Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Crofelemer

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

Active Ingredient: Crofelemer

Dosage Form; Route: Tablet, delayed release; oral

Strength: 125 mg

Recommendations for the Assessment of Identity and Quality of Botanical Raw Material (BRM):

Crofelemer is a botanical drug derived from BRM, the crude red latex of *Croton lechleri* Müll. Arg. [Fam. Euphorbiacae], which is also called dragon's blood (sangre de drago). Generic drug applicants should use the same plant species and perform BRM assessment:

1. Crofelemer BRM should be collected from the crude red latex of *Croton lechleri*. The plant species should be correctly identified and authenticated based on techniques such as macroscopic/microscopic and/or analysis of genetic material.
2. Crude red latex as BRM should be collected from the mature tree with defined eco-geographic regions (EGRs). Implementing and enforcing established good agricultural and collection practice (GACP) procedures will minimize variations in BRM and ensure batch-to-batch consistency of crofelemer.
3. BRMs should be analyzed for their crofelemer content, total phenolics and taspine content, as well as heavy metals and pesticides.

Recommendations for Demonstrating API Sameness:

API sameness can be established by showing equivalence between Test API and API from the reference listed drug (RLD) product with the three criteria described in detail below. Generic drug applicants are advised to perform side-by-side comparative studies using Test API and API obtained from the RLD product. It is recommended that at least three batches of Test and RLD product each should be characterized to assess API sameness and robustness in the manufacturing process. The following three criteria should be used to demonstrate API sameness:

1. Equivalence of physicochemical properties of crofelemer

The following physicochemical characterizations should be performed to demonstrate API sameness:

   a. Molecular weight distribution
   b. The overall characteristic structural properties of crofelemer, including but not limited

to:

i. Circular dichroism (CD)
ii. Elemental analysis (EA)
iii. Fourier transformation infrared spectroscopy (FT-IR)
iv. Ultraviolet (UV)
v. Ultra-high performance liquid chromatography (UPLC)
vi. Nuclear magnetic resonance spectra (^{1}H and ^{13}C NMR and 2D NMR)
vii. X-ray powder diffraction (XRPD)
viii. Liquid chromatography–mass spectrometry (LC-MS) profiles

The monomer building block composition, average monomer ratio of catechin/epicatechin to gallocatechin/epigallocatechin in the oligomers, mean degree of polymerization, and conversion yield after digestion (depolymerization) of the oligomers for the generic crofelemer should be equivalent to the drug substance in the RLD. Given the complexity of crofelemer, applicants should develop and use orthogonal analytical methods corresponding to each attribute as listed above, for comprehensive characterization and demonstration of sameness between the crofelemer in the generic drug product and the RLD.

2. Equivalence of chemical fingerprinting of crofelemer compositions and other concomitant components

Single or multiple analytical methods with different separation/detection principles may be used to generate full chemical fingerprinting profile for crofelemer as well as its concomitant components. All chemical constituents presented in the full chemical fingerprinting profile should be qualitatively and quantitatively comparable from generic to RLD.

3. Equivalence of biological assay results

A biological assay can serve as a confirmatory test of equivalence and provide complementary confirmation of crofelemer sameness. The FDA recommends applicants develop and validate a cell-based assay that may reflect the mechanism of action (MOA) of crofelemer to demonstrate equivalent bioactivity.

Recommendations for Demonstrating Bioequivalence:

Type of study: Bioequivalence study with clinical endpoint
Design: Randomized, double-blind, parallel, controlled
Strength: 125 mg
Subjects: HIV-positive males and females on antiretroviral therapy with associated secretory diarrhea, ages 18-60 years

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Analyte to measure: Not applicable

Bioequivalence based on (95% CI): Clinical endpoint

Dissolution test method and sampling times: The dissolution information for this drug product can be found in the FDA's Dissolution Methods database,

http://www.accessdata.fda.gov/scripts/cder/dissolution. Conduct comparative dissolution testing on 12 dosage units for each of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application.

Additional comments regarding the bioequivalence study with clinical endpoint:

1. The Office of Generic Drugs recommends conducting a bioequivalence study with a clinical endpoint in the treatment of secretory diarrhea in HIV-positive subjects being treated with antiretroviral therapy. Subjects are to be randomized to receive the Test crofelemer 125 mg delayed-release tablet, the RLD 125 mg delayed-release tablet or placebo orally twice daily for 4 weeks. The primary endpoint is the proportion of subjects who experience clinical response, defined as ≤ 2 watery bowel movements per week for at least 2 of the 4 weeks of the study. The study should include a 3-day run-in period prior to the 4 weeks collection of data in support of the primary endpoint.

2. Inclusion Criteria (the applicant may add additional criteria)
    a. Male or female, age between 18 and 60 years
    b. History of HIV-1 infection confirmed by standard serological tests (positive enzyme-linked immunosorbent assay (ELISA) and Western blot), and/or positive HIV titer confirmed by polymerase chain reaction (PCR) based HIV-1 viral load assay.
    c. Stable antiretroviral therapeutic regimen (no additions, deletions, or changes in type or dose of medication) for treatment of HIV disease and associated conditions (including prophylactic antibiotics for *Pneumocystis jirovecii* pneumonia or infection) for at least 4 weeks prior to screening, plus ability to remain on this regimen during the screening and baseline periods and throughout the study.
    d. Patient-reported history of refractory diarrhea, defined as persistently loose stools despite reported use of ≥ 2 anti-diarrheal medications (ADM), of at least 1 month's duration, and for the month prior to screening.
    e. Colonoscopy for colon cancer screening or any other condition within the past 5 years if ≥ 50 years of age. This examination must have demonstrated no evidence of colitis, infection, or neoplasm, with the exception of benign polyps of the colon.
    f. Willingness to discontinue ADM, other than assigned drug, during the course of the study.

3. Exclusion Criteria (the applicant may add additional criteria)
    a. Females who are pregnant, breast feeding, or planning a pregnancy.
    b. Females of childbearing potential who do not agree to utilize an adequate form of contraception.
    c. Immediate need for GI surgery or intervention for active GI bleeding, peritonitis, intestinal obstruction, or intra-abdominal abscess.
    d. History of gastric, small intestinal, or colonic surgery, excluding appendectomy.
    e. Symptoms of bowel obstruction or confirmed evidence of a stricture.
    f. Use of opiate pain medication within 2 weeks of screening. Subjects receiving the following opiate regimens and therapies do not need to be excluded from enrollment if taken within 2 weeks of screening:
        i. Stable methadone buprenorphine, or buprenorphine/naloxone treatment (no addition, deletion, or change in dose of medication) for the purpose of pain

management or addiction management for at least 3 months prior to screening plus the ability to remain on this dose throughout the study.

ii. Fentanyl transdermal patch therapy for pain management, on a stable dose for at least 4 weeks prior to screening plus the ability to remain on this dose throughout the study.

iii. Opiates used exclusively for control of diarrhea – loperamide (Imodium®), diphenoxylate (Lomotil®), codeine, paregoric, or tincture of opium. Note that due to these drugs action as ADMs, they must be stopped on the day following screening.

g. Positive urine test for opiates, unless the subject was taking an opiate or known to be on stable methadone, buprenorphine, buprenorphine/naloxone, or fentanyl transdermal patch therapy, or an opiate-based ADM as defined in Exclusion Criterion 3, and this opiate was identified on the drug screen.

h. Use of an antibiotic within 2 weeks prior to screening, with the exception of stable antibiotic therapy for prophylactic treatment of infection or an HIV-associated condition for at least 4 weeks prior to screening

i. CD4 counts < 100 cells/mm^3

j. Oral temperature greater than 38.0^{o}C, or unintentional weight loss of 5.0 kg or greater during the prior 2 months

k. Positive GI biopsy, GI culture, or stool test result in the past 4 months for any of the following:

i. Bacteria: *Salmonella, Shigella, Campylobacter, Yersinia, Mycobacterium*

ii. Bacterial toxin: *Clostridium difficile*

iii. Ova and parasites: *Giardia, Entamoeba, Isospora, Cyclospora, Cryptosporidium, Microsporidium*

iv. Viruses: *Cytomegalovirus*

v. Or any fecal pathogen requiring antibiotic treatment within 14 days of screening

l. Evidence on prior colonoscopy or upper endoscopy of colitis, enteritis, infection (HIV-associated or otherwise), or neoplasm, other than benign polyps.

m. Bright red blood per rectum.

n. History of ulcerative colitis, Crohn's disease, celiac sprue (gluten-enteropathy), chronic pancreatitis, malabsorption, or any other GI disease associated with diarrhea.

4. The recommended primary endpoint is the proportion of subjects who experience clinical response, defined as ≤ 2 watery bowel movements per week for at least 2 of the 4 weeks of the study.

5. Provide the Subject-Level Analysis Dataset (ADSL), one record per subject, using the following headings, if applicable:
   a. Study identifier
   b. Unique subject identifier
   c. Subject identifier for the study
   d. Study site identifier (if applicable)
   e. Age
   f. Age units (years)
   g. Sex

h. Race
i. Name of planned treatment
j. Name of actual treatment
k. Safety population flag (yes/no)
l. Reason for exclusion from safety population
m. Modified intent-to-treat (mITT) population flag (yes/no)
n. Reason for exclusion from mITT population
o. Per protocol (PP) population flag (yes/no)
p. Reason for exclusion from PP population
q. Randomized population flag (yes/no)
r. Date/time of first exposure to treatment
s. Date/time of last exposure to treatment
t. End of study date
u. End of study status
v. Subject required additional treatment due to unsatisfactory treatment response (yes/no)
w. Duration of diarrhea
x. Years since HIV diagnosis
y. Baseline watery bowel movements per day
z. Number of anti-diarrheal medications in the 4 weeks prior to screening
aa. Antiretroviral treatment regimen
bb. Number of watery bowel movements per week
cc. ≤ 2 watery bowel movements per week for at least two of the four weeks (yes/no)
dd. Compliance rate (%)
ee. Subject missed the pre-specified number of scheduled doses for more than pre-specified number of consecutive days (yes/no)
ff. Adverse event(s) reported (yes/no)
gg. Concomitant medication (yes/no)

6. Provide the basic data structure (BDS) dataset with records per subject, per analysis timepoint, using the following headings, if applicable:
   a. Study identifier
   b. Unique subject identifier
   c. Subject identifier for the study
   d. Study site identifier (if applicable)
   e. Name of planned treatment
   f. Name of actual treatment
   g. Safety population flag (yes/no)
   h. Modified ITT population flag (yes/no)
   i. Per-protocol (PP) population flag (yes/no)
   j. Analysis date
   k. Analysis visit
   l. Study visit within the designated window (yes/no)
   m. Analysis timepoint (e.g., week1, week 2, etc.) (if applicable)
   n. Number of watery bowel movements per week
   o. ≤ 2 watery bowel movements per week for at least two of the four weeks (yes/no)
   p. Additional treatment required during the visit (yes/no)

q. Adverse event reported during the visit (yes/no)
r. Concomitant medication during the visit (yes/no)

7. Please refer to the product-specific guidance on adapalene; benzoyl peroxide topical gel, 0.3%; 2.5% entitled *Guidance on Adapalene; Benzoyl Peroxide* for a recommended approach to statistical analysis and study design for bioequivalence studies with clinical endpoints.

8. Study data should be submitted in a standardized format. Please refer to the study data standards published at www.fda.gov[1]

[1] Study Data Standards for Submission to CDER and CBER available at: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm