

Draft Guidance on Cariprazine Hydrochloride

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Capsule; oral

Recommended Studies: One study

1. Type of study and design: Multiple-dose, steady state, two-way crossover in vivo
Strength: EQ 6.0 mg Base
Subjects: Patients already receiving a stable dose of cariprazine hydrochloride capsules, EQ 6.0 mg Base
Additional comments: Cariprazine and its two major active metabolites, desmethyl cariprazine (DCAR) and didesmethyl cariprazine (DDCAR), have long terminal elimination half-lives (>24 hours). Because of their long half-lives, changes in dose will not be fully reflected in plasma for several weeks. Due to safety concerns, investigators should monitor patients for adverse reactions and treatment response for several weeks after treating with VRAYLAR and its test drug products. However, measurement of active metabolites is not necessary during the bioequivalence study since they are not metabolized presystemically. Extrapyramidal symptoms and akathisia are among the most common and most clinically significant adverse reactions, even at the lowest cariprazine doses. Dyspepsia, vomiting, somnolence, and restlessness are also commonly seen in patients with bipolar mania. In addition, patients should be monitored for rhabdomyolysis, blood pressure elevation, hepatotoxicity, and ocular toxicity.

Analytes to measure: Cariprazine in plasma

Bioequivalence based on (90% CI): Cariprazine

Waiver request of in vivo testing: EQ 1.5 mg base, EQ 3 mg base and EQ 4.5 mg base strengths based on (i) acceptable bioequivalence studies on the EQ 6.0 mg base strength, (ii) comparable dissolution testing of all strengths, and (iii) proportional similarity in the formulations 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).