Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Tofacitinib Citrate

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

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 22 mg Base
   Subjects: Males and non-pregnant, non-lactating female subjects, general population
   Additional comments: 1) Test prospective study participants and exclude those with latent tuberculosis or with abnormal liver function tests, blood counts, or lipid profiles; 2) Exclude subjects with a history of or risk factors for venous/arterial thromboembolic events; 3) Females of reproductive potential should use effective contraception and should have a negative pregnancy test immediately before receiving each dose of tofacitinib. Advise females of reproductive potential of the potential risk to the fetus.

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2. Type of study: Fed
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: EQ 22 mg Base
   Subjects: Males and non-pregnant, non-lactating females, general population
   Additional comments: See comments above.

Analyte to measure: Tofacitinib in plasma

Bioequivalence based on (90% CI): Tofacitinib

Waiver request of in vivo testing: Not applicable

Additional Strength: Bioequivalence of the EQ 11 mg Base strength to the corresponding reference product strength may be demonstrated based on principles laid out in the FDA guidance for industry, *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA.*

Dissolution test method and sampling times: For modified release drug products, applicants should develop specific discriminating dissolution methods. Alternatively, applicants may use the dissolution method set forth in any related official United States Pharmacopeia (USP) drug product monograph or in the FDA's database, http://www.accessdata.fda.gov/scripts/cder/dissolution/, provided that applicants submit adequate dissolution data supporting the discriminating ability of such a method. If a new dissolution method is developed, submit the dissolution method development and validation report with the complete information/data supporting the proposed method. Conduct comparative dissolution testing on 12 dosage units for each strength of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application.

In addition to the method above, submit dissolution profiles on 12 dosage units for each strength of the 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). Agitation speeds may be increased if appropriate. It is acceptable to add a small amount of surfactant if necessary. 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.

Due to a concern of dose dumping of drug from this product when taken with alcohol, additional dissolution testing should be conducted using various concentrations of ethanol in the dissolution medium as follows:

Testing Conditions: 900 mL, 0.1 N HCl, USP apparatus 2 (paddle, with the option to use sinkers) at 50 rpm, with or without alcohol;

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

Conduct testing on both test and reference products accordingly, and provide data on individual unit, means, range and %CV.