Contains Nonbinding Recommendations

Draft Guidance on Miltefosine

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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: Miltefosine

Dosage Form/Route: Capsule/Oral

Recommended studies: In Vitro Options

I] Q1 (qualitative) and Q2 (quantitative) similarity. The test product formulations are qualitatively (Q1) and quantitatively (Q2) the same as the Reference Listed Drug (RLD) product with respect to active and inactive ingredients.

II] If the test product formulations are qualitatively (Q1) (i.e., contain all the same inactive ingredients) and quantitatively (Q2) the same as the reference listed drug (RLD) with respect to inactive ingredients, bioequivalence (BE) of all capsule strengths may be established based on the following comparative dissolution studies.

1) Type of Study: Dissolution**.** For test product formulations that are Q1 and Q2 the same as the RLD, dissolution data in the specified medium should be provided for 12 capsules each of test and reference products, as follows:

Apparatus: USP Apparatus 2 (paddle)
Rotation speed: 50 rpm
Medium: 0.1N HCl
Volume: 750 mL
Temperature: 37ºC
Sample times: 5, 10, 20, 30, and 30 minutes or as needed for profile comparison

An f2 test[1] should be performed using mean profiles to ensure comparable test (T) and reference (R) product drug

[1] 1Dissolution profiles may be compared using the following equation that defines a similarity factor (f2):
f2 = 50 LOG {[1+1/n Σn
t=1 (Rt-Tt)2]-0.5 x 100}
where Rt and Tt are the percent dissolved at each time point. An f2 value between 50 and 100 suggests the two dissolution profiles are similar. See Guidance for Industry Immediate Release Solid Oral Dosage Forms, Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation (November 1995), at 23

release under a range of pH conditions. The f2 test comparing T vs. R in each medium should be between 50 and 100.

2) Type of Study: Dissolution. In addition to performing the miltefosine dissolution testing listed as stated above, please provide comparative dissolution data for test and reference products under the following conditions:

Apparatus: USP apparatus 2 (paddle)
Rotational Speed: 50 rpm
Medium: Biorelevant FaSSGF[2]
Biorelevant FeSSGF2
Biorelevant FaSSIF2
Biorelevant FeSSIF2
Volume: 750 mL
Temperature: 37ºC
Sampling: 5, 10, 15, 20 and 30 minutes or as needed for profile comparison.

The above dissolution profiles, should be compared by the model independent approach using a 'f2' similarity factor[3].

Analytes to measure (in appropriate biological fluid): N/A

Bioequivalence based on (90% CI): N/A

Waiver request of in-vivo testing: N/A

[2] Jantratid E, Janssen N, Reppas C, and Dressman JB. Dissolution Media Simulating Conditions in the Proximal Human Gastrointestinal Tract: An Update. Pharm Res. 2008 July; 25(7):1663-1676.
[3] Guidance for Industry—Dissolution testing of Immediate Release Solid Oral Dosage Forms, finalized August 1997, page 8