Contains Nonbinding Recommendations

Draft Guidance on Leucovorin Calcium

Active ingredient: Leucovorin Calcium

Form/Route: Tablets/Oral

Recommended studies: 1 study

Type of study: Fasting
Design: Single-dose, two-way, crossover *in-vivo*
Strength: 25 mg
Subjects: Normal healthy males and females, general population
Additional Comments: Subjects should refrain from eating food high in folic acid prior to and during the study.

Analytes to measure: Leucovorin and its metabolite, 5-methyl-tetrahydrofolic acid in plasma using an achiral assay. 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 value (average of at least three pre-dose values, e.g. 0, -0.5 and -1.0 hr) 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 its metabolite, 5-methyl-tetrahydrofolic acid. If leucovorin cannot be reliably measured, you should analyze the metabolite data obtained from the study 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 dissolution testing across all strengths, and (iii) proportional similarity in the formulations across all strengths.

Dissolution test method and sampling times:

Please note that a **Dissolution Methods Database** is available to the public at the OGD website at http://www.fda.gov/cder/ogd/index.htm. Please find the dissolution information for this product at this website. Please 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 application.