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Draft Guidance on Paliperidone Palmitate

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This guidance, which interprets the Agency’s regulations on bioequivalence at 21 CFR part 320, provides product-specific recommendations on, among other things, the design of bioequivalence studies to support abbreviated new drug applications (ANDAs) for the referenced drug product. FDA is publishing this guidance to further facilitate generic drug product availability and to assist the generic pharmaceutical industry with identifying the most appropriate methodology for developing drugs and generating evidence needed to support ANDA approval for generic versions of this product.

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This is a new draft product-specific guidance for industry on generic paliperidone palmitate.

Active Ingredient: Paliperidone palmitate

Dosage Form; Route: Suspension, extended release; intramuscular

Recommended Study: One study

1. Type of study: Bioequivalence (BE) study with Pharmacokinetic (PK) endpoints
Design: Parallel or crossover steady state
Strengths: 273 mg/0.875 mL, 410 mg/1.315 mL, 546 mg/1.75 mL, 819 mg/2.625 mL
Subjects: Male and nonpregnant female patients with schizophrenia who are already receiving a stable regimen of 3-month paliperidone palmitate extended-release suspension via the intramuscular route. Patients who are already receiving any dosage regimen of 3-month paliperidone palmitate injection every three months would be eligible to participate in the study by continuing their established maintenance dose. Patients who are already receiving 78 mg/0.5 mL, 117 mg/0.75 mL, 156 mg/mL or 234 mg/1.5 mL of 1-month paliperidone palmitate injection monthly may be eligible to participate the study by switching to an equivalent dose of 3-month paliperidone palmitate injection.

Additional comments: (1) FDA does not recommend that studies be conducted using healthy subjects or patients on a different antipsychotic treatment. (2) Patients who are receiving monthly paliperidone palmitate injection should be adequately treated with 1-month paliperidone palmitate extended-release injectable suspension for at least four months at the time of initiation of 3-month paliperidone palmitate injection. (3) PK data should be submitted to demonstrate that steady state has been reached for each individual. (4) The applicant may select any one of the strengths (273 mg/0.875 mL, 410 mg/1.315 mL, 546 mg/1.75 mL, 819 mg/2.625 mL) to conduct PK BE study based on number of eligible patients, provided that all strengths of test product are from the same bulk.

Analyte to measure: 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} 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 [$=100 * (C_{\max} \text{ SS} - C_{\min} \text{ SS})/C_{\text{average}} \text{ SS}$]
- Individual and mean time to peak concentration

The 90% confidence interval for the ratio of the geometric means of the pharmacokinetic parameters (AUC ss and C_{\max} ss) 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.

Prospective applicants may also consider the use of quantitative methods and modeling (for example, model-integrated approach) to support demonstration of bioequivalence. In order to clarify the FDA's expectations for prospective applicants early in product development, and to assist prospective applicants to submit an ANDA as complete as possible, FDA strongly encourages prospective applicants to discuss their development program for an alternative approach to bioequivalence, with the FDA via the pre-ANDA meeting pathway.

Waiver request of in vivo testing: Strength(s) not studied in vivo based on (i) acceptable in vivo bioequivalence study, (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 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).

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