Contains Nonbinding Recommendations

Draft Guidance on Mesalamine

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Delayed release capsule; oral

Recommended Studies: Three studies

1. Type of study: Fasting
   Design: Single-dose, partially or fully replicated crossover designin vivo
   Strength: 400 mg
   Subjects: Healthy males and females, general population. Females should not be pregnant, and if applicable, should practice abstention or contraception during the study.
   Additional comments: Other study designs are acceptable if appropriate. Specific recommendations are provided below.

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2. Type of study: Fed
   Design: Single-dose, partially or fully replicated crossover design, in vivo
   Strength: 400 mg
   Subjects: Healthy males and females, general population. Females should not be pregnant, and if applicable, should practice abstention or contraception during the study.
   Additional comments: Other study designs are acceptable if appropriate. Specific recommendations are provided below.

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

Bioequivalence based on (90% CI): Mesalamine

Additional comments regarding the BE study with PK endpoints:

1. Applicants may consider using a reference-scaled average bioequivalence approach for mesalamine. For general information on this approach, please refer to the Progesterone Capsule Guidance for additional information regarding highly variable drugs.

2. For both fasting and fed studies, the following PK parameters are recommended to be evaluated: Log-transformed $AUC_{8\text{-}48}$, $AUC_{0\text{-}t}$, and C_{max}, where $AUC_{8\text{-}48}$ is the area under the plasma concentration vs. time curve from 8 to 48 hours, $AUC_{0\text{-}t}$ is the area under the curve from 0 hours to the last measurable time point, and C_{max} is the maximum plasma concentration. Applicants should have extensive sampling points around T_{max} to have accurate estimation of C_{max} and T_{max}, and at least four consecutive non-zero measurements of concentrations are recommended for $AUC_{8\text{-}48}$. Other partial AUCs may

be evaluated as supporting material to evaluate similarity of drug release throughout the gastrointestinal tract.

3. As AUC_{0-t} is recommended in place of $AUC_{0-\infty}$, the last sampling time point should be at least 72 hours.

3.	Type of study:	In vitro comparative dissolution study
	Strength:	400 mg
	Apparatus:	USP Apparatus 2 (paddle)
	Stage 1:	2 hours in 0.1 N HCl at 100 rpm (500 mL)
	Stage 2:	Each of (1) pH 4.5 Acetate buffer at 50 rpm (2) pH 6.0 Phosphate buffer at 50 rpm (3) pH 6.5 Phosphate buffer at 50 rpm (4) pH 6.8 Phosphate buffer at 50 rpm (5) pH 7.2 Phosphate buffer at 50 rpm (6) pH 7.5 Phosphate buffer at 50 rpm
	Volume:	900 mL
	Temperature:	37°C
	Sampling times:	The sampling time should be at least 150 minutes or as needed for profile comparison when applicable. The applicant should use at least 24 dosage units of the test product and at least 2 lots of the reference product (12 dosage units per lot). The f2 metric will be used to compare dissolution profiles.

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/. Please conduct comparative dissolution testing on 24 dosage units each of all strengths of the test and reference products (at least 2 different reference lots; 12 dosage units from each lot). Specifications will be determined upon review of the abbreviated new drug application (ANDA).

Due to a concern of dose dumping of drug from this drug product when taken with alcohol, the Agency currently requests that additional dissolution testing be conducted using various concentrations of ethanol in the dissolution medium, as follows:

Testing Conditions: 900 mL, 0.1 N HCl, USP apparatus 2 (paddle) @100 rpm, with or without alcohol;

Test 1: 12 units tested according to the proposed method (with 0.1N HCl), with data collected every 15 minutes for a total of 2 hours

Test 2: 12 units tested by substituting 5% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours

Test 3: 12 units tested by substituting 20% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours

Test 4: 12 units tested by substituting 40% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours

Both test and RLD products must be tested accordingly and data must be provided on individual unit, means, range, and %CV.