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Draft Guidance on Nitazoxanide

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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: Tablets; 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: 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: 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, 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 studies 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: 500 mg
Subjects: Immunocompetent subjects (12 years and older) with diarrhea caused by *Giardia lamblia*.
Additional comments: Specific recommendations are provided below.

In vivo BE studies 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.

Additional comments regarding the clinical endpoint study:

[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.

1. Infection with *Giardia lamblia* in immunocompetent male or female patients aged ≥ 12 years should be diagnosed at screening with the following criteria. The presence of *G. lamblia* must be reconfirmed on the day of enrollment:
   a. diarrhea (defined as the passage of three or more unformed stools per day) and
   b. a positive stool specimen with cysts of *Giardia lamblia* as the sole identifiable pathogen on the day of enrollment.

2. Patients should be excluded from enrollment if they meet any of the following 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. patients known or suspected of having Human Immunodeficiency Virus/Acquired Immune Deficiency Syndrome
   f. patients with compromised renal or hepatic function
   g. patients with chronic gastrointestinal illness
   h. subjects with malnutrition, defined as a Body Mass Index less than 18.5 kg/m^2 in adults and BMI < 5% for age based on Centers for Disease Control and Prevention growth chart in adolescents ≥12 years of age
   i. patients taking warfarin

3. Concomitant use of warfarin, antimicrobial drug(s) and drug(s) with antiprotozoan activity other than the study drugs is prohibited.

4. Patients should be randomized to receive the RLD, the generic nitazoxanide tablets 500 mg, or placebo twice daily for 3 days (i.e. on Study Days 1, 2 and 3).

5. The recommended primary endpoint is the proportion of patients 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. Patients enrolled with other causes of diarrhea (e.g., bacterial, *Entamoeba histolytica* or *Crytosporidium parvum*) and patients 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. To demonstrate BE, the 90% confidence interval of the difference in success proportion between the test product and RLD treatment groups must be within (-0.20, +0.20).

8. Both the test product and the RLD should demonstrate superiority over placebo in the mITT population to demonstrate sufficient activity to detect a difference between products.

9. The accepted per protocol (PP) population used for BE evaluation includes all randomized patients who meet inclusion/exclusion criteria, take a prespecified proportion of doses (usually at least 75% and no more than 125% of prescribed 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 use of patient diaries.

10. 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.

11. The mITT population includes all patients who are randomized, meet inclusion/exclusion criteria, have no identifiable cause of diarrhea, receive at least one dose of study medication, and return for at least one post-baseline visit.

12. Sufficient amount of patients must be enrolled to demonstrate non-inferiority of the test product compared to the RLD.

13. 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) 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 = "well" clinical response rate of test treatment
    p_R = "well" clinical response rate of reference treatment.

    Let
    n_T = sample size of test treatment group

$c n_T$ = number of patients with "well" clinical response in test treatment group

n_R = sample size of reference treatment group

$c n_R$ = number of patients with "well" clinical response in reference treatment group

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

and se = $(\hat{p}_T(1 - \hat{p}_T)/n_T + \hat{p}_R(1 - \hat{p}_R)/n_R)^{1/2}$.

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

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

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

We 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.

14. 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 *G. lamblia* cyst 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, number of stools per day, number of formed stools per day, number of unformed

stools per day, number of bright red bloody stools per day, 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.

15. 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 test product and RLD.

16. Refer to 21 CFR 320.38 and 320.63 regarding retention of study drug samples. For more information, 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."