Drug Monograph

Drug/Drug Class:	**Motegrity™ (prucalopride) film coated tablet / GI Motility Agents**
Prepared for:	MO HealthNet
Prepared by:	Conduent

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms & Manufacturer:	Motegrity is available as an oral tablet in 1 mg and 2 mg tablets of prucalopride. Distributed by: Shire US Inc., Lexington, MA 02421.
Summary of Findings:	The efficacy of Motegrity was demonstrated in 6 randomized, double-blind, placebo-controlled clinical trials in 1237 patients. The primary efficacy endpoint was an average of 3+ complete, spontaneous bowel movements (CSBM), over the 12-week treatment period. In 4 of the 6 studies, the primary endpoint was achieved ($p<0.001$). Improvement in the frequency of SCBMs/week were seen as early as week 1 and maintained through week 12 in all studies.
Status Recommendation:	☐ Prior Authorization (PA) Required ☐ Open Access ☐ Clinical Edit ☒ PDL
Type of PA Criteria:	☐ Increased Risk of ADE ☒ Under Solicitation ☐ Appropriate Indications ☐ No PA Required

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payers are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction [1,2]

Chronic constipation is defined by the presence of the following for at least 3 months: 2 or more of the following for more than 25% of defecations (straining, lumpy/hard stools, sensation of incomplete evacuation, sensation of anorectal obstruction or blockage, manual maneuvers to facilitate evacuation, fewer than 3 spontaneous bowel movements per week), loose stools are rarely present without the use of laxatives, and does not meet criteria for diagnosis of irritable bowel syndrome. Constipation is extremely common, with prevalence of 16% of adults (33% in adults > 60 years), and rarely causes life-threatening disease.

Dosage Form [3]

Motegrity is available as an oral tablet in 1 mg and 2 mg tablets of prucalopride.

Manufacturer [3]

Distributed by: Shire US Inc., Lexington, MA 02421.

Indication(s) [3]

Motegrity is indicated for the treatment of chronic idiopathic constipation in adults.

Clinical Efficacy [3,4,5] (mechanism of action/pharmacology, comparative efficacy)

Motegrity, a selective serotonin-4 ($5HT_4$) receptor agonist, is a gastrointestinal prokinetic agent that stimulates colonic peristalsis, increasing bowel motility.

Pharmacokinetics:

	Motegrity
Absorption	Time to peak: 2 - 3 hours
Metabolism	Substrate of CYP3A4
Excretion	Urine: 60-65% as prucalopride Feces: 5% as prucalopride
Half-life	1 day

Clinical Trials Experience

STUDY 1 DESIGN	Randomized, double-blind, placebo-controlled study (n = 620)
INCLUSION CRITERIA	• ≥18 years of age • History of constipation (2 or fewer spontaneous bowel movements per week that result in a feeling of complete evacuation, or one or

	more of the following for at least 6 months: - very hard stools - sensation of incomplete evacuation following at least a quarter of stools - straining at defecation at least a quarter of the time
EXCLUSION CRITERIA	• Drug induced constipation • Subjects suffering from endocrine, metabolic or neurologic disorders • Subjects with megacolon/megarectum or pseudo-obstruction diagnosis • Constipation as a result of surgery • Known or suspected organic disorders: obstruction, carcinoma, inflammatory bowel disease • Severe or uncontrolled cardiovascular, liver or lung disease, neurologic or psychiatric disorders, cancers, AIDS, or other gastrointestinal or endocrine disorders • Impaired renal functions • Clinically significant abnormalities of hematology, urinalysis, or blood chemistry • Females of child bearing potential without adequate contraceptive protection during trial
TREATMENT REGIMEN	Patients were randomized to receive Motegrity 2 mg (n=190) once daily or placebo (n=193) for 12 weeks.
RESULTS	The primary measure of efficacy was the proportion of subjects with an average of 3 or more complete spontaneous bowel movements per week. 29% of patients achieved the primary endpoint using Motegrity, compared to 13% in the placebo group (95% CI (8,24): p<0.001).
SAFETY	Discussed in the Adverse Effects section below.

Contraindications [3,4]

- Hypersensitivity to Motegrity
- 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.

Warnings and Precautions [3,4]

- Suicidal ideation and behavior: Monitor patients for persistent worsening of depression and emergence of suicidal thoughts and behavior. Instruct patients to discontinue Motegrity immediately and contact their provider if depression is persistently worse, or they experience emerging suicidal thoughts or behaviors.

Adverse Effects [3,4]

Most common, ≥ 1%	Motegrity (n = 1251) %
Headache	19
Abdominal pain [a]	16
Nausea	14
Diarrhea	13
Abdominal distension	5
Dizziness	4
Vomiting	3
Flatulence	3
Fatigue	2

a. Includes 93 patients who started on Motegrity 1 mg and increased to 2 mg

Drug Interactions [3,4]

- There are no known significant drug interactions

Dosage and Administration [3,4]

- 2 mg once daily
- Renal Impairment: CrCl ≥ 30mL/minute: no dosage necessary. CrCl <30 mL/minute: 1 mg once daily.
- Hepatic Impairment: There are no dosage adjustments provided in the manufacture's labeling.

Cost

Generic Name	Brand Name	Manufacturer	Dose	Cost**/ Month
Prucalopride	Motegrity	Shire	2 mg daily	$423.90
Linaclotide	Linzess	Allergan	145 mcg daily	$213

** Wholesale Acquisition Cost

Conclusion

Motegrity is indicated for the treatment of chronic idiopathic constipation in adults. The efficacy of Motegrity was demonstrated in 6 randomized, double-blind, placebo-controlled clinical trials in 1237 patients. In 4 of the 6 studies, there was a statistically significant improvement in complete spontaneous bowel movements compared to placebo. Improvement in the frequency of SCBMs/week were seen as early as week 1 and maintained through week 12. Across the six studies, the median time to first complete, spontaneous bowel movement after dosing of Motegrity on day 1 ranged from 1.4 to 4.7 days compared to 9.1 to 20.6 days with placebo. The most common adverse reactions in patients taking Motegrity (>10%) were headache, abdominal pain, nausea, and diarrhea.

Recommendation

This drug is being considered for inclusion in the state specific Preferred Drug List (PDL).

References

1) Hayat U, Dugum M, Garg S. Chronic constipation: Update on management. Cleveland Clinic Journal of Medicine. 2017 May;84(5):397-408. https://www.mdedge.com/ccjm/article/136631/drug-therapy/chronic-constipation-update-management. Accessed May 20, 2019.
2) American Gastroenterological Association Medical Position Statement on Constipation. https://www.gastrojournal.org/article/S0016-5085(12)01545-4/fulltext?referrer=https%3A%2F%2Fwww.ncbi.nlm.nih.gov%2F. Accessed May 20, 2019.
3) Product Information: Motegrity™ (prucalopride). Shire US Inc., Lexington, MA 02421.
4) Prucalopride: Drug Information. Lexi-Drugs. Wolters Kluwer Clinical Drug Information Inc.
5) A Double-blind, Placebo-controlled, Trial to Evaluate the Efficacy and Safety of Prucalopride (R108512) Tablets in Subjects With Chronic Consiptation. https://clinicaltrials.gov/ct2/show/NCT00483886?term=00483886&rank=1. Accessed May 20th, 2019.

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Date: May 20, 2019