

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Approval Package for:**

***APPLICATION NUMBER:***

**202292Orig1s000**

***Trade Name:*** Fulyzaq delayed-release tablets

***Generic Name:*** crofelemer

***Sponsor:*** Salix Pharmaceuticals, Inc

***Approval Date:*** December 31, 2012

***Indications:*** For the use of Fulyzaq (crofelemer) delayed-release tablets for the symptomatic relief of non-infectious diarrhea in adult patients with HIV/AIDS on antiretroviral therapy.

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*APPLICATION NUMBER:*

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**APPROVAL LETTER**



NDA 202292

**NDA APPROVAL**

Salix Pharmaceuticals, Inc  
Attention: Jennifer Richards  
Sr. Manager, Regulatory Affairs  
8510 Colonnade Center Drive  
Raleigh, NC 27615

Dear Ms. Richards:

Please refer to your New Drug Application (NDA) dated December 05, 2011, received December 05, 2011, submitted under section 505(b)/pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Fulyzaq (crofelemer) delayed-release tablets.

We acknowledge receipt of your amendments dated December 22, 2011, January 05, 2012, February 14, 2012, February 24, 2012, February 29, 2012, March 15, 2012, March 19, 2012, April 02, 2012, April 06, 2012, April 06, 2012, April 30, 2012, May 01, 2012, June 01, 2012, June 27, 2012, June 29, 2012, July 02, 2012, July 11, 2012, July 13, 2012, July 16, 2012, July 27, 2012, July 31, 2012, August 01, 2012, August 10, 2012, August 15, 2012, August 22, 2012, August 24, 2012, August 24, 2012, August 27, 2012, August 27, 2012, August 28, 2012, August 30, 2012, September 05, 2012, September 13, 2012, September 13, 2012, October 15, 2012, November 13, 2012, November 28, 2012, and December 07, 2012, December 12, 2012, December 14, 2012, December 19, 2012, and December 20, 2012.

This new drug application provides for the use of Fulyzaq (crofelemer) delayed-release tablets for the symptomatic relief of non-infectious diarrhea in adult patients with HIV/AIDS on anti-retroviral therapy.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

**CONTENT OF LABELING**

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert). Information

on submitting SPL files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

### **CARTON AND IMMEDIATE CONTAINER LABELS**

We acknowledge your December 12, 2012, submission containing final printed carton and container labels.

### **MARKET PACKAGE**

Please submit one market package of the drug product when it is available to the following address:

Kevin Bugin  
Food and Drug Administration  
Center for Drug Evaluation and Research  
White Oak Building 22, Room: 5143  
10903 New Hampshire Avenue  
Silver Spring, Maryland  
*Use zip code **20903** if shipping via United States Postal Service (USPS).*  
*Use zip code **20993** if sending via any carrier other than USPS (e.g., UPS, DHL, FedEx).*

### **ADVISORY COMMITTEE**

Your application for Fulyzaq (crofelemer) delayed-release tablets was not referred to an FDA 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.

### **REQUIRED PEDIATRIC ASSESSMENTS**

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.

We are waiving the pediatric study requirement for ages 0 to 30 days of age because necessary studies are impossible or highly impracticable as very few patients below 30 days of age are treated with anti-retroviral therapy.

We are deferring submission of your pediatric study for ages 1 month to 17 years of age for this application because this product is ready for approval for use in adults and the pediatric study has not been completed.

Your deferred pediatric study required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act (FDCA) is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. This required study is listed below.

1975-1      A pediatric study to evaluate pharmacokinetics (PK), efficacy for symptomatic relief of non-infectious diarrhea, and safety with different doses of Fulyzaq (crofelemer) over a four week period in HIV-positive pediatric patients, ages 1 month to 17 years of age, on anti-retroviral therapy.

Final Protocol Submission:    06/2013

Study Completion:            06/2017

Final Report Submission:     12/2017

Submit the protocol to your IND 051818 with a cross-reference letter to this NDA.

Reports of this required pediatric postmarketing study must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from this study. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

### **POSTMARKETING REQUIREMENTS UNDER 505(o)**

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of cancer in patients taking Fulyzaq (crofelemer) delayed-release tablets.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

- 1975-2 A six-month rodent carcinogenicity study of orally administered crofelemer in the mouse. The carcinogenicity protocol will be submitted for Special Protocol Assessment (SPA) prior to initiating the study.

The timetable you submitted on December 07, 2012, states that you will conduct this study according to the following schedule:

SPA Submission:	10/2013
Final Protocol Submission:	01/2014
Study Completion:	12/2014
Final Report Submission:	06/2015

- 1975-3 A two-year rodent carcinogenicity study of orally administered crofelemer in the rat. The carcinogenicity protocol will be submitted for Special Protocol Assessment (SPA) prior to initiating the study.

The timetable you submitted on December 07, 2012, states that you will conduct this study according to the following schedule:

SPA Submission:	12/2013
Final Protocol Submission:	04/2014
Study Completion:	10/2016
Final Report Submission:	06/2017

Submit the protocols to your IND 051818 with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **“Required Postmarketing Protocol Under 505(o)”**, **“Required Postmarketing Final Report Under 505(o)”**, **“Required Postmarketing Correspondence Under 505(o)”**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

**POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS  
UNDER SECTION 506B**

We remind you of your postmarketing commitments:

- 1975-4 An *in vitro* study to determine whether crofelemer is an inhibitor of the transporters P-glycoprotein and BCRP.

The timetable you submitted on November 28, 2012, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 03/2013  
Study Completion: 09/2013  
Final Report Submission: 03/2014

- 1975-5 An *in vivo* study in human subjects to evaluate whether crofelemer inhibits CYP 3A4 using a probe that is a pure substrate of CYP 3A4.

The timetable you submitted on November 28, 2012, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 06/2013  
Study Completion: 12/2013  
Final Report Submission: 06/2014

**POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING  
REQUIREMENTS UNDER SECTION 506B**

We remind you of your postmarketing commitments in your submission dated December 19, 2012. These commitments are listed below.

- 1975-6 Perform an elemental analysis to identify the source and identity of potential (b) (4) [REDACTED] impurities in crofelemer.

Final Report Submission: 12/2013

- 1975-7 Characterize the (b) (4) crofelemer (b) (4) [REDACTED]

Final Report Submission: 12/2013

1975-8 Revise the current HPLC methods for assay and related substances for the crofelemer drug substance and drug product or develop new methods. The revised or new methods must be stability indicating and appropriately validated.

Final Report Submission: 12/2013

We also remind you of your postmarketing commitments in your submission dated December 20, 2012. These commitments are listed below.

1975-9 Re-evaluate the specification, and revise as needed, for the crofelemer cell-based assay that use (b) (4) after one year of product lots of crofelemer (anticipated to be (b) (4) lots) have been manufactured.

Final Report Submission: 2/2014

1975-10 Validate and implement the cell-based potency assay that uses (b) (4)

Final Report Submission: 1/2014

Submit clinical protocols to your IND 051818 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled “**Postmarketing Commitment Protocol**,” “**Postmarketing Commitment Final Report**,” or “**Postmarketing Commitment Correspondence**.”

### **PROMOTIONAL MATERIALS**

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

### **REPORTING REQUIREMENTS**

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

### **MEDWATCH-TO-MANUFACTURER PROGRAM**

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at <http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm>.

### **POST-ACTION FEEDBACK MEETING**

New molecular entities and new biologics qualify for a post-action feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call Kevin Bugin, Regulatory Project Manager, at (301) 796-2302.

Sincerely,

*{See appended electronic signature page}*

Julie Beitz, M.D.  
Director  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

ENCLOSURE(S):  
Content of Labeling

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JULIE G BEITZ  
12/31/2012