

Draft Guidance on Treprostinil Diolamine

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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

Dosage Form; Route: Extended release tablet; oral

Recommended Studies: Two studies

1. Type of study: Fasting
Design: Single-dose, two-way crossover, in vivo
Strength: 2.5 mg (base)
Subjects: Healthy males and non-pregnant females, general population.
Additional comments: Females should practice abstinence or contraception during the study.

2. Type of study: Fed
Design: Single-dose, two-way crossover, in vivo
Strength: 2.5 mg (base)
Subjects: Healthy males and non-pregnant females, general population.
Additional comments: Same as above.

Analytes to measure (in appropriate biological fluid): Treprostinil in plasma.

Bioequivalence based on (90% CI): Treprostinil

Waiver request of in vivo testing: 1 mg (base); 0.25 mg (base) and 0.125 mg (base) strengths based on (i) acceptable bioequivalence studies on the 2.5 mg strength, (ii) acceptable in vitro dissolution testing of all strengths, and (iii) proportional similarity of the formulations across all strengths.

Dissolution test method and sampling times:

I. The dissolution information for this drug product can be found on the FDA-Recommended Dissolution Methods website 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).

- II. 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) 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. Applicants should 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.
- III. Due to concerns of dose dumping from this drug product when taken with alcohol, applicants should conduct additional dissolution testing using various concentrations of ethanol in the dissolution medium, as follows:
Testing conditions: 900 mL, 0.1 N HCl, apparatus 1 (basket) @ 100 rpm, with and without the alcohol (see below):
Test 1: 12 units tested according to the proposed method (with 0.1 N 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 all strengths.