Contains Nonbinding Recommendations

Draft Guidance on Mesalamine

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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: Mesalamine

Dosage Form; Route: Delayed release tablets; oral

Recommended Studies: Three studies

1. Type of study: Fasting
   Design: Single-dose, partially or fully replicated crossover design, in vivo
   Strength: 400 mg
   Subjects: Normal 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: Normal 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: 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 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_{8-48}, AUC_{0-t}, and C_{max}, where AUC_{8-48} is the area under the plasma concentration vs. time curve from 8 to 48 hours, AUC_{0-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_{8-48}. 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)
	Pretreatment Stage:	2 hours in 0.1 N HCl at 100 rpm (500 mL)
	Evaluation Stage:	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 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 all strengths of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application (ANDA).