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Draft Guidance on Gepirone Hydrochloride

May 2025

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

Active Ingredient:	Gepirone hydrochloride
Dosage Form:	Tablet, extended release
Route:	Oral
Strengths:	EQ 18.2 mg Base, EQ 36.3 mg Base, EQ 54.5 mg Base, EQ 72.6 mg Base
Recommended Studies:	Three in vivo bioequivalence studies with pharmacokinetic endpoints

1. Type of study: Fasting
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: EQ 72.6 mg Base
   Subjects: Healthy males and non-pregnant, non-lactating females
   Additional comments: Exclude subjects ≥65 years. Exclude subjects with risk factors (e.g., QTc interval >450 msec) for prolonged QTc interval and Torsdaes de Pointes. Monitor electrocardiogram and electrolytes during the study. Subjects should be evaluated prior to discharge for cognitive impairment such as drowsiness, dizziness, and confusion and instructed not to drive or operate machinery until their cognitive function returns to baseline level.

Applicants may consider using a reference-scaled average bioequivalence approach for gepirone. If using this approach, the applicant should provide evidence of high variability in the bioequivalence parameters (i.e., within-subject variability ≥30%) for the reference standard. For general information on this approach refer to the most recent version of the FDA guidance for industry, *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an Abbreviated New Drug Application*,[a] for additional information regarding highly variable drugs.

2. Type of study: Fasting
Design: Single-dose, two-treatment, two-period crossover in vivo
Strength: EQ 18.2 mg Base
Subjects: Healthy males and non-pregnant, non-lactating females
Additional comments: See comments above.

3. Type of study: Fed
Design: Single-dose, two-treatment, two-period crossover in vivo
Strength: EQ 18.2 mg Base
Subjects: Healthy males and non-pregnant, non-lactating females
Additional comments: See comments above.

Analytes to measure: Gepirone, 3-hydroxy gepirone, and 2-(1-piperazinyl) pyrimidine in plasma

Provide the data for 3-hydroxy gepirone and 2-(1-piperazinyl) pyrimidine as supportive evidence of comparable therapeutic outcome. For 3-hydroxy gepirone and 2-(1-Piperazinyl) pyrimidine, the following data should be submitted: individual and mean concentrations, individual and mean pharmacokinetic parameters, and geometric means and ratios of means for AUC and C_{max}.

Bioequivalence based on (90% CI): Gepirone

Additional strengths: Bioequivalence of the EQ 36.3 mg Base and EQ 54.4 mg Base strengths to the corresponding reference listed drug (RLD)[1] strengths may be demonstrated based on principles laid out in the most recent version of the FDA guidance for industry on *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an Abbreviated New Drug Application*.[a]

Dissolution test method and sampling times: For modified release drug products, applicants should develop specific discriminating dissolution methods. Alternatively, applicants may use the dissolution method set forth in any related official United States Pharmacopeia (USP) drug product monograph, or in the FDA's database, http://www.accessdata.fda.gov/scripts/cder/dissolution/, provided that applicants submit adequate dissolution data supporting the discriminating ability of such a method. If a new dissolution method is developed, submit the dissolution method development and validation report with the complete information/data supporting the proposed method. Conduct comparative

[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.*

dissolution testing on 12 dosage units for each strength of the test (T) product and RLD.[1] Specifications will be determined upon review of the abbreviated new drug application.

In addition to the method above, submit dissolution profiles on 12 dosage units for each strength of the T product and RLD generated using USP Apparatus 1 at 100 rpm and/or Apparatus 2 at 50 rpm in at least three dissolution media (e.g., pH 1.2, 4.5 and 6.8 buffer). Agitation speeds may be increased if appropriate. It is acceptable to add a small amount of surfactant if necessary. Include early sampling times of 1, 2, and 4 hours and continue every 2 hours until at least 80% of the drug is released to provide assurance against premature release of drug (dose dumping) from the formulation.

Alcohol dose dumping studies: Due to concerns of dose dumping of drug from this product when taken with alcohol, conduct additional dissolution testing on all strengths using various concentrations of ethanol in the dissolution medium as follows:

Testing conditions: 900 mL, 0.1N HCl, USP Apparatus 2 (paddle) at 50 rpm, with or without alcohol

> Test 1: 12 units tested according to the proposed method (with 0.1 N HCl) with data collected every 15 minutes for a total of 2 hours
>
> Test 2: 12 units analyzed by substituting 5% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours
>
> Test 3: 12 units analyzed by substituting 20% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours
>
> Test 4: 12 units analyzed by substituting 40% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours

Conduct testing on both T product and RLD accordingly, and provide data on individual unit, means, range and %CV.

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[a] For the most recent version of a guidance, check the FDA guidance website at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.