

Draft Guidance on Asenapine Maleate

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Active ingredient: Asenapine Maleate

Form/Route: Tablet/Sublingual

Recommended studies: 1 study

1. Type of study: Steady-state
Design: Multiple-dose, two-way, crossover in vivo
Strength: EQ 10 mg base
Subjects: Male and non-pregnant female patients who are receiving a stable twice daily dose of asenapine maleate EQ 10 mg base. FDA recommends that studies not be conducted using healthy subjects.

Additional comments: 1) According to the randomization schedule, an equal number of patients would receive either the generic formulation (Treatment A) or the reference formulation (Treatment B) in the same dose as administered prior to the study, i.e., a twice daily dose of asenapine maleate EQ 10 mg base, for 7 days, 2) Patients would then be switched to the other product for a second period of 7 days. There should be no washout period between the two treatment periods, 3) After the study is completed, patients could be continued on twice daily dose of asenapine maleate EQ 10 mg base using an approved asenapine maleate product as prescribed by their clinicians, 4) Tablets should not be crushed, chewed, or swallowed, 5) Subjects should not eat or drink for 10 minutes after drug administration, 6) Applicants may consider using a reference-scaled average bioequivalence approach for this drug product. If using this approach, please provide evidence of high variability in the bioequivalence parameters, AUC and/or C_{max} (i.e., within-subject variability $\geq 30\%$) for the reference product. For general information on this approach, please refer to the Progesterone Capsule Draft Guidance for additional information regarding reference-scaled average bioequivalence approach. 7) Steady-state asenapine concentrations should be confirmed by obtaining at least three consecutive measurements of plasma asenapine concentrations prior to dosing.

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

Bioequivalence based on (90% CI): Asenapine

Waiver request of in vivo testing: EQ 5 mg base, based on (i) acceptable bioequivalence studies on the EQ 10 mg base strength, (ii) acceptable in vitro disintegration and dissolution testing of all strengths, and (iii) proportional similarity of the formulations across all strengths. Please refer to the Mirtazapine Tablet Draft Guidance for additional information regarding waivers of in vivo testing

Disintegration and Dissolution test method and sampling times:

Please conduct the disintegration test as per the USP. Please note that a **Dissolution Methods Database** is available to the public at the OGD website at <http://www.accessdata.fda.gov/scripts/cder/dissolution/>.

Please find the dissolution information for this product at this website. Please conduct comparative disintegration and dissolution testing on 12 dosage units each of all strengths of the test and reference products. Specifications will be determined upon review of the application.

Additional comments regarding the bioequivalence study:

Before the study begins, the proposed protocol must be approved by an institutional review board (IRB).¹

The FDA recommends that applicants enroll a sufficient number of patients to ensure adequate statistical power.

Blood samples should be collected over a dosing interval on day 7, following preliminary sampling on days 5 and 6 to confirm steady-state conditions. The last dose of asenapine maleate sublingual tablet, EQ 10 mg base to be taken before blood sampling for each period should be administered at the clinical site to assure exact timing of sampling.

1. Patient Entry Criteria and Facilities

To enter into this study, patients should be appropriate candidates for asenapine maleate sublingual tablet, EQ 10 mg base twice daily therapy (as stated in product labeling, e.g. exclude subjects with severe hepatic impairment, history of allergic or adverse responses to asenapine maleate or any comparable or similar product, history of drug induced leukopenia/neutropenia, history of congenital prolongation of the QT interval, history of cardiac arrhythmias, recent history of myocardial infarction or unstable heart disease) and have been taking a stable dose of asenapine maleate sublingual tablet, EQ 10 mg base twice daily therapy for at least three months. Patients should be otherwise healthy as determined by physical examination, medical history, and routine hematologic and biochemical tests (e.g., exclude subjects with screening low white blood cell count, neutropenia, hypomagnesemia, hypokalemia, prolonged QT interval or bradycardia).

Outpatients should be hospitalized for at least 2 days during the collection of each set of pharmacokinetic samples. The clinical and analytical laboratories used for the study should be identified in the study report, along with the names, titles, and curriculum vitae of the medical and scientific/analytical directors.

2. Safety Monitoring

White blood cell (WBC) counts should be monitored and asenapine maleate sublingual tablet treatment modified, if necessary, in accordance with the leukopenia, neutropenia and agranulocytosis warning in the labeling of the reference listed drug product. Patients requiring modification of asenapine maleate sublingual tablet treatment should be dropped from the study and provided with prompt medical care. Blood pressure, heart rate, and body temperature should be monitored during the study and immediate medical care provided for any significant abnormalities.

3. Restrictions

Patients should fast for at least 8 hours prior to and 4 hours after the administration of the morning dose of the test or reference treatment on day 7 of each period (i.e., the days on which blood samples are to be collected to assess the concentration-time curve). All meals on day 7 should be standardized during the study. Water may be allowed, except for 1 hour before and 1 hour after drug administration, when no liquid should be permitted.

¹ See 21 CFR 314.94(a)(7)(iii)

Patients with any of the following should be excluded from the study:

- A history of allergic or adverse reactions to asenapine maleate or any comparable or similar product
- A history of severe hepatic impairment, drug induced leukopenia/neutropenia, congenital prolongation of the QT interval, cardiac arrhythmias, myocardial infarction or unstable heart disease
- Concurrent primary psychiatric or neurological diagnosis, including organic mental disorder, severe tardive dyskinesia, or idiopathic Parkinson's disease
- A total white blood cell count below 4000/mL, or an absolute neutrophil count below 2000/mL
- A history of granulocytopenia or myeloproliferative disorders (drug-induced or idiopathic)
- Significant orthostatic hypotension (i.e., a drop in systolic blood pressure of 30 mm Hg or more and/or a drop in diastolic blood pressure of 20 mm Hg or more on standing)
- Concurrent use of antihypertensive medication or any medication that might predispose to orthostatic hypotension
- A medical or surgical condition that might interfere with the absorption, metabolism, or excretion of asenapine maleate
- A history of epilepsy or risk for seizures
- Concurrent use of other drugs known to suppress bone marrow function
- Expected changes in concomitant medications during the period of study
- Positive tests for drug or alcohol abuse at screening or baseline
- A history of alcohol or drug dependence by *Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV)* criteria during the 6-month period immediately prior to study entry
- Compliance with outpatient medication schedule not expected
- History of multiple syncopal episodes

4. Blood Sampling

Venous blood samples should be collected after the day 7 morning dose to assess the concentration-time curve at predose (0 hours) and at 0.25, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0 hours. The predose blood sampling should include at least three successive trough level samples (C_{\min}). These samples should be collected on the last 3 days of dosing in each period to ensure that steady-state blood plasma/serum levels are achieved in each study period.

Other Recommendations

1. Precautions and Safety Issues

- Patients should be confined for at least 12 hours after the first dose of the test and reference products.
- Patients should remain in the supine position for the first 6 hours after the first dose, even if they were previously on a stable dose of asenapine maleate.
- Patients should be adequately hydrated. This may be achieved by administering 240 mL of water before the overnight fast, 240 mL of water one hour before dosing, and beginning no sooner than 1 hour after drug administration, 240 mL of water every 2 hours for 6 hours post-dosing. Subjects should not eat or drink for 10 minutes after drug administration.
- Patients must be adequately informed of possible cardiovascular adverse effects in the consent form.²

2. Statistical Analysis of Pharmacokinetic Data (Blood Plasma/Serum)

The following pharmacokinetic data should be used for the evaluation of bioequivalence of the multiple-dose study:

- Individual and mean blood drug concentration levels
- 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 statistically to verify that steady-state was achieved prior to Period 1 and Period 2 pharmacokinetic sampling.

3. Clinical Report and Adverse Reactions

- Patient medical histories, physical examination and laboratory reports, and all incidents of possible adverse reactions should be reported.

² See 21 CFR 50.25