

Contains Nonbinding Recommendations
Draft Guidance on Divalproex Sodium

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Delayed release tablets; oral

Recommended Studies: Two studies

1. Type of study: Fasting
Design: Single-dose, 2-treatment, 2-sequence, 4-period, fully replicated crossover in vivo
Strength: 500 mg
Subjects: Normal healthy males and nonpregnant females, general population
Additional comments: Please evaluate for normal liver function tests prior to dosing with divalproex sodium in bioequivalence studies.

2. Type of study: Fed
Design: Single-dose, 2-treatment, 2-sequence, 4-period, fully replicated crossover in vivo
Strength: 500 mg
Subjects: Normal healthy males and nonpregnant females, general population
Additional comments: Please see comment above.

Analytes to measure: Valproic Acid in plasma

Bioequivalence based on (90% CI): Valproic Acid

Waiver request of in vivo testing: 125 mg and 250 mg based on (i) acceptable bioequivalence studies on the 500 mg strength, (ii) acceptable in vitro dissolution testing for all strengths, and (iii) proportional similarity in the formulations across all strengths.

Dissolution test method and sampling times: 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).

For modified release products, dissolution profiles 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, water) 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. The following sampling times are recommended: 1, 2, and 4 hours and every 2 hours thereafter, until at least 80% of the drug is dissolved. Comparative dissolution profiles should include individual tablet data as well as the mean, range, and standard deviation at each time point for twelve tablets. Specifications will be determined upon review of the data submitted in the application.

Explanation: FDA has concluded that valproic acid is a narrow therapeutic index (NTI) drug based on the following evidence:

- The range between the effective valproic acid concentrations and the concentrations associated with serious toxicity is narrow;
- Sub-optimal doses or concentrations lead to therapeutic failure or severe toxicity;
- Valproic acid is subject to therapeutic monitoring based on pharmacokinetics measures;
- Valproic acid has low-to-moderate within-subject variability.

The study should be a fully replicated crossover design in order to:

- Scale bioequivalence limits to the variability of the reference product; and
- Compare test and reference products' within-subject variability.

For details about the “Method for Statistical Analysis Using the Reference-Scaled Average Bioequivalence Approach” for NTI drugs, see the guidance on warfarin sodium.