

Draft Guidance on Morphine Sulfate; Naltrexone Hydrochloride

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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

Form/Route: Capsule, Extended Release; Oral

Recommended studies: 4 studies

1. Type of study: Fasting
Design: Single-dose, two-way crossover in vivo
Strength: 60mg/2.4mg
Subjects: Healthy males and non-pregnant females, general population
Additional Comments: Due to safety concerns, bioequivalence studies on the highest strength are not recommended. A naltrexone blockade is NOT recommended because a lower strength (60mg/2.4mg) is the recommended reference listed drug for the BE studies.

2. Type of study: Fed
Design: Single-dose, two-way crossover in vivo
Strength: 60mg/2.4mg
Subjects: Healthy males and non-pregnant females, general population
Additional Comments: Please see comments above. Please refer to the Amantadine Hydrochloride Tablet Draft Guidance for additional information regarding fed studies.

3. Type of study: Fasting sprinkle in applesauce
Design: Single-dose, two-way crossover in vivo
Strength: 60mg/2.4mg
Subjects: Healthy males and non-pregnant females, general population
Additional Comments: Fasting study, with contents sprinkled over a spoonful of applesauce in accordance with the approved labeling of the RLD.

4. Type of study: Fasting, crushed drug product
Design: Single-dose, two-way crossover in vivo
Strength: 60mg/2.4mg
Subjects: Healthy males and non-pregnant females, general population
Additional Comments: Please see comments above. The crushing of capsules damages the integrity of the modified-release beads, releasing the Naltrexone present in the core of the beads. This allows for the assessment of Naltrexone bioequivalence in a potential abuse situation.

Analytes to measure (in appropriate biological fluid): Morphine, morphine-6-glucuronide, naltrexone, and 6- β -naltrexol in plasma

Bioequivalence based on (90% CI): Morphine and Naltrexone (or 6- β -naltrexol)

If naltrexone can be reliably measured, a confidence interval approach for bioequivalence determination should be used for naltrexone, and 6- β -naltrexol data should be submitted as supportive evidence of comparable therapeutic outcome. If naltrexone cannot be reliably measured, a confidence interval approach for bioequivalence determination should be used for 6- β -naltrexol.

Plasma naltrexone and 6- β -naltrexol concentrations may be low and highly variable following single administration of morphine sulfate; naltrexone hydrochloride capsules. Please develop a method of adequate sensitivity to measure plasma naltrexone and 6- β -naltrexol concentrations. If naltrexone and 6- β -naltrexol pharmacokinetic profiles for over the entire dose interval cannot be characterized, the Agency may consider bioequivalence analysis based on subjects in which the test and reference product result in at least four consecutive plasma samples that contain peak drug concentration (C_{max}) as described in the Agency response to Docket No. CP-FDA-2004-P-0469-0004, dated February 22, 2006.

Waiver request of in-vivo testing: 20mg/0.8mg, 30mg/1.2mg, 50mg/2mg, 80mg/3.2mg and 100mg/4mg based on (i) acceptable bioequivalence studies on the 60mg/2.4mg strength, (ii) acceptable in vitro dissolution testing of all strengths, and (iii) proportional similarity in the formulations across all strengths. Please refer to the Mirtazapine Tablet Draft Guidance for additional information regarding waivers of in-vivo testing.

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.

In addition to the method above, for modified release products, dissolution profiles on 12 dosage units each of test and reference products generated using USP Apparatus I at 100 rpm and/or Apparatus II at 50 rpm in at least three dissolution media (pH 1.2, 4.5 and 6.8 buffer) and water should be submitted in the application. Agitation speeds may have to be increased, if appropriate. It is acceptable to add a small amount of surfactant, if necessary. Please include early sampling times of 1, 2, and 4 hours and continue every 2 hours until at least 80% of the drug is released, to provide assurance against premature release of drug (dose dumping) from the formulation. Specifications will be determined upon review of the data submitted in the application.

Due to a concern of dose dumping from this drug product when taken with alcohol, please conduct additional dissolution testing using various concentrations of ethanol in the

dissolution medium, as follows:

Testing Conditions: 500 mL, 0.1 N HCl, USP apparatus 2 (paddle) @50 rpm, with or without alcohol (see below):

- 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 analyzed 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 analyzed 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 analyzed 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 on morphine and naltrexone components of test and reference products of all strengths.