

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202292Orig1s000

OFFICE DIRECTOR MEMO

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: December 31, 2012

FROM: Julie Beitz, MD

SUBJECT: Approval Action

TO: NDA 202292 Fulyzaq (crofelemer) delayed-release tablets
Salix Pharmaceuticals, Inc.

Summary

Fulyzaq (crofelemer) delayed-release tablets are enteric-coated tablets containing an oligomeric proanthocyanidin mixture, a botanical drug substance that is derived from the red latex of *Croton lechleri*. This plant species is widely distributed throughout Western Amazonian South America and the red latex from this plant is known for its medicinal properties, including relief of diarrhea.

Crofelemer has been found to decrease chloride ion secretion at the luminal membrane of enterocytes, targeting two structurally unrelated apical membrane chloride channels: the cystic fibrosis transmembrane conductance regulator (CFTR), a cAMP-stimulated chloride channel; and calcium-activated chloride channels (CaCCs).^{1,2} Crofelemer is thought to act by blocking chloride ion secretion and accompanying high volume water loss, thereby normalizing the flow of chloride and water in the gastrointestinal tract. In clinical trials, crofelemer has been evaluated as an anti-diarrheal agent for the symptomatic relief of infectious (traveler's) diarrhea and of non-infectious diarrhea in patients with HIV/AIDS on anti-retroviral therapy.

Diarrhea is experienced by over half of HIV-infected patients at some time during the course of their illness. It can have a substantial negative impact on quality of life and is a common reason for discontinuing or switching highly active anti-retroviral therapy (HAART) regimens.³ In 15-46% of HIV-infected patients with diarrhea, no pathogen can be identified.⁴

Etiologies of noninfectious diarrhea include effects of HIV on the gastrointestinal tract (HIV enteropathy), adverse effects of HAART, particularly with use of protease inhibitors such as ritonavir, and chronic pancreatitis and exocrine insufficiency. HAART-associated diarrhea may be caused by a variety of mechanisms, including increased calcium-dependent chloride conductance and cellular apoptosis, necrosis and decreased proliferation of intestinal epithelial cells.⁵

There are no currently FDA-approved therapies for HIV-associated diarrhea. Modification of HAART regimens may be attempted. Dietary assessment should be performed, and modification of dietary fiber and use of nutritional supplements should be considered. Treatment is primarily supportive; non-narcotic,

¹ Gabriel SE, Davenport SE, Steagall RJ, Vimal V, Carlson T, and Rozhon EJ. A novel plant-derived inhibitor of cAMP-mediated fluid and chloride secretion. *Am J Physiology* 1999; 276:G58-G63.

² Tradtrantip L, Namkung W, and Verkman AS. Crofelemer, an antisecretory antidiarrheal proanthocyanidin oligomer extracted from *Croton lechleri*, targets two distinct intestinal chloride channels. *Mol Pharmacol* 2010; 77:69-78.

³ MacArthur RD and Dupont HL. Etiology and pharmacologic management of noninfectious diarrhea in HIV-infected individuals in the highly active antiretroviral era. *Clin Inf Dis* 2012; 55:860-7.

⁴ Kartalija M, and Merle AS. Diarrhea and AIDS in the era of highly active antiretroviral therapy. *Clin Inf Dis* 1999; 28:701-7.

⁵ MacArthur and Dupont, 2012.

narcotic or anti-secretory medications may be used. There are no clinical data to support the use of anti-motility agents in this condition.⁶

This memo documents my concurrence with the Division of Gastroenterology and Inborn Errors Product's (DGIEP's) recommendation for approval of NDA 202292 for Fulyzaq (crofelemer) delayed-release tablets for the symptomatic relief of non-infectious diarrhea in adult patients with HIV/AIDS on anti-retroviral therapy. The applicant has provided:

- adequate evidence for raw material quality controls, and good agricultural and collection practices;
- adequate analytic tests for the identity of the crofelemer drug substance and drug product;
- a validated, clinically relevant bioassay to determine the relative inhibitory potency of post-approval crofelemer drug substance and drug product batches;
- acceptable relative potency specifications for the crofelemer drug substance and drug product;
- data suggesting that therapeutic efficacy will not be seriously impacted by batch-to-batch variations;
- information about the historical use of crofelemer formulations for diarrhea.

Discussions regarding the product labeling, and postmarketing study requirements and commitments have been satisfactorily completed. There are no inspectional issues that preclude approval.

Dosing

The recommended dose of Fulyzaq (crofelemer) delayed-release tablets is 125 mg taken orally twice a day, with or without food. This dose regimen is estimated to result in a small bowel luminal drug concentration of 240 μ M, which is several fold-higher than the IC₅₀ for CFTR-mediated inhibition of chloride secretion. Tablets should be swallowed whole and not crushed or chewed.

Regulatory History

[REDACTED] (b) (4)

On November 1, 1996, Shaman submitted IND 051818 to the Division of Gastrointestinal and Coagulation Drug Products (DGCDP, now known as DGIEP) [REDACTED] (b) (4)

[REDACTED] (b) (4)

On April 23, 2002, Shaman also transferred IND 051818 to PS Pharmaceuticals, Inc. which later changed its name to Napo Pharmaceuticals, Inc. and the product name to crofelemer. At an End-of-Phase 2 meeting held with Napo representatives on May 5, 2004, DGCDP agreed to transfer the previously granted Fast Track designation to IND 051818.

On October 20, 2006, Napo submitted the ADVENT trial protocol for consideration under a Special Protocol Assessment. Although a No Agreement letter was issued on December 4, 2006, protocol discussions continued through 2007 regarding the proposed adaptive trial design, the primary endpoint definition, and statistical methodologies. On December 9, 2009, IND 051818 was transferred to Salix Pharmaceuticals, Inc.

⁶ *Ibid.*

A pre-NDA meeting was held on January 19, 2011, during which FDA stated that adequate documentation would need to be provided in the NDA regarding raw material quality controls, and the applicant's ability to reproducibly manufacture a commercial product that is comparable to the product tested in clinical trials. In particular, Salix would need to provide assurance of its ability to reproduce the catechin/gallocatechin monomer ratio from batch to batch, and demonstrate the comparability of this ratio in clinical trial batches and commercial batches.

A second pre-NDA meeting to discuss issues related to the chemistry, manufacturing, and controls (CMC) of crofelemer was held on May 24, 2011. Salix indicated that it was not feasible to determine the monomer ratio in the crofelemer drug substance due to "the natural variation in monomer unit sequences, unit bonding, and chain length." Staff from the Office of New Drug Quality Assessment (ONDQA) emphasized that the ratio of catechin to gallocatechin monomers will need to be determined as an identity test for the drug substance. Determination of the stereochemistry of the two monomers will not be required. Salix was advised to evaluate the effect of varying the monomer ratio on clinical efficacy; this could be accomplished as part of the ongoing open-label safety trial, if appropriately amended to add assessments of efficacy. Alternatively, there may be sufficient data with previous clinical trial material to assess the impact of the monomer ratio on efficacy. Upon review of the available information, assuming there is no correlation of efficacy to the monomer ratio, FDA would consider whether the requirement for a monomer ratio identity test could be waived.

In addition, Salix was advised to establish raw material quality controls with appropriate specifications to ensure that the latex is collected from only legitimate sources (and not from plant species grown in the same area that may be confused with *Croton lechleri*).

On December 5, 2011, Salix submitted NDA 202292. The application was granted a priority review. A major amendment received on April 6, 2012 extended the review clock by 90 days. A Center-level briefing was held on August 6, 2012, to discuss potential paths to approval given that the identity of the crofelemer drug substance and drug product has not been fully characterized. The regulatory action on this application was delayed past the PDUFA goal date (September 5, 2012) to allow time for 1) implementation by the applicant of validated, clinically relevant bioassay(s) to be used for the determination of the relative potency of crofelemer drug substance and drug product post-approval batches, and 2) inspection by FDA of the facility performing the bioassay(s) in accordance with cGMPs.

This application was not referred to an advisory committee because the application did not raise significant public health questions on the role of the drug in the diagnosis, cure, mitigation, treatment or prevention of disease, and outside expertise was not necessary.

Product Quality Considerations

Crofelemer is a complex oligomeric/polymeric drug substance composed of catechin, gallocatechin and their epimers. Molecules vary in monomer composition, linkage and chain length. Crofelemer is prepared by extraction and purification (b) (4) from the red latex sap of the plant *Croton lechleri*. The applicant proposed to use only sap harvested from trees in a specific geographical region in (b) (4) and identify the drug substance utilizing IR (b) (4) (b) (4) and HPLC.

Acid hydrolysis degradation of the oligomeric/polymeric material into its constituent monomers allows calculation of: 1) the monomer ratio of (epi)catechin to (epi)gallocatechin; 2) average molecular weight; and 3) conversion yield. When subjected to (b) (4) the conversion yield for the crofelemer drug substance ranged between (b) (4) (o) (4) The composition of the remaining (b) (4) material has not been identified.

Forced degradation studies showed a significant increase in the crofelemer peak area when the drug substance was subjected to strong oxidizing conditions or elevated temperatures, causing the crofelemer

peak to increase by as much as (b) (4). This increase in crofelemer peak area was evident in both HPLC methods (for assay and related substances), suggesting that neither method is stability indicating.

Initial ONDQA Assessment. In a review dated July 13, 2012, the ONDQA primary reviewer recommended a complete response action for NDA 202292 in accordance with CFR 314.125(b)(1). This recommendation was based on concerns that 1) the IR (b) (4) tests were not specific, and 2) the HPLC methods were not suitable as tests for identity without further development. Thus, the applicant's proposed tests for identity failed to meet the minimal recommendations cited in existing regulations and summarized in the 2004 *Guidance for Industry: Botanical Drug Products* (hereafter referred to as the Botanical Guidance).

For the drug substance, the applicant had not:

- Provided either chemical identification for the active constituents or characteristic markers in the drug substance, or a representative spectroscopic and/or chromatographic fingerprint;
- Established a biological assay for characterization and quality control of the drug substance, given that the active chemical constituents are not known or quantifiable.

For the drug product, the applicant had not provided:

- Chemical identification for the active constituents or characteristic markers;
- Stability-indicating analytical methods capable of monitoring the stability of the drug product and detecting degradants formed during storage.

Botanical Review Team Assessment. Crofelemer is a highly complex mixture of oligomers. In the BRT's view, the applicant's characterization of crofelemer represents the state of the art and that further characterization (e.g., further separation of HPLC peaks) is limited by currently available analytical techniques. The Botanical Guidance acknowledges that conventional CMC measures may not be adequate to ensure the intended therapeutic effect of a botanical drug product and recommends that "pre-CMC" and "post-CMC" measures be considered.

Pre-CMC steps would include raw material quality controls, and good agricultural and collection practices (GACPs). In BRT's view, the crofelemer plant can be easily recognized by trained workers, the plant latex is less variable than other plant parts, harvesting will be limited to wild growth in (b) (4) eco-geographic regions, and the applicant will develop measures to ensure forest renewal.

Post-CMC measures could include use of clinically relevant bioassay(s), if available, to ensure quality control of post-approval batches. Other measures could include consideration of 1) the sensitivity of clinical response to dose (i.e., a flat dose response would suggest that batch variations may be tolerable), and 2) the clinical effects of various manufactured batches used in Phase 3 trials (i.e., a negative "treatment-by-batch" interaction would suggest that therapeutic effects will not be seriously affected by batch-to-batch variations). In addition, historical information regarding clinical effects of the botanical drug product with indigenous use may be supportive.

In the case of crofelemer, inhibition of intestinal chloride channels is fully saturated at crofelemer doses used in the applicant's clinical trial (i.e., 125-500 mg twice daily). Three dose regimens and multiple crofelemer batches were used in the trial; clinical efficacy was generally similar irrespective of dose regimen or batch used. In addition, various formulations derived from the latex of *Croton lechleri* available ex-US have been used for diarrhea and have been reported to be effective and well-tolerated.

The applicant's original application did not include implementation of validated, clinically relevant bioassay(s) that could be used to ensure quality control of post-approval batches. Nevertheless, the BRT concluded that the applicant's raw material controls were sufficient, and that crofelemer's clinical effects at the recommended 125 mg dose taken twice daily are not sensitive to variations in oligomer composition. Thus, the BRT concluded that there is adequate assurance of therapeutic effect of post-approval batches and recommended NDA approval. The BRT further recommended that a clinically relevant bioassay, if

available, could be used to qualify future manufacturing changes and new eco-geographical regions. Alternatively, new cultivated sources of latex may be qualified by clinical trials for the same or other related diarrheal conditions.

Center-Level Briefing. On August 6, 2012, a Center-level briefing was held to present the available CMC and clinical information and discuss the likelihood that future post-approval batches will provide assurance of the intended therapeutic effect, given that crofelemer provides for the symptomatic relief of HIV-associated diarrhea, a condition with no approved therapies. A potential path forward was discussed, namely, implementation of validated, clinically relevant bioassay(s), such as those measuring crofelemer's (b) (4), for release and stability testing of post-approval batches.

Post-Briefing Activities – Bioassay Development. On August 6, 2012, following the briefing, the applicant was contacted regarding the feasibility of developing, validating and implementing clinically relevant bioassay(s) to assess the potency of post-approval batches of crofelemer. At a teleconference held on August 8, 2012, Salix informed the Agency that it had engaged (b) (4) to develop validated (b) (4) assays and that (b) (4) would test the potency of each new batch of crofelemer drug substance and drug product. As the (b) (4) facility typically performs such assays under GLP specifications, FDA further requested that (b) (4) develop and validate the assays under cGMP conditions and inform FDA when the facility would be ready for inspection.

On November 6, 2012, draft analytical method validation protocols were submitted for bioassays that would measure crofelemer (b) (4)

On December 4, 2012, Salix informed FDA in a teleconference that results for (b) (4) Salix submitted results from method validation studies for the (b) (4) assay in draft and final reports dated December 10 and 14, 2012, respectively. Staff from the Office of Biotechnology Products, Division of Therapeutic Proteins (OBP/DTP) reviewed the results and concluded that the studies demonstrated acceptable method specificity, linearity, accuracy, precision (intra-assay and inter-assay), and elements of robustness. A forced-degradation study was also performed and demonstrated the method to be stability-indicating.

Salix initially proposed acceptance criteria for the crofelemer drug substance and drug product of (b) (4) relative potency as assessed by the CFTR inhibition assay. The estimated small intestine luminal concentration of crofelemer following administration of a 125 mg tablet is approximately 240 µM, or approximately 24 times the IC₅₀ observed for the tablet in assay validation studies. Concentrations of 120 µM and 240 µM result in maximum blockade of CFTR function; therefore, a reduction in relative potency of up to (b) (4) would not be expected to affect therapeutic efficacy. At a teleconference with Salix on December 14, 2012, staff from OBP/DTP accepted a specification of (b) (4) on a provisional basis, and the inspection of the (b) (4) facility was scheduled. The relative potency specification was further revised to (b) (4) using data from pooled method precision and intermediate precision validation assays. The specification was based on the observed mean relative potency of (b) (4)

The inspection of the (b) (4) facility was conducted on (b) (4) The inspector raised a concern about (b) (4)

(b) (4) The Office of Compliance deemed the facility acceptable on December 31, 2012.

Final ONDQA Assessment. During the months of June - August, 2012, Salix amended its original application with additional CMC information, including 1) updates to the drug substance specifications with limits that define the oligomer distribution, 2) comparable IR spectra from different lots of crofelemer

7 (b) (4)

drug substance and drug product when compared to a reference standard, and 3) information regarding monomer ratios, mean degree of polymerization, and conversion yield after hydrolysis. This information was deemed sufficient to establish the identity of the crofelemer drug substance and drug product, if a validated, clinically relevant bioassay were implemented as part of the crofelemer drug substance and drug product release specifications. With the successful implementation of a validated (b) (4) assay at the (b) (4) facility, the ONDQA primary reviewer completed a second review and Dr. Terrance Ocheltree completed a tertiary review on December 31, 2012, both recommending approval of the application.

Postmarketing Commitments. The applicant has agreed to 1) identify the source and identity of potential (b) (4) impurities, 2) characterize (b) (4) crofelemer (b) (4), and 3) revise the current HPLC methods for assay and related substances for the drug substance and drug product or develop new methods; the revised or new methods must be stability-indicating and appropriately validated. In addition, the applicant has agreed to 1) re-evaluate, and revise as needed, the relative potency specification for the (b) (4) assay after one year of product lots of crofelemer have been manufactured (anticipated to be (b) (4) lots), and 2) validate and implement the (b) (4) assay.

Clinical Pharmacology

Absorption of crofelemer is minimal following oral dosing in healthy adult subjects and HIV-positive patients; concentrations of crofelemer in plasma are below the level of quantitation (50 ng/mL). Therefore, standard pharmacokinetic parameters cannot be estimated.

Consistent with its purported mechanism of action, stool chloride concentrations decreased in patients treated with crofelemer 500 mg four times a day (n=26) for four days relative to placebo (n=24). Stool chloride concentrations decreased in all race subgroups treated with Fulyzaq.

In vitro studies have shown that crofelemer has the potential to inhibit CYP 3A4 and transporters MRP2 and OATP1A2 at concentrations expected in the gut. Due to the minimal absorption of crofelemer however, it is unlikely to inhibit cytochrome P450 isoenzymes systemically.

In a crossover study in 28 healthy adult subjects, crofelemer 500 mg was administered orally four times daily for 5 days, and nelfinavir, zidovudine, and lamivudine were administered as a single dose together on Day 5. Crofelemer had no effect on the exposure of zidovudine and nelfinavir in this study; a 20% decrease in lamivudine exposure was observed but was not considered to be clinically important. Nelfinavir is not a preferred probe for drug interaction studies as it is both a CYP 3A4 inhibitor and a substrate of CYP 3A4.

In a randomized, blinded, four-period crossover thorough QT study involving 48 healthy adult subjects, there was no QT prolonging effect observed for either the therapeutic (125 mg) or the supratherapeutic dose (1250 mg) of crofelemer.

Postmarketing Commitments. The majority of anti-retroviral drugs used in HIV are either metabolized by CYP isoenzymes or eliminated unchanged by the kidney. Because crofelemer is not significantly absorbed into the systemic circulation, it is not expected to either alter the systemic concentrations of these drugs due to alteration of enzyme/transporter activity or compete for transporters in the renal proximal tubule. Nevertheless, the applicant has agreed to conduct the following studies to further explore the potential for drug-drug interactions as post-approval commitments: 1) an *in vitro* study of the effects of crofelemer on P-glycoprotein and BCRP transporters, and 2) an *in vivo* study in human subjects of the effects of crofelemer on CYP 3A4 using a probe that is a pure substrate of CYP 3A4 (such as midazolam or an anti-retroviral drug other than nelfinavir).

Efficacy

The efficacy of crofelemer in patients with HIV-associated diarrhea was evaluated in a double-blind, placebo-controlled trial (the ADVENT trial) in 374 patients, aged 21-68 years (median 45 years), on stable anti-retroviral therapy, and with a history of diarrhea for one month or more.⁸ Patients with infectious or other causes of diarrhea (such as inflammatory bowel disease, celiac sprue, chronic pancreatitis) were excluded. Most patients were male (85%); 46% were Caucasian and 32% were African American. The median time since HIV diagnosis among enrollees was 12 years, the median time since diarrhea started was 4 years, and the median number of watery bowel movements was 2.5 *per day*.

The trial had a two-stage adaptive design. The purpose of the first stage was to select an optimal dose for the treatment of HIV-associated diarrhea; this dose would be the only dose assessed in the second stage. Patients participated in either the first or second stage, but not both. The statistical analysis plan called for combining the results from both stages.

In both stages, patients received placebo for 10 days (screening period) followed by randomization to either crofelemer or placebo for 31 days (double-blind period). Only patients with one or more watery bowel movements per day on at least 5 of the last 7 days of the screening period were randomized to the double-blind treatment. In the first stage, patients were randomized 1:1:1 to receive either crofelemer 125, 250 or 500 mg twice daily or placebo. In the second stage, patients were randomized 1:1 to receive either crofelemer 125 mg twice daily or placebo; the 125 mg dose was selected based on an interim analysis of efficacy from patients treated in the first stage.

In each stage, the double-blind period was followed by a 20 week placebo-free period. Patients treated with crofelemer continued on the same dose in the placebo-free period. In the first stage, patients treated with placebo were re-randomized 1:1:1 to receive crofelemer 125, 250 or 500 mg twice daily. In the second stage, patients that received placebo were switched to crofelemer 125 mg twice daily.

Clinical response was defined as the proportion of patients with 2 or less watery bowel movements *per week* during at least 2 of the 4 weeks of the double-blind period. Patients who received concomitant anti-diarrheal medications or opiates were considered non-responders.

The results of the two double-blind periods (i.e., from each stage) were combined for the primary efficacy analysis. A total of 136 patients received crofelemer 125 mg twice daily and 138 patients received placebo. Completion rates among patients enrolled in these groups was high (92% for the crofelemer 125 mg twice daily group and 94% for patients on placebo). Most patients received concomitant protease inhibitors during the double-blind period. A significantly larger proportion of patients treated with crofelemer 125 mg twice daily experienced a clinical response as compared to patients in the placebo group (17.6% vs. 8.0%, $p < 0.01$). Although the magnitude of the treatment effects appears to be modest, the choice of efficacy endpoint was deemed “an extremely stringent criterion for demonstrating efficacy” by members of the trial’s Interim Analysis Committee.⁹

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 treatment effect of crofelemer 125 mg twice daily among these subgroups. There were too few female patients and patients with 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.

⁸ Diarrhea was defined as either persistently loose stools despite regular use of anti-diarrheal medication (ADM) (e.g., loperamide, diphenoxylate, and bismuth subsalicylate) or one or more watery bowel movements per day without regular ADM use.

⁹ See minutes of the Interim Analysis Committee meeting dated August 3, 2009.

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

Safety

A total of 696 HIV-positive patients received crofelemer in three placebo-controlled trials for a mean of 78 days; 229 patients received the recommended dose of 125 mg twice daily for a mean of 141 days. Doses of 500 mg four times a day for a mean duration of 14 days have been administered to 242 patients. Crofelemer was generally well tolerated. The most common adverse events reported in at least 2% of patients treated with the 125 mg twice daily regimen were: upper respiratory tract infection (5.7%), bronchitis (3.9%), cough (3.5%), flatulence and increased bilirubin (3.1% each).

The **Warnings and Precautions** section of the product label will emphasize the importance of ruling out infectious causes of diarrhea before starting treatment with crofelemer.

Long-term, non-clinical carcinogenicity studies have not been performed. In accordance with agreements reached at the January 19, 2011, pre-NDA meeting, the applicant will conduct carcinogenicity studies in two rodent species post-approval.

Tradename Review

The applicant's proposed tradename "Fulyzaq" is acceptable from both a promotional and safety perspective. The applicant was informed of this determination on September 12, 2012.

Pediatric Considerations

Pediatric Use. The **Use in Specific Populations** section, **Pediatric Use** subsection, of the product label will state that the safety and effectiveness of Fulyzaq have not been established in patients less than 18 years of age.

Required Pediatric Studies. Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

FDA will waive the pediatric study requirement for ages birth to 30 days because necessary studies are impossible or highly impracticable as very few patients below 30 days of age are treated with anti-retroviral therapy.

The pediatric study requirement will be deferred for patients greater than 1 month through 17 years since the product is ready for approval in adults. The deferred study will be designed to evaluate the pharmacokinetics, efficacy and safety of Fulyzaq (crofelemer) over a four week period in HIV+ pediatric patients ages 1 month to 17 years on anti-retroviral therapy.

Postmarketing Requirements under 505(o)

The applicant will be required to conduct the following postmarketing studies to identify an unexpected serious risk of cancer in patients taking Fulyzaq (crofelemer) delayed-release tablets:

1. A six-month carcinogenicity study with orally administered crofelemer in mice.
2. A two-year carcinogenicity study with orally administered crofelemer in rats.

Protocols for both studies will be submitted for Special Protocol Assessment prior to study initiation.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JULIE G BEITZ
12/31/2012