Contains Nonbinding Recommendations

Draft Guidance on Amantadine Hydrochloride

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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

Form/Route: Tablet/Oral

Recommended studies: 2 studies

1. Type of study: Fasting
   Design: Single-dose, two-way crossover in-vivo
   Strength: 100 mg
   Subjects: Healthy males and nonpregnant females, general population
   Additional Comments:

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2. Type of study: Fed
   Design: Single-dose, two-way crossover in-vivo
   Strength: 100 mg
   Subjects: Healthy males and nonpregnant females, general population
   Additional Comments: See attachment for recommendations regarding fed studies

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

Bioequivalence based on (90% CI): Amantadine

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 the test and reference products. Specifications will be determined upon review of the application.

Attachment:

Co-administration of food with oral drug products can influence bioequivalence (BE). Therefore, fed BE studies can determine whether test and RLD products are bioequivalent when co-administered with meals. We usually recommend a single-dose, two-period, two-treatment, two-sequence, crossover study for fed BE studies.

When a fasting in vivo BE study is indicated for an orally administered, immediate release product, we also recommend that applicants conduct a fed study, except as follows:

- When both test product and RLD are rapidly dissolving, have similar dissolution profiles, and contain a drug substance with high solubility and high permeability (BCS Class I)

- When the *dosage and administration* section of the RLD labeling states that the product should be taken only on an empty stomach (e.g., the labeling states that the product should be administered one hour before or two hours after a meal).

For orally administered, immediate release products labeled to be taken only with food, fasting and fed studies are recommended, except when serious adverse events are anticipated with fasting administration. In these cases, we recommend that applicants conduct only a fed study; a fasting study is not recommended.

For all orally administered, modified release drug products, we recommend that applicants conduct a fed BE study in addition to a fasting BE study. These studies are usually conducted on the highest strength of the drug product, unless safety considerations preclude the use of that dose in study subjects.

Test Meal Composition:

We recommend that applicants conduct fed BE studies using meals that provide the greatest effects on GI physiology and systemic drug availability. We recommend a high-fat (approximately 50 percent of total caloric content of the meal), high-calorie (approximately 800 to 1000 calories) test meal for fed BE studies. This test meal should derive approximately 150, 250, and 500-600 calories from protein, carbohydrate, and fat, respectively. The caloric breakdown of the test meal should be provided in the study report.

An example test meal would be: two eggs fried in butter, two strips of bacon, two slices of toast with butter, four ounces of hash brown potatoes and eight ounces of whole milk. Substitutions in this test meal (e.g., beef instead of bacon) can be made as long as the meal provides a similar amount of calories from protein, carbohydrate, and fat and has comparable meal volume, density, and viscosity.