PDL DRUG REVIEW

Proprietary Name: Motegrity®
Common Name: prucalopride
PDL Category: GI, Constipation-IBS-OIC

Comparable Products	Preferred Drug List Status
Amitiza	Preferred with Conditions
Linzess	Non-Preferred with Conditions
Trulance	Non-Preferred with Conditions

Summary

Pharmacology/Usage: Prucalopride succinate, the active ingredient of Motegrity®, is a serotonin type 4 (5-HT4) receptor agonist. It is a gastrointestinal (GI) prokinetic agent that stimulates colonic peristalsis (high-amplitude propagating contractions [HAPCs]), which increases bowel motility. In isolated GI tissues from various animal species, prucalopride facilitated acetylcholine release to enhance the amplitude of contractions and stimulate peristalsis.

Indication: For the treatment of chronic idiopathic constipation (CIC) in adults.

There is no pregnancy category for this medication; however, the risk summary indicates that the available data from case reports with use in pregnant women are insufficient to identify any drug-associated risks of miscarriage, major birth defects, or adverse maternal or fetal outcomes. The safety and efficacy of use in the pediatric population have not been established.

Dosage Forms: Film-Coated Tablets: 1mg, 2mg

Recommended Dosage: Take 2mg PO QD, with or without food. In patients with severe renal impairment (Cr Cl <30ml/min), take 1mg QD. Dose adjustments are not required with mild and moderate renal impairment, as well as with hepatic impairment. Use in patients with end-stage renal disease requiring dialysis should be avoided.

Drug Interactions: There are currently no reported drug interactions with this product.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Motegrity®) minus reported % incidence for placebo. Please note that an incidence of 0% means the incidence was the same as or that the active drug was less than placebo.* The most frequently reported adverse events included headache (10%), abdominal pain (5%), nausea (7%), diarrhea (8%), abdominal distension (1%), dizziness (2%), vomiting (1%), flatulence (1%), and fatigue (1%).

In clinical trials, suicides, suicide attempts, and suicidal ideation have been reported. A causal association between treatment with Motegrity® and an increased risk of suicidal ideation and behavior has not been established. It is recommended to monitor all patients treated with Motegrity® for persistent worsening of depression or the emergence of suicidal thoughts and behaviors.

Contraindications: With a history of hypersensitivity to prucalopride or any component of the product; In patients with intestinal perforation or obstruction due to structural or functional disorder of the gut wall, obstructive ileus, severe inflammatory conditions of the intestinal tract such as Crohn's disease, ulcerative, colitis, and toxic megacolon/megarectum.

Manufacturer: Shire US Manufacturing, Inc

Analysis: The safety and efficacy of Motegrity® were assessed in 6 double-blind, placebo-controlled, randomized multicenter studies that included adults with CIC (N=2484). Studies 1 through 5 were 12-weeks in duration and study 6 was 24 weeks in duration. Overall, the majority of patients were female (76%) and white (76%). The mean adult age was 47 years and the mean duration of constipation was 16 years, with 28% having chronic constipation for at least 20 years.

Eligible patients required a history of chronic constipation, defined as having fewer than 3 spontaneous bowel movements (SBMs) per week that resulted in a feeling of complete evacuation (complete, spontaneous bowel movement [CSBM]) and 1 or more of the following symptoms for >25% of bowel movements in the preceding 3 months, with symptoms onset more than 6 months prior to screening: lumpy or hard stools, sensation of incomplete evacuation, straining at defecation. Patients who never had SBMs were eligible. In study 1, eligibility also included sensation of ano-rectal obstruction or blockade or the need for digital manipulation in more than 25% of bowel movements. In all studies, patients were excluded if constipation was due to secondary causes or suspected to be drug-induced.

For the primary efficacy endpoint, a responder was defined as a patient with an average of 3 or more CSBMs per week, over the 12-week treatment period. The table below includes the results, which was adapted from the prescribing information.

Study	Motegrity® 1 or 2mg QD		Placebo		Treatment difference	p-value
	N	n (%)	N	n (%)		
Study 1	249	83 (33%)	252	26 (10%)	23	<0.001
Study 2	177	67 (38%)	181	32 (18%)	20	<0.001
Study 3	236	46 (19%)	240	23 (10%)	10	0.002
Study 4	190	55 (29%)	193	25 (13%)	16	<0.001
Study 5	214	50 (24%)	212	25 (12%)	12	<0.001
Study 6	171	43 (25%)	169	34 (20%)	5	0.341

In all studies, improvement in the frequency of CSBMs per week was seen as early as week 1 and was maintained through week 12.

Of the 6 studies, the median time to first CSBM after dosing of Motegrity® on day 1 ranged from 1.4 to 4.7 days compared with 9.1 to 20.6 days in the placebo group. The median time to first SBM after dosing on day 1 ranged from 0.1 to 0.4 days in the Motegrity® group compared with 1.0 to 1.6 days in the placebo group.

Using an alternative efficacy endpoint, a responder was defined as a patient who had at least 3 CSBMs and an increase of at least 1 CSBM from baseline in a given week for at least 9 weeks out of the 12-week treatment period and for at least 3 of the last 4 weeks of the treatment period. The differences in response rates between Motegrity® and placebo can be seen in the table below, which was adapted from the prescribing information.

Study	Motegrity® 1 or 2mg QD		Placebo		Treatment difference
	N	n (%)	N	n (%)	
Study 1	249	65 (26%)	252	22 (9%)	17
Study 2	177	57 (32%)	181	25 (14%)	18
Study 3	236	30 (13%)	240	13 (5%)	8
Study 4	190	37 (19%)	193	15 (8%)	11
Study 5	214	34 (16%)	212	11 (5%)	11
Study 6	171	29 (17%)	169	22 (13%)	4

Place in Therapy: Motegrity® is an oral selective serotonin type 4 (5-HT4) receptor agonist indicated for the treatment of chronic idiopathic constipation in adults. It is a GI prokinetic agent that stimulates colonic peristasis, which increases bowel motility and it is the only 5-HT4 currently FDA approved. It was found in clinical trials to have a significantly higher responder rate in 5 of the 6 studies, with a responder being defined as a patient with an average of ≥3 CSBMs per week, over the 12-week treatment period.

A 2018 systematic review and meta-analysis by Nee et al[2] included 27 placebo-controlled trials to assess the safety and efficacy approved treatments for OIC. The most common primary outcome was 3 or more complete SBMs a week over the trial period. Results suggested that overall, the mu-opioid receptor antagonists, lubiprostone, and prucalopride were superior to placebo for the treatment of OIC.

There is no evidence at this time that Motegrity® is safer or more effective than the currently preferred, more cost-effective medications. It is therefore recommended that Motegrity® remain non-preferred and require prior authorization and be available to those who are unable to tolerate or who have failed on preferred medications.

PDL Placement: ☐ **Preferred**
☒ **Non-Preferred with Conditions**

Reference

[1] Motegrity [package insert]. Lexington, MA: Shire US Inc; 2018.
[2] Nee J, Zakari M, Sugarman MA, et al. Efficacy of treatments for opioid-induced constipation: systematic review and meta-analysis. *Clin Gastroneterol Hepatol*. 2018; 16(10): 1569-1584.