

Draft Guidance on Diroximel Fumarate

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Delayed release capsule; oral

Recommended Studies: Two studies

1. Type of study: Fasting
Design: Single-dose, two-treatment, two-period crossover in vivo
Strength: 231 mg
Subjects: Males and non-pregnant, non-lactating females, general population
Additional comment: Exclude subjects with preexisting low lymphocyte counts based on a complete blood cell count test within 6 months.

2. Type of study: Fed
Design: Single-dose, two-treatment, two-period crossover in vivo
Strength: 231 mg
Subjects: Males and non-pregnant, non-lactating females, general population
Additional comment: See comment above.

Analyte to measure: Monomethyl fumarate in plasma

Bioequivalence based on (90% CI): Monomethyl fumarate

Additional Strengths: Not applicable

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 (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, 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 of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application.

Alcohol dose dumping studies:

Due to concerns of dose dumping of drug from this product when taken with alcohol, conduct additional dissolution testing using various concentrations of ethanol in the dissolution medium as follows:

Testing Conditions: 750 mL, 0.1 N HCl, USP apparatus 2 (paddle) at 75 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.