Prucalopride (Motegrity™) New Drug Update

January 2019

Drug Name	**prucalopride**
Trade Name (Manufacturer)	**Motegrity (Shire)**
Form	Oral tablet
Strength	1 mg, 2 mg
FDA Approval	December 14, 2018
Market Availability	2019 (anticipated)
FDA Approval Classification	Standard Review
Classification	To be determined

INDICATION[1]

Prucalopride (Motegrity) is a serotonin-4 (5-HT_4) receptor agonist indicated for the treatment of chronic idiopathic constipation (CIC) in adults.

Prucalopride's effects as 5-HT_4 receptor agonist serve as a gastrointestinal (GI) prokinetic agent; it stimulates colonic peristalsis, increasing bowel motility.

PHARMACOKINETICS

Notable pharmacokinetics include an absolute bioavailability of > 90%, plasma protein binding of approximately 30%, significant renal elimination, and a half-life of approximately 1 day. Food does not have a significant effect on the oral bioavailability. It is a substrate of cytochrome P450 3A4 and has several minor metabolites.

CONTRAINDICATIONS/WARNINGS

Prucalopride is contraindicated in patients with a history of hypersensitivity; hypersensitivity reactions, including dyspnea, rash, pruritus, urticaria, and facial edema have been observed with prucalopride. It is also contraindicated in patients with intestinal perforation or obstruction due to structural or functional disorder of the gut wall, obstructive ileus, or severe inflammatory conditions of the intestinal tract (e.g., Crohn's disease, ulcerative colitis, toxic megacolon/megarectum).

Prucalopride also carries a warning for suicidal ideation and behavior. Suicide completions, attempts, and ideation have been reported with prucalopride; however, a causal association between prucalopride and suicidal ideation has not been established. Patients, caregivers, and family members should be advised of these risks and instructed to contact a healthcare provider if the patient experiences these symptoms. In blinded trials, 1 patient reported an attempted suicide 7 days following prucalopride discontinuation, and 2 patients reported suicide attempts, 1 patient reported suicide ideation, and 2 patients had completed suicides (prucalopride discontinued ≥ 1 month prior) in open-label trials.

DRUG INTERACTIONS

Drug interactions with prucalopride are not described in the product labeling.

COMMON ADVERSE EFFECTS

The most common adverse reactions (≥ 2%) reported with prucalopride compared to placebo, respectively, in clinical trials were headache (19% versus 9%), abdominal pain (16% versus 11%), nausea (14% versus 7%), diarrhea (13% versus 5%), abdominal distension (5% versus 4%), dizziness (4% versus 2%), vomiting (3% versus 2%), flatulence (3% versus 2%), and fatigue (2% versus 1%).

SPECIAL POPULATIONS

Pregnancy

Data on the use of prucalopride use in pregnant women are insufficient to determine if there are any drug-associated risks of miscarriage, major birth defects, or adverse maternal or fetal outcomes.

Pediatrics

The safety and effectiveness of prucalopride have not been established in pediatric patients.

Geriatrics

No overall differences in safety and effectiveness were observed between elderly and younger patients using prucalopride in clinical trials; however, pharmacokinetic data suggests that elderly patients have a higher exposure to prucalopride compared to younger patients, likely due to decreased renal function.

Hepatic Impairment

Pharmacokinetic studies assessing prucalopride in hepatically impaired patients suggest that differences in these populations (Child-Pugh B and C) are not clinically significant.

Renal Impairment

As prucalopride is extensively excreted by the kidney, a decreased dose is recommended in patients with severe renal impairment and should be avoided in patients with end-stage renal disease (ESRD) requiring dialysis.

DOSAGES

The recommended dose is 2 mg orally once daily with or without food.

The recommended dose in patients with severe renal impairment (CrCl < 30 mL/min) is 1 mg once daily.

CLINICAL TRIALS[2,3,4,5]

A literature search was performed using "prucalopride" and "chronic idiopathic constipation."

Six, multicenter, randomized, double-blind, placebo-controlled clinical trials evaluated the efficacy and safety of prucalopride in the treatment of 2,484 adult patients with CIC (Study 1, n=501; Study 2, n=358; Study 3, n=476; Study 4, n=383; Study 5, n=426; Study 6, n=340). Five of the studies consisted

of 12 weeks of treatment while the sixth trial lasted for 24 weeks. Included patients were required to have a history of chronic idiopathic constipation, defined as ≤ 3 spontaneous bowel movements (SBMs) per week that result in a feeling of complete evacuation (complete spontaneous bowel movements [CSBMs]), and ≥ 1 of the select symptoms (lumpy or hard stools, sensation of incomplete evacuation, or straining at defecation) for > 25% of the bowel movements in the prior 3 months, with the onset of symptoms > 6 months prior to the screening. In Study 1, sensation of ano-rectal obstruction or blockade or the need for digital manipulation were also eligible select symptoms.

In Study 1, 2, and 6, only 2 mg doses were included for most adults, while in Study 3, 4, and 5, patients were randomized to either 2 or 4 mg daily. Notably, Study 2 and 6 initiated geriatric patients on 1 mg, and the dose could be increased to 2 mg after a few weeks if the response was inadequate (dose was increased in 88% of these patients). Results below include data for placebo and 1 or 2 mg. Study 2 included only males; however, the majority of patients across all trials were female (76%). Baseline demographics included 76% Caucasians a mean age of 47 years (range, 17 to 95 years), and the mean duration of constipation was 16 (±15 years) years.

The primary efficacy endpoint in all studies was response, defined as those with an average of ≥ 3 CSBMs/week over the 12-week treatment period, assessed using patient-reported diary entries. A statistically significant difference in response was found in all studies favoring treatment with prucalopride versus placebo, with the exception of Study 6 (see table below). An alternative definition of response, defined as those with ≥ 3 CSBMs/week and an increase of ≥ 1 CSBMs from baseline for ≥ 9 weeks of the 12-week treatment period and ≥ 3 of the last 4 weeks of treatment, was also assessed.

Study	Prucalopride Response (%)	Placebo Response (%)	Treatment Difference (95% Confidence Interval [CI])	P-value
1 (NCT01116206) Primary endpoint	33	10	23 (16 to 30)	< 0.001
Alternative endpoint	26	9	17 (11 to 24)	not reported
2 (NCT01147926) Primary endpoint	39	18	20 (11 to 29)	0.002
Alternative endpoint	32	14	18 (10 to 27)	not reported
3 (NCT00488137) Primary endpoint	19	10	10 (4 to 16)	< 0.001
Alternative endpoint	13	5	8 (2 to 12)	not reported
4 (NCT00483886) Primary endpoint	29	13	16 (8 to 24)	< 0.001
Alternative endpoint	19	8	11 (5 to 18)	not reported
5 (NCT00485940) Primary endpoint	24	12	12 (4 to 19)	< 0.001
Alternative endpoint	16	5	11 (5 to 16)	not reported
6 (NCT01424228) Primary endpoint	25	20	5 (-4 to 14)	0.341
Alternative endpoint	17	13	4 (-4 to 12)	not reported

OTHER DRUGS USED FOR CONDITION[6]

Key other competitors that are approved for chronic idiopathic constipation include linaclotide (Linzess®), lubiprostone (Amitiza®), and plecanatide (Trulance®). Both linaclotide and plecanatide are guanylate cyclase-C (GC-C) agonists, ultimately increasing intestinal fluid and accelerated gastrointestinal transit. Lubiprostone (Amitiza) activates ClC-2 chloride channels which produces a chloride-rich intestinal fluid secretion without altering serum electrolyte concentrations.

Several other laxatives (oral, enemas, or suppositories) may be used for the treatment of constipation, such as fiber supplements, bisacodyl, docusate, magnesium citrate, sodium phosphate, senna, milk of magnesia, lactulose, mineral oil, polyethylene glycol, and castor oil.

PLACE IN THERAPY[7,8,9]

The American Gastroenterological Association (AGA) classifies constipation as a syndrome that is defined by bowel symptoms specific to the difficult passage of stool, infrequent passage of stool, abnormal hardness of stool, or a feeling of incomplete evacuation after a bowel movement. Though constipation can occur secondary to another disease (e.g., Parkinson's disease, spinal cord injury), idiopathic constipation occurs independent of any other underlying disorder. Chronic idiopathic constipation (CIC) is diagnosed if there are < 3 spontaneous bowel movements (SBMs) per week with symptoms occurring for ≥ 6 months and at least 2 of the previously mentioned bowel symptoms.

Nonpharmacologic management of constipation includes dietary changes (e.g., increasing fiber intake) and biofeedback therapy. The AGA's 2013 guidelines on constipation suggest that a newer agent (e.g., lubiprostone, linaclotide) should be considered when symptoms do not respond to laxatives; however, these guidelines do not address CIC specifically and other newer agents were not available at the time of guideline preparation.

In 2014, the American College of Gastroenterology (ACG) provided a monograph on the Management of Irritable Bowel Syndrome and Chronic Idiopathic Constipation in an effort to assess the evidence of efficacy of IBS and constipation agents. The osmotic laxatives, polyethylene glycol (PEG) and lactulose, and stimulant laxatives, sodium picosulfate and bisacodyl, have been shown to be effective in chronic constipation. Other stimulant laxatives have not been adequately studied and are not recommended. Linaclotide (Linzess), lubiprostone (Amitiza), and plecanatide (Trulance) are all effective in CIC and are well tolerated, but comparative studies are not currently available to guide their place in CIC therapy.

Prucalopride (Motegrity), as a 5-HT_4 receptor agonist, offers an alternative option for the treatment of CIC in adults, with a mechanism of action that differs from other currently available treatments.

REFERENCES

1 Motegrity [package insert]. Lexington, MA; Shire; December 2018.
2 Motegrity [package insert]. Lexington, MA; Shire; December 2018.
3 Yiannakou Y, Piessevaux H, Bouchoucha M, et al. A randomized, double-blind, placebo-controlled, phase 3 trial to evaluate the efficacy, safety, and tolerability of prucalopride in men with chronic constipation. Am J Gastroenterol. 2015;110(5):741-8. DOI: 10.1038/ajg.2015.115..
4 Tack J, van Outryve M, Beyens G, et al. Prucalopride (Resolor) in the treatment of severe chronic constipation in patients dissatisfied with laxatives. Gut. 2009;58(3):357-65. DOI: 10.1136/gut.2008.162404.
5 Camilleri M, Kerstens R, Rykx A, et al. A placebo-controlled trial of prucalopride for severe chronic constipation. N Engl J Med. 2008;358(22):2344-54. DOI: 10.1056/NEJMoa0800670.
6 Clinical Pharmacology. Available at: https://www.clinicalpharmacology.com/. Accessed January 11, 2019.
7 Bharucha A, Pemberton J, Locke III G. AGA technical review on constipation. Gastroenterology 2013; 144:218-238. DOI: 10.1053/j.gastro.2012.10.028. Available at: http://www.gastro.org/guidelines. Accessed January 11, 2019.

8 Bharucha AE, Dorn SD, Lembo A, et al for the American Gastroenterological Association. American Gastroenterological Association medical position statement on constipation. Gastroenterology. 2013;144(1):211-7. DOI: 10.1053/j.gastro.2012.10.029. Available at: https://www.gastrojournal.org/article/S0016-5085(12)01545-4/pdf. Accessed January 11, 2019.
9 Ford AC, Moayyedi P, Lacy BE, et al. American College of Gastroenterology monograph on the management of irritable bowel syndrome and chronic idiopathic constipation. Am J Gastroenterol. 2014; 109 Suppl 1:S2-26; quiz S27. DOI: 10.1038/ajg.2014.187. Available at: http://www.nature.com/ajg/journal/v109/n1s/abs/ajg2014187a.html. Accessed January 11, 2019.