Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Sodium Phenylbutyrate; Taurursodiol

October 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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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 Ingredients: Sodium phenylbutyrate; Taurursodiol

Dosage Form: For suspension

Route: Oral

Strength: 3 gm/packet; 1 gm/packet

Recommended Study: One in vivo bioequivalence study with pharmacokinetic endpoints

1. Type of study: Fed
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 3 gm/packet; 1 gm/packet
   Subjects: Healthy males and non-pregnant, non-lactating females
   Additional comments: Avoid concomitant use of bile acid sequestering agents, inhibitors of bile acid transporters, aluminum-based antacids, probenecid, histone deacetylase inhibitors and inhibitors of organic anion transporting polypeptides 1B3 during the study to prevent taurursodiol from absorption from the gastrointestinal lumen.

Analytes to measure: Phenylbutyrate and taurursodiol in plasma

Post-dose taurursodiol measurements should be corrected by the baseline taurursodiol value. Multiple baseline concentrations should be measured from each individual subject in the period before administration of the study drug and subtract the time-averaged baseline or time-matched baseline from post-dose concentrations for those subjects in an appropriate manner consistent with the pharmacokinetic properties of the drug.

Baseline concentrations of taurursodiol should be determined for each dosing period, and baseline corrections should be period specific. The pharmacokinetic and statistical analyses should be performed on both uncorrected and corrected data.

Bioequivalence based on (90% CI): Phenylbutyrate and baseline-corrected taurursodiol

Waiver request of in vivo testing: Not applicable

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 the test product and reference listed drug (RLD).[1] Specifications will be determined upon review of the abbreviated new drug application.

Product-specific testing conditions for in vitro feeding tube studies: The approved labeling for the RLD states that the product may be administered by a nasogastric (NG) or gastrotomy (G) tube. Conduct the in vitro feeding tube studies, including comparative recovery testing, sedimentation volume and redispersibility testing, particle size distribution study, and in-use stability in designated dispersion media (i.e., water). For general procedures of in vitro feeding tube studies, refer to the most recent version of the FDA guidance for industry on *Oral Drug Products Administered Via Enteral Feeding Tube: In Vitro Testing and Labeling Recommendations*.[a]

Testing tube: NG tube (8 French) and G tube (12 French)

1. Three types of tube configurations including different materials and/or different designs with at least one PEG tube tested with an inflated balloon design
2. Reporting of the pH value of the water
3. Holding times of 0 and 1 hour after constitution

Sedimentation volume and redispersibility testing

Particle size distribution study

In-use stability in designated dispersion media (i.e., water)

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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.

[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.*