Recommended Mar 2020

Draft Guidance on Upadacitinib

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

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: 15 mg
   Subjects: Males and non-pregnant, non-lactating females, general population
   Additional comments: 1) Study protocol should incorporate appropriate screening and monitoring of subjects as per applicable recommendations from the reference listed drug’s label; 2) Study subjects should be tested and confirmed negative for latent tuberculosis before enrolling in a bioequivalence study; 3) Enrolled subjects should have normal liver function tests, blood counts, and lipid profiles at baseline prior to study drug administration; 4) Subjects at an increased risk for thrombosis should be excluded from the bioequivalence study; 5) Female subjects of reproductive potential should practice abstention or contraception during the study and for 4 weeks after the final dose.

2. Type of study: Fed
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 15 mg
   Subjects: Males and non-pregnant, non-lactating females, general population
   Additional comments: See comments above.

Analyte to measure (in appropriate biological fluid): Upadacitinib in plasma

Bioequivalence based on (90% CI): Upadacitinib

Additional strengths: Not applicable

Dissolution test method and sampling times:
For modified release drug products, FDA recommends that applicants develop specific discriminating dissolution methods. Applicants may also use the dissolution method set forth in any related official United States Pharmacopeia (USP) drug product monograph, or in the FDA’s database (available at 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, FDA recommends that the submission includes 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 the test and reference products. Specifications will be determined upon review of the abbreviated new drug application.

In addition to the method above, dissolution profiles on 12 dosage units for 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) should be submitted. 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 when taken with alcohol, the Agency currently requests that additional dissolution testing be conducted using various concentrations of ethanol in the dissolution medium as follows:

Testing Conditions: Volume: 900 mL 0.1N HCl, USP Apparatus 1 (Basket) at 100 rpm, with and without alcohol:

Test 1: Twelve units tested according to the proposed method, with data collected every 15 minutes for a total of 2 hours

Test 2: Twelve 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: Twelve 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: Twelve 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 reference products should be tested accordingly and data should be provided on individual unit, means, range and %CV.