Dear Healthcare Professional,

At MPR we strive to bring you important drug information in a concise and timely fashion. In keeping with this goal, we are pleased to bring you this PRESCRIBING ALERT about Fulyzaq™ (crofelemer) 125 mg delayed-release tablets, a product of Salix Pharmaceuticals, Inc. Diarrhea is a known side effect of multiple classes of drugs used in antiretroviral therapy (ART) regimens.¹ As diarrhea continues to be a problem for many patients with HIV, Fulyzaq is the only anti-diarrheal approved by the FDA specifically for the symptomatic relief of noninfectious diarrhea in adult patients with HIV/AIDS on ART. Fulyzaq provides a unique antisecretory effect without affecting gut motility or the efficacy of ARTs. More than twice as many patients with chronic diarrhea had improvements with Fulyzaq vs those on placebo.² 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.² In this PRESCRIBING ALERT you will learn more about Fulyzaq and its unique antisecretory effect for the relief of noninfectious diarrhea in HIV patients on ART.

For more information see the current edition of MPR.

For your reference, please see additional Important Safety Information on the next page and complete Prescribing Information.

Sincerely,

Madonna Krawczyk, PharmD
Director of Clinical Communications
MPR Custom Programs

REFERENCES
INDICATION
FULYZAQ™ (crofelemer) is an anti-diarrheal indicated for the symptomatic relief of non-infectious diarrhea in adult patients with HIV/AIDS on anti-retroviral therapy.

IMPORTANT SAFETY INFORMATION ABOUT FULYZAQ
FULYZAQ delayed-release tablets should not be used for the treatment of infectious diarrhea. Rule out infectious etiologies of diarrhea before starting FULYZAQ. If infectious etiologies are not considered, and FULYZAQ 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.

Based on animal data, FULYZAQ may cause fetal harm. Safety and effectiveness of FULYZAQ have not been established in patients less than 18 years of age.

In clinical studies, the most common adverse reactions (occurring in ≥3% patients and at a rate greater than placebo) were upper respiratory tract infection, bronchitis, cough, flatulence and increased bilirubin.

Salix obtained rights to crofelemer under license from Napo Pharmaceuticals, Inc.

Please see complete Prescribing Information.
**Fulyzaq™**
(crofelemer) 125 mg Delayed-Release Tablets

**Company:** Salix Pharmaceuticals, Inc.
**Pharmacologic Class:** Antidiarrheal.
**Formulations:** 125 mg delayed-release tablets.
**Indication:** Symptomatic relief of noninfectious diarrhea in patients with HIV/AIDS on antiretroviral therapy.
**Adults:** ≥18yrs: One tablet twice a day.
**Children:** <18yrs: Not established.

**Warnings & Precautions:** Rule out infectious etiologies of diarrhea before starting crofelemer.
**Special Populations:** Pregnancy (Cat.C). Nursing mothers: use caution. Based on animal data, may cause fetal harm.
**Adverse Reactions:** Upper respiratory tract infection, bronchitis, cough, flatulence, increased bilirubin.
**How Supplied:** Tablets–60/bottle

Diarrhea is a known side effect of multiple classes of drugs
- Antiretroviral therapies (ARTs), including protease inhibitors (PIs), nucleoside reverse transcriptase inhibitors (NRTIs), and non-nucleoside reverse transcriptase inhibitors (NNRTIs), can cause diarrhea in HIV patients.¹

Diarrhea occurred in up to 27% of patients on common NNRTI- and PI-based regimens over the course of the first year of therapy²,³
- Results were seen in pivotal trials published in 2012²,³

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Please see additional Important Safety Information on last page and complete Prescribing Information.

(continued on next page)
[✓] **Fulyzaq™ (crofelemer)** is indicated for symptomatic relief of noninfectious diarrhea in adult patients with HIV/AIDS on ART

[✓] **Fulyzaq** normalizes the flow of chloride and water in the GI tract

- The unique mechanism of action (MOA) of Fulyzaq results in an antisecretory effect that does not affect gut motility

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**MECHANISM OF ACTION**

- The MOA targets and controls dual chloride channels: cystic fibrosis transmembrane conductance regulator and calcium-activated chloride ion channels

- Chloride channels are key regulators in the intestinal tract that actively transport chloride ions, driving water secretion into the lumen

- Unlike other antidiarrheal medications, Fulyzaq acts by blocking chloride secretion and accompanying high-volume water loss in diarrhea

In clinical studies, the most common adverse reactions (occurring in ≥3% patients and at a rate greater than placebo) were upper respiratory tract infection, bronchitis, cough, flatulence and increased bilirubin.

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*Source: Fulyzaq [prescribing information].*

*CaCC = calcium-activated chloride ion channels; CFTR = cystic fibrosis transmembrane conductance regulator.*

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*Please see additional Important Safety Information on last page and complete Prescribing Information.*
Fulyzaq™ (crofelemer) is the only antidiarrheal studied in an adequate and well-controlled trial for patients with ART-related diarrhea

- Fulyzaq was evaluated in a randomized, double-blind, placebo-controlled (1 month) and 125 mg active treatment extension multicenter study.
- The study enrolled 374 HIV patients on stable ART with a history of diarrhea for ≥1 month. Patients enrolled were only those with 1 or more daily watery bowel movements on at least 5 out of 7 days prior to their entry in the trial.
- The primary efficacy end point 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.

Fulyzaq provides significant improvement in noninfectious ART-related diarrhea

- At enrollment, patients receiving Fulyzaq had a median of 2.5 watery bowel movements per day.

*Clinical response was defined as ≤2 watery bowel movements per week during at least 2 weeks of the 4-week trial period.

Fulyzaq offers convenient, scheduled dosing

- Patients should take one 125 mg, delayed-release tablet orally twice daily.
- No dose modifications are required with respect to CD4 cell count and HIV viral load.

Individual adverse events in ≥2% of patients treated with Fulyzaq in the ADVENT trial were comparable to placebo during the 4-week placebo controlled phase.

Please see additional Important Safety Information on last page and complete Prescribing Information.
Confirmed safety profile over a 6-month period

- Fulyzaq™ (crofelemer) had a safety profile similar to placebo in clinical studies
  - In the ADVENT study, Fulyzaq did not have clinically relevant drug-drug interactions with commonly used ART
  - HIV viral load and CD4 count did not appear to change over the 1-month, placebo-controlled period

- Fulyzaq is minimally absorbed
  - Following oral dosing in healthy adults and HIV-positive patients
  - Concentrations of Fulyzaq in plasma were below the level of quantitation (50 ng/mL)

Fulyzaq demonstrated a low incidence of adverse events compared to placebo

- In clinical trials, the incidence of constipation was low and similar to placebo

INDICATION
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