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Draft Guidance on Paliperidone Palmitate

May 2023

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In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

Active Ingredient: Paliperidone palmitate

Dosage Form; Route: Suspension, extended release; Intramuscular

Recommended Study: One in vivo bioequivalence study with pharmacokinetic endpoints

1. Type of study: Bioequivalence study with pharmacokinetic 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 non-pregnant 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) Patients who are receiving oral paliperidone, oral risperidone, risperidone intramuscular injectable may be eligible to participate the study by switching to paliperidone palmitate extended-release suspension. The decision for switching a patient from other antipsychotics (oral paliperidone, oral risperidone, risperidone intramuscular injectable) should be made by a healthcare professional based upon their knowledge and experience with the patient, and assessment of the benefits and risks. The transitioning should not be considered solely for the purpose of satisfying enrollment criteria for the bioequivalence study. (3) The applicant may conduct the study using one site of injection (either gluteal or deltoid). If both sites of injection (gluteal and deltoid) are included in the study, proportions of the patients should be similar between test and reference groups. (4) More than three doses may be required to reach steady state. pharmacokinetic data should be submitted to demonstrate that steady state has been reached for each individual. (5) The applicant may select any one of the strengths (39 mg/0.25 mL, 78 mg/0.5 mL, 117 mg/0.75 mL, 156

mg/mL, 234 mg/1.5 mL) to conduct pharmacokinetic bioequivalence study based on number of eligible patients, provided that all strengths of test product only differ in fill volume.

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 [$=100 * (C_{max}$ ss $- C_{min}$ ss$)/C_{average}$ 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 in the FDA's Dissolution Methods database, 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).

Additional information:

Device:
The reference listed drug (RLD) is presented as a kit that contains one prefilled syringe and two safety needles with integrated needle protection systems. The prefilled syringe and safety needles with the needle protection system are the device constituent parts.

FDA recommends that prospective applicants examine the size and shape, the external critical design attributes, and the external operating principles of the RLD devices when designing the Test (T) devices including:

- Single-use, fixed-dose, pre-filled syringe format
- Needle gauge and length
- Needle protection system

User interface assessment:
An ANDA for this product should include complete comparative analyses so FDA can determine whether any differences in design for the user interface of the proposed generic product, as compared to the RLD, are acceptable and whether the product can be expected to have the same clinical effect and safety profile as the RLD when administered to patients under the conditions specified in the labeling. For additional information, refer to the most recent version of the FDA guidance for industry on *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA*. [a]

Revision History: Recommended August 2011; Revised December 2013, December 2015, July 2016, May 2023

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[a] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.