Contains Nonbinding Recommendations

Draft Guidance on Treprostinil Diolamine

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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: Treprostinil diolamine

Dosage Form; Route: Extended release tablet; Oral

Recommended Studies: Two studies

1. Type of study: Fasting
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: EQ 1 mg base
   Subjects: Males and non-pregnant, non-lactating females, general population
   Additional Comments: Women of child-bearing potential should practice abstention or contraception during the study.

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2. Type of study: Fed
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: EQ 1 mg base
   Subjects: Males and non-pregnant, non-lactating females, general population
   Additional Comments: Same as above.

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

Bioequivalence based on (90% CI): Treprostinil

Additional strengths: Bioequivalence of EQ 5 mg base, EQ 2.5 mg base, EQ 0.25 mg base and EQ 0.125 mg base to the corresponding reference product strengths may be demonstrated based on principles laid out in the FDA guidance on "Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA[1]".

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.

[1]https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064964.htm

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.