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Draft Guidance on Leucovorin Calcium

October 2024

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Active Ingredient: Leucovorin calcium

Dosage Form: Tablet

Route: Oral

Strengths: EQ 5 mg Base, EQ 10 mg Base, EQ 15 mg Base, EQ 25 mg Base

Recommended Study: One in vivo bioequivalence study with pharmacokinetic endpoints

1. Type of study: Fasting
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: EQ 25 mg Base
   Subjects: Healthy males and non-pregnant, non-lactating females
   Additional comments: Subjects should refrain from folate and folic acid intake prior to and during the study.

Analytes to measure: Leucovorin and the 5-methyl tetrahydrofolic acid metabolite in plasma

If leucovorin plasma concentrations can be reliably measured and its pharmacokinetic parameters accurately determined, 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, analyze the metabolite data using the confidence interval approach.

Waiver request of in vivo testing: EQ 5 mg Base, EQ 10 mg Base, and EQ 15 mg Base strengths based on (i) acceptable bioequivalence study on the EQ 25 mg Base strength, (ii) acceptable in vitro dissolution testing of all strengths, and (iii) proportional similarity of the formulations across all strengths

Dissolution test method and sampling times: The dissolution information for this drug product can be found in the FDA's Dissolution Methods database, http://www.accessdata.fda.gov/scripts/cder/dissolution/. Conduct comparative dissolution testing on 12 dosage units for each of all strengths of the test product and reference listed drug (RLD).[1] Specifications will be determined upon review of the abbreviated new drug application.

Document History: Recommended July 2008; Revised July 2018, October 2024

Unique Agency Identifier: PSG_018342

[1] If the RLD is not available, refer to the most recent version of the FDA guidance for industry on *Referencing Approved Drug Products in ANDA Submissions*.