-NAPO (6276). I understand that revoking this Authorization will end further uses and disclosure of my Protected Health Information by the parties identified above except to the extent those uses and disclosures have been made in reliance upon this Authorization as permitted by applicable law. I am entitled to receive a copy of this Authorization.

The personal and health insurance information I have provided on this form is complete and accurate to the best of my knowledge. I will update my information promptly if any of the information reflected on this Form changes by contacting the Program at (888) 527-NAPO (6276).

SIGN HERE

PATIENT SIGNATURE (PLEASE SIGN HERE **AND** ON PAGE 4)

DATE

SIGN HERE

PATIENT LEGAL REPRESENTATIVE (IF APPROPRIATE)

RELATIONSHIP TO PATIENT (OPTIONAL)

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napocares@napopharma.com
napocares.com

NAPOCARES™ PATIENT SUPPORT ENROLLMENT (CONTINUED)

PRESCRIBER INFORMATION

PRESCRIBER FIRST NAME / LAST NAME

STREET ADDRESS

CITY | STATE | ZIP

NPI # | EMAIL (OPTIONAL)

PHONE #

FAX #

OFFICE CONTACT NAME (OPTIONAL) | OFFICE CONTACT PHONE # (OPTIONAL)

PREFERRED METHOD OF CONTACT: ☐ Phone ☐ Email ☐ Fax

PRESCRIPTION

PATIENT FIRST NAME / LAST NAME

PREFERRED PHARMACY | PREFERRED PHARMACY PHONE #

☐ **NEW AND MAINTENANCE PATIENTS** QTY: 60 tablets REFILLS: _____
Mytesi (crofelemer 125 mg delayed-release tablets)
SIG: One (1) tablet BID

☐ **QUICK START FOR NEW PATIENTS** QTY: 30 tablets REFILLS: 1 REFILL (IF ELIGIBLE)
Mytesi (crofelemer 125 mg delayed-release tablets)
SIG: One (1) tablet BID

Quick Start prescription is at no cost, for eligible patients within labeled indication only, and not contingent on purchase of any kind. Quick Start prescription is intended to support access to therapy if there is a delay in insurance coverage determination. By checking the box above for Quick Start prescription, I, as the prescriber, with my signature below on this form, agree and attest that I will not submit a claim to or seek payment from the patient or any third-party payer (eg, Medicaid, Medicare, private insurance, etc.) for payment/reimbursement for any free product(s) provided by Napo Pharmaceuticals, Inc. I agree and understand that any free product provided by Napo Pharmaceuticals, Inc. may not be sold, traded, bartered, transferred, or returned for credit and will only be used for the patient named above on the form. Napo Pharmaceuticals, Inc. reserves the right to modify or terminate the program without notice at any time.

SIGN HERE

PRESCRIBER SIGNATURE (DISPENSE AS WRITTEN) | DATE

PRESCRIBER AUTHORIZATION

By signing below, I certify that (1) the above therapy is appropriate and medically necessary and in the best interest of the named patient; (2) I have received the appropriate permission from the patient (or the patient's Legal Representative) and met any other applicable legal or regulatory requirements such as those imposed under the Health Insurance Portability and Accountability Act of 1996 and/or state law needed to release the above information to Napo Pharmaceuticals, Inc. (Napo) and its agents; (3) I have obtained the patient's authorization to release the above information and such other information as may be required by AssistRx, as Napo Pharmaceuticals, Inc.'s agent, and its employees to assist in obtaining coverage for Mytesi; and (4) I appoint AssistRx as my agent for the purpose of conveying this prescription to the appropriate dispensing pharmacy, verifying the patient's insurance coverage for MYTESI (crofelemer) 125 mg tablets, providing information regarding payer coverage and benefits and how to prepare prior authorization requests, coverage determination appeals, or other coverage issues, and providing my patient and me with educational and support services associated with MYTESI (crofelemer).

I certify that I have reviewed the additional terms available at https://ebvterms.com, which are specifically incorporated herein by reference, and acknowledge and consent to their application and enforceability in regards to this certification.

SIGN HERE

PRESCRIBER SIGNATURE | DATE

MEDICAL INFORMATION

DIAGNOSIS ICD-10 CODE

- ☐ R19.7 Diarrhea, unspecified
- ☐ K59.1 Functional diarrhea
- ☐ K52.9 Noninfective gastroenteritis and colitis, unspecified
- ☐ B23.2 HIV disease resulting in haematological and immunological abnormalities, not elsewhere classified
- ☐ Other _____

DIARRHEA MEDICATION HISTORY (CHECK ALL THAT APPLY)

Mytesi	Loperamide	Lomotil	Other: _____
☐ Current treatment	☐ Current treatment	☐ Current treatment	☐ Current treatment
☐ Tried	☐ Tried	☐ Tried	☐ Tried
☐ Failed	☐ Failed	☐ Failed	☐ Failed
☐ Responded	☐ Responded	☐ Responded	☐ Responded

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NAPOCARES™ PATIENT SUPPORT ENROLLMENT (CONTINUED)

1. **OVERVIEW** NapoCares Patient Support Program is designed to provide Mytesi to those for whom a medical need has been established, who cannot afford the cost of therapy, and who are below the maximum income requirements adjusted by household size and have no other insurance coverage or federally funded health benefit options available to access Mytesi.

2. **DEFINITIONS** For the purpose of this enrollment form and NapoCares Patient Support Program, the following definitions shall apply: **"Patient"** means one on whose behalf an application has been submitted for Benefits under NapoCares; **"Applicant"** means a person who submits an application for Benefits under NapoCares; **"Beneficiary"** means an Applicant whose application for access to Mytesi under the Patient Support Program has been granted in full or part pursuant to the NapoCares program; **"Benefits"** means Mytesi Delayed-Release Tablets that are provided pursuant to the NapoCares program; **"You"** means the Applicant and/or a Beneficiary, as appropriate from the context of this use; and **"NapoCares"** means the NapoCares Patient Support Program.

3. **SIGNATURES REQUIRED** In order to be considered for Benefits under NapoCares, both You (or your legal representative) and your prescribing healthcare provider must complete and sign the appropriate sections of the application form.

4. **ACCESS TO INFORMATION** Your application for Benefits allows access to financial, medical, and other information about You. In order for NapoCares to receive certain medical information about You in your application, the Health Insurance Portability and Accountability Act of 1996 and the related Privacy Rule 45 CFR Parts 160 and 164 (collectively "HIPAA") require NapoCares to obtain your written authorization. If You do not sign the enrollment form, NapoCares cannot process your application and You will not be able to participate in NapoCares.

5. **ELIGIBILITY** Eligibility for NapoCares varies by program:
   - Quick Start Program: Applicant must be covered under a commercial insurance policy or Medicare.

6. **US RESIDENTS ONLY** Only US Residents (excluding Puerto Rico and other US territories) are eligible for Benefits under NapoCares.

7. **LIMIT ON SUPPLY**
   - Quick Start Program: A maximum of one 30-day supply of Mytesi over the lifetime of the Beneficiary may be awarded to a Beneficiary.

8. **NO RIGHT TO ASSISTANCE** An applicant for Benefits under NapoCares has no legal right to receive assistance from NapoCares. Any award of Benefits from NapoCares will involve the assessment of many criteria among potentially qualified Applicants. Therefore, we reserve the right to grant or deny an application, in whole or in part, on the basis of such criteria as we deem appropriate. In particular, the fact that an Applicant may be granted an award of Benefits at one time does not mean that the Applicant is entitled to, or will be granted, an award of Benefits at any time. Napo Pharmaceuticals, Inc. reserves the right to rescind, revoke, or amend this program at any time without notice.

9. **DISTRIBUTION** NapoCares uses contracted partners for all of its distribution activities, including distribution of Mytesi. NapoCares' contracted distributors are responsible for the distribution activities provided, including any delays in shipment or other problems that might occur with the delivery of Mytesi.

10. **DRUG SHORTAGE** NapoCares will attempt to provide You with sufficient quantities of Mytesi to cover your needs while You are enrolled in the NapoCares program. However, in the event that a shortage of drug exists at any time during a period of time for which You have been awarded drug under NapoCares, NapoCares will give You written or verbal notice of such shortage.

11. **WAITING LISTS** NapoCares may receive numerous applications, resulting in requests for more Mytesi than is available through the NapoCares program. Therefore, NapoCares may not be able to approve all applications for Benefits. Moreover, a waiting list of Applicants may accrue, which may delay processing applications until a sufficient supply of Mytesi becomes available through the NapoCares program.

12. **RIGHT TO MODIFY BENEFIT** We, during the time period of any award to Beneficiary, reserve the right to review the award and/or the Patient's medical and financial situation. Based on that review, we reserve the right to increase, decrease, or terminate Benefits previously awarded to You.

13. **ADDITIONAL RESTRICTIONS** In the course of reviewing an application and/or administering an award of Benefits under NapoCares, we reserve the right to impose such other conditions and/or require that You provide such other information and/or that You take such actions as we deem appropriate.

14. **NO WARRANTIES** NapoCares does not make any representations or warranties, either expressed or implied, concerning any aspect of NapoCares.

15. **TERMINATION OF PROGRAM** NapoCares may be amended or terminated, without prior notice, at any time.

SIGN HERE _____ PATIENT SIGNATURE _____ DATE

SIGN HERE _____ PATIENT LEGAL REPRESENTATIVE (IF APPROPRIATE) _____ RELATIONSHIP TO PATIENT (OPTIONAL)

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use MYTESI safely and effectively. See full prescribing information for MYTESI.

MYTESI® (crofelemer) delayed-release tablets, for oral use

Initial U.S. Approval: 2012

----------RECENT MAJOR CHANGES----------

Dosage and Administration (2)	02/2018
Warnings and Precautions (5.1)	02/2018

----------INDICATIONS AND USAGE----------

MYTESI is an anti-diarrheal indicated for the symptomatic relief of non-infectious diarrhea in adult patients with HIV/AIDS on anti-retroviral therapy. (1)

----------DOSAGE AND ADMINISTRATION----------

Before starting MYTESI, rule out infectious etiologies of diarrhea. (2, 5.1)

The recommended adult dosage is 125 mg taken orally twice a day, with or without food. (2)

Do not crush or chew the tablets. Swallow whole. (2)

----------DOSAGE FORMS AND STRENGTHS----------

Delayed-Release Tablets: 125 mg (3)

----------CONTRAINDICATIONS----------

None (4)

----------WARNINGS AND PRECAUTIONS----------

Risks of Treatment in Patients with Infectious Diarrhea: Consider infectious etiologies of diarrhea before starting treatment to reduce the risk of inappropriate therapy and worsening disease. (2, 5.1)

----------ADVERSE REACTIONS----------

Most common adverse reactions (≥ 3%) are: upper respiratory tract infection, bronchitis, cough, flatulence and increased bilirubin. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Napo Pharmaceuticals at 1-844-722-8256 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION

Revised 02/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

MYTESI is indicated for symptomatic relief of non-infectious diarrhea in adult patients with HIV/AIDS on anti-retroviral therapy.

2 DOSAGE AND ADMINISTRATION

Before starting MYTESI, rule out infectious etiologies of diarrhea *[see Warnings and Precautions (5.1)]*.

The recommended adult dosage of MYTESI is 125 mg taken orally two times a day, with or without food.

Do not crush or chew MYTESI tablets. Swallow whole.

3 DOSAGE FORMS AND STRENGTHS

Delayed-Release Tablets: 125 mg of crofelemer as a white, oval, delayed-release tablet printed on one side with 125SLXP.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Risks of Treatment in Patients with Infectious Diarrhea

Before starting MYTESI, rule out infectious etiologies of diarrhea. If infectious etiologies are not considered, and MYTESI is initiated based on a presumptive diagnosis of non-infectious diarrhea, then there is a risk that patients with infectious etiologies will not receive the appropriate treatments, and their disease may worsen. MYTESI is not indicated for the treatment of infectious diarrhea.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

A total of 696 HIV-positive patients in three placebo-controlled trials received MYTESI for a mean duration of 78 days. Of the total population across the three trials, 229 patients received a dosage of 125 mg twice a day for a mean duration of 141 days, and 171 patients received one of four higher than recommended dosages for a mean duration of 139 days (N=69) 14 days (N=102), 146 days (N=54), and 14 days (N=242), respectively.

Adverse reactions in patients treated with MYTESI 125 mg twice daily that occurred in at least 2% of patients and at a higher incidence than placebo are provided in Table 1.

Table 1: Common Adverse Reactions* in HIV-Positive Patients in Three Placebo-Controlled Trials

Adverse Reaction	MYTESI 125 mg Twice Daily N = 229 n (%)	Placebo N = 274 n (%)
Upper respiratory tract infection	13 (6)	4 (2)
Bronchitis	9 (4)	0
Cough	8 (4)	3 (1)
Flatulence	7 (3)	3 (1)
Increased bilirubin	7 (3)	3 (1)
Nausea	6 (3)	4 (2)
Back pain	6 (3)	4 (2)
Arthralgia	6 (3)	0
Urinary tract infection	5 (2)	2 (1)
Nasopharyngitis	5 (2)	2 (1)
Musculoskeletal pain	5 (2)	1 (<1)
Hemorrhoids	5 (2)	0
Giardiasis	5 (2)	0
Anxiety	5 (2)	1 (<1)
Increased alanine aminotransferase	5 (2)	3 (1)
Abdominal distension	5 (2)	1 (<1)

* occurring in at least 2% of patients and at a higher incidence than placebo

Less common adverse reactions that occurred in between 1% and 2% of patients taking 125 mg twice daily of MYTESI were abdominal pain, acne, increased aspartate aminotransferase, increased conjugated bilirubin, increased unconjugated blood bilirubin, constipation, depression, dermatitis, dizziness, dry mouth, dyspepsia, gastroenteritis, herpes zoster, nephrolithiasis, pain in extremity, pollakiuria, sinusitis and decreased white blood cell count.

7 DRUG INTERACTIONS

7.1 Nelfinavir, Zidovudine, and Lamivudine

MYTESI administration did not have a clinically relevant interaction with nelfinavir, zidovudine, or lamivudine in a drug-drug interaction trial *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Reproduction studies performed with crofelemer in rats at oral doses up to 177 times the recommended daily human dose of 250 mg (approximately 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.

8.3 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.

8.4 Pediatric Use

The safety and effectiveness of MYTESI have not been established in pediatric patients.

8.5 Geriatric Use

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

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

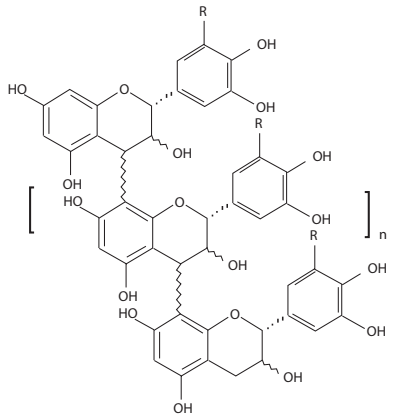
No dose modifications are recommended with respect to CD4 cell count and HIV viral load, based on the findings in subgroups of patients defined by CD4 cell count and HIV viral load.

The safety profile of MYTESI was similar in patients with baseline CD4 cell count less than 404 cells/microL (lower limit of normal range) (N=388) and patients with baseline CD4 cell counts greater than or equal to 404 cells/microL (N=289).

The safety profile of crofelemer was similar in patients with baseline HIV viral loads less than 400 copies/mL (N = 412) and patients with baseline HIV viral loads greater than or equal to 400 copies/mL (N = 278).

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* Müll. Arg. Crofelemer is an oligomeric proanthocyanidin mixture primarily composed of (+)–catechin, (–)–epicatechin, (+)–gallocatechin, 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 degradation.



R = H or OH range n = 3 to 5.5

Inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, and microcrystalline cellulose.

Coating ingredients: ethylacrylate and methylacrylate 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 cyclic adenosine monophosphate (cAMP)-stimulated cystic fibrosis 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 regulate 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 gastrointestinal tract.

12.2 Pharmacodynamics

Consistent with the mechanism of action of crofelemer (i.e., inhibition of CFTR and CaCC in the gastrointestinal lumen), data suggest stool chloride concentrations decreased in patients treated with crofelemer 500 mg four times daily (8-times the recommended daily dosage) (n=25) for four days relative to placebo (n=24); stool chloride concentrations decreased in both African American patients treated with crofelemer (n=3) relative to placebo (n=5) and non-African American patients treated with MYTESI (n=22) relative to placebo (n=19).

7003689 1

MYTESI
(CROFELEMER) DELAYED-RELEASE TABLETS

REV: February 2018

Cardiac Electrophysiology

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 quantitation (50 ng/mL). Therefore, standard pharmacokinetic parameters such as area under the curve, maximum concentration, and half-life cannot be estimated.

Effect of Food

Administration of crofelemer with a high-fat meal was not associated with an increase in systemic exposure of crofelemer in healthy subjects. In the clinical trial, a single 500 mg dose of crofelemer (4-times the recommended dose) was administered one-half hour before the morning and evening meals *[see Dosage and Administration (2)]*.

Drug Interaction Studies

In vitro studies have shown that crofelemer has the potential to inhibit cytochrome P450 isoenzyme 3A and transporters MRP2 and OATP1A2 at concentrations expected in the gut. Due to the minimal absorption of crofelemer, crofelemer is unlikely to inhibit cytochrome P450 isoenzymes 1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1 and CYP3A4 systemically.

Nelfinavir, Zidovudine, Lamivudine

Results of a crossover study in healthy subjects showed crofelemer 500 mg administered four times daily (8-times the recommended dosage) for five days had no effect on the exposure of zidovudine and nelfinavir when administered as a single dose. A 20% decrease in lamivudine exposure was also observed in the same study but was not considered to be clinically important.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of crofelemer.

Mutagenesis

Crofelemer was negative in the bacterial reverse mutation assay, chromosomal aberration assay, and rat bone marrow micronucleus assay.

Impairment of Fertility

Crofelemer, at oral doses of up to 738 mg/kg/day (177 times the recommended human daily dose of 125 mg twice daily), had no effects on fertility or reproductive performance of male and female rats.

14 CLINICAL STUDIES

The efficacy of MYTESI was evaluated in a randomized, double-blind, placebo-controlled (one month) and placebo-free (five month), multi-center study. The study enrolled 374 HIV-positive patients on stable anti-retroviral therapy with a history of diarrhea for one month or more. Diarrhea was defined as either persistently loose stools despite regular use of anti-diarrheal medication (e.g., loperamide, diphenoxylate, and bismuth subsalicylate) or one or more watery bowel movements per day without regular anti-diarrheal medicine use.

Patients were excluded if they had a positive gastrointestinal biopsy, gastrointestinal culture, or stool test for multiple bacteria (Salmonella, Shigella, Campylobacter, Yersinia, Mycobacterium), bacterial toxin (*Clostridium difficile*), ova and parasites (Giardia, Entamoeba, Isospora, Cyclospora, Cryptosporidium, Microsporidium), or viruses (Cytomegalovirus). Patients were also excluded if they had a history of ulcerative colitis, Crohn's disease, celiac sprue (gluten-enteropathy), chronic pancreatitis, malabsorption, or any other gastrointestinal disease associated with diarrhea.

The study had a two-stage adaptive design. In both stages, patients received placebo for 10 days (screening period) followed by randomization to crofelemer or placebo for 31 days of treatment (double-blind period). Only patients with 1 or more watery bowel movements per day on at least 5 of the last 7 days in the screening period were randomized to 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 dosage regimens (125 mg twice daily, or one of two higher dosage regimens) or placebo. In the second stage, patients were randomized 1:1 to MYTESI 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 MYTESI 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 dosage regimens (125 mg twice daily, or one of the two higher dosage regimens) in the placebo-free period. In the second stage, patients that received placebo were treated with MYTESI 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 1000, 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 MYTESI 125 mg twice daily, 101 patients received one of the two higher dosage regimens and 138 patients received placebo. The percentages of patients that completed the double-blind period were 92% in the MYTESI 125 mg group and 94% in the placebo arm.

Most patients received concomitant protease inhibitors during the double-blind period (Table 2). The most frequently used anti-retroviral therapies in the MYTESI 125 mg and placebo groups were tenofovir/emtricitabine, ritonavir, and lopinavir/ritonavir.

Table 2: Concomitant Anti-Retroviral Therapy Used in the Double-Blind Period in Patients with HIV

	MYTESI 125 mg twice daily (N = 136)n (%)	Placebo N = 138 n (%)
Any antiretroviral therapy	135 (99)	134 (97)
Any protease inhibitor	87 (64)	97 (70)
Tenofovir/Emtricitabine	45 (33)	52 (38)
Ritonavir	46 (34)	49 (36)
Lopinavir/Ritonavir	30 (22)	40 (29)
Efavirenz/Tenofovir/Emtricitabine	30 (22)	21 (15)
Tenofovir disoproxil fumarate	18 (13)	14 (10)
Atazanavir sulfate	19 (14)	22 (16)
Abacavir w/ lamivudine	17 (13)	18 (13)
Darunavir	19 (14)	14 (10)
Raltegravir	16 (12)	11 (8)
Valaciclovir hydrochloride	12 (9)	16 (12)
Fosamprenavir	12 (9)	13 (9)
Zidovudine w/lamivudine	12 (9)	15 (11)
Lamivudine	7 (5)	6 (4)
Nevirapine	8 (6)	9 (7)
Atazanavir	5 (4)	2 (1)

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

A significantly larger proportion of patients in the MYTESI 125 mg twice daily group experienced clinical response compared with patients in the placebo group (18% vs. 8%, 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 patients and patients 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 MYTESI 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

MYTESI (crofelemer) 125 mg delayed-release tablets are white, oval tablets printed on one side with 125SLXP. They are available in the following package size:

Bottles of 60: NDC 70564-802-60

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 to swallow MYTESI tablets whole and not to crush or chew the tablets.

Manufactured by Patheon, Inc. for

napo® pharmaceuticals

Napo Pharmaceuticals, Inc., San Francisco, CA 94105

US Patent Nos. 7,341,744 and 7,323,195.

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