Contains Nonbinding Recommendations

Draft Guidance on Mebendazole

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Tablet, chewable; oral

Recommended Studies: Two studies

1. Type of study: Bioequivalence study with PK endpoints under fed conditions
   Design: Single dose, two-way, crossover in vivo
   Strength: 500 mg
   Subjects: Healthy males, healthy non-pregnant and non-lactating females
   Additional comments: A fasting study is not recommended. The tablets must be chewed completely before swallowing. Do not swallow the tablet whole.

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2. Type of study: Bioequivalence study with clinical endpoints
   Design: Randomized, double blind, parallel, placebo controlled in vivo
   Strength: 500 mg
   Subjects: Patients infected with *Trichuris trichiura* (whipworm)
   Additional comments are after the dissolution testing recommendations. Currently available data on clinical studies indicate that a study in the treatment of *Ascaris lumbricoide*s would not be sufficiently sensitive to detect differences between products due to the high cure rate in the treatment of *Ascaris lumbricoide*s.

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

Bioequivalence based on (90% CI): Mebendazole (Fed PK bioequivalence study only) and clinical endpoints (BE study with clinical endpoints only)

Waiver request of in-vivo testing: Not Applicable

Dissolution test method and sampling times: The dissolution information for this drug product can be found on the FDA-Recommended Dissolution Methods website available to the public at the following location: http://www.accessdata.fda.gov/scripts/cder/dissolution/. 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 Abbreviated New Drug Application (ANDA).

Additional comments regarding the clinical endpoint study:

1. The Office of Generic Drugs (OGD) recommends conducting a BE study with a clinical endpoint in the treatment of patients with *Trichuris trichiura* infection. Subjects are to be randomized to receive the generic (T) mebendazole chewable tablets, the reference listed drug (R), or a placebo tablet at a single dose of 500 mg. The tablets must be chewed completely before swallowing. Do not swallow the tablet whole. For patients who have difficulty chewing the tablet, the test or reference tablet can be placed in a spoon and approximately 2 mL to 3 mL of drinking water added onto the tablet using a dosing syringe. Within 2 minutes, the tablet absorbs the water and turns into a soft mass with semi-solid consistency, which can then be swallowed.

2. Infection with *Trichuris trichiura* should be diagnosed by positive identification of eggs, worms, or larvae on microscopic examination of two separate stool specimens at baseline. Specimens should be obtained on two separate days in order to adequately cover the egg shedding cycle of 24-48 hours. The method used for identification should be consistent across clinical trial sites. The Kato-Katz technique is one acceptable technique that has been widely reported in the literature.

3. Patients should be excluded from enrollment if they have severe complications due to worm infestations, including chronic dysentery, significant abdominal pain, abdominal distension, significant weight loss, malnutrition, anemia, hypoalbuminemia, inflammatory bowel disease, or rectal prolapse.

4. Patients should be evaluated at baseline for parasitic infections other than *Trichuris* by testing stool, blood, and urine samples. Patients infected with a parasite other than soil transmitted helminths should be excluded from enrollment and provided with effective treatment.

5. Due to the reported variability in cure rates and Egg Reduction Rates (ERR) in different geographical areas, test sites should be located in the same geographical area. Otherwise, analysis of results should be stratified by test site and evaluated for a treatment-by-site interaction to ensure that pooling of results across sites is appropriate.

6. Stool specimen evaluations at baseline should include worm identification and larva, ova, and parasite count and number of eggs per gram of stool.

7. A placebo arm is needed to ensure that the study drugs are active and that the study design is adequately sensitive to detect differences between products. Given that most *Trichuris* infestations are asymptomatic, a placebo arm is considered reasonably safe with appropriate rescue criteria and provision of effective therapy at the end of the study for those patients receiving placebo.

8. The study protocol should include rescue criteria to ensure that patients with complications or worsening symptoms will be discontinued and provided with effective treatment. These patients should be included in the Per Protocol (PP) analysis as treatment failures, and a Last Observation Carried Forward (LOCF) analysis should be used for the ERR.

9. Stool specimens should be collected at 1 and 3 weeks after the end of treatment and evaluated for worm identification and larva, ova, and parasite count and number of eggs per gram of feces. Test of Cure (TOC) is to be evaluated at 3 weeks after the end of treatment.

10. The recommended primary endpoint is the proportion of patients with cure, defined as absence of worm, larva, and ova in 2 stool samples collected on 2 separate days at 3 weeks after completion of treatment.

11. ERR and the percentage reduction in number of eggs per gram of feces should be evaluated at 1 and 3 weeks after the end of treatment. A rising egg count would be a criterion for rescue therapy. The ERR at TOC should be analyzed as a secondary endpoint.

12. To demonstrate bioequivalence, the 90% confidence interval of the difference in cure rates between the test and reference treatment groups must be within (-0.20, +0.20) in the PP analysis population. In addition, the ERR for test and reference treatment groups should be compared and should not be substantially different between the two treatment groups. For both cure rate and ERR, test and reference treatments should be superior to placebo in the Intent-To-Treat (ITT) analysis population in order to establish that the treatments are active and that the study is sensitive enough to demonstrate a difference between products.

13. The accepted PP population used for bioequivalence evaluation includes all randomized patients who take a pre-specified 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.

14. The 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. To ensure adequate sensitivity of the study to detect product differences, both active products should show statistical superiority over the placebo ($p<0.05$) with regard to the cure rate, using the ITT study population and LOCF.

15. The following Statistical Analysis Method is recommended for bioequivalence testing for a dichotomous variable (cure/failure):

    <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 (-0.20, +0.20) in order to establish equivalence.

    The compound hypothesis to be tested is:

    H_0: $P_T - P_R < -0.20$ or $P_T - P_R > 0.20$ Versus H_A : $-0.20 \leq P_T - P_R \leq 0.20$

    Where P_T = cure rate of test treatment and P_R = cure rate of reference treatment.

Let

n_T = sample size of test treatment group
c n_T = number of cured patients in test treatment group
n_R = sample size of reference treatment group
c n_R = number of cured patients in reference treatment group

$\hat{P}_T = c\, n_T/n_T$, $\hat{P}_R = c\, n_R/n_R$,

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:

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

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

We reject H_0 if $L \geq -0.20$ and $U \leq 0.20$

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

16. Study data should be submitted to the OGD in electronic format. A list of file names, 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. Please provide a "pdf" document with a detailed description of the codes that are used for each variable in each of the SAS datasets (for example, Y=yes, N=no for analysis population). 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 files 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, laboratory results, baseline stool analysis from each of two separate stool samples (including worm identification and larva, ova and parasite count, and dichotomized outcome (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, egg reduction rate (ERR, percentage reduction in egg intensity as measured by eggs per gram of feces following treatment), adverse events, reason for discontinuation, need for rescue treatment.

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 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.

17. 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.

18. 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 International Council for Harmonisation E6, "Good Clinical Practice: Consolidated Guideline."