Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Tenapanor Hydrochloride

December 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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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:	Tenapanor hydrochloride
Dosage Form:	Tablet
Route:	Oral
Strengths:	EQ 10 mg Base, EQ 20 mg Base, EQ 30 mg Base
Recommended Studies:	Two options: (1) one in vitro bioequivalence study (comparative dissolution), or (2) one comparative clinical endpoint bioequivalence study

I. Option 1: One in vitro bioequivalence study

If the test product formulation is qualitatively (Q1) and quantitatively (Q2) the same as the reference listed drug (RLD) in inactive ingredients, the active pharmaceutical ingredient is present in the same solid form as the RLD, and the absolute change in total tablet weight relative to the RLD is within 5%, bioequivalence may be established by conducting one in vitro comparative dissolution study.

Type of study: In vitro comparative dissolution study

Comparative dissolution testing should be conducted using 12 dosage units each of the test product and the RLD in multiple media, including three compendial media covering pH 1.2 - 6.8 (e.g., pH 1.2, 4.5, and 6.8) and the quality control medium (unless identical to the compendial media).

Provide a dissolution method development report for the test product containing information and data that demonstrate the appropriateness of the selected dissolution method and sampling times, such as the discriminating ability to detect changes in critical quality attributes that could potentially impact drug product performance.

II. Option 2: One comparative clinical endpoint bioequivalence study

1. Type of study: Comparative clinical endpoint bioequivalence study
Design: Randomized, double-blind, parallel-group, placebo-controlled, in vivo
Strength: EQ 30 mg Base
Subjects: Males and non-pregnant, non-lactating females with chronic kidney disease on dialysis
Additional comments: Specific recommendations are provided below.

    1. FDA recommends conducting a bioequivalence study with clinical endpoint in subjects with chronic kidney disease on dialysis who have an inadequate response to phosphate binders or who are intolerant of any dose of phosphate binder therapy. After a 2-4 weeks run-in period during which existing phosphate binder treatment is maintained, subjects are to be randomized to receive the test product, RLD, or placebo twice daily for 2 weeks. The primary endpoint is the change from baseline in serum phosphorus concentration at Week 2.

    2. Inclusion criteria (the sponsor may add additional criteria):
        a. Males or females aged ≥18 years.
        b. Chronic maintenance hemodialysis 3 times per week for at least 3 months or chronic maintenance peritoneal dialysis for a minimum of 6 months. If modality of dialysis had changed, subject must have met 1 of the 2 dialysis criteria above and been on the new modality of dialysis for a minimum of 1 month.
        c. Stable vascular access
        d. If receiving active vitamin D or calcimimetics, the dose should have been unchanged for the last 4 weeks
        e. Dialysis adequacy Kt/V ≥1.2 at most recent measurement
        f. Prescribed and taking phosphate binder medication at least 3 times per day. The prescribed dose should have been unchanged during the last 4 weeks.
        g. Serum phosphorus concentrations ≥5.5 and ≤10.0 mg/dL

    3. Exclusion criteria (the sponsor may add additional criteria):
        a. Severe hyperphosphatemia defined as having a serum phosphorus concentration >10.0 mg/dL on phosphate binders at any time point during routine clinical monitoring for the 3 preceding months
        b. Serum/plasma parathyroid hormone >1200 pg/mL
        c. Clinical signs of hypovolemia
        d. History of inflammatory bowel disease or irritable bowel syndrome with diarrhea
        e. Scheduled for living donor kidney transplant

f. Persistent metabolic acidosis defined as serum carbon dioxide <18 mmol/L
g. Diarrhea or loose stools during the week before randomization defined as Bristol stool form scale ≥6 and frequency ≥3 for 2 or more days
h. Previous exposure to tenapanor

4. Study doses (EQ 30 mg Base twice daily) should be administered prior to breakfast and dinner (unless the meal is immediately prior to dialysis, in which case it should be administered just prior to the next meal after dialysis).

5. The study should include a list of prescription and over-the-counter drug products, procedures, and activities that are prohibited from the study, such as non-study medications that may increase bowel movement frequency and/or loosen stool.

6. Serum phosphorus should be obtained weekly pre-dialysis on a day of short dialysis interval. Consider analyzing serum phosphorus in a single laboratory if the study is conducted at multiple sites.

7. The parallel treatment arms should be balanced in baseline serum phosphorus concentrations, type of dialysis, and type of phosphate binder therapy.

8. Subjects requiring tenapanor dose adjustments (e.g., due to gastrointestinal tolerability) or additional therapy for phosphate lowering effect or major changes in dialysis (e.g., frequency or modality of dialysis) during the treatment period (2 weeks) should be excluded from analysis.

9. Temporary interruption or permanent discontinuation of treatment should be considered for subjects experiencing treatment-limiting adverse reactions (e.g., diarrhea). Criteria for terminating and resuming treatments should be specified in the protocol.

10. After completing the study, all subjects should continue the treatment using the RLD or alternative therapy based on the investigators' or their healthcare providers' discretion.

11. Provide Subject-Level Analysis Dataset (ADSL), one record per subject, using the following headings, if applicable:
    a. Study identifier
    b. Unique subject identifier
    c. Subject identifier for the study
    d. Study site identifier (if applicable)
    e. Age
    f. Age units (years)
    g. Sex
    h. Race
    i. Type of phosphate binder
    j. Type of dialysis

k. Name of planned treatment
l. Name of actual treatment
m. Safety population flag (yes/no)
n. Reason for exclusion from safety population
o. Modified intent-to-treat (mITT) population flag (yes/no)
p. Reason for exclusion from mITT
q. Per-Protocol (PP) population flag (yes/no)
r. Reason for exclusion from PP population
s. Completers population flag (yes/no)
t. Randomized population flag (yes/no)
u. Date/time of first exposure to treatment
v. Date/time of last exposure to treatment
w. End of study date
x. End of study status
y. Subject required additional treatment due to unsatisfactory treatment response (yes/no)
z. Compliance rate (%)
aa. Subject missed the scheduled dose for more than the pre-specified number of days (yes/no)
bb. Serum phosphorus at Baseline, Week 1, and Week 2
cc. Reason for premature discontinuation of subject
dd. Compliance rate (%)
ee. Subject missed pre-specified number of scheduled doses for more than pre-specified number of consecutive days (yes/no)
ff. Adverse event reported (yes/no)
gg. Concomitant medication (yes/no)

12. Provide basic data structure (BDS) dataset with records per subject, per visit, per analysis timepoint, using the following headings, if applicable:
    a. Study identifier
    b. Unique subject identifier
    c. Subject identifier for the study
    d. Study site identifier (if applicable)
    e. Name of planned treatment
    f. Name of actual treatment
    g. Safety population flag (yes/no)
    h. mITT population flag (yes/no)
    i. PP population flag (yes/no)
    j. Completers population flag (yes/no)
    k. Analysis date
    l. Analysis visit
    m. Study visit within designated window (yes/no)
    n. Serum phosphorus
    o. Analysis timepoint (e.g., Week 1)
    p. Additional treatment required during the visit (yes/no)
    q. Rescue medication/anti-diarrheal use reported (yes/no)

r. Concomitant medication during the visit (yes/no)
s. Adverse event reported during the visit (yes/no)
t. Laboratory testing during the visit (yes/no)

13. Refer to the most recent version of the FDA product-specific guidance *Adapalene; Benzoyl Peroxide Topical Gel* (NDA 207917)[a] for a recommended approach to statistical analysis and study design for the comparative clinical endpoint bioequivalence study.

14. Refer to the study data standards resources, https://www.fda.gov/industry/fda-resources-data-standards/study-data-standards-resources.

Waiver request of in vivo testing: EQ 10 mg Base and EQ 20 mg Base strengths based on (i) an acceptable comparative clinical endpoint bioequivalence study on the EQ 30 mg Base strength, (ii) acceptable in vitro dissolution testing of all strengths, and (iii) proportional similarity of the formulations across all strengths

---

Document History: Recommended December 2025

Unique Agency Identifier: PSG_213931

[a] For the most recent version of a product-specific guidance, check the FDA product-specific guidance website at https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm.