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Draft Guidance on Aripiprazole

October 2024

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Active Ingredient: Aripiprazole

Dosage Form: Tablet

Route: Oral

Strengths: 2 mg, 5 mg, 10 mg, 15 mg, 20 mg, 30 mg

Recommended Study: One in vivo bioequivalence study with pharmacokinetic endpoints

1. Type of study: Fasting
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 10 mg
   Subjects: Healthy males and non-pregnant, non-lactating females
   Additional comments: Exclude geriatric subjects (aged 65 years and over) due to higher risks of orthostatic hypotension and central nervous system adverse events (e.g., cognitive impairment). Exclude CYP2D6 poor metabolizers. Ensure an adequate washout period between treatments in the crossover study due to the long elimination half-life of aripiprazole. Alternatively, a parallel study design may be considered. See notes below for additional information on study design.

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 and the unknown dose response relationship of this event, the following safety precautions are recommended for studies conducted in healthy subjects of aripiprazole at all doses:

1. Study protocols should specify standard procedures to diagnose and treat dystonic reactions if they occur.
2. Subjects younger than 45 years of age should be excluded. The occurrence of dystonia appears to be rare at ages of approximately 45 years and higher.
3. 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.
4. Exclude subjects with a prior personal or family history of dystonic reactions to medications (e.g., neuroleptic drugs).

Aripiprazole can cause nausea, vomiting, dizziness, syncope, insomnia, headache, fatigue, hypotension, hot flashes, weakness, diaphoresis, and confusion and may lead to its discontinuation. To minimize the occurrence of adverse events and to ensure the safety of healthy subjects in clinical trials of aripiprazole, the following is recommended:

1. Monitor vital signs and adverse events associated with orthostatic hypotension. The protocol should include safety measures (e.g., sufficient hydration prior to dosing and remaining in supine position for at least 8 hours post-dose) to prevent adverse events associated with orthostatic hypotension.
2. Subjects should be informed of the symptoms of orthostatic hypotension and advised to rise slowly when changing their position (supine or sitting to or standing positions). Subjects should also be encouraged to use urinals or bedpans and should be assisted when using the bathroom during the first 8 hours after dosing and at any time if the subject is experiencing adverse events such as nausea, dizziness, or hypotension.
3. Subjects should be closely monitored at study unit until adverse events have resolved.

Analyte to measure: 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 strengths, based on (i) an acceptable bioequivalence study on the 10 mg strength (ii) acceptable in vitro dissolution testing of all strengths, and (iii) proportional similarity of the formulations across all 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 for each of all strengths of the test product and reference listed drug (RLD).[1] Specifications will be determined upon review of the abbreviated new drug application.

[1] If the RLD is not available, refer to the most recent version of the FDA guidance for industry on *Referencing Approved Drug Products in ANDA Submissions.*

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