National PBM Drug Monograph

Lubiprostone (Amitiza™)

September 2006

VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel

Executive Summary:

Indication

Lubiprostone is indicated for the treatment of chronic idiopathic constipation (CIC) in the adult population. CIC is generally defined by infrequent or difficult passage of stool.

Goals of Therapy

The goal of therapy is to improve symptom control by either increasing the frequency of defecation or increasing the episodes of complete evacuation while at the same time decreasing symptoms associated with constipation-like defecatory straining.

Mechanism of Action of Lubiprostone (Amitiza™) in Chronic Idiopathic Constipation

Lubiprostone is a bicyclic fatty acid prostaglandin E 1 derivative that is a locally acting chloride channel activator that enhances a chloride-rich intestinal fluid secretion without altering sodium and potassium concentrations in the serum. Lubiprostone acts by specifically activating CIC-2, which is a normal constituent of the apical membrane of the human intestine, in a protein kinase A-independent fashion. By increasing intestinal fluid secretion, lubiprostone increases motility in the intestine, thereby increasing the passage of stool and alleviating symptoms associated with CIC.

Efficacy

The approval of lubiprostone by the FDA for treatment of chronic constipation was based on two randomized, placebo controlled efficacy trials published only as abstracts. These identical-design, double blind, placebo controlled studies were designed to investigate the efficacy of the drug in increasing spontaneuous bowel movement (SBM) frequency. A total of 479 patients went through a 2 week drug-free washout/baseline, followed by randomization to receive either 24 mcg lubiprostone or placebo twice daily for 4 weeks. Trial data indicated that subjects receiving the drug experienced significantly more SBMs at the end of week 1 than placebo. Similar results were observed for weeks 2-4, and no significant "rebound-effect" relapse was noted following the conclusion of treatment. Further, patients receiving the drug were more likely to experience their first SBM within 24 hours of dosing than placebo (56.7% vs. 36.9% for study 1; 62.9% vs. 31.9% for study 2), and time to first SBM was reduced. Signs and symptoms of constipation (including bloating, discomfort, poor stool consistency and straining) were also reduced for subjects receiving lubiprostone.

Adverse Effects

The most common adverse effects include nausea, diarrhea, and headache. There have been no reported cases of ischemic colitis at this time. Nausea related to lubiprostone most often occurs after the first few doses and is not transient.

Dosing

The recommended dosing for lubiprostone is 24 micrograms taken twice daily orally with food.

Recommendations

Based on currently available literature, lubiprostone should be reserved for patients who do not respond to all formulary alternatives (*e.g., bulking agents, stimulant laxatives, polyethylene glycol (PEG) osmotic laxatives*), including adequate dietary change and proper hydration, to relieve chronic idiopathic constipation. It is important to obtain appropriate evaluation and/or referral to a specialist for work-up of intractable constipation. Since the FDA approval for lubiprostone does not exclude patients > 65 years of age (as does the indication for tegaserod), lubiprostone may be a viable alternative in patients with an inadequate response to traditional therapy who are > 65 years of age (10.6% of N=479 in the efficacy trials and 18.4% of N=871 in the long term safety trials were age > or = 65 years) who are not candidates for tegaserod therapy. It may also be an alternative to other osmotic diuretics, in the case of patients at risk for electrolyte imbalances who do not have the degree of abdominal pain per Rome II Criteria to establish a diagnosis of Constipation predominant Irritable Bowel Syndrome (IBS-C). Efficacy should be established and regularly monitored. Efficacy studies indicate that approximately 72.1% of patients will fully respond to lubiprostone by the end of week one and 61.3% by 24 hours after initiation. If response is not seen within this time frame, it is reasonable to consider discontinuation.

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Introduction

The purposes of this monograph are to (1) evaluate the available evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to evaluating lubiprostone for possible addition to the VA National Formulary; (2) define its role in chronic idiopathic constipation; and (3) identify parameters for its rational use in the VA.

Pharmacology[1]

Chronic idiopathic constipation is generally defined by infrequent or difficult passage of stool. The signs and symptoms associated with chronic idiopathic constipation (i.e., abdominal pain or discomfort, bloating, straining, and hard or lumpy stools) may be the result of abnormal colonic motility that can delay the transit of intestinal contents and impede the evacuation of rectal contents. One approach to the treatment of chronic idiopathic constipation is the secretion of fluid into the abdominal lumen through the activation of chloride channels in the apical membrane of the gastrointestinal epithelium.

Lubiprostone is a bicyclic fatty acid prostaglandin E 1 derivative locally acting chloride channel activator that enhances a chloride-rich intestinal fluid secretion without altering sodium and potassium concentrations in the serum. Lubiprostone acts by specifically activating CIC-2, which is a normal constituent of the apical membrane of the human intestine, in a protein kinase A-independent fashion. By increasing intestinal fluid secretion, lubiprostone increases motility in the intestine, thereby increasing the passage of stool and alleviating symptoms associated with chronic idiopathic constipation. Patch clamp cell studies in human cell lines have indicated that the majority of the beneficial biological activity of lubiprostone and its metabolites is observed only on the apical (luminal) portion of the gastrointestinal epithelium.

Pharmacokinetics[1]

Lubiprostone has low systemic availability following oral administration and concentrations of lubiprostone in plasma are below the level of quantization (10pg/mL). Therefore, standard pharmacokinetic parameters such as area under the curve (AUC), C_{max}, and $t_{½}$ cannot be reliably calculated. However, the pharmacokinetic parameters of M3 (only measurable active metabolite) have been characterized.

Absorption

Peak plasma levels of M3, after a single dose of 24 mcg of lubiprostone, occurred at approximately 1.14 hours. The C_{max} was 41.9 pg/mL and the mean AUC was 59.1 pg•hr/mL. AUC of M3 increases proportionally after single 24-mcg and 144-mcg doses of lubiprostone.

Distribution

In vitro protein binding studies indicate lubiprostone is approximately 94% bound to human plasma proteins. Studies in rats with radio labeled lubiprostone indicate minimal distribution beyond the gastrointestinal tissues. Concentrations of radio labeled compound at 48 hours post-administration were minimal in all tissues. Patients requiring special attention with regards to protein binding issues include those with low albumin such as geriatric patients, those with

nephritic syndrome, recent myocardial infarction, surgical recovery, inflammatory diseases such as rheumatoid arthritis, liver disease and/or pregnancy.

Metabolism

The results of both human and animal studies indicate that lubiprostone is rapidly and extensively metabolized by 15-position reduction, α-chain β-oxidation, and ω–chain ω-oxidation. These biotransformations are not mediated by the hepatic cytochrome P450 system but rather appear to be mediated by the ubiquitously expressed carbonyl reductase. M3, a metabolite of lubiprostone in both humans and animals, is formed by the reduction of the carbonyl group at the 15-hydroxy moiety that consists of both α-hydroxy and β-hydroxy epimers. M3 makes up less than 10% of the dose of radio labeled lubiprostone. Animal studies have shown that metabolism of lubiprostone rapidly occurs within the stomach and jejunum, most likely in the absence of any systemic absorption. This is presumed to be the case in humans as well.

Elimination

Lubiprostone could not be detected in plasma; however, M3 has a $t_{½}$ ranging from 0.9 to 1.4 hours. After a single oral dose of 72 □g of ^{3}H-labeled lubiprostone, 60% of total administered radioactivity was recovered in the urine within 24 hours and 30% of total administered radioactivity was recovered in the feces by 168 hours. Lubiprostone and M3 are only detected in trace amounts in feces in humans.

Food Effect

A study was conducted with a single 72-mcg dose of ^{3}H-labeled lubiprostone to evaluate the potential of a food effect on lubiprostone absorption, metabolism, and excretion (AME). Pharmacokinetic parameters of total radioactivity demonstrated that C_{max} decreased by 55% while $AUC_{0-\infty}$ was unchanged when lubiprostone was administered with a high-fat meal. The clinical relevance of the effect of food on the pharmacokinetics of lubiprostone is not clear. However, lubiprostone was administered with food in a majority of clinical trials.

Special Populations

Gender

Gender has no effect on the pharmacokinetics of M3 when lubiprostone is administered.

Hepatic Impairment

Lubiprostone has not been studied in hepatically impaired populations.

Renal Impairment

Lubiprostone has not been studied in renally impaired populations.

Table 1 Pharmacokinetic Comparison of FDA-Approved Agents for Treatment of Constipation

Parameter	Lubiprostone	Tegaserod	Polyethylene glycol 3350
Metabolism	Oxidation and reduction in the stomach and jejunum	Presystemic acid catalyzed hydrolysis in stomach followed by oxidation and conjugation	n/a
Elimination	60% urine; 30% feces	2/3 excreted unchanged in feces, 1/3 excreted as main metabolite in urine	Feces primarily; <0.1% renal excretion
Half-life	0.9-1.4 hrs (M3)	11 +/- 5 hrs	n/a
Protein Binding	94%	98%	n/a
Bioavailability	n/a	10%	n/a

FDA Approved Indication(s) and Off-label Uses

Approved Indications: Lubiprostone is indicated for the treatment of chronic idiopathic constipation in the adult population.

Current Alternatives

Based on currently available literature, lubiprostone should be reserved for patients who do not respond to all formulary alternatives (*e.g., bulking agents, stimulant laxatives, polyethylene glycol (PEG) osmotic laxatives*), including adequate dietary change and proper hydration, to relieve chronic idiopathic constipation. An "adequate therapeutic trial" of the available alternatives should be considered per AGA expert consensus.[3] However, this adequate trial is not defined in terms of days to response and should be based on clinical judgment and patient parameters. *At this time, lubiprostone and tegaserod are the only agents FDA approved for the treatment of chronic idiopathic constipation.*

Tegaserod (Zelnorm): nonformulary for treatment of patients less than 65 years of age with chronic idiopathic constipation. Efficacy was not seen in patients > 65 years of age as they may have age related decreases in relevant 5HT4 receptors resulting in lack of efficacy.

Polyethylene glycol 3350 (Miralax): for treatment of occasional constipation.

Dosage and Administration

The recommended dosage of lubiprostone is 24mcg taken twice daily orally with food. Providers and patients should periodically assess the need for continued therapy. At this point, clinical trials have established safety for use of lubiprostone in patients who are responders to the drug for up to 48 months. The FDA did not require cessation and or interruption in therapy with drug approval.

Renal Impairment: Dosing has not been defined.

Hepatic Impairment: Dosing has not been defined.

Elderly: Dosing has not been defined.

Efficacy (refer to Appendix: Clinical Trials)[4-12]

The efficacy of lubiprostone has only been evaluated in placebo-controlled trials. Head to head comparisons of lubiprostone and other available treatments for chronic constipation are not currently available. Lubiprostone at a dose of 24 mcg twice daily has demonstrated efficacy in the treatment of chronic idiopathic constipation. Within 24 hours of the first dose, subjects in double blind placebo controlled trials had significant improvements in spontaneous bowel movements, which were sustained throughout trial duration of 4 weeks. Subjects reported improvements in stool consistency, straining, constipation severity and global assessment scores for constipation. Impact on visceral hypersensitivity of irritable bowel syndrome (IBS) constipation predominant could not be demonstrated, and is under investigation. Upon discontinuation of treatment, rebound constipation or worsening of constipation did not occur in a blinded randomized withdrawal trial, although significantly more patients experienced a relapse of symptoms. Safety and efficacy have been demonstrated for up to 48 weeks at this time. Additional data from open label trials out to 12 months support long term efficacy with respect to abdominal bloating, discomfort, and constipation severity.

Adverse Events (Safety Data)[1]

System/Adverse Event	Placebo (%) (n=316)	Lubiprostone (%)		
		24 mcg once daily (n=29)	24 mcg twice daily (n=1113)	Any Active Dose* (n=1175)
Gastrointestinal disorders				
Nausea	5.1	17.2	31.1	30.9
Diarrhea	0.9	10.3	13.2	13.2
Abdominal Distension	2.2	0.0	7.1	6.8
Abdominal pain	2.8	3.4	6.7	6.8
Flatulence	1.9	3.4	6.1	5.9
Vomiting	0.9	0.0	4.6	4.4
Loose stools	0.0	0.0	3.4	3.2
Dyspepsia	1.3	0.0	2.9	2.7
Abdominal pain upper	1.9	0.0	2.2	2.1
Abdominal pain lower	0.6	0.0	1.9	1.8
Gastroesophageal reflux disease	0.6	0.0	1.8	1.7
Abdominal discomfort	0.0	3.4	1.5	1.5
Dry mouth	0.3	0.0	1.5	1.4
Constipation	0.9	0.0	1.1	1.0
Stomach discomfort	0.3	0.0	1.1	1.0
Infections and infestations				
Sinusitis	1.6	0.0	4.9	4.8
Urinary tract infection	1.9	3.4	4.4	4.3
Upper respiratory infection	0.9	0.0	3.7	3.6
Nasopharyngitis	2.2	0.0	2.9	2.7
Influenza	0.6	0.0	2.0	1.9
Bronchitis	0.3	3.4	1.6	1.7
Gastroenteritis viral	0.0	3.4	1.0	1.0
Viral infection	0.3	3.4	0.5	0.6
Nervous system disorders				
Headache	6.6	3.4	13.2	13.0
Dizziness	1.3	3.4	4.1	4.0
Hypoasthesia	0.0	3.4	0.5	0.6
General disorders and site administration conditions				
Edema peripheral	0.3	0.0	3.8	3.6
Fatigue	1.9	6.9	2.3	2.5
Chest discomfort	0.0	3.4	1.6	1.6
Chest pain	0.0	0.0	1.1	1.0
Pyrexia	0.3	0.0	1.1	1.0
Musculoskeletal and connective tissue disorders				
Arthralgia	0.3	0.0	3.1	3.0
Back Pain	0.9	3.4	2.3	2.3
Pain in extremity	0.0	3.4	1.9	1.9
Respiratory, thoracic, and mediastinal disorders				
Dyspnea	0.0	3.4	2.4	2.5
Pharyngolaryngeal pain	2.2	0.0	1.7	1.6
Cough	0.6	0.0	1.6	1.5
Investigations				
Weight increased	0.0	0.0	1.0	0.9
Psychiatric disorders				
Depression	0.0	0.0	1.4	1.4
Anxiety	0.3	0.0	1.4	1.4
Insomnia	0.6	0.0	1.4	1.4
Vascular disorders				
Hypertension	0.0	0.0	1.0	0.9

*Includes subjects receiving 24 mcg daily, 24 mcg twice daily, and 24 mcg three times daily.

Deaths and Other Serious Adverse Events

Thirty-six subjects (4 receiving placebo, 32 receiving lubiprostone) had at least 1 serious adverse events (SAE) during phase I-III lubiprostone trials. All subjects receiving lubiprostone were receiving 24 mcg twice daily. All SAEs reported by subjects receiving placebo were considered unrelated to treatment compared to 2 SAEs in the subjects receiving lubiprostone that were considered possibly treatment related by the investigator; 1 subject gave birth to a baby with club feet after becoming pregnant while taking lubiprostone, and the other had severe diarrhea while receiving lubiprostone. No deaths were reported during any of the phase I-III trials. There have been no reported cases of ischemic colitis at this time.

Common Adverse Events

Nausea, diarrhea, headache, abdominal distension, abdominal pain, flatulence, sinusitis, vomiting, urinary tract infection, dizziness, upper respiratory infection, peripheral edema, loose stools, arthralgia, dyspepsia, nasopharyngitis, fatigue, dyspnea, back pain

Other Adverse Events

Gastrointestinal disorders: watery stools, fecal incontinence, abnormal bowel sounds, frequent bowel movements, retching

Nervous system disorders: syncope, tremor, dysgeusia, paresthesia

General disorders and administration conditions: rigors, pain, asthenia, malaise, edema

Respiratory, thoracic, and mediastinal disorders: asthma, painful respiration, throat tightness

Skin and subcutaneous tissue disorders: hyperhidrosis, uritcaria, rash

Psychiatric disorders: nervousness

Vascular disorders: flushing, palpitations

Metabolism and nutrition disorders: decreased appetite

Ear and labyrinth disorders: vertigo

Tolerability

Approximately 19.7% of subjects exposed to lubiprostone discontinued treatment secondary to an AE compared to 1.4% of subjects receiving placebo across all clinical trials. The most common AEs leading to discontinuation in subjects receiving lubiprostone during phase II and III trials included nausea (8.7%), diarrhea (2.2%), abdominal pain (1.5%), abdominal distension (1.4%), vomiting (1.3%), flatulence (1.1%), headache (3.7%), dizziness (1.1%), and dyspnea (1.3%).

For further details on the safety results of the clinical trials, refer to *Appendix: Clinical Trials.*

Precautions/Contraindications

Warnings

Patients with symptoms suggestive of mechanical gastrointestinal obstruction should be evaluated prior to initiating lubiprostone treatment. These “Red Flag Symptoms” according to the American College of Gastroenterology include: Pain that awakens/interferes with sleep, diarrhea that awakens/interferes with sleep, blood in the stool (visible or occult), weight loss, fever, or abnormal physical examination.

Lubiprostone is classified as a Pregnancy Category C medication. The safety of lubiprostone in pregnancy has not been evaluated in humans. In guinea pigs, lubiprostone has been shown to have the potential to cause fetal loss. Lubiprostone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Women who could become pregnant should have a negative pregnancy test prior to beginning therapy with lubiprostone and should be capable of complying with effective contraceptive measures.

Precautions

Lubiprostone may cause nausea. If this occurs, concomitant administration of food with lubiprostone may reduce symptoms of nausea. Lubiprostone should not be administered to patients that have severe diarrhea. Patients should be aware of the possible occurrence of diarrhea during treatment. If the diarrhea becomes severe, the patients should be instructed to consult their provider.

Contraindications

Lubiprostone is contraindicated in those patients with a known hypersensitivity to the drug or any of its excipients, and in patients with a history of mechanical gastrointestinal obstruction.

Carcinogenesis

Two 2-year oral (gavage) carcinogenicity studies (one in Crl:B6C3F1 mice and one in Sprague-Dawley rats) were conducted with lubiprostone. In the study in mice, lubiprostone doses of 25, 75, 200, and 500 mcg/kg/day (approximately 2, 6, 17, and 42 times the recommended human dose, respectively, based on body surface area) were used. In the rat study, lubiprostone doses of 20, 100, and 400 mcg/kg/day (approximately 3, 17, and 68 times the recommended human dose, respectively, based on body surface area) were used. In the mouse carcinogenicity study, there was no significant increase in any tumor incidences. There was a significant increase in the incidence of interstitial cell adenoma of the testes in male rats at the 400 mcg/kg/day dose. In female rats, treatment with lubiprostone produced hepatocellular adenoma at the 400 mcg/kg/day dose.

Mutagenesis

Lubiprostone was not genotoxic in the in vitro Ames reverse mutation assay, the in vitro mouse lymphoma (L5178Y TK+/−) forward mutation assay, the in vitro Chinese hamster lung (CHL/IU) chromosomal aberration assay, and the in vivo mouse bone marrow micronucleus assay.

Fertility impairment:

Lubiprostone, at oral dosages of up to 1,000 mcg/kg/day, had no effect on the fertility and reproductive function of male and female rats. The 1,000 mcg/kg/day dosage in rats is approximately 166 times the recommended human dosage of 48 mcg/day, based on the body surface area.

Teratogenic Effects

Teratology studies with lubiprostone have been conducted in rats at oral dosages up to 2,000 mcg/kg/day (approximately 332 times the recommended human dosage, based on body surface area), and in rabbits at oral dosages of up to 100 mcg/kg/day (approximately 33 times the recommended human dosage, based on body surface area). Lubiprostone was not teratogenic in rats and rabbits. In guinea pigs, lubiprostone caused fetal loss at repeated dosages of 10 and 25 mcg/kg/day (approximately 2 and 6 times the human dosage, respectively, based on body surface area) administered on days 40 to 53 of gestation.

There are no adequate and well controlled studies in pregnant women. However, during clinical testing of lubiprostone at 24 mcg twice daily, 4 women became pregnant. Per protocol,

lubiprostone was discontinued upon pregnancy detection. Three of the 4 women delivered healthy babies. The fourth woman was monitored for 1 month following discontinuation of study drug, at which time the pregnancy was progressing as expected; the patient was subsequently lost to follow-up. During phase I-III lubiprostone trials of 24 mcg twice daily, one patient gave birth to a baby with club feet after becoming pregnant while taking lubiprostone. This could not be directly correlated to ingestion of the medication, nor could it be ruled out.

Lubiprostone should only be used during pregnancy if the potential benefit justifies the potential risk to the fetus. If a woman is or becomes pregnant while taking the drug, apprise the patient of the potential hazard to the fetus. Women who could become pregnant should have a negative pregnancy test prior to beginning therapy with lubiprostone and should be capable of complying with effective contraceptive measures.

Lactation:
It is not known whether lubiprostone is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in breast-feeding infants from lubiprostone, the provider should determine whether to discontinue breast-feeding or the drug, taking into account the importance of the drug to the mother.

Look-alike / Sound-alike (LA / SA) Error Risk Potential

The VA PBM and Center for Medication Safety is conducting a pilot program which queries a multi-attribute drug product search engine for similar sounding and appearing drug names based on orthographic and phonologic similarities, as well as similarities in dosage form, strength and route of administration. Based on similarity scores as well as clinical judgment, the following drug names may be potential sources of drug name confusion:

LA/SA for generic name **lubiprostone:** dinoprostone gel, Lupron 1mg inj, Lunesta 1mg tab, Loprox susp, Lubrex lotion, mifepristone 200mg tab, misoprostol 100mcg tab, unoprostone 0.15gm solution, progesterone cream

LA/SA for trade name **AMITIZA**: Alinia 500mg tab, Alimta 500mg vial inj, Avita gel, Amitex 30mg tab, Avinza 120mg cap, Antara 130mg cap, Arixtra 10mg inj, Emtriva 200mg cap

Drug Interactions

Drug-Drug Interactions
Based upon the results of *in vitro* human microsome studies, there is low likelihood of drug-drug interactions. *In vitro* studies using human liver microsomes indicate that cytochrome P450 isoenzymes are not involved in the metabolism of lubiprostone. Further *in vitro* studies indicate microsomal carbonyl reductase may be involved in the extensive biotransformation of lubiprostone to M3. Additionally, *in vitro* studies in human liver microsomes demonstrate that lubiprostone does not inhibit cytochrome P450 isoforms 3A4, 2D6, 1A2, 2A6, 2B6, 2C9, 2C19, or 2E1, and *in vitro* studies in primary cultures of human hepatocytes show no induction of the cytochrome P450 isoforms 1A2, 2B6, 2C9, and 3A4. No additional drug-drug interaction studies have been performed. Based on the available information, no protein binding-mediated drug interactions of clinical significance are anticipated.

Drug-Food, Drug-Lab, Drug-Disease Interactions
No reports of drug-food, drug-lab or drug-disease interactions at this time.

Acquisition Costs

Cost Comparison of available treatments for chronic constipation.

Medication	Packaging	Price/Pack	Dose Range	Cost/Day	Cost/Month	Cost/Year
Psyllium (Metamucil)	3.4g/5g	$5.59/30 pack	1 po qd-tid	$0.18 - 0.54	$5.40 – 16.20	$64.8-194
Psyllium (Konsel)	10.6 oz	$3.56/bottle	1 tsp qd – tid	$0.07 – 0.21	$2.10 – 6.30	$25.6–76.7
Milk-of-Mg	480 mL	$0.89/bottle	15-60 ml po qhs	$0.003 - 0.11	$0.08 – 3.30	$1.00 - 39.60
Bisacodyl 5mg	100 tabs	$0.75/bottle	10-15mg po qhs	$0.025	$0.50 – 0.74	$5.90-8.86
Bisacodyl 10mg	500 supp	$23.28/box	10mg pr prn	$0.046	$1.40	$16.76
Senna 8.6mg	100 tabs	$0.82/bottle	8.6-34.4 mg po bid	$0.01 - 0.04	$0.32 - 1.27	$3.82 - 15.26
Docusate Na 250mg	100 caps	$2.07/bottle	250mg po qd	$0.022	$0.67	$8.00
PEG 3350*	255 g	$9.95/bottle	1 tbsp po qd	$0.69	$20.70	$248
Lactulose 10g/15ml	480 mL	$2.44/bottle	15-60ml po qd	$0.085 - 0.35	$2.63 - 10.50	$31.50-126
Tegaserod 2mg	60 tabs	$95.99/bottle	2mg po bid	$3.20	$95.99	$1152
Tegaserod 6mg	60 tabs	$106.07/bottle	6mg po bid	$3.54	$106.07	$1273
Tegaserod 6mg (split-tablets)	60 tabs	$106.07/bottle	3mg po bid	$1.77	$53.04	$636.42
Lubiprostone 24mcg	100 caps	$167.27	24 mcg po bid	$3.35	$100.36	$1204

** polyethylene glycol (Miralax)*

Pharmacoeconomic Analysis

At this time, the only other treatment option available for Chronic Idiopathic Constipation is tegaserod. From the above, acquisition costs for lubiprostone are similar to that of tegaserod, however, lubiprostone offers the availability of the agent for those patients > 65 years old, who do not respond to traditional pharmacotherapy for constipation. Cost per month for tegaserod utilizing tablet splitting is approximately half that of lubiprostone.

Conclusions

Lubiprostone has been shown to be safe and efficacious at a dose of 24 mcg twice daily for Chronic Idiopathic Constipation, with significant improvement in spontaneous bowel movements within 24 hours of the first dose. Subjects have reported improvements in consistency of stools, straining, constipation severity, and global assessment of constipation during clinical trials. The degree of relief from the pain of visceral hypersensitivity related to IBS-C has not been established and should not be expected based on the mechanism of this medication. Long term safety and efficacy have been evaluated for this medication at periods of 24 weeks, and 48 weeks in an open-label extension study where the drug was taken on an as needed basis. The agent is well tolerated with most common side effects reported being headache and nausea. When taken with food, nausea is reported to be reduced, however, nausea related to the medication is not transient. No clinically significant electrolyte imbalances have occurred secondarily related to lubiprostone administration. Federal pricing for lubiprostone is similar to tegaserod, depending on the dose. Lubiprostone offers a second alternative to tegaserod, as last line agents, after lack of response to formulary alternatives, in the treatment of CIC, with the added indication in patients > 65 years of age. It offers safety data out to 48 weeks, in comparison to 12 week data available for tegaserod.

Recommendations

Based on currently available literature, lubiprostone should be reserved for patients who do not respond to all formulary alternatives, including adequate dietary change, to relieve chronic idiopathic constipation. It is important to obtain appropriate evaluation and/or referral to a specialist for work-up of intractable constipation. Lubiprostone may be a viable alternative in patients who do not respond to traditional therapy who are > 65 years of age who are not

candidates for tegaserod therapy. It may also be an alternative to other osmotic diuretics, in the case of patients at risk for electrolyte imbalances who have a confirmed diagnosis of CIC. Efficacy should be established and regularly monitored. Efficacy studies indicate that approximately 72.1% of patients will fully respond to lubiprostone by the end of week one and 61.3% by 24 hours after initiation. If response is not seen within this time frame, it is reasonable to consider discontinuation.

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Prepared July 2006.

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Appendix: Clinical Trials

A literature search was performed on PubMed/Medline (1966 to present) using the search terms <lubiprostone> and <amitiza>. The search was limited to studies performed in humans and published in English language. Reference lists of review articles and the manufacturer's AMCP dossier were searched for relevant clinical trials. All randomized controlled trials published in peer-reviewed journals were included. Animal studies were not included.

<table>
<tr><td>Citation</td><td>Camilleri M, Bharucha AE, Ueno R, Burton D, Thomforde GM, Baxter K, McKinzie S, and Zinmeister AR. Effect of a selective chloride channel activator, lubiprostone, on gastrointestinal transit, gastric sensory, and motor functions in healthy volunteers. American Journal of Physiology-Gastroenterology and Liver Physiology 2006 May; 290 (5): G942-G947.[4]</td></tr>
<tr><td>Study Goals</td><td>The goal of this study was to analyze the gastrointestinal and colonic effects of lubiprostone, a selective type 2 chloride channel activator, specifically the gastrointestinal transit, gastric motor and sensory functions.</td></tr>
<tr><td>Methods</td><td>Study Design
The study was a randomized, parallel-group, single-dose, multiple administration, double-blind, placebo-controlled trial. Thirty-two patients (N= 32) were given either 24mcg lubiprostone twice daily or an equivalent amount of placebo using identical capsules. Standardized dosing and testing were performed on 4 different days. Patients received one dose of lubiprostone the evening prior to testing and one dose the following morning. Evaluation of gastrointestinal effects included scintigraphic gastric, small bowel, and colonic transit of solids, gastric volume using SPECT technique, MTV, and postprandial symptoms using satiation test. Primary efficacy end points included gastric emptying half life, small bowel transit t10%, geometric center at 24 hours, ascending colon emptying half life, fasting and postprandial gastric volumes, and maximum tolerated volume (MTV).

Data Analysis
Analysis of covariance was used to compare the treatment group with placebo. This study demonstrated 80% power to detect a significant difference in primary end points based on a two-sided z-test with α-level of 0.05.</td></tr>
<tr><td>Criteria</td><td>Inclusion criteria
Inclusion criteria were healthy patients aged 18-60 years. Patients were able to take low-dose aspirin, estrogen replacements, birth control pills, depot estrogen injections, or thyroid replacements as indicated.
Exclusion criteria
Patients were excluded if they had taken any other medications within 48 hours of treatment initiation or if they had any gastrointestinal diseases/conditions including dyspepsia and irritable bowel syndrome. Other patients were excluded for participating in another clinical trial within 30 days of the study.</td></tr>
<tr><td>Results</td><td>Data analysis (in minutes)
<table>
<tr><th></th><th>Lubiprostone (95% CI)</th><th>Placebo (95% CI)</th><th>p-value</th></tr>
<tr><td>Gastric emptying half life</td><td>106.1 (5.5)</td><td>132.4 (5.9)</td><td>0.003</td></tr>
<tr><td>Ascending colon half life</td><td>15 (1.6)</td><td>13.6 (1.7)</td><td>NS</td></tr>
<tr><td>Posttreatment MTV*, ml</td><td>1242 (51)</td><td>1091 (51)</td><td>0.05</td></tr>
<tr><td>Posttreatment 30 min postsatiation, mm</td><td></td><td></td><td></td></tr>
<tr><td>Nausea</td><td>13.3 (3.9)</td><td>16 (4.2)</td><td>NS</td></tr>
<tr><td>Fullness</td><td>68.5 (3.1)</td><td>55.4 (3.4)</td><td>0.008</td></tr>
<tr><td>Bloating</td><td>41.6 (5)</td><td>30.4 (5.4)</td><td>NS</td></tr>
<tr><td>Pain</td><td>12.2 (3.4)</td><td>12.2 (3.6)</td><td>NS</td></tr>
<tr><td>Aggregate score</td><td>137 (9.7)</td><td>114.3 (10.3)</td><td>NS</td></tr>
</table>
*Maximum Tolerated Volume
Small bowel transit time in the lubprostone group was faster than the placebo group (P=0.017). Colonic transit was also accelerated after 24 hours in the lubiprostone group compared with placebo (P=0.033); however, there was no statistical significance between groups after 48 hours (P=0.084). Fasting gastric volumes were increased in the lubiprostone group (P=0.049); however, postprandial gastric volumes were not statistically different (no P value reported).</td></tr>
<tr><td>Conclusions</td><td>The authors concluded that activation of selective chloride channels by lubiprostone slows gastric emptying and speeds up small bowel and colonic transit time in a small population of healthy patients. These effects did not show any statistically significant association with the aggregate score of postprandial symptoms measured (nausea, fullness, bloating, and pain). This data provides support that lubiprostone has a potential use in patients with delayed colonic transit, as seen in chronic constipation. Impact of lubiprostone on visceral hypersensitivity merits further study and was not determined in this trial. Slowing in GI transit explains increase in nausea and GI symptomatology.</td></tr>
<tr><td>Critique</td><td>Strengths
• Randomized, double-blind, placebo-controlled trial
• 80% power to determine statistical significance
• Baseline characteristics of patients are similar except MTV values in lubiprostone group were slightly less
Limitations</td></tr>
</table>

	• Small population of patients (N=32) • Study not analyzed on an intention-to-treat method, 2 patients lost to follow-up • Mean patient population age 29-33 years, not reflective of average patient in VA population; study conducted in healthy volunteers • Potential bias, study funded by Sucampo Pharmaceuticals Inc. • Clinical significance unknown at this point, further research needed

Analysis of Abstracts [Bolded citations were used in FDA approval

Citation Design Analysis type	Eligibility Criteria	Interventions	Patient Population Profile	Efficacy Results	Safety Results	Author's conclusions
Johanson JF et al.[5] 2002 (A315) Randomized, controlled clinical trial with ITT	Inclusion criteria: Constipation defined as <3 BMs per week, a 6 month history of at least one of the following symptoms, occurring 25% of the time: straining, hard stools, or sensation of incomplete evacuation.	Patients were randomized to either placebo, or RU-0211 (24, 48, or 72mcg per day for 3 weeks).	129 subjects Majority were female and Caucasian *115 female, 12 male, 48 median age, 20-78 range*	N_R = 127 Statistically significant improvement was found in average weekly number of BMs during weeks 1-2, stool consistency, bloating, and assessment of constipation severity for the patients receiving RU-0211. These results were found in patients receiving 48 or 72 mcg dose.	Incidence of nausea in patients receiving RU-0211 was statistically more than placebo. Four patients withdrew due to nausea, and they were equally dispersed between treatment groups. The incidence of other AEs, most commonly headache, diarrhea, and bloating, was similar between groups.	RU-0211 increases the number of BMs per week, decreases symptoms of constipation, and is well tolerated at doses of 48mcg or 72 mcg per day.
Ueno R[6] 2005 (Abstract) Phase I Study, placebo-controlled	Patients had to be confined for 24 hours before initiation of treatment and for 24 hours after the end of therapy.	Patients were randomized to either placebo or lubiprostone at different doses. Group 1: 24 mcg TID or placebo; Group 2: 24mcg + 6mcg TID or placebo; Group 3: 24 mcg + 12mcg TID or placebo. Drug administered for 6 days TID with a final dose on day 7.	26 subjects *Demographics not detailed in abstract*	N_R = 26 The 24mcg TID lubiprostone group had 2.3 times the number of bowel movements than the placebo group. No increased pharmacodynamic effects were found in doses higher than 24mcg TID.	2 patients withdrew from study after day one, but did not experience AEs. The most common AEs were nausea, abdominal cramps, and vomiting. Laboratory parameter changes were not clinically significant. Frequency of diarrhea was greater in the lubiprostone groups compared with placebo.	24mcg TID was an effective dose of lubiprostone in this population of subjects. Also, lubiprostone 24mcg TID was found to be safe and well-tolerated.
Johanson JF et al.[7] 2003 (Abstract) Phase III randomized, placebo controlled, multicenter trial	Constipation was defined as an average of <3 SBMs per week. Patients also had at least a 6 month history of 1 or more of the Rome II criteria for functional constipation.	Patients were randomized to either placebo or RU-0211 24mcg BID. Treatment lasted 4 weeks with a 2 week drug-free period for follow-up. A daily diary was used by patients to document SBMs and symptoms.	242 Mean age 48.6 years 90% female 86% Caucasian	N_R = 242 SBM frequency: 5.1-5.7 SBMs/ week in the RU-0211 group vs. 2.8-3.5 in placebo (P<0.002 at all weeks) Time to first SBM: 57% in RU-0211 group vs. 37% in placebo (P=0.0024)	9 patients withdrew from study due to AEs Most commonly observed AEs included nausea, diarrhea, and headache.	RU-0211 demonstrated significant benefits over placebo at a dose of 24mcg BID, and was well-tolerated and safe in this population of patients.

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				Degree of straining and Stool consistency: RU-0211 showed significant improvement compared with placebo (P<0.001 at all weeks) Treatment effectiveness (global assessment done by subjects): significantly better in RU-0211 group vs. placebo (P<0.0001 at all weeks).		
Johanson JF et al.[8] 2005 (Abstract 884) Phase III multicenter, randomized, parallel-group, double blind trial.	Patients had a history of CIC. Constipation was defined as <3 SBMs per week. Patients also had constipation symptoms including hard stools, sensation of incomplete evacuation, or straining during at least 25% of bowel movements for at least a 6-month period before the study. Exclusion criteria were patients with mechanical obstruction, large or small intestinal disorders, and conditions/treatments that could affect results.	After a 15 day drug-free period, patients were randomized to either placebo or lubiprostone 24mcg BID, taken with food and water, for 28 days. A diary was used by patients to document SBMs and symptoms.	119 patients lubiprostone; 118 patients placebo *88.9% female, mean age 47.2 years, range 20.0-81 years* *80.8% Caucasian* *9.6% African American* *10.9% ≥ 65*	N_R = 237 *Number of patients where* SBM *occurred* within 24hr after first dose: 73/119 (61.3%) in the lubiprostone group and 37/118 (31.4%) in the placebo group, p<0.0001. SBM frequency after 48 hr: 79.3% in lubiprostone group and 65.5% in placebo group. Time to first SBM: lubiprostone showed statistically significance over placebo (p<0.001). Mean SBM frequency/ week: statistically greater in lubiprostone group and sustained throughout study (p<0.05)	No information on safety data was included in the abstract.	Lubiprostone 24mcg BID was effective in rapid relief and sustained treatment of chronic idiopathic constipation for a 4 week period.
Johanson JF et al.[9] 2004 (Abstract 749) Randomized, blinded withdrawal study	Patients went through a drug-free baseline period of 2 weeks before the study.	All patients received RU-0211 24mcg BID for 4 weeks. The subjects were randomized to either RU-0211 24mcg BID or placebo BID for 3 weeks. A daily diary was use by patients to document bowel activity and symptoms.	128 received at least one dose of study drug *104 females, 24 males, median age 50, range 20-82 years*	N_R = 128 Primary endpoints: Weekly spontaneous bowel movements (SBMs) were increased at all 4 weeks (p<0.0001); consistency and straining, abdominal bloating and discomfort, and constipation severity assessments all significantly improved (p<0.0001). Response rates: SBM frequency was 5.59 in RU-0211 group vs. 3.04 in placebo group (p=0.0464). SBM frequency was still improved from baseline in the placebo group (p=0.002). Relapse rates: 44.4% for placebo vs. 18.2% for RU-0211 group (p=0.0223).	No serious AEs reported. Other AEs were comparable with previous studies.	RU-0211 was rapidly effective in treatment of constipation. Also, there was no withdraw effect found after taking patients off RU-0211
Johanson JF et al.[10] 2005 (Abstract 896) Phase III multicenter, parallel-group, double-	Patients had a history constipation, defined as <3 SBMs per week and at least 6 months of hard stools, sensation of	Patients were randomized to lubiprostone 24mcg BID or placebo plus food and water for 28 days after a 15 day drug-free period. Baseline	Majority of were female and Caucasian Both study	N_R = 237 Primary endpoints: SBM frequency was 5.89 in lubiprostone group vs. 3.99 in placebo (p<0.0001) at week 1. The results were	Mild to moderate nausea was the most common AE,, which occurred in 21% of patients in lubiprostone	Lubiprostone is safe and effective for rapid, sustained treatment of chronic constipation at a dose of 24mcg BID, and showed

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blind, randomized, placebo-controlled trial.	incomplete evacuation or straining in 25% of bowel movements.	evaluations were performed and weekly assessments made throughout study.	groups were similar. 209 female, 28 male, median age 46, range 20-81 years	sustained throughout the 4 weeks. Secondary endpoints: The lubiprostone group had improvements in % of patients with SBM in first 24 hours (61.3% vs., 31.4%), and response classification including stool consistency (p<0.0001), straining (p<0.002), and severity (p<0.03).	groups and 4.2% in placebo. There were no reported serious AEs.	significant improvement compared with placebo.
Johanson JF et al.[11] 2005 (Abstract 899) Phase III multicenter, parallel-group, double-blind, placebo-controlled trial.	Patients had chronic idiopathic constipation, which was defined as <3 SBMs per week. Patients also had at least 6 months of hard stools, sensation of incomplete evacuation or straining in 25% of bowel movements. Exclusion criteria included patients with conditions or treatments that could affect results of the study.	Patients were randomized to either lubiprostone 24mcg BID or placebo, after a 15 day drug-free period. They received treatment plus food and water for 28 days. Patient assessments of treatment success were recorded in daily diaries at baseline and weekly throughout study.	244 *Demographics not provided in abstract*	Significant improvements found in following endpoints for lubiprostone group compared with baseline: stool consistency (p<0.001), degree of straining (p<0.03). Significant improvements found in these endpoints for lubiprostone group compared with placebo: SBM frequency (p<0.0001 at Week 1, p<0.05 at Weeks 2-4), stool consistency (p<0.0001), straining (p<0.002), constipation severity (p<0.006 at Week 1, p<0.03 at Weeks 2-4). Patient assessments reported significantly higher effectiveness rating in lubiprostone group than placebo (rating: 1.88 vs. 1.22 on a scale of 0-4, p<0.0001).	No safety endpoints reported in this abstract.	Lubiprostone positively affected chronic constipation symptoms, according to patient assessments during a 4 week period of treatment.
Johanson J et al.[12] 2005 Multicenter, open label study	New and continuing subjects from a previous study enrolled. Patients with conditions and treatments that could potentially affect safety and efficacy data were excluded.	14 day drug free period, symptomatic subjects with documented CIC defined as < 3 BM per week received oral lubiprostone at 48 mcg/day with food and water for 24 weeks on prn basis at the discretion of the subjects perceived need.	N=308, 306 were analyzed at weeks 1, 4, 8, 12, 18 and 24 for safety, N=304 for efficacy. Female, Caucasian with mean age of 49	Statistically significant improvements in constipation severity, bloating, and abdominal discomfort related to bloating. Pt perceived treatment efficacy week 4 to week 24 (2.12 to 2.35 p = 0.01) *Dosing was 48 mcg daily in BID divided doses.*	51.6% of patients reported AEs most likely related to therapy. All were classified as not serious. 19.6% patients discontinued due to AE. Most often headache and nausea. No changes in vitals or physical exams.	Treatment with oral lubiprostone (24 mcg BID) as directed by subjects perceived need for relief is well tolerated and is associated with improvement in constipation severity and abdominal bloating.

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N_R, Number randomized.
ITT, intent-to-treat analysis
BID, twice daily
TID, three times daily
BM, bowel movement
SBM, spontaneous bowel movement
AE, adverse event
CIC, chronic idiopathic constipation