Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Olanzapine; Samidorphan L-Malate

February 2023

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Active Ingredients: Olanzapine; Samidorphan L-malate

Dosage Form; Route: Tablet; oral

Recommended Studies: Two in vivo bioequivalence studies with pharmacokinetic endpoints

1. Type of study: Fasting
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 5 mg; EQ 10 mg Base
   Subjects: Health males and non-pregnant, non-lactating females
   Additional comments: Exclude geriatric subjects (aged 65 years and over) due to higher incidences of orthostatic hypotension and central nervous system adverse events (e.g., cognitive impairment). Monitor vital sign and adverse reactions associated with orthostatic hypotension during the study. Subjects should not engage in potentially hazardous activities requiring complete mental alertness, such as driving a motor vehicle or operating machinery, until they have completely returned to their baseline level of cognitive functioning after taking olanzapine/samidorphan L-malate tablet. Ensure an adequate washout period between treatments in the crossover study due to the long elimination half-life of olanzapine. Alternatively, a parallel study design may be considered.

2. Type of study: Fed
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 5 mg; EQ 10 mg Base
   Subjects: Healthy males and non-pregnant, non-lactating females
   Additional comments: See comments above.

Analytes to measure: Olanzapine and samidorphan in plasma

Bioequivalence based on (90% CI): Olanzapine and samidorphan

Waiver request of in vivo testing: 10 mg; EQ 10 mg Base, 15 mg; EQ 10 mg Base and 20 mg; EQ 10 mg Base strengths based on (i) acceptable bioequivalence studies on the 5 mg; EQ 10 mg Base strength, (ii) acceptable in vitro dissolution testing of all strengths, and (iii) proportional similarity of the formulations across 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).

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