Contains Nonbinding Recommendations

Guidance on Aripiprazole

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Tablet; Oral

Recommended Studies: Two studies

1. Type of study: Fasting
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 10 mg
   Subjects: Males and non-pregnant, non-lactating females, general population
   Additional comments: None

---

2. Type of study: Fed
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 10 mg
   Subjects: Males and non-pregnant, non-lactating females, general population
   Additional comments: None

Notes:

Life-threatening adverse events attributed to acute laryngeal dystonia have been reported following administration of a single dose of 30 mg aripiprazole to healthy subjects in bioequivalence studies. Although such events have not been reported at doses lower than 30 mg, because of the life-threatening nature of these events, and because the dose response relationship is not known for this event, the following safety precautions are recommended for healthy subject studies of aripiprazole at all doses:

- Study protocols should specify standard procedures to diagnose and treat dystonic reactions should they occur.
- Subjects younger than 45 years of age should be excluded. There appears to be an inverse linear relationship between age and the incidence of acute dystonic reactions. Adults under 35 years of age were reported to have a 15-fold higher rate of neuroleptic-induced dystonia compared to a group of patients 60-80 years of age. The occurrence of dystonias appears to be rare at ages of approximately 45 years and higher.
- Protocols should include stringent drug screening procedures to ensure that subjects are free of illicit drugs at the time of administration of each study drug dose.

- The screening interview should include specific questions to exclude subjects with a prior personal or family history of dystonic reactions to medications. Prospective study subjects should also be specifically questioned about prior neuroleptic drug exposures.

Aripiprazole has been poorly tolerated by healthy subjects in some bioequivalence studies, particularly at the 15 and 30 mg dose levels. In several cases, adverse events have resulted in a high incidence of dropouts. Adverse events in aripiprazole studies have included nausea, vomiting, dizziness, syncope, insomnia, headache, fatigue, hypotension, hot flashes, weakness, diaphoresis and confusion. To minimize the occurrence of adverse events, and to ensure the safety of healthy subjects in clinical trials of aripiprazole, the following is recommended:

- Subjects should be monitored in-house for at least 3 days after dosing and until adverse events have resolved.
- Subjects should be kept supine for at least 8 hours starting no longer than 15 minutes after each dose.
- Subjects should be asked to use the bathroom soon before dosing. Subjects should be encouraged to use urinals or bedpans during the first 8 hours after dosing and at any time after dosing if the subject is experiencing adverse events such as nausea, dizziness or hypotension. If subjects do use the bathroom during the first 8 hours after dosing or while experiencing adverse events such as nausea, dizziness or hypotension, they should be assisted to and from the bathroom by study personnel.
- At a minimum, routine 12-lead electrocardiograms (ECG) should be performed at 3-5 hours after dosing and at 8-12 hours after dosing. Continuous ECG monitoring during those time periods may be considered as an alternative.
- Vital signs monitoring should continue post dosing throughout the period that subjects are housed, commencing no later than 30 minutes following dosing. Vital signs should be monitored frequently (at least every 0.5-1 hour) for at least the first 8 hours after dosing and the first hour after subjects are allowed to rise from the supine position.
- Prespecified limits should be defined for reporting adverse events related to vital signs (e.g. hypotension, bradycardia, etc.). Vital sign readings that meet these predefined limits should be reported as adverse events, even if they are not performed during a scheduled assessment (e.g. vital signs performed as part of an assessment of an adverse event).
- The protocol should include standard procedures for the assessment and management of potential adverse events, including vital signs and ECG monitoring as appropriate for adverse events possibly associated with hypotension.
- Women of childbearing potential should be enrolled only if they are using effective contraceptives. A negative pregnancy test is needed within 24 hours prior to each dose. These subjects should also be informed of the potential teratogenicity of the study drug as part of the informed consent process.
- The protocol should include measures to prevent relative dehydration at the time of dosing, such as encouragement of water intake whenever possible prior to dosing. Consideration should be made to providing a standard meal just prior to the standard fasting period before dosing.
- During the informed consent process, subjects should be advised of the high incidence of adverse events that have occurred in some healthy subject studies of aripiprazole.

Aripiprazole has a long terminal elimination half-life. Ensure adequate washout periods between treatments in the crossover studies due to its long terminal elimination half-life. Also consider using a parallel study design due to its long half-life. For long half-life drug products with low intra-subject variability in distribution and clearance, an area under the curve (AUC) truncated to 72 hours may be used in place of AUC0-t or AUC0-∞. For either a crossover or parallel study, sample collection time should be adequate to ensure completion of gastrointestinal transit of the drug product and absorption of the drug substance. Collect sufficient blood samples in the bioequivalence studies to adequately characterize the peak concentration (Cmax) and time to reach peak concentration (Tmax).

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

Bioequivalence based on (90% CI): Aripiprazole

Waiver request of in vivo testing: 2 mg, 5 mg, 15 mg, 20 mg and 30 mg, based on (i) acceptable bioequivalence studies on the 10 mg strengths (ii) proportionally similar 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 web site, 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).