

## Draft Guidance on Leucovorin Calcium

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

**Dosage Form; Route:** Tablet; oral

**Recommended Studies:** Two studies

1. Type of study: Fasting  
Design: Single-dose, two-treatment, two-period crossover in vivo  
Strength: EQ 25 mg BASE  
Subjects: Normal healthy males and females  
Additional comments: Subjects should refrain from folate and folic acid intake prior to and during the study
  
2. Type of study: Fed  
Design: Single-dose, two-treatment, two-period crossover in vivo  
Strength: EQ 25 mg BASE  
Subjects: Normal healthy males and females  
Additional comments: Same as comments above

---

**Analytes to measure (in appropriate biological fluid):** leucovorin and the 5-methyl tetrahydrofolic acid metabolite in plasma. If leucovorin plasma concentrations can be reliably measured and its pharmacokinetic parameters accurately determined, please analyze the leucovorin data using the confidence interval approach. The metabolite data can be used to provide supportive evidence of comparable therapeutic outcome.

The post-dose plasma concentrations should be corrected for baseline by subtracting the mean pre-dose baseline (average of at least three pre-dose values, e.g. 0, -0.5, and -1.0 hour) from individual post-dose values. The baseline corrected and uncorrected data and statistical analyses should be submitted to the Agency. Bioequivalence should be determined based on the baseline corrected pharmacokinetic data.

**Bioequivalence based on (90% CI):** leucovorin or 5-methyl tetrahydrofolic acid. If leucovorin cannot be reliably measured, you should analyze the metabolite data using the confidence interval approach.

**Waiver request of in vivo testing:** 5 mg, 10 mg and 15 mg based on (i) acceptable bioequivalence studies on the 25 mg strength, (ii) acceptable discussion testing across 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 web site, 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).