

Draft Guidance on Nortriptyline Hydrochloride

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Capsules; oral

Recommended Studies: Two in vivo studies

1. Type of study: Fasting

Design: Single-dose, two-way crossover in vivo

Strength: EQ 75 MG BASE

Subjects: Healthy males and nonpregnant females, general population

Additional comments:

- a. Female subjects should not be pregnant or lactating, and, if applicable, should practice abstinence or contraception during the study.
- b. Ensure adequate washout periods between treatments in the crossover studies due to nortriptyline's long terminal elimination half-life. Also consider using a parallel study design due to its long half-life. For long half-life drug products with low intra-subject variability in distribution and clearance, an AUC truncated to 72 hours may be used in place of AUC_{0-t} or $AUC_{0-\infty}$. For either a crossover or parallel study, sample collection time should be adequate to ensure completion of gastrointestinal transit of the drug product and absorption of the drug substance. Collect sufficient blood samples in the bioequivalence (BE) studies to adequately characterize the peak concentration (C_{max}) and time to reach peak concentration (t_{max}).

2. Type of study: Fed

Design: Single-dose, two-way crossover in vivo

Strength: EQ 75 MG BASE

Subjects: Healthy males and nonpregnant females, general population

Additional comments: Same as comments above

Analytes to measure (in appropriate biological fluid): Nortriptyline and its active metabolite, E-10-hydroxynortriptyline, in plasma

Submit the metabolite data as supportive evidence of comparable therapeutic outcome. For the metabolite, the following data should be submitted: individual and mean concentrations, individual and mean pharmacokinetic parameters, and geometric means and ratios of means for AUC and C_{max} .

Bioequivalence based on (90% CI): Nortriptyline

Waiver request of in vivo testing: EQ 10 MG BASE, EQ 25 MG BASE, and EQ 50 MG BASE strengths based on (i) acceptable BE studies on the EQ 75 MG BASE strength, (ii) proportionally similar formulation across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths

Dissolution test method and sample 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 the test and reference products. Specifications will be determined upon review of the abbreviated new drug application (ANDA).