Contains Nonbinding Recommendations

Draft Guidance on Brexpiprazole

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Tablets; oral

Recommended Studies: Two studies

1. Type of study: Fasting
   Design: Single-dose, two-way, two-period crossover or parallel design in-vivo
   Strength: 2 mg
   Subjects: Healthy males and nonpregnant females.
   Additional comments:

---

2. Type of study: Fed
   Design: Single-dose, two-way, two-period crossover or parallel design in-vivo
   Strength: 2 mg
   Subjects: Healthy males and nonpregnant females.
   Additional comments:

Notes:
Dystonia has been reported among healthy subjects who received brexpiprazole tablets. To avoid potential risk of dystonia, subjects who are younger than 45 years or have a history of dystonia should be excluded. Adverse events associated with brexpiprazole appear comparable to those associated with the atypical antipsychotic class of drugs (i.e., aripiprazole). All the safety precautions for healthy volunteer studies of brexpiprazole are the same as those recommended for healthy volunteer studies of aripiprazole. Please refer to the product specific guidance on aripiprazole tablets.

Brexpiprazole has a long terminal elimination half-life. Please ensure adequate washout periods between treatments in the crossover studies. For long half-life drug products, an AUC truncated to 72 hours may be used in place of AUC_{0-t} or AUC_{0-inf}. Please collect sufficient blood samples in the bioequivalence studies to adequately characterize the peak plasma concentration (C_{max}) and time for peak plasma concentration (T_{max}).

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

Bioequivalence based on (90% CI): Brexpiprazole

Waiver request of in-vivo testing:
0.25 mg, 0.5 mg, 1 mg, 3 mg and 4 mg based on (i) acceptable bioequivalence studies on the 2 mg strength, (ii) proportional similarity of the formulations 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).