

Draft Guidance on Plecanatide

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Active Ingredient: Plecanatide

Dosage Form; Route: Tablet; oral

Strength: 3 mg

Overview: This draft guidance provides recommendations for the development of generic drug product, Plecanatide Tablet, using synthetic plecanatide as the active pharmaceutical ingredient (API). FDA provides recommendations for the following:

1. characterizations to support a demonstration of API sameness.
2. demonstrating bioequivalence (BE) of this product.
3. product specific testing conditions for in vitro feeding tube studies.

Recommendations for Demonstrating API Sameness:

Sameness of synthetic plecanatide can be demonstrated based on comparative physicochemical and biological characterizations. The characterizations should include the following categories to support API sameness:

1. Primary peptide sequence and related molecular properties such as molecular formula, specific optical rotation, and spectroscopic properties
2. Configuration of the two disulfide bonds
3. In vitro biological activity (e.g., binding, functional assays)

Recommendations for Demonstrating BE:

BE can be demonstrated through either in vitro or in vivo studies.

1. In vitro option

If the test product formulation is qualitatively (Q1) and quantitatively (Q2) the same as the reference listed drug (RLD) in terms of inactive ingredients, then BE of the drug product may be established based solely on comparative dissolution.

Dissolution data in each specified medium should be provided for 12 tablets each of test and RLD as follows:

Apparatus: USP Apparatus 2 (paddle)
Media: water, 0.1N HCl, pH 4.5 buffer and pH 6.8 buffer
Volume: 500 mL
Temperature: 37°C
Rotation speed: 50 rpm
Sampling time points: 5, 10, 15, 20, 30 minutes

An f2 test should be performed using mean profiles to assure comparable test (T) and reference (R) product drug release under a range of pH conditions. The f2 test comparing T vs. R in each media should be 50 or greater. Note that the f2 test is not necessary when both T and R dissolve 85% or more in 15 minutes or less using all four media.

2. In vivo option

Type of study: BE Study with Clinical Endpoint
Design: Randomized, double blind, parallel, placebo controlled in vivo
Strength: 3 mg
Subjects: Male and female (nonpregnant and nonlactating) subjects with chronic idiopathic constipation
Additional comments: Specific recommendations on BE study with clinical endpoint are provided below after the section about feeding tube studies.

Bioequivalence based on (90% CI): Clinical endpoint

Dissolution test method and sampling times: The dissolution information for this drug product can be found on the FDA-Recommended Dissolution Methods web site, available to the public at the following location: <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 (ANDA).

Product specific testing conditions for in vitro feeding tube studies:

The approved labeling for the reference product states that the product may be administered by a nasogastric (NG) tube or gastric (G) tube. Conduct the in vitro feeding tube studies including comparative recovery testing and sedimentation volume testing. Refer to the Lansoprazole Delayed-Release Orally Disintegrating Tablet Draft Guidance for additional information regarding procedures of in vitro feeding tube studies.

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

Testing strength: 3 mg

Dispersion medium: 30 mL water

Specific recommendations on BE study with clinical endpoint:

1. The Office of Generic Drugs (OGD) recommends conducting a BE study with a clinical endpoint in the treatment of chronic idiopathic constipation. After a 2-week baseline/washout period, subjects are to be randomized to receive the generic plecanatide tablet, the RLD tablet, or placebo once daily. The primary endpoint is the number of spontaneous bowel movements (SBM) during Week 1 (study Days 1-7) compared to baseline.
2. Inclusion Criteria (the Applicant may add additional criteria)
 - a. Male or nonpregnant female aged ≥ 18 years with a clinical diagnosis of chronic idiopathic constipation defined as < 3 SBMs per week and confirmed by daily diary during baseline/pre-treatment period. An SBM is defined as any bowel movement that did not occur within 24 hours after rescue medication use.
 - b. Have one or more of the following symptoms related to bowel movements for at least 6 months before the baseline visit and confirmed by daily diary during the 2-week baseline/washout period:
 - straining during defecation more than 25% of the time
 - lumpy or hard stools for more than 25% of the bowel movements (Bristol Stool Form Scale 1 to 2)
 - sensation of incomplete evacuation following more than 25% of the bowel movements
 - sensation of anorectal obstruction/blockage more than 25% of the time
 - c. Meet the colonoscopy requirements defined by the American Gastroenterological Association (AGA) guidelines.
 - d. Willing to discontinue any laxatives used before the Pretreatment Visit in favor of the protocol-defined Rescue Medicine.
 - e. No major changes in life-style that may have affected CIC symptoms (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 (the Applicant may add additional criteria)
 - a. Pregnant, breast feeding, or planning a pregnancy.
 - b. Subject 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 Irritable Bowel Syndrome or 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 trial, 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 gastrointestinal 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 within 4 weeks prior to baseline of systemic antibiotic.
- 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, if 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.]
- 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 drug products, procedures, and activities that are prohibited during the study, such as:
 - a. Prescription and over-the-counter (OTC) laxatives other than those prescribed as a rescue medication during the baseline/washout period by the Investigator. Note: the use of fiber supplement or bulk laxatives, and probiotics are acceptable, if 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.
 - b. Antibiotics, including rifaximin
 - c. Oral anticholinergic agents
 - d. Antidiarrheal agents including bismuth subsalicylate and kaolin
 - e. Drugs known to cause diarrhea (e.g., orlistat, acarbose, misoprostol, colchicine)
 - f. Drugs with activity at 5-HT₄, 5-HT₃, 5HT_{2b} receptors
 - g. Bile acid sequestrants
 - h. Opioids
 - i. Anticonvulsants, antidepressants, calcium channel blockers, antihistamines with primary anti-H₁ activity, proton pump inhibitors, and H₂ antagonists are acceptable only if the subject 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.
 - j. Significant changes in diet.
5. The study should include a 2-week screening and pretreatment period to assess study eligibility and baseline SBM frequency. Over-the-counter or prescription laxatives cannot be administered beginning the day prior to pre-treatment visit(s).
6. The recommended primary endpoint is the number of spontaneous bowel movement (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.
7. Rescue medications (e.g. bisacodyl 5 mg tablets) 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. The Applicant should submit a data set that includes daily rescue medication use for each subject who used the rescue medication at any point during the study. The Applicant should pre-specify rescue medication use (amount, frequency), maximum daily rescue medication use, and any limitations on rescue medication use during the study.
8. The protocol should clearly define the per-protocol (PP), modified intent-to-treat (mITT) and safety populations.
 - a. The accepted PP population used for bioequivalence evaluation includes all randomized subjects who meet all inclusion/exclusion criteria, dosed a pre-specified proportion of the scheduled doses (generally at least 75% and no more than 125%) of the assigned product for the specified duration of the study, do not miss a pre-specified number of scheduled doses for more than pre-specified number of days, and complete the evaluation within the designated visit window with no protocol

- violations that would affect the treatment evaluation. The protocol should specify how compliance will be verified, (e.g., by subject diaries).
- b. The mITT and safety populations include all randomized subjects who use at least one dose of product.
9. Subjects who are discontinued early from the study due to lack of treatment effect should be included in the PP population. Subjects whose condition worsens and who require alternate or supplemental therapy, excluding pre-specified rescue therapies, for the treatment of constipation during the treatment phase of the study should be discontinued, included in the mITT and PP population analysis, and provided with effective treatment. Subjects discontinued early for other reasons should be excluded from the PP population, but included in the mITT population. The protocol should clearly state how missing data will be handled in the statistical analyses and provide appropriate justification for the method chosen.
 10. The start and stop date calendar date (e.g. mm/dd/yyyy) and study day (e.g. Day X) of concomitant medication use should be provided in the data set in addition to the reason for the medication use. The Applicant should clearly explain whether the medication was used prior to baseline visit, during the study, or both.
 11. All adverse events (AEs) should be reported, whether or not they are considered to be related to the treatment. The report of AEs should include date of onset, description of the AE, severity, relation to study medication, action taken, outcome and date of resolution. This information is needed to determine if the incidence and severity of adverse reactions is different between the test product and RLD.
 12. All pregnancies should be reported, including outcome information
 13. If the inactive ingredients are different than those contained in the RLD or in significantly different amounts, then the Applicant is to clearly describe the differences and provide information to show that the differences will not affect the safety, efficacy and/or systemic or local availability of the drug.
 14. The method of randomization should be described in the protocol. It is recommended that an independent third party generate and hold the randomization code throughout the conduct of the study to minimize bias. The Applicant may generate the randomization code if not involved in the packaging and labeling of the study medication. A sealed copy of the randomization scheme should be retained at the study site and should be available to FDA investigators at the time of site inspection to allow for verification of the treatment identity of each subject.
 15. A detailed description of the blinding procedure is to be provided in the protocol. The packaging of the test, reference and placebo products should be similar in appearance to make differences in treatment less obvious to the subjects and to maintain adequate blinding of evaluators. When possible, neither the subject nor the investigator should be

able to identify the treatment. The containers should not be opened by the subject at the study center.

16. Please refer to 21 CFR 320.38, 320.63 and the Guidance for Industry, “Handling and Retention of BA and BE Testing Samples”, regarding retention of study drug samples and 21 CFR 320.36 for requirements for maintenance of records of bioequivalence testing. In addition, the investigators should follow the procedures of 21 CFR 58 and ICH E6, “Good Clinical Practice: Consolidated Guideline”, for retention of study records and data to conduct their studies in compliance with Good Laboratory Practices (GLP) and Good Clinical Practices (GCP). Retention samples should be randomly selected from the drug supplies received prior to dispensing to subjects. Retention samples should not be returned to the Applicant at any time.
17. It is the Applicant's responsibility to enroll sufficient subjects for the study to demonstrate bioequivalence between the products.
18. A placebo control arm is recommended to demonstrate that the test product and RLD are active and as a parameter to establish that the study is sufficiently sensitive to detect differences between products.
19. To establish bioequivalence for a continuous endpoint, it is recommended the following compound hypotheses be tested using the per protocol population:
$$H_0: \mu_T / \mu_R < \theta_1 \quad \text{or} \quad \mu_T / \mu_R > \theta_2 \quad \text{versus} \quad H_A : \theta_1 \leq \mu_T / \mu_R \leq \theta_2$$
where μ_T = mean of the primary endpoint for the test group, and
 μ_R = mean of the primary endpoint for the reference group

The null hypothesis, H_0 , is rejected with a type I error (α) of 0.05 (two one-sided tests) if the estimated 90% confidence interval for the ratio of the means between test and reference products (μ_T / μ_R) is contained within the interval $[\theta_1, \theta_2]$, where $\theta_1 = 0.80$ and $\theta_2 = 1.25$. Rejection of the null hypothesis supports the conclusion of equivalence of the two products.
20. To establish sensitivity within the study for a continuous primary endpoint, the test and reference products should both be statistically superior to the placebo. Conduct an appropriate two-sided inferential test with a type I error (α) of 0.05, using the mITT population and the primary endpoint.
21. The study data should be submitted in standardized format. Please refer study data standards published at www.FDA.gov¹.
22. The protocol should include a full detailed statistical analysis plan and describe how missing data will be prevented and handled if exist.

¹ Study Data Standards for Submission to CDER available at:
<https://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm587508.htm>

23. Please provide the Subject-Level Analysis Dataset (ADSL), 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. Adverse event reported (yes/no)
 - bb. Concomitant medication (yes/no)
24. Please provide the basic data structure (BDS) 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. Per-Protocol (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. Rescue medication/ laxative use reported (yes/no)
- s. If reported, provide name, dose, date(s), and time of rescue medication use
- t. Concomitant medication reported during this visit (yes/no)
- u. Adverse event reported during this visit (yes/no)
- v. Laboratory testing during this visit (yes/no)