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Draft Guidance on Aripiprazole

November 2024

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

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: Aripiprazole

Dosage Form: Suspension, extended release

Route: Intramuscular

Strengths: 720 mg/2.4 mL (300 mg/mL), 960 mg/3.2 mL (300 mg/mL)

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: 960 mg/3.2 mL
   Subjects: Male and non-pregnant female patients with schizophrenia or bipolar I disorder who are already receiving a stable regimen of aripiprazole extended-release injectable suspension (960 mg/3.2 mL) for intramuscular use.
   Additional comments:
   a. FDA does not recommend that studies be conducted using healthy subjects or patients on a different antipsychotic treatment.
   b. Patients who are receiving oral aripiprazole or aripiprazole extended-release injectable suspension once monthly dosing may be eligible to participate the study by switching to aripiprazole extended-release injectable suspension (960 mg/3.2 mL). The decision for switching a patient from oral aripiprazole or aripiprazole extended-release injectable suspension once monthly dosing 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.

c. Trough concentration data should be analyzed using appropriate statistical method to demonstrate that the steady state of test and reference listed drug (RLD) [1] has been reached for each individual prior to pharmacokinetic sampling.

Analyte to measure: Aripiprazole in plasma

Bioequivalence based on (90% CI): Aripiprazole

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

- 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 RLD.

Waiver request of in vivo testing: 720 mg/2.4 mL strength based on (i) acceptable bioequivalence study on the 960 mg/3.2 mL strength, and (ii) evidence supporting identical formulation composition between both 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 both strengths of the test product and RLD. Specifications will be determined upon review of the abbreviated new drug application (ANDA).

Additional information:

Device:
RLD is presented as a kit that consists of one prefilled syringe of aripiprazole suspension, and two needles with needle guards. The prefilled syringe and the needles with needle guard systems are the device constituent parts.

[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.*

FDA recommends that prospective applicants examine the external critical design attributes, and the external operating principles of the RLD device when designing the test device including:

- Single-dose, fixed-dose prefilled syringe format
- Needle gauge and length
- Needle guard 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]

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