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Draft Guidance on Mesalamine

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Recommended Studies: Three studies

1. Type of study: Fasting
   Design: Single-dose, two-way crossover design, in vivo
   Strength: 375 mg (Recommended dose: 4 x 375 mg capsules)
   Subjects: Males and non-pregnant, non-lactating females, general population
   Additional comments: Alternate study design is acceptable if appropriate. Specific recommendations are provided below.

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2. Type of study: Fed
   Design: Single-dose, two-way crossover design, in vivo
   Strength: 375 mg (Recommended dose: 4 x 375 mg capsules)
   Subjects: Males and non-pregnant, non-lactating females, general population
   Additional comments: Alternate study design is acceptable if appropriate. Specific recommendations are provided below.

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

Bioequivalence based on (90% CI): Mesalamine

Additional comments regarding the bioequivalence (BE) study with pharmacokinetic (PK) endpoints:

1) Applicants may consider using a reference-scaled average BE approach for mesalamine. If this approach is used, the applicant should provide evidence of high variability, in their studies, in the BE parameters (i.e., within-subject variability $\geq$ 30%) for the reference product. For general information on this approach, refer to the Progesterone Capsule Guidance for additional information regarding highly variable drugs.

2) For the fasting study, the following PK parameters will be evaluated: Log-transformed area under the plasma concentration time curve from 3 to the last measurable time point (AUC_{3-t}), AUC from 0 hours to the last measurable time point

(AUC_{0-t}), and maximum plasma concentration (C_{max}). Applicants should have extensive sampling points around T_{max} (time of maximum plasma concentration observed) to have accurate estimation of C_{max}, and at least four non-zero measurements of concentration are recommended for each partial AUC.
Note: Submit AUC_{0-3} data for the fasting study, where AUC_{0-3} is the AUC from 0 to 3 hours.

3) For the fed study, the following PK parameters will be evaluated: Log-transformed AUC_{0-t}, and C_{max}. Submit AUC_{0-3} and AUC_{3-t} data as supportive evidence of comparable therapeutic outcome.

4) Because AUC_{0-t} is recommended in lieu of $AUC_{0-\infty}$, the last sampling time point should be at least 72 hours post-dose for both fasted and fed studies.

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3. Type of study: In vitro comparative dissolution study
Strength: 375 mg
Apparatus: USP Apparatus 1 (basket)
Pretreatment Stage: 2 hours in 750 mL 0.1 N HCl at 100 rpm
Evaluation Stage: Each of the following:
(1) pH 4.5 Acetate buffer at 100 rpm
(2) pH 6.0 Phosphate buffer at 100 rpm
(3) pH 6.5 Phosphate buffer at 100 rpm
(4) pH 6.8 Phosphate buffer at 100 rpm
(5) pH 7.2 Phosphate buffer at 100 rpm
(6) pH 7.5 Phosphate buffer at 100 rpm
Volume: 1000 mL
Temperature: 37ºC
Sample times: 0.5, 1, 2, 4, 7 and 9 hours or as needed for profile comparison
Additional comments: Use at least 12 dosage units per test. The f2 metric should be used to compare dissolution profiles.

Additional strengths: Not applicable

Dissolution test method and sampling times (for product specification):
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 of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application.