Contains Nonbinding Recommendations

Draft Guidance on Olanzapine Pamoate

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Extended Release Suspension; intramuscular

Recommended Studies: One study

1. Type of study: In vivo steady-state fasting
   Design: Multiple-dose (1) Parallel group, or (2) two period, crossover
   Strength: 405 mg/vial
   Subjects: Male and nonpregnant female patients with schizophrenia who are already on the 405 mg / 4 week maintenance dose of olanzapine pamoate extended release suspension.

   Additional Comments: (1) FDA recommends that studies not be conducted using healthy subjects or patients on a different antipsychotic treatment or who are not already receiving the 405 mg / 4 week dosage regimen. (2) PK data should be submitted to demonstrate that steady state has been reached for each individual. (3) Due to the risk of post-injection delirium sedation syndrome (PDSS) Zyprexa Relprevv (olanzapine pamoate) was approved with a Risk Evaluation and Mitigation Strategy (REMS) and an Elements to Assure Safe Use (ETASU) plan. All pertinent elements of the REMS and ETASU must be incorporated into the protocol and informed consent.

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

Bioequivalence based on (90% CI): Olanzapine

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

- 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 $AUC_{interdose}$ ($AUC_{interdose}$ 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 mean 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. 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: 210 mg/vial and 300 mg/vial based on (i) acceptable in vitro and in vivo bioequivalence studies on the 405 mg/vial strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro drug release 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 the test and reference products. Specifications will be determined upon review of the abbreviated new drug application (ANDA).