Contains Nonbinding Recommendations

Draft Guidance on Nitazoxanide

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: For Suspension; oral

Recommended Studies: Two options

Option 1:
If the Test product formulation is qualitatively and quantitatively (Q1[1]/Q2[2]) the same as the Reference Listed Drug (RLD) with respect to inactive ingredients, bioequivalence (BE) may be established by conducting both in vivo BE studies with pharmacokinetic (PK) endpoints and in vitro dissolution studies.

In vivo BE study with PK endpoints:

1. Type of study: Fasting
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 100 mg/ 5 mL (Dose: 500 mg)
   Subjects: Healthy males and nonpregnant, nonlactating females, general population.
   Additional Comments: None

2. Type of study: Fed
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 100 mg/ 5 mL (Dose: 500 mg)
   Subjects: Healthy males and nonpregnant, nonlactating females, general population.
   Additional Comments: None

Analytes to measure (in appropriate biological fluid): Tizoxanide in plasma

Bioequivalence based on (90% CI): Tizoxanide

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 Web site, 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 both strengths of the Test

[1] Q1 (qualitative sameness) means that the Test product uses the same inactive ingredient(s) as the Reference product.
[2] Q2 (quantitative sameness) means that the concentrations of the inactive ingredient(s) used in the Test product are within ±5% of those used in the Reference product.

and Reference products. Specifications will be determined upon review of the abbreviated new drug application (ANDA).

In addition to performing the nitazoxanide dissolution testing listed at the above website, please provide comparative dissolution data for Test and Reference products under the following conditions:

Apparatus:	USP apparatus 2 (paddle)
Rotational speed:	75 rpm
Medium:	Biorelevant FaSSGF[3]
	Biorelevant FeSSGF[3]
	Biorelevant FaSSGF-V2[3]
	Biorelevant FeSSGF-V2[3]
	pH 6.8 phosphate buffer/hexadecyltrimethyl ammonium bromide (cetrimide) concentrations of 2%, 4%, 6%
	pH 7.5 phosphate buffer/cetrimide concentrations of 2%, 4%, 6%
Volume:	900mL
Temperature:	37°C
	15, 30, 45, 60 and 90 minutes or as needed for profile comparison.
Sampling:	Report combined nitazoxanide and tizoxanide concentrations.

Option 2:
If the Test product formulation is not Q1/Q2 the same as the RLD with respect to inactive ingredients, BE should be established by conducting an in vivo study with clinical endpoints, in vivo study with PK endpoints, and in vitro comparative dissolution testing.

In vivo BE study with clinical endpoints:

Type of study: BE study with clinical endpoints
Design: Randomized, double blind, parallel, placebo-controlled in vivo
Strength: 100 mg/ 5mL
Subjects: Immunocompetent subjects (12 years and older) with diarrhea caused by *Giardia lamblia*.
Additional comments: Specific recommendations are provided below.

In vivo BE study with PK endpoints:

The same studies as recommended under Option 1.

Waiver request of in vivo testing: Not applicable

Dissolution test method and sampling times: The same studies as recommended under Option 1.

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[3] 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.

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 diarrhea caused by Giardia lamblia (G. lamblia). Subjects are to be randomized to receive the generic nitazoxanide oral suspension, the RLD, or placebo. The study drug is to be taken every 12 hours with food for 3 days (i.e. Study Days 1, 2, and 3). The primary endpoint is the proportion of subjects with a "well" clinical response evaluated 4 to 7 days following the end of treatment.

2. Inclusion Criteria (the Applicant may add additional criteria)
   a. male or female subjects ≥ 12 years with
   b. diarrhea (defined as the passage of three or more unformed stools per day) AND
   c. a positive stool specimen with cysts of G. lamblia as the sole identifiable pathogen on the day of enrollment. The presence of G. lamblia must be reconfirmed on the day of enrollment.

3. Exclusion Criteria (the Applicant may add additional criteria)
   a. an additional intestinal pathogen that might contribute to the presenting symptoms (e.g. pathogenic bacteria such as Salmonella, Shigella, Entamoeba histolytica, Cryptosporidium parvum)
   b. administration of drug(s) known to affect intestinal motility or diarrhea within 7 days of enrollment
   c. administration of drug(s) with antiprotozoan activity within 2 weeks of enrollment (e.g., metronidazole, tinidazole, paromomycin, nitazoxanide, azithromycin)
   d. females who are pregnant or breast feeding
   e. subjects known or suspected of having HIV/AIDS
   f. subjects with compromised renal or hepatic function
   g. subjects with chronic gastrointestinal illness
   h. subjects with malnutrition, defined as a BMI less than 18.5 kg/m2 in adults and BMI<5% for age based on the CDC growth chart in adolescents ≥ 12 years of age.
   i. subjects taking warfarin

4. The protocol should include a list of the prescription and over-the counter- drug products, procedures, and activities that are prohibited during the study, such as
   a. warfarin,
   b. antimicrobial drug(s), and
   c. drug(s) with antiprotozoan activity other than the study drug

5. The recommended primary endpoint is the proportion of subjects with a "well" clinical response evaluated 4 to 7 days following end of treatment (i.e., evaluated on Study Days 7, 8, 9 or 10). A clinical response of "well" is defined as either 1) "no symptoms, no watery stool and no more than 2 soft stools with no hematochezia within the past 24 hours" or 2) "no symptoms and no unformed stools within the past 48 hours."

6. Subjects enrolled with other causes of diarrhea (e.g., bacterial, Entamoeba histolytica or Cryptosporidium parvum) and subjects with no cysts of Giardia lamblia at baseline should be excluded from the modified intent-to-treat (mITT) and per protocol (PP) analysis populations.

7. The protocol should clearly define the PP, modified mITT and safety populations.
   a. The accepted PP population used for BE evaluation includes all randomized subjects who:
      i. Meet all inclusion/exclusion criteria
      ii. Are dosed a pre-specified proportion of the scheduled doses (Generally At least 75% and no more than 125%) of the assigned product for the specified duration of the study. The protocol should specify how compliance will be verified (e.g., use of subject diaries).
      iii. Do not miss a pre-specified number of scheduled doses for more than pre-specified number of consecutive days.
      iv. Complete the evaluation within the designated visit window with no protocol violations that would affect the treatment evaluation.
   b. The mITT and safety populations include all randomized subjects who use at least one dose of product.

8. Subjects who are discontinued early from the study due to lack of treatment effect should be included in the PP population as treatment failures. Subjects whose condition worsens and who require alternate or supplemental therapy for the treatment of their condition during the treatment phase of the study should be discontinued, included in the mITT and PP population analyses as treatment failures and provided with effective treatment. Subjects discontinued early for other reasons should be excluded from the PP population, but included in the mITT population, using Last Observation Carried Forward (LOCF). Applicants should provide a pre-specified definition of lack of treatment effect.

9. The start and stop calendar date (e.g., mm/dd/yyyy) and study day (e.g. Day X) of concomitant medication use should be provided in the data set in addition to the reason for the medication use. The Applicant should clearly note whether the medication was used prior to baseline visit, during the study, or both.

10. If the study allows for the use of a rescue medication, the Applicant should submit a data set that includes the date and time of each rescue medication use for each subject who used the rescue medication at any point during the study. The Applicant should pre-specify rescue medication use (name, type, amount, frequency, reason to use), maximum allowable amount of daily rescue medication use, and any limitations (e.g., cannot use rescue medication within pre-specified number of hours prior to primary endpoint evaluation) for rescue medication use during the study.

11. All adverse events (AEs) should be reported, whether or not they are considered to be related to the treatment. The report of AEs should include date of onset, description of the AE, severity, relation to study medication, action taken, outcome and date of resolution. This information is needed to determine if the incidence and severity of adverse reactions is different between the Test product and RLD.

12. All pregnancies should be reported, including outcome information.

13. If the inactive ingredients are different than those contained in the RLD or in significantly different amounts, then the Applicant is to clearly describe the differences and provide information to show that the differences will not affect the safety, efficacy, or systemic or local availability of the drug. Inactive ingredients used should provide adequate margins of safety for the proposed clinical exposure in the target population (e.g., 1 year and older).

14. The method of randomization should be described in the protocol and the randomization schedule should be provided. It is recommended that an independent third party generate and hold the randomization code throughout the conduct of the study in order to minimize bias. The Applicant may generate the randomization code if not involved in the packaging and labeling of the study medication. A sealed copy of the randomization scheme should be retained at the study site and should be available to FDA investigators at the time of site inspection to allow for verification of the treatment identity of each subject.

15. A detailed description of the blinding procedure is to be provided in the protocol. The packaging of the Test, Reference and placebo products should be similar in appearance to make differences in treatment less obvious to the subjects and to maintain adequate blinding of evaluators. When possible, neither the subject nor the investigator should be able to identify the treatment. The containers should not be opened by the subject at the study center.

16. Please refer to 21 CFR 320.38, 320.63 and the Guidance for Industry, "Handling and Retention of BA and BE Testing Samples", regarding retention of study drug samples and 21 CFR 320.36 for requirements for maintenance of records of BE testing. In addition, the investigators should follow the procedures of 21 CFR 58 and ICH E6, "Good Clinical Practice: Consolidated Guideline", for retention of study records and data in order to conduct their studies in compliance with Good Laboratory Practices (GLP) and Good Clinical Practices (GCP). Retention samples should be randomly selected from the drug supplies received for each shipment prior to dispensing to subjects. Retention samples should not be returned to the Applicant at any time.

17. It is the Applicant's responsibility to enroll sufficient subjects for the study to demonstrate BE between the product.

18. To establish sensitivity within the study for either a dichotomous or continuous primary endpoint, the Test and Reference products should both be statistically superior to the placebo. Conduct an appropriate two-sided inferential test with a type I error (α) of 0.05, using the mITT population and the primary endpoint.

19. The study data should be submitted in standardized format. Please refer to study data standards published at www.FDA.gov.

20. The protocol should include a section with fully detailed statistical analysis plan.

21. Please 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. mITT population flag (yes/no)
n. Reason for exclusion from mITT population
o. 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. Baseline stool analysis
x. Baseline G. lamblia cyst count
y. Well clinical response evaluated on Days 7, 8, 9, or 10 (Yes/No)
z. Compliance rate (%)
aa. Subject missed the pre-specified number of scheduled doses for more than pre-specified number of consecutive days (yes/no)
bb. Adverse event reported (yes/no)
cc. Concomitant medication (yes/no)

22. Please provide the basic data structure (BDS) dataset with records per subject, per visit, 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. 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., hour 0, hour 2) (if applicable)
n. Number of stools per day
o. Number of formed stools per day
p. Number of unformed stools per day
q. Number of bright red bloody stools per day
r. Clinical symptoms (e.g. nausea, abdominal pain or cramping, anorexia, etc.)
s. Well clinical response evaluated on Days 7, 8, 9, or 10 (Yes/No)
t. Results of stool analysis
u. Laboratory results
v. Additional treatment required during the visit (yes/no)
w. Adverse event reported during the visit (yes/no)
x. Concomitant medication during the visit (yes/no)