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Draft Guidance on Clonazepam

November 2024

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

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Active Ingredient: Clonazepam

Dosage Form: Suspension[1]

Route: Oral

Strength: 1 mg/5 mL

Recommended Studies: Two options: (1) two in vivo bioequivalence studies with pharmacokinetic endpoints using the designated reference standard (RS) for clonazepam tablets or (2) one in vivo bioequivalence study with pharmacokinetic endpoints using the designated RS for clonazepam suspension

I. Option 1: Two in vivo bioequivalence studies with pharmacokinetic endpoints using the designated RS for clonazepam tablets[2]

1. Type of study: Fasting
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 1 mg/5 mL at a dose of 1 mg (5 mL)
   Subjects: Healthy males and non-pregnant, non-lactating females
   Additional comments: Conduct the study by testing 1 mg (5 mL) of the clonazepam suspension compared to 1 mg of the RS. Females of reproductive potential should use effective contraception during the study and for 2 weeks after the last dose. Ensure an adequate washout period between treatments in the crossover study due to the long

[1] Dosage form identified is the subject of an approved suitability petition (FDA-2003-P-0122).
[2] The currently designated RS for clonazepam tablets is the reference listed drug, NDA 017533, clonazepam tablets, 1 mg.

elimination half-life of clonazepam. Alternatively, a parallel study design may be considered.

2. Type of study: Fed
Design: Single-dose, two-treatment, two-period crossover in vivo
Strength: 1 mg/5 mL at a dose of 1 mg (5 mL)
Subjects: Healthy males and non-pregnant, non-lactating females
Additional comments: See comments above.

II. Option 2: One in vivo bioequivalence study with pharmacokinetic endpoints using the designated RS for clonazepam suspension[3]

1. Type of study: Fasting
Design: Single-dose, two-treatment, two-period crossover in vivo
Strength: 1 mg/5 mL at a dose of 1 mg (5 mL)
Subjects: Healthy males and non-pregnant, non-lactating females
Additional comments: Conduct the study by testing 1 mg (5 mL) of the clonazepam suspension compared to 1 mg (5 mL) of the RS. Females of reproductive potential should use effective contraception during the study and for 2 weeks after the last dose. Ensure an adequate washout period between treatments in the crossover study due to the long elimination half-life of clonazepam. Alternatively, a parallel study design may be considered. An additional bioequivalence study under fed conditions may be necessary if clonazepam suspension is deemed high-risk. High-risk products are those where the drug substance characteristics in combination with the complexity of the formulation design or manufacturing process lead to an increased likelihood that in vivo performance may be impacted differently by varying gastrointestinal conditions between the fasted and fed conditions. Refer to the most recent version of the FDA guidance for industry on *M13A Bioequivalence for Immediate-Release Solid Oral Dosage Forms*.[4]

Analyte to measure: Clonazepam in plasma

Bioequivalence based on (90% CI): Clonazepam

Waiver request of in vivo testing: Not applicable

Dissolution test method and sampling times: The dissolution information for the RS 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 the test product and the RS. Specifications will be determined upon review of the abbreviated new drug application.

[3] This option can be used when a petitioned ANDA for clonazepam suspension is approved and designated as the RS. There is currently no approved petitioned ANDA for clonazepam suspension.
[4] https://www.fda.gov/media/165049/download

Document History: Recommended November 2024

Unique Agency Identifier: PSG_017533-Sus