Formulary Drug Reviews: Plecanatide

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Generic Name: Plecanatide

Proprietary Name: Trulance (Synergy Pharmaceuticals)

Approval Rating: 1S

Therapeutic Class: Gastrointestinal Agents, Guanylate Cyclase C Agonists

Similar Drugs: Linaclotide

Sound-/Look-Alike Names: Linaclotide

Indications

Plecanatide is approved for the treatment of chronic idiopathic constipation (CIC) in adults.^{1,2} It is also being evaluated for the treatment of irritable bowel syndrome with constipation (IBS-C).^{3,4,5}

Constipation is characterized by dysfunction of colonic motility and the defecation process. CIC is a functional type of constipation. Constipation is defined as a symptom-based disorder characterized by infrequent stools and/or difficult stool passage; it tends to be more common in females, older patients, and those of lower socioeconomic status.^{6,7}

Linaclotide is approved for the treatment of CIC or IBS-C in adults.⁸ Other drugs used in the treatment of these conditions include laxatives, prokinetic agents, serotonergic agents, prosecretory agents (including linaclotide and plecanatide), and bile acid modulators.^{9,10} Based on its pharmacology, plecanatide may also be effective in the treatment of ulcerative colitis.¹¹

Clinical Pharmacology

Plecanatide is a uroguanylin analog. Uroguanylin and guanylin are natriuretic peptides involved in the maintenance of normal bowel movements. Uroguanylin and guanylin are agonists of guanylate cyclase C (GC-C) receptors in the gastrointestinal (GI) tract; however, their binding affinity may be affected by pH within the GI tract. Activation of GC-C receptors in the GI tract stimulates intracellular production of cyclic guanosine monophosphate (cGMP), which then activates cystic fibrosis transmembrane conductance regulator (CFTR) and cGMP-dependent protein kinase G-II. The activation of both CFTR and cGMP-dependent protein kinase G-II produces an efflux of chloride ions from enterocytes lining the GI tract, resulting in an efflux of water into the intestinal lumen.^{2,12,13,14,15}

Plecanatide is a peptide containing 16 amino acids that is structurally similar to uroguanylin. The structural difference

between plecanatide and uroguanylin is a single amino acid (ie, replacement of the penultimate aspartate at the N-terminus with glutamate in plecanatide).^{9,13,14,15} Plecanatide's effect on the GI tract is expected to be similar to that of uroguanylin.^{14,15} Linaclotide, also a GC-C agonist, may have less variation in its binding affinity to GC-C receptors along the longitudinal axis of the GI tract because of its relative insensitivity to changes in pH between 5 and 8.^{8,12} The clinical significance of this difference in binding affinity between plecanatide and linaclotide relative to pH has not been determined.

Pharmacokinetics

Plecanatide does not appear to be absorbed from the GI tract; no detectable plasma concentrations were observed after single oral doses of plecanatide ranging from 0.1 to 48.6 mg.^{2,14,16} Linaclotide is minimally absorbed, with low systemic availability following oral administration.⁸

Plecanatide is metabolized in the GI tract to an active metabolite. Both plecanatide and its active metabolite are proteolytically degraded within the intestinal lumen to smaller peptides and naturally occurring amino acids.²

Comparative Efficacy

Indication: CIC

Guidelines. Guideline: American College of Gastroenterology (ACG) monograph on the management of IBS and CIC

Reference: American College of Gastroenterology⁶

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Comments: Treatment of CIC may include fiber supplements, polyethylene glycol, lactulose, sodium picosulfate, bisacodyl, linaclotide, lubiprostone, and/or biofeedback. According to the ACG monograph, linaclotide is considered effective in the treatment of CIC (high-quality evidence, strong recommendation). Plecanatide is not mentioned in this monograph.

Guideline: American Society of Colon and Rectal Surgeons' clinical practice guideline for the evaluation and management of constipation

Reference: American Society of Colon and Rectal Surgeons⁷

Comments: Initial management of symptomatic constipation is dietary modification, which may include fiber and fluid supplements. Osmotic laxatives are recommended for the treatment of chronic constipation. Stimulant laxatives are recommended for short-term, second-line treatment of chronic constipation. When dietary modifications as well as osmotic and stimulant laxative therapy have failed, linaclotide and lubiprostone may be considered. Surgery may be appropriate in certain refractory cases. Plecanatide is mentioned in this guideline as an investigational agent.

Studies. Drug: Plecanatide versus placebo

Reference: Miner PB, et al, 2013^{17,18}

Study Design: Randomized, double-blind, multicenter study

Study Funding: Synergy Pharmaceuticals

Patients: 951 patients with CIC. Patients had to meet modified Rome III criteria for CIC diagnosis and have fewer than 3 complete spontaneous bowel movements (CSBMs) per week. Exclusion criteria were loose or watery stool in the absence of laxative use for more than 25% of bowel movements during 3 months prior to screening or during the 14-day pretreatment period; Rome III IBS-C diagnosis; active peptic ulcer disease not adequately treated; history of cathartic colon, laxative or enema abuse, or ischemic colitis; fecal impaction within 3 months of screening; disease or condition associated with constipation; structural abnormality of the GI tract or gastric bypass surgery; pelvic floor dysfunction; pseudo-obstruction; active infectious gastritis; diverticulitis; anal fissures or disease/condition that can affect GI motility or defecation or that is associated with abdominal pain; unexplained GI bleeding, iron deficiency anemia, weight loss, or systemic signs of infection or colitis; and major surgery within 60 days of screening. Of the 951 patients enrolled, 946 received at least 1 dose of the study medication and had at least 1 postdose efficacy assessment. Plecanatide-treated patients had a mean age of 47 years, and 86.5% were female; demographics of the placebo group were similar.

Intervention: Patients were randomized to receive placebo or plecanatide 0.3 mg, 1 mg, or 3 mg once daily for 12 treatment weeks.

Results

Primary End Point(s)

- Proportion of weekly responders, defined as those having at least 3 CSBMs per week and an increase of at least 1 CSBM per week from baseline, was 11.5% with placebo ($P = \text{NS}$), 19% with plecanatide 0.3 mg ($P < .05$), 17.2% with plecanatide 1 mg ($P = \text{NS}$), and 21.5% with plecanatide 3 mg ($P < .01$).
- Proportion of durable overall responders, defined as patients who were weekly responders for at least 9 of 12 treatment weeks, including 3 of the last 4 treatment weeks, was 10.7% with placebo ($P = \text{NS}$), 18.6% with plecanatide 0.3 mg ($P < .05$), 16.8% with plecanatide 1 mg ($P = \text{NS}$), and 19% with plecanatide 3 mg ($P < .01$). The number needed to treat (NNT) for durable overall CSBM response over 12 weeks of therapy was 12.1 with plecanatide 3 mg.

Secondary End Point(s)

- Change in frequency of spontaneous bowel movements (SBMs) and CSBMs per week from baseline occurred within the first week and were maintained through week 12 with plecanatide 3 mg. Weekly CSBMs increased by 1 or more from baseline over 12 weeks in 36.8% of patients with placebo ($P = \text{NS}$), 42.6% with plecanatide 0.3 mg ($P = \text{NS}$), 50% with plecanatide 1 mg ($P < .01$), and 52.3% with plecanatide 3 mg ($P < .001$).

Comments: This phase 2b/3 dose-ranging study was designed to assess the efficacy and safety of plecanatide in the treatment of CIC. Electronic diaries were used to track SBMs, CSBMs, and symptoms; missing diary data were imputed using mean data as replacement. The study used a modified intention-to-treat (mITT) population for analysis.

Limitations: Study results are only available as a published abstract.

Reference: Miner PB, et al, 2016 (Study-00)^{19,20}

Study Design: Randomized, double-blind, multicenter study

Study Funding: Synergy Pharmaceuticals

Patients: 1346 adults with CIC. Patients had to meet modified Rome III criteria for CIC diagnosis and had to have experienced symptoms for at least 3 months, with symptom onset at least 6 months prior to diagnosis. Exclusion criteria were loose or watery stool in the absence of laxative use for more than 25% of bowel movements during 3 months prior to screening or during the 14-day pretreatment period; active peptic ulcer disease, diabetes, or hypertension not adequately treated; history of cathartic colon, laxative or enema abuse, or ischemic colitis; fecal impaction within 3 months of screening; disease or condition associated with constipation; structural abnormality of the GI tract or gastric bypass surgery;

pelvic floor dysfunction; pseudo-obstruction; active infectious gastritis; diverticulitis; anal fissures or disease/condition that can affect GI motility or defecation or that is associated with abdominal pain; unexplained GI bleeding, iron deficiency anemia, weight loss, or systemic signs of infection or colitis; and participation in a previous plecanatide clinical trial.

Intervention: Patients were randomized (1:1:1) to receive placebo or plecanatide 3 mg or 6 mg once daily for 12 treatment weeks.

Results

Primary End Point(s)

- Proportion of durable overall responders, defined as patients who were weekly responders (3 or more CSBMs and an increase of 1 or more CSBM from baseline) for at least 9 of 12 treatment weeks, including 3 of the last 4 weeks, was 10.2% with placebo, 21% with plecanatide 3 mg, and 19.5% with plecanatide 6 mg ($P < .001$ vs placebo for both). The NNT for durable overall CSBM response over 12 weeks of therapy was 9.3 with plecanatide 3 mg and 10.8 with plecanatide 6 mg.

Secondary End Point(s)

- Changes in the frequency of SBMs and CSBMs per week from baseline occurred within the first week and were maintained through week 12. SBMs increased from baseline at week 12 by 1.4 with placebo, 3.3 with plecanatide 3 mg, and 3.2 with plecanatide 6 mg ($P < .001$ vs placebo for both). CSBMs increased from baseline by 1.2 per week with placebo, by 2.5 per week with plecanatide 3 mg, and by 2.2 per week with plecanatide 6 mg ($P < .001$ vs placebo for both).

Comments: This phase 3 study was designed to assess the efficacy and safety of plecanatide in the treatment of CIC. Electronic diaries were used to track SBMs, CSBMs, and symptoms. The study used an mITT population for analysis and was conducted in the United States and Canada.

Limitations: Study results are only available as a published abstract.

Reference: Miner PB, et al, 2016 (Study-03)^{21,22}

Study Design: Randomized, double-blind, multicenter study

Study Funding: Synergy Pharmaceuticals

Patients: 1337 adults with CIC. Patients had to meet modified Rome III criteria for CIC diagnosis and had to have experienced symptoms for at least 3 months, with symptom onset at least 6 months prior to diagnosis.

Intervention: Patients were randomized (1:1:1) to receive placebo or plecanatide 3 mg or 6 mg once daily for 12 treatment weeks.

Results

Primary End Point(s)

- Proportion of durable overall responders, defined as patients who were weekly responders (3 or more CSBMs and an increase of 1 or more CSBM from baseline) for at least 9 of 12 treatment weeks, including 3 of the last 4 weeks, increased by 12.8% with placebo, 20.1% with plecanatide 3 mg, and 20% with plecanatide 6 mg ($P = .004$ vs placebo for both). The NNT for durable overall CSBM response over 12 weeks of therapy was 13.7 with plecanatide 3 mg and 13.9 with plecanatide 6 mg.

Secondary End Point(s)

- Changes in the frequency of SBMs and CSBMs per week from baseline occurred within the first week and were maintained through week 12. SBMs increased from baseline at week 12 by 1.8 with placebo, 3.2 with plecanatide 3 mg, and 3.2 with plecanatide 6 mg ($P < .001$ vs placebo for both). CSBMs increased from baseline by 1.4 per week with placebo, by 2.3 per week with plecanatide 3 mg, and by 2.2 per week with plecanatide 6 mg ($P < .001$ vs placebo for both).

Comments: This study used the same design as Study-00 and was conducted only in the United States.^{19,22} Pooled analysis of Study-00 and Study-03 demonstrated improvements in Bristol Stool Form Scale scores, Patient Global Assessments of constipation severity, treatment satisfaction scores, and treatment continuation scores with both doses of plecanatide compared with placebo.^{23,24} Patients from these 2 studies were eligible to enroll in a multicenter, open-label, 52-week safety and tolerability study of plecanatide.²⁵

Limitations: Study results are only available as a published abstract.

Contraindications, Warnings, and Precautions

Contraindications

Plecanatide is contraindicated in patients younger than 6 years due to the risk of serious dehydration, and in patients with known or suspected mechanical GI obstruction.² Linaclotide has similar contraindications.⁸

Although not stated in the prescribing information, a potential contraindication is hypersensitivity to plecanatide or any of its inactive ingredients (magnesium stearate and microcrystalline cellulose).²

Warnings and Precautions

According to the boxed warning for plecanatide, use in children 6 years to younger than 18 years is not recommended;

death from dehydration occurred in young juvenile mice administered a single dose of plecanatide in nonclinical studies.² The safety and effectiveness of plecanatide in patients younger than 18 years have not been determined; use in this age group should be avoided.²

Clinical studies of plecanatide did not include sufficient numbers of patients 65 years and older to determine whether they respond differently from younger patients. In general, dose selection in elderly patients should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.²

Diarrhea can occur with plecanatide therapy. Severe diarrhea was reported in 0.6% of patients in clinical trials. If severe diarrhea occurs, suspend plecanatide therapy and start rehydration therapy.²

Because plecanatide and its active metabolites are not well absorbed following oral administration, maternal use is not expected to result in fetal exposure to plecanatide; however, evidence in humans is insufficient to support this conclusion. In animal development studies, administration of plecanatide to pregnant mice and rabbits at doses higher than the recommended human dosage showed no effects on embryofetal development.²

There is no information regarding the presence of plecanatide in human milk or its effects on milk production or breastfeeding infants.²

The warnings and precautions for linaclotide are similar to those for plecanatide.⁸

Adverse Reactions

In clinical trials, diarrhea occurred in 5% of plecanatide-treated patients compared with 1% of placebo patients and was the main reason for discontinuation of plecanatide therapy (2% of patients in the plecanatide group vs 0.5% of the placebo group). The majority of cases of diarrhea occurred within 4 weeks of starting plecanatide therapy.² In linaclotide clinical trials, diarrhea occurred in 16% of patients treated with linaclotide compared with 5% of placebo patients. The main reasons for discontinuation of linaclotide therapy were diarrhea (5% vs less than 1% of the placebo group) and abdominal pain (1% vs less than 1% of the placebo group).⁸

Other adverse reactions reported with plecanatide included sinusitis, upper respiratory tract infection, abdominal distension, flatulence, abdominal tenderness, and increased liver biochemical tests (2 patients with alanine aminotransferase [ALT] levels greater than 5 to 15 times the upper limit of normal, and 3 patients with aspartate aminotransferase [AST] levels greater than 5 times the upper limit of normal).²

Drug Interactions

No clinically important drug-drug interactions have been reported with plecanatide. In vitro tests show that plecanatide and its active metabolite are neither substrates nor

inhibitors of the transporters P-glycoprotein (P-gp) or breast cancer resistance protein.² No clinically important drug-drug interactions have been reported with linaclotide, and linaclotide has not been shown to interact with the cytochrome P450 enzyme system or with P-gp.⁸

Recommended Monitoring

Patients who develop severe diarrhea should be assessed for electrolyte abnormalities and the need for rehydration therapy.

Dosing

The recommended plecanatide dosage is 3 mg orally once daily with or without food.² A dosage of 6 mg was used in clinical studies but is not recommended due to a lack of additional benefit and a greater incidence of adverse reactions.²

Plecanatide tablets should be swallowed whole. If the patient has difficulty swallowing, the tablet can be crushed and administered orally in applesauce or with water; the entire mixture should be immediately consumed after mixing. If the patient has a nasogastric or gastric feeding tube, the tablet can be crushed and administered with water through the tube immediately after mixing. Prior to administration, the feeding tube should be flushed with 30 mL of water using an appropriate syringe; after administration of the water/drug mixture, the feeding tube should be flushed with at least 10 mL of water.²

The recommended dosage of linaclotide is 145 mcg orally once daily on an empty stomach, at least 30 minutes prior to the first meal of the day. The capsules should not be crushed or chewed. If the patient has difficulty swallowing, the capsule can be opened and mixed with applesauce or water. A water/linaclotide mixture can be administered through a nasogastric or gastric feeding tube.⁸

Product Availability

The New Drug Application for plecanatide was filed with the US Food and Drug Administration in 2016, and was approved in January 2017.^{1,5}

Plecanatide is available as a 3-mg tablet. It is supplied in bottles of 30 and in child-resistant, aluminum foil unit-dose blister packs of 30.² It should be stored in a dry place at 20°C to 25°C (68°F-77°F), with excursions permitted to 15°C to 30°C (59°F-86°F). The tablets should be protected from moisture and stored in the original bottle with the desiccant; they should not be subdivided or repackaged.²

Drug Safety/REMS

No Risk Evaluation and Mitigation Strategy (REMS) is required for plecanatide or linaclotide.^{1,2,8}

Conclusion

Plecanatide is approved for the treatment of CIC in adults. In placebo-controlled studies, plecanatide improved the frequency of both SBMs and CSBMs. Head-to-head comparison studies with linaclotide have not been conducted. Although linaclotide is approved for both CIC and IBS-C, plecanatide is only approved for CIC. Outcome data to evaluate the impact on health care costs (eg, changes in frequency of clinic visits, frequency of acute exacerbations) are not available.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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References

- Beitz J. NDA approval letter: *Trulance* (plecanatide NDA 208745). Food and Drug Administration. http://www.access-data.fda.gov/drugsatfda_docs/applletter/2017/208745Orig1s000ltr.pdf. Published January 19, 2017. Accessed January 23, 2017.
- Trulance* (plecanatide) [prescribing information]. New York, NY: Synergy Pharmaceuticals; 2017.
- Plecanatide. ClinicalTrials.gov. <https://clinicaltrials.gov/ct2/results?term=plecanatide&Search=Search>. Accessed January 21, 2017.
- Synergy Pharmaceuticals. The plecanatide irritable bowel syndrome with constipation study (IBS-C) (CIBS). NLM Identifier: NCT01722318. ClinicalTrials.gov. <https://clinicaltrials.gov/ct2/show/NCT01722318?term=NCT01722318&rank=1>. Updated January 13, 2015. Accessed January 21, 2017.
- Synergy Pharmaceuticals. Synergy Pharmaceuticals announces acceptance of new drug application for plecanatide, a novel uroguanylin analog, in chronic idiopathic constipation [news release]. <http://ir.synergypharma.com/press-releases/detail/1809/synergy-pharmaceuticals-announces-acceptance-of-new-drug>. Published April 19, 2016. Accessed January 21, 2017.
- Ford AC, Moayyedi P, Lacy BE, et al; Task Force on the Management of Functional Bowel Disorders. American College of Gastroenterology monograph on the management of irritable bowel syndrome and chronic idiopathic constipation. *Am J Gastroenterol*. 2014;109(suppl 1):S2-S26.
- Paquette IM, Varma M, Ternent C, et al. The American Society of Colon and Rectal Surgeons' clinical practice guideline for the evaluation and management of constipation. *Dis Colon Rectum*. 2016;59(6):479-492.
- Linzess* (linaclotide) [prescribing information]. Cambridge, MA: Forest Pharmaceuticals; 2016.
- Camilleri M. Pharmacology of the new treatments for lower gastrointestinal motility disorders and irritable bowel syndrome. *Clin Pharmacol Ther*. 2012;91(1):44-59.
- Jadallah KA, Kullab SM, Sanders DS. Constipation-predominant irritable bowel syndrome: a review of current and emerging drug therapies. *World J Gastroenterol*. 2014;20(27):8898-8909.
- Pitari GM. Pharmacology and clinical potential of guanylyl cyclase C agonists in the treatment of ulcerative colitis. *Drug Des Devel Ther*. 2013;7:351-360.
- Busby RW, Ortiz S. Clarification of linaclotide pharmacology presented in a recent clinical study of plecanatide. *Dig Dis Sci*. 2014;59(5):1066-1067.
- Jarmuż A, Zielkińska M, Storr M, Fichna J. Emerging treatments in neurogastroenterology: perspectives of guanylyl cyclase C agonists use in functional gastrointestinal disorders and inflammatory bowel diseases. *Neurogastroenterol Motil*. 2015;27(8):1057-1068.
- Shailubhai K, Comiskey S, Foss JA, et al. Plecanatide, an oral guanylate cyclase C agonist acting locally in the gastrointestinal tract, is safe and well-tolerated in single doses. *Dig Dis Sci*. 2013;58(9):2580-2586.
- Shailubhai K, Palejwala V, Arjunan KP, et al. Plecanatide and dolcanatide, novel guanylate cyclase-C agonists, ameliorate gastrointestinal inflammation in experimental models of murine colitis. *World J Gastrointest Pharmacol Ther*. 2015;6(4):213-222.
- Shailubhai K, Barrow L, Talluto C, et al. Plecanatide, a guanylate cyclase-C agonist, improves bowel habits and symptoms associated with chronic constipation in a phase IIa clinical study [poster P1174]. Poster presented at: 2011 American College of Gastroenterology Annual Scientific Meeting; October 28-November 8, 2011; Washington, DC. http://content.stockpr.com/synergypharma/db/Posters/93/poster_file/Synergy_Poster_P1174.pdf. Accessed May 16, 2016.
- Miner PB, Surowitz R, Fogel R, et al. Plecanatide, a novel guanylate cyclase-C (GC-C) receptor agonist, is efficacious and safe in patients with chronic idiopathic constipation (CIC): results from a 951 patient, 12 week, multi-center trial [abstract 925g]. *Gastroenterology*. 2013;144(5)(suppl 1):S163.
- Synergy Pharmaceuticals. The plecanatide chronic idiopathic constipation (CIC) study. NLM Identifier: NCT01429987. ClinicalTrials.gov. <https://clinicaltrials.gov/ct2/show/NCT01429987?term=plecanatide&rank=3>. Updated April 26, 2016. Accessed January 21, 2017.
- Miner PB, Prieto B, De La Portilla M, et al. A phase III study of the efficacy and safety of plecanatide in the treatment of chronic idiopathic constipation (CIC) (study-00) [abstract Sa1440]. *Gastroenterology*. 2016;150(4)(suppl 1):S316.
- Synergy Pharmaceuticals. 12-week study of plecanatide for CIC (the CIC3 study). NLM Identifier: NCT01982240. ClinicalTrials.gov. <https://clinicaltrials.gov/ct2/show/record/NCT01982240?term=plecanatide&rank=1>. Updated April 26, 2016. Accessed January 21, 2017.
- Miner PB, Lentz JD, Berenguer R, et al. Efficacy and safety of plecanatide in the treatment of chronic idiopathic constipation (CIC): results from a multicenter phase III study (study-03) [abstract Su1214]. *Gastroenterology*. 2016;150(4)(suppl 1):s497-s498.
- Synergy Pharmaceuticals. 12-week study of plecanatide for CIC (the National CIC3 Study). NLM Identifier: NCT02122471. ClinicalTrials.gov. <https://clinicaltrials.gov/ct2/show/NCT02122471?term=plecanatide&rank=2>. Updated April 26, 2016. Accessed January 21, 2017.

23. Krause R, Foehl H, Koltun W, Barrow L, Griffin P. Effect of plecanatide on stool consistency in the treatment of chronic idiopathic constipation (CIC): Results from two phase III studies [abstract Sa1444]. *Gastroenterology*. 2016;150(4)(suppl 1):S317.
24. Nualart M, Morgan W, Berenguer R, Nguyen A, Barrow L, Magnus L. Effect of plecanatide on patient assessments in chronic idiopathic constipation (CIC): Results from two phase III studies [abstract Sa1443]. *Gastroenterology*. 2016;150(4)(suppl 1):S317.
25. Synergy Pharmaceuticals. Open-label extension (OLE) study of plecanatide for chronic idiopathic constipation (CIC). NLM Identifier: NCT01919697. ClinicalTrials.gov. <https://clinicaltrials.gov/ct2/show/NCT01919697?term=plecanatide&rank=4>. Updated August 11, 2016. Accessed January 21, 2017.