Contains Nonbinding Recommendations

Draft Guidance on Mebendazole

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

Active ingredient: Mebendazole

Form/Route: Tablet, Chewable/Oral

Recommended studies: 2 studies

1. Type of study: Fed PK Bioequivalence Study
   Design: Single dose, two-way, crossover *in-vivo*
   Strength: 100 mg
   Subjects: Normal healthy males and females, general population.
   Additional comments: A fasting study is not recommended. The tablets should be swallowed whole during the conduct of the fed study.

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2. Type of study: Clinical Endpoint Bioequivalence Study
   Design: An *in vivo* randomized, double blind, parallel bioequivalence study with clinical endpoints
   Strength: 100 mg
   Subjects: Patients infected with *Ascaris lumbricoides* (common roundworm).
   Additional comments: Please find additional comments after the dissolution testing recommendations. Please submit a protocol for review to the Clinical Team.

Analytes to measure (in appropriate biological fluid): Mebendazole in plasma (Fed PK study only)

Bioequivalence based on (90% CI): Mebendazole (Fed PK study only)

Waiver request of in-vivo testing: Not Applicable

Dissolution test method and sampling times:

Please note that a **Dissolution Methods Database** is available to the public at the OGD website at http://www.fda.gov/cder/ogd/index.htm. Please find the dissolution information for this product at this website. Please conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products. Specifications will be determined upon review of the application.

Additional comments regarding the clinical endpoint study:

a. Patients should be diagnosed by positive stool specimen microscopic examination at baseline.

b. Patients should be randomized to receive the reference or the generic mebendazole chewable tablets 100 mg twice daily for 3 days.

c. Stool specimens should be collected at one and three weeks post dosing and evaluated for worm identification and larva, ova, and parasite count.

d. The recommended primary endpoint is the proportion of cured patients, with cure defined as absence of worm, larva, and ova in stool samples collected one and three weeks after treatment.

e. To demonstrate bioequivalence, the 90% confidence interval of the difference in success proportion between the generic and reference treatment groups must be within (-0.20, +0.20).

f. The accepted per protocol (PP) population used for bioequivalence evaluation includes all randomized patients who take a prespecified proportion of doses of the assigned medication and complete the evaluation within the designated visit window with no protocol violations that would affect the treatment evaluation. Patients discontinued for lack of treatment effect should also be included in the PP population as treatment failures. The protocol should specify how compliance will be verified, e.g., by the use of patient diaries.

g. The usual intent-to-treat (ITT) population includes all patients who are randomized, receive at least one dose of study medication, and return for at least one post-baseline visit.

h. The following Statistical Analysis Method is recommended:

<u>Equivalence Analysis</u>

Based on the usual method used in OGD for binary outcomes, the 90% confidence interval for the difference in proportions between the test and reference treatments should be contained within (-.20, +.20) in order to establish equivalence.

The compound hypothesis to be tested is:

H_0: $p_T - p_R < -.20$ or $p_T - p_R > .20$

versus

H_A : $-.20 \leq p_T - p_R \leq .20$

where p_T = cure rate of test treatment p_R = cure rate of reference treatment.

Let

n_T = sample size of test treatment group

cn_T = number of cured patients in test treatment group

n_R = sample size of reference treatment group

cn_R = number of cured patients in reference treatment group

$\hat{p}_T$ = cn_T / n_T , $\hat{p}_R$ = cn_R / n_R,

and se = ($\hat{p}_T$(1 - $\hat{p}_T$)/n_T + $\hat{p}_R$(1 - $\hat{p}_R$)/n_R)^{½}.

The 90% confidence interval for the difference in proportions between test and reference was calculated as follows, using Yates' correction:

$$L = (\hat{p}_T - \hat{p}_R) - 1.645\ se - (1/n_T + 1/n_R)/2$$

$$U = (\hat{p}_T - \hat{p}_R) + 1.645\ se + (1/n_T + 1/n_R)/2$$

Reject H_0 if $L \geq -.20$ and $U \leq .20$

Rejection of the null hypothesis H_0 supports the conclusion of equivalence of the two products.

i. Study data should be submitted to the OGD in electronic format. A list of file names included in the CD or diskette(s), with a simple description of the content of each file, should be included. Such a list should include an explanation of the variables included in each of the data sets. All SAS transport files should include .xpt as the file extension and should not be compressed. A simple SAS program to open the data transport files and SAS decode format file should be included.

Primary data sets should consist of two data sets: No Last Observation Carried Forward (No-LOCF – pure data set) and Last Observation Carried Forward (LOCF – modified data set). Per each patient, the following variables should be contained in the data set:

> Center/site, patient number, sex, race, age, drug/treatment, safety population (yes/no), reason for exclusion from safety population, ITT population (yes/no), reason for exclusion from ITT population, PP population (yes/no), reason for exclusion from PP population, baseline stool analysis (including worm identification and larva/ova and parasite count (no findings=none, 1-2=few, 3-10=moderate, >10=many), dichotomized cure versus failure.

Per each visit including baseline visit if data exist per each patient, the following variables should be contained in the data sets:

> Visit number, date of visit, visit days from baseline, reason for exclusion from ITT population per visit, reason for exclusion from PP population per visit, results of stool analysis, laboratory results, adverse events, reason for discontinuation.

The methods used to derive the variables such as ITT population, PP population, cure or failure, etc., should be included and explained.

Secondary data sets: SAS transport files should cover all variables collected in the Case Report Forms (CRF) per patient. You should provide a single file for each field such as demographics, baseline admission criteria and vital variables, clinical variables per each visit plus visit date, adverse events, reasons for discontinuation of treatment, medical history, compliance, and comments, etc.

j. All adverse events should be reported, whether or not they are considered to be related to the treatment. This information is needed to determine if the incidence of adverse reactions is different between the generic and reference products.

k. A placebo arm is not recommended because of the high cure rate with mebendazole, the low spontaneous resolution rate, and the risk of complications associated with this infection if not adequately treated.

l. Please refer to 21 CFR 320.38 and 320.63 regarding retention of study drug samples. For more information, please refer to the Guidance for Industry: "Handling and Retention of BA and BE Testing Samples" (May 2004). Retention samples should be randomly selected from each drug shipment by each study site and retained by the investigator or an independent third party not involved with packaging and labeling of the study products. Retention samples should not be returned to the sponsor at any time. These regulations apply to both studies. In addition, the investigators should follow the procedures of 21 CFR 58 and ICH E6, "Good Clinical Practice: Consolidated Guideline."