Contains Nonbinding Recommendations

Draft Guidance on Aripiprazole

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Active Ingredient: Aripiprazole

Dosage Form; Route: Extended-release injectable suspension; intramuscular

Recommended Studies: One study

1. Type of study: In vivo steady-state fasting
   Design: Multiple-dose, randomized, crossover, in vivo
   Strength: 400 mg
   Subjects: Patients who are already receiving a stable regimen of aripiprazole extended-release injection via the intramuscular route. Patients who are already receiving 400 mg of aripiprazole extended-release injection every four weeks would be eligible to participate in the study by continuing their established maintenance dose.
   Additional comments: FDA recommends that studies not be conducted using healthy subjects or patients on a different antipsychotic treatment. Aripiprazole is a potent antipsychotic drug and its administration could be associated with some serious adverse events. Due to the nature of these adverse events, FDA recommends that bioequivalence of generic versions of potent antipsychotic drugs be assessed in patients already receiving the products on established regimens.

As per 21 CFR § 314.94, the proposed parenteral drug product should be qualitatively (Q1) and quantitatively (Q2) the same to the reference product for both strengths (300 mg/vial and 400 mg/vial).

Analytes to measure (in appropriate biological fluid): 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 plasma 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 $AUC_{interdose}$ ($AUC_{interdose}$ 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 median time to peak concentration

The log-transformed AUC and C_{max} data should be analyzed statistically using analysis of variance. 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.

In period 2 (when patients are switched from reference to test or vice versa), individual and mean blood drug concentration levels should also be reported during the first three dosing intervals. Intensive sampling should be performed during this period to accurately capture changes in trough and peak levels. This information will be used as supporting data for bioequivalence to confirm that any differences in T_{lag} does not result in significant transient differences in C_{min}.

Waiver request of in vivo testing:
300 mg based on (i) acceptable bioequivalence studies on the 400 mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of 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).