

Draft Guidance on Mesalamine

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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

Form/Route: Extended Release Capsule/Oral

Recommended studies 3 studies

1. Type of study: Fasting
Design: Single-dose, two-way crossover design, in vivo
Strength: 500 mg (Recommended dose: 2 x 500 mg capsules)
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.

2. Type of study: Fed
Design: Single-dose, two-way crossover design, in vivo
Strength: 500 mg (Recommended dose: 2 x 500 mg capsules)
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 (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. If using this approach, the applicant should provide evidence of high variability in the bioequivalence 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 AUC_{0-3} , AUC_{3-t} , AUC_{0-t} , and C_{max} , where AUC_{0-3} is the area under the plasma concentration vs. time curve from 0 to 3 hours, AUC_{3-t} is the area under the plasma concentration vs. time curve from 3 to the last measurable time point, 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 non-zero measurements of concentration are recommended for each partial AUC.

- 3) For the fed study, the following PK parameters will be evaluated: Log-transformed AUC_{0-t} , and C_{max} . Please submit AUC_{0-3} and AUC_{3-t} data as supportive evidence of comparable therapeutic outcome.
- 4) As AUC_{0-t} is recommended in place of $AUC_{0-\infty}$, the last sampling time point should be at least at 72 hours.

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3. Type of study: In vitro comparative dissolution study
Strength: 250 mg and 500 mg
Apparatus: USP 2 (paddles)
Speed: 100 rpm
Media: 0.1 N HCl and appropriate buffers at pH values of 4.5, 6.0, 6.5, 6.8, 7.2, 7.5
Volume: 900 mL
Temperature: 37°C
Sampling times: 1, 2, 4, 6, 8, and 12 hours or as needed for profile comparison
Additional Comments: The applicant should use at least 12 dosage units per test. The f2 metric will be used to compare dissolution profiles.
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Waiver request of in vivo testing: Mesalamine extended release capsules, 250 mg, may be considered for a waiver of in vivo bioequivalence testing based on (1) acceptable bioequivalence studies on the 500 mg strength, (2) acceptable dissolution testing of the 250 mg and 500 mg strengths, and (3) proportional similarity in the formulations of the 250 mg and 500 mg strengths.

Dissolution test method and sampling times:

Please note that a **Dissolution Methods Database** is available to the public at the OGD website at <http://www.accessdata.fda.gov/scripts/cder/dissolution/>. Please find the dissolution information for this product at this website. Please 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 application.