Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Sodium Oxybate

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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

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:	Sodium oxybate
Dosage Form:	For suspension, extended release
Route:	Oral
Strengths:	4.5 gm/packet, 6 gm/packet, 7.5 gm/packet, 9 gm/packet
Recommended Studies:	Two in vivo bioequivalence studies with pharmacokinetic endpoints

1. Type of study: Fasting
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 4.5 gm/packet
   Subjects: Healthy males and non-pregnant, non-lactating females
   Additional comments: Exclude subjects with a history of obstructive sleep apnea. Exclude subjects with a history of recreational drug use or substance abuse. Exclude geriatric subjects due to risk of central nervous system effects. Monitor vital signs (e.g., respiratory rate and pulse oximetry) 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. Sodium oxybate extended release for suspension is approved under a Risk Evaluation and Mitigation Strategy (REMS) with Elements to Assure Safe Use (ETASU), which restricts its use. All pertinent elements of the REMS/ETASU must be incorporated into the protocol and informed consent. Follow the preparation and administration instructions in the reference listed drug (RLD) labeling.

2. Type of study: Fed
Design: Single-dose, two-treatment, two-period crossover in vivo
Strength: 4.5 gm/packet
Subjects: Healthy males and non-pregnant, non-lactating females
Additional comments: See comments above.

Analyte to measure: Gamma-hydroxybutyrate[1] in plasma

Bioequivalence based on (90% CI): Gamma-hydroxybutyrate

Additional strengths: Bioequivalence of the 6 gm/packet, 7.5 gm/packet, and 9 gm/packet strengths to the corresponding RLD 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 dissolution testing on 12 dosage units for each strength of the test and RLD products. Specifications will be determined upon review of the abbreviated new drug application (ANDA).

In addition to the method above, submit dissolution profiles on 12 dosage units for each strength of the test and RLD products 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 using various concentrations of ethanol in the dissolution medium as follows:

Testing Conditions: 900 mL, 0.1 N HCl, USP Apparatus 2 (paddle) at 100 rpm, with or without alcohol

[1] The drug name "sodium oxybate" is used to describe the salt form of the chemical gamma-hydroxybutyrate and the two names are often used synonymously.

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 test and reference products accordingly, and provide data on individual unit, means, range and %CV.

Additional information:

Device:
The RLD is presented in single-dose packets co-packaged with a mixing cup. The mixing cup is the device constituent part.

FDA recommends that prospective applicants examine the size and shape, the external critical design attributes, and the external operating principles of the RLD device when designing the test device including:

- Multi-use design
- Fill lines
- Screw-on cap

User interface assessment:
An ANDA for this product should include complete comparative analyses so FDA can determine whether any differences in design for the user interface of the proposed generic product, as compared to the RLD, are acceptable and whether the product can be expected to have the same clinical effect and safety profile as the RLD when administered to patients under the conditions specified in the labeling. For additional information, refer to the most recent version of the FDA guidance for industry on *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA*.[a]

Document History: Recommended May 2024

Unique Agency Identifier: PSG_214755

[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.