

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

FULYZAQ™ (crofelemer) delayed-release tablets, for oral use
Initial U.S. Approval: 2012

INDICATIONS AND USAGE
FULYZAQ 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
One 125 mg delayed-release tablet taken orally twice a day, with or without food (2)

DOSAGE FORMS AND STRENGTHS
Delayed-Release Tablets: 125 mg (3)

CONTRAINDICATIONS
None. (4)

WARNINGS AND PRECAUTIONS
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. (5.1)

ADVERSE REACTIONS
Most common adverse reactions (incidence ≥ 3%) are upper respiratory tract infection, bronchitis, cough, flatulence and increased bilirubin. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Salix Pharmaceuticals at 1-866-669-7597 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

USE IN SPECIFIC POPULATIONS
• *Pregnancy*: Based on animal data, may cause fetal harm (8.1)
• *Pediatric Use*: Safety and effectiveness of FULYZAQ has not been established in patients less than 18 years of age (8.4)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 12/2012

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*Sections or subsections omitted from the Full Prescribing Information are not listed.

1 **FULL PRESCRIBING INFORMATION**

2 **1 INDICATIONS AND USAGE**

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

5 **2 DOSAGE AND ADMINISTRATION**

6 The recommended dose of FULYZAQ is one 125 mg delayed-release tablet taken orally two
7 times a day, with or without food. FULYZAQ tablets should **not be crushed or chewed**. Tablets
8 should be swallowed whole.

9 **3 DOSAGE FORMS AND STRENGTHS**

10 FULYZAQ is a white, oval, enteric-coated 125 mg delayed-release tablet printed on one side
11 with 125SLXP.

12 **4 CONTRAINDICATIONS**

13 None.

14 **5 WARNINGS AND PRECAUTIONS**

15 **5.1 Risks of Treatment in Patients with Infectious Diarrhea**

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

21 **6 ADVERSE REACTIONS**

22 **6.1 Clinical Trials Experience**

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

26 A total of 696 HIV-positive patients in three placebo-controlled trials received FULYZAQ for a
27 mean duration of 78 days. Of the total population across the three trials, 229 patients received a
28 dose of 125 mg twice a day for a mean duration of 141 days, 69 patients received a dose of 250
29 mg twice a day for a mean duration of 139 days, 102 patients received a dose of 250 mg four
30 times a day for a mean duration of 14 days, 54 patients received a dose of 500 mg twice a day for

31 a mean duration of 146 days, and 242 patients received a dose of 500 mg four times a day for a
32 mean duration of 14 days.

33 Adverse reactions for FULYZAQ that occurred in at least 2% of patients and at a higher
34 incidence than placebo are provided in Table 1.

35 **Table 1: Adverse Reactions Occurring in at Least 2% of Patients in the 125 mg**
36 **Twice Daily Group**

Adverse Reaction	Crofelemer 125 mg BID*	Placebo
	N = 229 n (%)	N = 274 n (%)
Upper respiratory tract infection	13 (5.7)	4 (1.5)
Bronchitis	9 (3.9)	0
Cough	8 (3.5)	3 (1.1)
Flatulence	7 (3.1)	3 (1.1)
Increased bilirubin	7 (3.1)	3 (1.1)
Nausea	6 (2.6)	4 (1.5)
Back pain	6 (2.6)	4 (1.5)
Arthralgia	6 (2.6)	0
Urinary tract infection	5 (2.2)	2 (0.7)
Nasopharyngitis	5 (2.2)	2 (0.7)
Musculoskeletal pain	5 (2.2)	1 (0.4)
Hemorrhoids	5 (2.2)	0
Giardiasis	5 (2.2)	0
Anxiety	5 (2.2)	1 (0.4)
Increased alanine aminotransferase	5 (2.2)	3 (1.1)
Abdominal distension	5 (2.2)	1 (0.4)

* Twice daily

37 Adverse reactions that occurred in between 1% and 2% of patients taking a 250 mg daily dose of
38 FULYZAQ were abdominal pain, acne, increased aspartate aminotransferase, increased
39 conjugated bilirubin, increased unconjugated blood bilirubin, constipation, depression,
40 dermatitis, dizziness, dry mouth, dyspepsia, gastroenteritis, herpes zoster, nephrolithiasis, pain in
41 extremity, pollakiuria, procedural pain, seasonal allergy, sinusitis and decreased white blood cell
42 count.

43

44 Adverse reactions were similar in patients who received doses greater than 250 mg daily.

45 **7 DRUG INTERACTIONS**

46 **7.1 Drug Interaction Potential**

47

48 *In vitro* studies have shown that crofelemer has the potential to inhibit cytochrome P450
49 isoenzyme 3A and transporters MRP2 and OATP1A2 at concentrations expected in the gut. Due
50 to the minimal absorption of crofelemer, it is unlikely to inhibit cytochrome P450 isoenzymes
51 1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1 and CYP3A4 systemically [see *Clinical Pharmacology*
52 (12.3)].

53 **7.2 Nelfinavir, Zidovudine, and Lamivudine**

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

57 **8 USE IN SPECIFIC POPULATIONS**

58 **8.1 Pregnancy**

59 **Pregnancy Category C**

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

70 **8.3 Nursing Mothers**

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

75 **8.4 Pediatric Use**

76 The safety and effectiveness of FULYZAQ have not been established in pediatric patients less
77 than 18 years of age.

78 **8.5 Geriatric Use**

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

81 **8.6 Use in Patients with Low CD4 Counts and High Viral Loads**

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

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

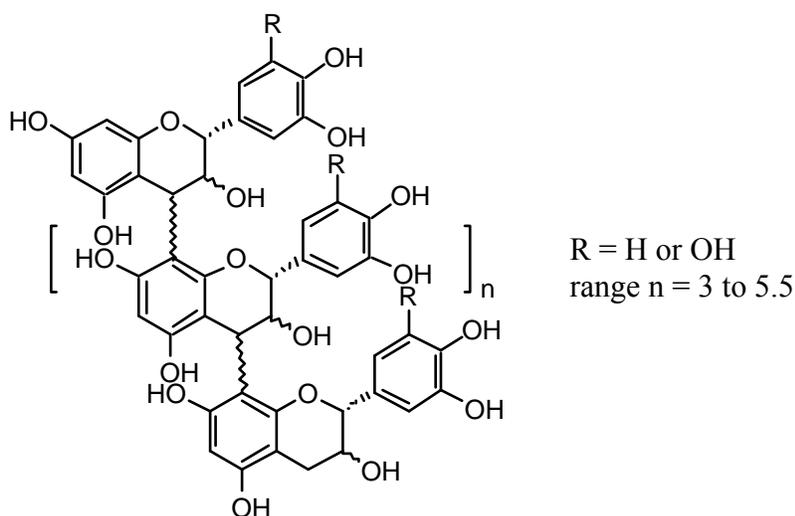
87 The safety profile of crofelemer was similar in patients with baseline HIV viral loads less
88 than 400 copies/mL (N = 412) and patients with baseline HIV viral loads greater than or equal to
89 400 copies/mL (N = 278).

90 **10 OVERDOSAGE**

91 There has been no reported experience with overdosage of crofelemer.

92 **11 DESCRIPTION**

93 FULYZAQ (crofelemer) delayed-release tablets is an anti-diarrheal, enteric-coated drug product
94 for oral administration. It contains 125 mg of crofelemer, a botanical drug substance that is
95 derived from the red latex of *Croton lechleri* Müll. Arg. Crofelemer is an oligomeric
96 proanthocyanidin mixture primarily composed of (+)-catechin, (-)-epicatechin, (+)-gallocatechin,
97 and (-)-epigallocatechin monomer units linked in random sequence, as represented below. The
98 average degree of polymerization for the oligomers ranges between 5 and 7.5, as determined by
99 phloroglucinol degradation.



100

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

103 Coating ingredients: ethylacrylate and methylacrylate copolymer dispersion, talc, triethyl citrate,
104 and white dispersion which contains xanthan gum, titanium dioxide, propyl paraben, and methyl
105 paraben.

106

107 **12 CLINICAL PHARMACOLOGY**

108 **12.1 Mechanism of Action**

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

115 **12.2 Pharmacodynamics**

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

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

124 **12.3 Pharmacokinetics**

125 *Absorption*

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

130 *Distribution*

131 The distribution of crofelemer has not been determined.

132 *Metabolism*

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

134 *Elimination*

135 The elimination route has not been identified in humans.

136 *Food Effect*

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

141 *Drug-Drug Interactions*

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

146 **13 NONCLINICAL TOXICOLOGY**

147 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

148 *Carcinogenesis*

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

151 *Mutagenesis*

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

154 *Impairment of Fertility*

155 Crofelemer, at oral doses of up to 738 mg/kg/day (177 times the recommended human daily dose
156 of 4.2 mg/kg), had no effects on fertility or reproductive performance of male and female rats.

157 **14 CLINICAL STUDIES**

158 The efficacy of FULYZAQ 125 mg delayed-release tablets twice daily was evaluated in a
159 randomized, double-blind, placebo-controlled (one month) and placebo-free (five month), multi-
160 center study. The study enrolled 374 HIV-positive patients on stable anti-retroviral therapy
161 (ART) with a history of diarrhea for one month or more. Diarrhea was defined as either
162 persistently loose stools despite regular use of anti-diarrheal medication (ADM) (e.g.,
163 loperamide, diphenoxylate, and bismuth subsalicylate) or one or more watery bowel movements
164 per day without regular ADM use.

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

171 The study had a two-stage adaptive design. In both stages, patients received placebo for 10 days
172 (screening period) followed by randomization to crofelemer or placebo for 31 days of treatment
173 (double-blind period). Only patients with 1 or more watery bowel movements per day on at least
174 5 of the last 7 days in the screening period were randomized to the double-blind period. Each
175 stage enrolled patients separately; the dose for the second stage was selected based on an interim
176 analysis of data from the first stage. In the first stage, patients were randomized 1:1:1:1 to one of
177 three crofelemer dose regimens (125, 250, or 500 mg twice daily) or placebo. In the second
178 stage, patients were randomized 1:1 to crofelemer 125 mg twice daily or placebo. The efficacy
179 analysis was based on results from the double-blind portion of both stages.

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

186 The median time since diagnosis of HIV was 12 years. The percentage of patients with a CD4
187 cell count of less than 404 was 39%. The percentage of patients with a HIV viral load greater
188 than or equal to 1000, 400 to 999, and less than 400 HIV copies/mL was 7%, 3%, and 9%,
189 respectively; the remainder had a viral load that was not detectable. The median time since
190 diarrhea started was 4 years. The median number of daily watery bowel movements was 2.5 per
191 day.

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

195 In the double-blind period of the study, 136 patients received crofelemer 125 mg twice daily, 54
196 patients received 250 mg twice daily, 47 patients received 500 mg twice daily, and 138 patients
197 received placebo. The percentages of patients that completed the double-blind period were 92%,
198 100%, 85%, and 94% in the 125 mg, 250 mg, 500 mg, and placebo arms, respectively.

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

202 **Table 2: Concomitant ART Use in the Double-Blind Period**

	125 mg BID (N = 136) n (%)	250 mg BID (N = 54) n (%)	500 mg BID (N = 46) n (%)	Placebo BID (N = 138) n (%)
Any ART	135 (99)	53 (98)	45 (98)	134 (97)
Any PI	87 (64)	41 (76)	33 (72)	97 (70)
Tenofovir/Emtricitabine	45 (33)	22 (41)	16 (35)	52 (38)
Ritonavir	46 (34)	18 (33)	15 (33)	49 (36)
Lopinavir/Ritonavir	30 (22)	21 (39)	15 (33)	40 (29)
Efavirenz/Tenofovir/ Emtricitabine	30 (22)	7 (13)	7 (15)	21 (15)
Tenofovir disoproxil fumarate	18 (13)	8 (15)	5 (11)	14 (10)
Antazanavir sulfate	19 (14)	3 (6)	6 (13)	22 (16)
Abacavir w/ lamivudine	17 (13)	5 (9)	5 (11)	18 (13)
Darunavir	19 (14)	4 (7)	4 (9)	14 (10)
Raltegravir	16 (12)	4 (7)	5 (11)	11 (8)
Valaciclovir hydrochloride	12 (9)	8 (15)	5 (11)	16 (12)
Fosamprenavir	12 (9)	6 (11)	4 (9)	13 (9)
Zidovudine w/ lamivudine	12 (9)	3 (6)	3 (7)	15 (11)
Lamivudine	7 (5)	6 (11)	4 (9)	6 (4)
Nevirapine	8 (6)	6 (11)	3 (7)	9 (7)
Atazanavir	5 (4)	6 (11)	2 (4)	2 (1)

203 Abbreviations: ART = antiretroviral therapy; PI = Protease Inhibitor; BID = twice daily.

204 * greater than 10% of Any Treatment Group

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

209 A significantly larger proportion of patients in the crofelemer 125 mg twice daily group
 210 experienced clinical response compared with patients in the placebo group (17.6% vs. 8.0%,
 211 1-sided $p < 0.01$).

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

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

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

225

226 **15 REFERENCES**

227 **16 HOW SUPPLIED/STORAGE AND HANDLING**

228 Crofelemer delayed-release tablets, 125 mg, are white, oval enteric-coated tablets printed on one
229 side with 125SLXP. They are available in the following package size:

230 Bottles of 60: NDC 65649-802-02

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

233 **17 PATIENT COUNSELING INFORMATION**

- 234
- Instruct patients that FULYZAQ tablets may be taken with or without food.
- 235
- Instruct patients that FULYZAQ tablets should not be crushed or chewed. Tablets
236 should be swallowed whole.

237 Manufactured for Salix Pharmaceuticals, Inc., Raleigh, NC 27615 by Patheon, Inc. FULYZAQ
238 is distributed by Salix Pharmaceuticals, Inc. under license from Napo Pharmaceuticals, Inc.

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

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

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/s/

JULIE G BEITZ
12/31/2012