

Draft Guidance on Paliperidone Palmitate

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Extended Release Suspension; Intramuscular

Recommended Studies: One study

1. Type of study: Bioequivalence (BE) study with pharmacokinetic (PK) endpoints
Design: Parallel or crossover steady-state
Strength: 39 mg/0.25 mL, 78 mg/0.5 mL, 117 mg/0.75 mL, 156 mg/mL, 234 mg/1.5 mL
Subjects: Male and nonpregnant female patients with schizophrenia or schizoaffective disorder who are already receiving a stable regimen of paliperidone palmitate extended release suspension via the intramuscular route. Patients who are already receiving any dosage regimen of paliperidone palmitate injection every month would be eligible to participate in the study by continuing their established maintenance dose.
Additional comments: (1) FDA does not recommend that studies be conducted using healthy subjects or patients on a different antipsychotic treatment. (2) Both sites of injection (gluteal and deltoid) should be included in the study design for adequate site representation to support the results of the study. (3) More than three doses may be required to reach steady state. PK data should be submitted to demonstrate that steady state has been reached for each individual. (4) All strengths of the test product need to be from the same bulk in order for all strengths of the Test to be administered in the PK BE study.

Analytes to measure (in appropriate biological fluid): Paliperidone in plasma

Bioequivalence based on (90% CI): Paliperidone

In the evaluation of bioequivalence of the multiple dose study, the following pharmacokinetic data should be submitted for paliperidone:

- Individual and mean blood drug concentration levels in a dosing interval after steady state is reached
- Individual and mean trough levels (C_{\min} ss)

- Individual and mean peak levels ($C_{\max \text{ ss}}$)
- Calculation of individual and mean steady-state AUC_{τ} (AUC_{τ} is AUC during a dosing interval at steady-state)
- Individual and mean percent fluctuation [$=100 * (C_{\max \text{ SS}} - C_{\min \text{ SS}})/C_{\text{average SS}}$]
- Individual and mean time to peak concentration

The 90% confidence interval for the ratio of the geometric means of the pharmacokinetic parameters (AUC and C_{\max}) should be within 80-125%. Fluctuation for the test product should be evaluated for comparability with the fluctuation of the reference product. The trough concentration data should also be analyzed to verify that steady-state was achieved prior to pharmacokinetic sampling.

Waiver request of in vivo testing: 39 mg/0.25 mL, 78 mg/0.5 mL, 117 mg/0.75 mL, and 234 mg/1.5 mL (if not studied in vivo) based on (i) acceptable bioequivalence study on the 156 mg/mL 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 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).