PDL NEW DRUG REVIEW

Proprietary Name: Fulyzaq®
Common Name: crofelemer, delayed-release tablets
PDL Category: GI- Antidiarrheal/Antacid- Misc

Comparable Products	Preferred Drug List Status
Diphenoxylate w/atropine	Preferred
Loperamide	Preferred

Summary

Indications and Usage: Symptomatic relief of non-infectious diarrhea in patients with HIV/AIDS on anti-retroviral therapy. This is a pregnancy category C medication. The safety and efficacy of use in children under the age of 18 have not been established.

Drug Interactions: Clinically relevant drug interactions were not seen when Fulyzaq® was used with nelfinavir, zidovudine, or lamivudine. *In vitro* studies found that crofelemer has the potential to inhibit CYP3A4.

Dosage Forms: Delayed-release tablets: 125mg. Not to be crushed or chewed, only swallowed whole.

Recommended Dosage: To be taken as one tablet twice daily, with or without food. There was no information found regarding use in those with renal or hepatic impairment, and if dosage reductions are required. In addition, dose modifications are not needed with respect to CD4 cell count and HIV viral load.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions = reported % incidence for drug minus reported % incidence for placebo.* The most common adverse events reported with Fulyzaq® include upper respiratory tract infection (4.2%), bronchitis (3.9%), cough (2.4%), flatulence (2%), increased bilirubin (2%), nausea (1.1%), back pain (1.1%), arthralgia (2.6%), urinary tract infection (1.5%), nasopharyngitis (1.5%), musculoskeletal pain (1.8%), hemorrhoids (2.2%), giardiasis (2.2%), anxiety (1.8%), increased alanine aminotransferase (1.1%), and abdominal distension (1.8%).

Contraindications: There are currently no contraindications listed in the prescribing information.

Manufacturer: Salix Pharmaceuticals, Inc.

Analysis: Crofelemer, the active ingredient of Fulyzaq®, is a botanical drug substance derived from the red latex of *Croton lechleri* Mull. Arg, a species of the flowering plant in the spurge family. It acts as an inhibitor of the cyclic adenosine monophosphate (cAMP)-stimulated cystic fibrosis transmembrane conductance regulator (CFTR) chloride ion (Cl^-) channel, as well as the calcium-activated Cl^- channels (CaCC) at the luminal membrane of enterocytes. These channels regulate Cl^- and fluid secretion by intestinal epithelial cells. As an inhibitor of both of these channels, crofelemer normalizes the flow of Cl^- and water in the GI tract.

Crofelemer is an anti-diarrheal agent for use in those with HIV/AIDs on anti-retroviral agents. It is not FDA approved for the treatment of infectious diarrhea. It is therefore recommended that prior to initiating therapy

with Fulyzaq®, infectious etiologies of diarrhea are ruled out. If Fulyzaq® treatment is started without infectious diarrhea being ruled out, there is a risk of not receiving appropriate treatment and a worsening of the condition.

A one-month placebo-controlled, randomized, double-blind study and a 5-month placebo-free period were performed to assess the safety and efficacy of crofelemer use in HIV-positive patients (N=374) on stable anti-retroviral therapy who had a one month or more history of diarrhea. Patients were randomized 1:1 to crofelemer 125mg BID or placebo. Furthermore, there was a five month placebo-free period that followed the double-blind phase. The primary endpoint was the proportion with a clinical response, defined as ≤2 watery bowel movements per week during at least 2 of the 4 weeks of the placebo-controlled phase. Those who took concomitant anti-diarrheal medications or opiates were considered non-responders.

Results suggest that significantly more in the crofelemer 125mg group had a clinical response as compared to the placebo group (17.6% vs 8%; p<0.01). [IME Comment: This calculates to an NNT of 11.] Furthermore, of the 24 clinical responders to crofelemer 125mg, 22 went into the placebo-free period. Results suggested that there were 16 responders at the end of month 3 and 14 responders at the end of month 5.

As this is a first in a new class of anti-diarrhea agents, there were no comparator clinical trials. It is recommended that Fulyzaq® remain non-preferred and require prior trials of preferred, more cost-effective anti-diarrheal agents.

PDL Placement:

- ☐ **Preferred**
- ☒ **Non-Preferred**
- ☐ **Preferred with Conditions**

References

[1] Fulyzaq® [package insert]. Raleigh, NCL Salix Pharmaceuticals, Inc; 2013.