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Draft Guidance on Tenapanor Hydrochloride

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This guidance, which interprets the Agency's regulations on bioequivalence at 21 CFR part 320, provides product-specific recommendations on, among other things, the design of bioequivalence studies to support abbreviated new drug applications (ANDAs) for the referenced drug product. FDA is publishing this guidance to further facilitate generic drug product availability and to assist the generic pharmaceutical industry with identifying the most appropriate methodology for developing drugs and generating evidence needed to support ANDA approval for generic versions of this product.

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This is a new draft product-specific guidance for industry on generic tenapanor hydrochloride.

Active Ingredient: Tenapanor hydrochloride

Dosage Form; Route: Tablet; oral

Recommended study: One study

1. Type of study: Bioequivalence study with a clinical endpoint
   Design: Randomized, double blind, parallel, placebo controlled, in vivo
   Strength: EQ 50 mg Base
   Subjects: Males and non-pregnant and non-lactating females with irritable bowel syndrome with predominant constipation
   Additional comments: See comments below

Bioequivalence based on (90% CI): Clinical endpoint

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 each of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application.

Additional comments regarding the bioequivalence study with a clinical endpoint:

1. After a 2-week baseline/washout period, randomize patients to receive the generic tenapanor tablet, the reference drug tablet, or placebo twice daily for 7 days. The primary endpoint is the number of spontaneous bowel movements (SBM) during Week 1 (study days 1-7) compared to baseline. An SBM is defined as any bowel movement that did not occur within 24 hours after rescue medication use.

2. Inclusion Criteria (add additional criteria as needed)

    a. Males and non-pregnant females aged ≥18 years with a clinical diagnosis of irritable bowel syndrome with predominant constipation defined as <3 SBMs per week and confirmed by daily diary during baseline/pre-treatment period
    b. Have recurrent abdominal pain, on average, at least 1 day per week for at least 6 months before the baseline visit, and confirmed by daily diary during the 2-week baseline/washout period which is associated with 2 or more of the following criteria:
        - Related to defecation
        - Associated with a change in frequency of stool
        - Associated with a change in form (appearance) of stool
    c. Meet the colonoscopy requirements defined by the American Gastroenterological Association guidelines
        - Patients who are 50 years or older must have had a colonoscopy within 10 years of enrollment
        - Patients of any age with unexplained warning symptoms (e.g., lower gastrointestinal (GI) bleeding, iron deficiency anemia, clinically significant weight loss, systemic signs of infection or colitis) must have had a colonoscopy, with non-significant findings, after the onset or worsening of the warning symptoms
    d. Willing to discontinue any laxatives used before the Pretreatment Visit in favor of the protocol-defined Rescue Medicine
    e. No major changes in lifestyle that may have affected irritable bowel syndrome with predominant constipation (e.g., starting a new diet or changing his or her exercise pattern) at least 30 days prior to the Screening Visit, and agree to refrain from making any new major life-style changes from the time of screening to the last trial visit

3. Exclusion Criteria (add additional criteria as needed):

    a. Pregnant, breast feeding, or planning a pregnancy
    b. Patient of any age with evidence of weight loss, anemia, or rectal bleeding and without documentation of the results of either a flexible sigmoidoscopy or colonoscopy performed during the 6 months prior to dosing
    c. Documented mechanical bowel obstruction (e.g., bowel obstruction due to tumor, hernia), megacolon/megarectum, or diagnosis of pseudo-obstruction
    d. History of a disease or condition that is associated with constipation, such as Hirschsprung's disease, descending perineum syndrome, solitary rectal ulcer syndrome, collagen vascular disease, or systemic sclerosis
    e. Structural abnormality of the GI tract or a disease or condition that could affect GI motility
    f. History of bowel resection, malignant polyps, colitis, abdominal adhesions, intestinal ischemia, or esophageal atresia
    g. Known or suspected organic disorders of the large or small bowel (e.g., inflammatory bowel disease, ulcerative colitis, Crohn's Disease) or constipation secondary to a documented cause (e.g., surgery, bowel resection)
    h. Fecal impaction that required hospitalization or emergency room treatment within 3 months of the Screening Visit
    i. History of cathartic colon, laxative or enema abuse, ischemic colitis, or pelvic floor dysfunction
    j. Meet the Rome IV criteria for Opioid-Induced Constipation
    k. Diagnosis or family history of familial adenomatous polyposis, hereditary nonpolyposis colorectal cancer, or any other form of familial colorectal cancer
    l. Unexplained and clinically significant alarm symptoms (non-hemorrhoid lower GI bleeding [rectal bleeding or heme-positive stool], iron-deficiency anemia, weight loss) or systemic signs of infection or colitis
    m. Current active peptic ulcer disease
    n. Taking pharmacologic treatment for reflux that has not been stable for 15 days prior to Screening Visit
    o. History of diverticulitis or any chronic condition (e.g., chronic pancreatitis, polycystic kidney disease, ovarian cysts, endometriosis) that could be associated with abdominal pain or discomfort and could confound the assessments in this study, unless the patient was considered to have been cured of the condition
    p. Bariatric surgery for treatment of obesity or surgery to remove a segment of the GI tract at any time before the Screening Visit, surgery of the abdomen, pelvis, or retroperitoneal structures during the 6 months before the Screening Visit, an appendectomy or cholecystectomy during the 60 days before the Screening Visit
    q. Potential central nervous system cause of constipation (e.g., Parkinson's disease, spinal cord injury, and multiple sclerosis)
    r. Untreated hypothyroidism or treated hypothyroidism for which the dose of thyroid hormone had not been stable for at least 6 weeks at the time of the Screening Visit
    s. Hospitalized for any GI or abdominal surgical procedure during the 3 months prior to dosing

t. Clinically significant cardiovascular, liver, lung, neurologic, renal, or psychiatric disorder, or clinically significant laboratory abnormalities
u. Use of antibiotics within 4 weeks prior to baseline
v. Reported using barium enema within 7 days of the Screening Visit or reported using a prohibited medicine within 15 days of the Screening Visit or during the Pretreatment Period (note: the use of fiber supplement or bulk laxatives, and probiotics are acceptable, provided that the patient has been on a stable dose for 30 days before the Screening Visit and plans to continue stable dosing for the duration of the trial.)
w. Use of rescue medication for >2 days in either of the two weeks in the Pretreatment period or use of rescue medication within 72 hours before the first dose of the study drug

4. The protocol should include a list of the prescription and over-the-counter (OTC) drug products, procedures, and activities that are prohibited during the study, such as:

    a. Prescription and OTC laxatives other than those prescribed as a rescue medicine during the baseline/washout period by the Investigator (note: the use of fiber supplement or bulk laxatives, and probiotics are acceptable, provided that the subject has been on a stable dose for 30 days before the Screening Visit and plans to continue stable dosing for the duration of the trial.) Antibiotics, including rifaximin
    b. Oral anticholinergic agents
    c. Antidiarrheal agents including bismuth subsalicylate and kaolin
    d. Drugs known to cause diarrhea (e.g., orlistat, acarbose, misoprostol, colchicine)
    e. Drugs with activity on 5-HT4, 5-HT3, 5HT2b receptors
    f. Bile acid sequestrants
    g. Opioids
        - Anticonvulsants, antidepressants, calcium channel blockers, antihistamines with primary anti-H1 activity, proton pump inhibitors, and H2 antagonists are acceptable only if the patient has been on a stable dose for 15 days prior to Screening Visit and will remain on this same dose for the duration of the study
    h. Significant changes in diet

5. The study should include a 2-week screening and pretreatment period to assess study eligibility and baseline SBM. OTC or prescription laxatives other than those prescribed as a rescue medicine should not be administered prior to pre-treatment visit(s).

6. The recommended primary endpoint is the number of SBM during Week 1 (study days 1-7), compared to baseline.

7. Abdominal pain should be measured during the study period in a similar manner as the screening period.

8. Rescue medications (e.g., bisacodyl 5 mg tablets or 10 mg suppository) should be available if ≥72 hours have passed since the previous bowel movement and should be restricted to no more than 2 days each week, including pretreatment period. Submit a data set that includes daily rescue medication use for each patient who used the rescue medication at any point during the study. Pre-specify rescue medication use (amount, frequency), maximum daily rescue medication use, and any limitations on rescue medication use during the study.

9. Provide the Subject-Level Analysis Dataset, one record per subject, using the following headings, if applicable:

    a. Study identifier
    b. Subject identifier
    c. Study site identifier (if applicable)
    d. Age
    e. Age units (years)
    f. Sex
    g. Race
    h. Name of planned treatment
    i. Name of actual treatment
    j. Safety population flag (yes/no)
    k. Reason for exclusion from safety population
    l. Modified Intent-to-Treat (mITT) population flag (yes/no)
    m. Reason for exclusion from mITT population
    n. Per-Protocol (PP) population flag (yes/no)
    o. Reason for exclusion from PP population
    p. Completers population flag (yes/no)
    q. Randomized population flag (yes/no)
    r. Date/time of first exposure to treatment
    s. Date/time of last exposure to treatment
    t. End of study date
    u. End of study status
    v. Subject required alternate or supplemental treatment due to unsatisfactory treatment response (yes/no)
    w. Compliance rate (%)
    x. Subject missed the scheduled dose for more than the pre-specified number of days (yes/no)
    y. Number of spontaneous bowel movements at Baseline
    z. Number of spontaneous bowel movements during Week 1 (study days 1-7)
    aa. Average weekly abdominal pain score at Baseline
    bb. Average weekly abdominal pain score during Week 1 (study days 1-7)
    cc. Adverse event reported (yes/no)
    dd. Concomitant medication (yes/no)

10. Provide the basic data structure dataset with records per subject, per visit, per analysis time point, using the following headings, if applicable:

a. Study identifier
b. Unique subject identifier
c. Study site identifier
d. Name of planned treatment
e. Name of actual treatment
f. Safety population flag (yes/no)
g. mITT population flag (yes/no)
h. PP population flag (yes/no)
i. Completers population flag (yes/no)
j. Analysis date
k. Analysis visit
l. Study visit within the designated window (yes/no)
m. Number of SBMs on Baseline Day 1 (study day -13), Day 2 (study day -12), etc., to Baseline Day 14 (study day 0)
n. Number of BMs with lumpy or hard stools on Baseline Day 1, Day 2, etc., to Baseline Day 14
o. Number of BMs followed by sensation of incomplete evacuation on Baseline Day 1, Day 2, etc., to Baseline Day 14
p. Number of BMs with straining at defecation on Baseline Day 1, Day 2, etc., to Baseline Day 14
q. Number of SBMs on treatment Day 1 (study day 1), Day 2 (study day 2), etc., to treatment Day 7 (study day 7)
r. Number of SBMs on Baseline Day 1 (study day -13), Day 2 (study day -12), etc., to Baseline Day 14 (study day 0)
s. Abdominal pain on Baseline Day 1, Day 2, etc., to Baseline Day 14
t. Abdominal pain on treatment Day 1 (study day 1), Day 2 (study day 2), etc., to treatment Day 7 (study day 7)
u. Rescue medication/ laxative use reported (yes/no)
v. If reported, provide name, dose, date(s), and time of rescue medication use.
w. Concomitant medication reported during this visit (yes/no)
x. Adverse event reported during this visit (yes/no)
y. Laboratory testing during this visit (yes/no)

11. Refer to the draft product-specific guidance on *Adapalene; Benzoyl Peroxide, Gel; Topical, 0.3%; 2.5%* for a recommended approach to statistical analysis and study design for bioequivalence studies with a clinical endpoint.

12. Study data should be submitted in a standardized format. Refer to the study data standards published at www.fda.gov[1]

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[1] Study Data Standards Resources: https://www.fda.gov/industry/fda-resources-data-standards/study-data-standards-resources