



Gastrointestinal (GI) Motility, Chronic Therapeutic Class Review (TCR)

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MANAGEMENTSM

FDA-APPROVED INDICATIONS

Drug	Manufacturer	Indication(s)
alosetron (Lotronex®) ¹	Prometheus	Treatment of severe, diarrhea-predominant irritable bowel syndrome (IBS-D) in women who have chronic IBS symptoms and have failed conventional therapy
linaclotide (Linzess®) ²	Forest	Treatment of chronic idiopathic constipation (CIC) Treatment of irritable bowel syndrome with constipation (IBS-C)
lubiprostone (Amitiza®) ³	Takeda	Treatment of chronic idiopathic constipation (CIC) Treatment of irritable bowel syndrome with constipation (IBS-C) in females ≥ 18 years old Treatment of opioid-induced constipation (OIC) in adults with chronic, non-cancer pain*
methylnaltrexone (Relistor®) ⁴	Salix	Treatment of opiate-induced constipation (OIC) in adult patients with advanced illness who are receiving palliative care when response to laxative therapy has been insufficient** Treatment of OIC in patients taking opioids for chronic non-cancer pain
naloxegol (Movantik®) ⁵	Astra Zeneca	Treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain

*Effectiveness of lubiprostone in the treatment of opioid-induced constipation (OIC) in patients taking diphenylheptane opioids (e.g., methadone) has not been established.

**Use of methylnaltrexone beyond 4 months has not been studied in the advanced illness population.

OVERVIEW

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.⁶ Chronic idiopathic constipation (CIC) is diagnosed if there are less than 3 spontaneous bowel movements (SBMs) per week with symptoms occurring for 6 months or more and at least 2 of the previously mentioned bowel symptoms.

Irritable bowel syndrome (IBS) is a functional bowel disorder which can be chronic, relapsing, and often life long.^{7,8} IBS occurs in up to 15% of the population and is up to 2.5 times more common in women than men. IBS is characterized by symptoms of abdominal pain or discomfort associated with abnormal stool frequency, abnormal stool form, abnormal stool passage, and/or bloating or abdominal distension, which may or may not be relieved by defecation at least 3 days per month in the past 3 months. Patients present with a combination of symptoms that are typically constipation predominant (IBS-C), diarrhea predominant (IBS-D), and/or alternating between both, or mixed (IBS-M). Patients with IBS experience significant negative impact on their quality of life due to adverse symptoms. Causes of IBS have not been fully identified, but could potentially include gut hypersensitivity, disturbed colonic motility, post-infective bowel dysfunction, or a defective anti-nociceptive system. There may also be contributing factors (e.g., stress, food intolerance, abnormal intestinal flora) which can hinder the effectiveness of treatment if left unresolved.

Symptoms of IBS are common to other gastrointestinal (GI) disorders and it is important to assess the presence of warning signs (e.g., fever, unintended weight loss, blood in stool, anemia, abnormal physical finding or blood studies, family history of inflammatory bowel disease or cancer), which might be indicative of a more serious condition.^{9,10,11} Diagnosis of IBS usually occurs in the presence of symptoms while excluding organ disease or other GI disorders. IBS can also present with non-colonic features (e.g., functional urinary and gynecologic problems, gallbladder and stomach symptoms, back pain, migraine, and depression) which can lead to inappropriate patient referrals.

IBS is a chronic condition without a cure. Therefore, treatment of IBS is based on management of the patient's symptoms and may require a combination of modalities to achieve relief. 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.¹² The evidence of quality was graded by standard criteria with recommendations developed based on the quality of the evidence in addition to other factors (e.g., risk, cost). A brief overview of the monograph indicates the following: insoluble fiber may exacerbate symptoms and provide little relief while soluble fiber and psyllium may provide some relief in IBS. Loperamide is an effective antidiarrheal; however, there is no evidence to support the use of loperamide for relief of symptoms in IBS. 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) and lubiprostone (Amitiza) are effective in CIC and are well tolerated, but comparative studies are not currently available to guide the agents place in CIC therapy.

The 2014 AGA guidelines recommend laxatives as well as both linaclotide and lubiprostone in patients with IBS-C over no drug treatment; however, they note that patients may prefer alternatives due to cost. They also recommend rifaximin (Xifaxan®), an antibacterial indicated for IBS-D, and alosetron (Lotronex) over no drug treatment in patients with IBS-D.¹³ Patients with mild symptoms often respond to dietary changes, such as increasing fiber intake and reducing exposure to intolerant foods, while pharmacologic intervention is typically reserved for patients with moderate to severe symptoms.^{14,15,16} As needed usage of antispasmodics (e.g., dicyclomine, hyoscyamine) and antidiarrheals (e.g., loperamide, atropine/diphenoxylate) can be used to treat mild to moderate symptoms of IBS-D, while more severe symptoms may necessitate scheduled dosing. Laxatives (e.g., docusate, bisacodyl, sennosides, polyethylene glycol, and magnesium hydroxide,) can be used to treat mild to moderate symptoms of IBS-C, while linaclotide and lubiprostone are reserved for patients with moderate to severe symptoms. Other considerations can include rifaximin for moderate to severe IBS-D and tricyclic antidepressants (TCAs) for moderate to severe IBS-C and IBS-D. Newly released agents acting at the 5-HT receptor (e.g. alosetron) may help painful symptoms, and must be used based on whether the stool habit is primarily diarrhea or constipation.^{17,18,19,20} No data exist as to the role in mixed or alternating IBS, and recommendations as to their use as first- or second-line treatments need to be determined based on issues of efficacy, safety, and cost. Alosetron was voluntarily withdrawn from the U.S. market in 2000 due to ischemic colitis and serious complications of severe constipation.²¹ In 2002, it returned to market but with tight restrictions.

Opioid-induced constipation (OIC) is a common adverse effect of opioid therapy. The 2009 American Pain Society (APS) and American Academy of Pain Medicine (AAPM) clinical guidelines for chronic opioid therapy in patients with non cancer pain recommend that common adverse effects, including

constipation, should be anticipated and addressed appropriately.²² The 2012 American Society of Interventional Pain Physicians (ASIPP) guidelines for responsible opioid prescribing in chronic non cancer pain recommend that prescribers initiate a prophylactic bowel regimen even before the development of constipation and definitely after its development.^{23,24}

PHARMACOLOGY^{25,26,27,28,29}

Alosetron (Lotronex) is a selective serotonin 5-HT₃ receptor antagonist. The 5-HT₃ receptors are ligand-gated cation channels that are located extensively throughout the GI tract, as well as other peripheral and central sites. When activated, these channels regulate processes that cause many of the symptoms of IBS-D, including visceral pain, colonic transit, and gastrointestinal secretions. The 5-HT₃ receptor antagonists inhibit the activation of these channels resulting in modulation of the GI tract.

Linaclotide (Linzess) is a guanylate cyclase-C (GC-C) agonist. Both linaclotide and its active metabolite bind to GC-C and act locally on the luminal surface of the intestinal epithelium. Activation of GC-C results in an increase in both intracellular and extracellular concentrations of cyclic guanosine monophosphate (cGMP). Elevation in intracellular cGMP stimulates secretion of chloride and bicarbonate into the intestinal lumen, mainly through the activation of the cystic fibrosis transmembrane conductance regulator (CFTR) ion channel. This results in increased intestinal fluid and accelerated transit. In animal models, linaclotide has been shown to both accelerate GI transit and reduce intestinal pain. The linaclotide-induced reduction in visceral pain in animals is thought to be mediated by increased extracellular cGMP, which was shown to decrease the activity of pain-sensing nerves.

Lubiprostone (Amitiza) activates ClC-2 chloride channels which produces a chloride-rich intestinal fluid secretion without altering serum electrolyte concentrations. The majority of the beneficial biological activity of lubiprostone and its metabolites are observed only on the apical (luminal) portion of the gastrointestinal epithelium. By increasing intestinal fluid secretion, lubiprostone increases motility in the intestine, thereby facilitating the passage of stool and alleviating symptoms associated with chronic idiopathic constipation.

Methylnaltrexone (Relistor) and naloxegol (Movantik) are both mu-opioid receptor antagonists. Naloxegol is a pegylated form of naloxone. When administered at the recommended dose, naloxegol decreases the constipating effects of opioids in the GI tract tissues. As a result of being both a substrate for the P-glycoprotein transporter (P-gp) and containing a PEG moiety, the ability to cross the blood-brain barrier is limited, and it functions primarily in the periphery. Thus, naloxegol does not interfere with the analgesic effects of opioids in the central nervous system. Similar to naloxegol, the ability of methylnaltrexone to cross the blood-brain barrier is restricted and functions peripherally at the mu-opioid receptor in the GI tract tissues. This mechanism of action decreases the constipating effects of opioids without inhibiting opioid-mediated analgesic effects on the central nervous system; therefore, it does not block the opioid analgesic effect.

PHARMACOKINETICS

Drug	Bioavailability (%)	Half-Life	Metabolism	Excretion
alosetron (Lotronex) ³⁰	50–60	1.5 hr	Predominately metabolized by cytochrome P450 enzymes 2C9, 3A4, and 1A2	Urine (74%) Feces (11%)
linaclotide (Linzess) ³¹	n/a*	n/a*	Proteolytically degraded in the lumen to smaller peptides and naturally occurring amino acids	Feces
lubiprostone (Amitiza) ³²	n/a*	n/a*	Rapidly and extensively metabolized by carbonyl reductase mediated oxidation and reduction	Feces
methylnaltrexone (Relistor) ³³	nr	8 hrs	Primarily metabolized to methyl-6-naltrexol isomers and methylnaltrexone sulfate	Urine (53.6%) Feces (17.3%)
naloxegol (Movantik) ³⁴	nr	6 to 11 hrs	Primarily metabolized by the CYP3A enzyme system	Urine (16%) Feces (68%)

*Standard pharmacokinetic parameters cannot be calculated due to immeasurable plasma concentrations following therapeutic oral doses.

nr=not reported

CONTRAINDICATIONS/WARNINGS^{35,36,37,38,39}

Alosetron (Lotronex) is contraindicated in patients with a history of severe bowel or hepatic disorders (e.g., GI obstruction/perforation, stricture, toxic megacolon, or GI adhesions) and in patients coadministered fluvoxamine. The use of alosetron (Lotronex) in patients with impaired intestinal circulation, diverticulitis, Crohn’s disease, thrombophlebitis, hypercoagulable state, ischemic or ulcerative colitis is also contraindicated. Additionally, therapy should not be initiated in patients with constipation.

Both linaclotide (Linzess) and lubiprostone (Amitiza) are contraindicated in patients with known or suspected mechanical GI obstruction. Both methylnaltrexone (Relistor) and naloxegol (Movantik) are contraindicated in patients with known/suspected GI obstruction or increased risk of recurrent obstruction due to the potential for GI perforation.

Use of naloxegol is contraindicated in patients who have experienced a severe reaction to naloxegol or any of the excipients contained in the drug. Concomitant use of naloxegol with strong CYP3A4 inhibitors (e.g., clarithromycin, ketoconazole) is contraindicated as these agents can significantly increase exposure to naloxegol and potentially precipitate opioid withdrawal symptoms.

Cases of gastrointestinal (GI) perforation have been reported with administration of a different peripherally-acting opioid antagonist in patients with medical conditions associated with localized or diffuse reduction in the structural integrity of the GI tract wall (e.g., peptic ulcer disease, Ogilvie’s syndrome, diverticular disease, infiltrative GI tract malignancies, or peritoneal metastases). Therefore, the overall risk-benefit profile should be assessed in patients administered naloxegol. If treatment is deemed necessary, patients should be monitored for severe, persistent, and/or worsening abdominal pain. If symptoms are observed, the drug should be discontinued.

Use of linaclotide (Linzess) in children up to 6 years of age is contraindicated and carries a boxed warning and should be avoided in children up to 17 years of age.

Allergic-type reactions have been reported with the use of lubiprostone.

DRUG INTERACTIONS^{40,41,42,43,44}

Based on data from *in vivo* studies, alosetron (Lotronex) is predominately metabolized by cytochrome P450 (CYP) 1A2, with minor contributions from CYP3A4 and CYP2C9. Inducers or inhibitors of these enzymes, such as fluvoxamine or ketoconazole, may alter the metabolism and clearance of alosetron (Lotronex).

No drug-drug interaction studies have been conducted for linaclotide (Linzess) or lubiprostone (Amitiza); however, there is a low potential for serious or significant drug interactions due to very low systemic bioavailability. Neither linaclotide (Linzess) nor lubiprostone (Amitiza) is a substrate, inhibitor, or inducer of any cytochrome P450 metabolic pathway. Drug interactions mediated by protein binding are not anticipated with linaclotide or lubiprostone. Pharmacodynamic drug interactions can be anticipated with agents that oppose the action of drugs to treat constipation. This includes medications that decrease GI motility or have anticholinergic effects.

Naloxegol (Movantik) is primarily metabolized by the cytochrome P450 3A4 enzyme system. Administration with moderate CYP3A4 inhibitors (e.g., diltiazem, erythromycin, verapamil) may increase naloxegol concentrations; therefore, concomitant use is not recommended. However, if concomitant use is unavoidable, the dosage of naloxegol (Movantik) should be decreased and the patient should be monitored for adverse effects. Use of naloxegol with strong CYP3A4 inducers (e.g., rifampin) is not recommended as well due to a decrease in naloxegol concentrations. Furthermore, both methylnaltrexone (Relistor) and naloxegol have the potential for additive effects if given with other opioid agents and should be avoided.

In vitro, methylnaltrexone (Relistor) did not significantly inhibit the activity of cytochrome P450 (CYP) isozymes 1A2, 2A6, 2C9, 2C19, or 3A4. In healthy subjects, a subcutaneous dose of methylnaltrexone 0.3 mg/kg did not significantly affect the metabolism of the CYP2D6 substrate, dextromethorphan.

ADVERSE EFFECTS^{45,46,47,48,49}

Drug	Constipation	Diarrhea	Nausea	Abdominal Pain	Flatulence	Abdominal Distension	Viral Gastroenteritis	Headache	Dyspnea
alosetron (Lotronex) n=8,328	29 (6)	nr	6 (5)	7 (4)	nr	2 (1)	nr	nr	nr
linaclotide (Linzess) n=807 (IBS-C)	nr	20 (3)	nr	7 (5)	4 (2)	2 (1)	3 (1)	4 (3)	nr
n=430 (CIC)	nr	16 (5)	nr	7 (6)	6 (5)	3 (2)	reported	nr	nr
lubiprostone (Amitiza) n=1,113 (CIC)	nr	12 (<1)	29 (3)	8 (3)	6 (2)	6 (2)	nr	11 (5)	2 (0)
n=1,011 (IBS-C)	nr	7 (4)	8 (4)	nr	nr	3 (2)	nr	nr	nr
n=860 (OIC)	nr	8 (2)	11 (5)	4 (1)	nr	3 (2)	nr	2 (1)	nr
methylnaltrexone (Relistor) n=150 (OIC non-cancer pain)	nr	6 (4)	9 (6)	21 (6)	nr (advanced illness-reported in 13%)	nr	nr	nr	nr
naloxegol (Movantik) n=446 (25 mg dose)	nr	9 (5)	8 (5)	21 (7)	6 (3)	nr	nr	4 (3)	nr

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all inclusive. Incidences for placebo groups are indicated in parentheses.

nr = not reported.

Constipation is a dose-related adverse effect of alosetron (Lotronex) and the most frequently reported adverse effect in clinical trials. Constipation associated with alosetron (Lotronex) is generally reported as mild to moderate in intensity, transient in nature, and resolved either spontaneously or upon discontinuation of the drug. There have been reports of serious complications of constipation in clinical trials and post-marketing data, including obstruction, ileus, impaction, toxic megacolon, and secondary bowel ischemia. Due to the risk associated with using alosetron, prescribers must be enrolled in the Prescribing Program for Lotronex (PPL). Patients who are elderly, debilitated, or taking other medications that decrease GI motility may be at greater risk for complications of constipation. Alosetron should be discontinued immediately in any patient experiencing constipation.

Severe diarrhea was reported in approximately 2% of the patients taking linaclotide (Linzess) and lubiprostone (Amitiza). If severe diarrhea occurs, the patient should be instructed to contact their provider and dosing of the drug may need to be interrupted or suspended.

The most common adverse effect associated with lubiprostone is nausea. The incidence of nausea increases in a dose-dependant manner with the highest percentage being reported in patients

receiving the 24 mcg twice daily dosing regimen. It is recommended that lubiprostone be given with food and water, which has shown to decrease reported nausea.

Dyspnea with lubiprostone has been reported and usually occurs within 30 to 60 minutes of taking the first dose. Described as a sensation of chest tightness and difficulty taking in a breath, these symptoms generally resolve within three hours after taking the dose but recurrence has been frequently reported with subsequent doses.

The most common adverse effects associated with methylnaltrexone (Relistor) in adult patients with opioid-induced constipation and advanced illness are abdominal pain, flatulence, nausea, dizziness, and diarrhea.

In clinical trials, patients receiving both methadone and naloxegol (Movantik) were observed to have a higher frequency of GI adverse reactions that may have been related to opioid withdrawal compared to patients receiving other opioid agents. Additionally, consider the overall risk benefit of naloxegol and methylnaltrexone in patients with disruptions to the blood-brain barrier, as they may be at increased risk of opioid withdrawal symptoms (e.g., hyperhidrosis, chills, diarrhea, abdominal pain, anxiety, irritability, yawning) or reduced analgesia. Discontinue methylnaltrexone if severe or persistent diarrhea occurs during treatment.

SPECIAL POPULATIONS^{50,51,52,53,54}

Pediatrics

Safety and effectiveness have not been established in pediatric patients for alosetron (Lotronex), linaclotide (Linzess), lubiprostone (Amitiza), methylnaltrexone (Relistor), or naloxegol (Movantik).

Linaclotide is contraindicated in pediatric patients up to 6 years of age and should be avoided in patients 6 years through 17 years of age.

Pregnancy

Alosetron (Lotronex) is classified as FDA pregnancy risk category B.

Linaclotide (Linzess), lubiprostone (Amitiza), methylnaltrexone (Relistor), and naloxegol (Movantik) are classified as FDA pregnancy risk category C. Methylnaltrexone and naloxegol should only be used during pregnancy if the potential benefit outweighs the potential risk to the fetus, as the agents could precipitate opioid withdrawal in a fetus.

Renal Impairment

No dose adjustment is necessary based on renal function for alosetron (Lotronex), linaclotide (Linzess), or lubiprostone (Amitiza). A reduced dose (12.5 mg daily) of naloxegol (Movantik) is recommended for patients with moderate, severe, or end-stage renal impairment (CrCL <60 mL/min). Methylnaltrexone (Relistor) does not require a dose adjustment in patients with mild or moderate renal function. However, the dose should be reduced by one half in patients with severe renal impairment (CrCL <30 mL/min).

Hepatic Impairment

Alosetron (Lotronex) is contraindicated in patients with severe hepatic impairment and should be used cautiously in patients with mild to moderate hepatic impairment.

No dose adjustment is needed based on hepatic function for linaclotide (Linzess).

For the treatment of CIC with lubiprostone (Amitiza), the recommended dose for patients with moderately impaired hepatic function (Child-Pugh Class B) is 16 mg twice daily. For patients with severely impaired hepatic function (Child-Pugh Class C), the recommended dose is 8 mcg twice daily. If tolerated, the dose can be escalated to full dosing with appropriate monitoring of patient response.

For the treatment of IBS-C, there is no dose adjustment of lubiprostone needed for patients with moderately impaired hepatic function (Child-Pugh Class B). For patients with severely impaired hepatic function (Child-Pugh Class C), the recommended dose is 8 mcg once daily. If tolerated, the dose can be escalated to full dosing with appropriate monitoring of patient response.

In mild to moderate hepatic impairment, an adjustment is not required for methylnaltrexone (Relistor).

Naloxegol (Movantik) has not been evaluated in severe hepatic impairment and its use should be avoided. No dose adjustments are required in patients with mild to moderate hepatic impairment taking naloxegol.

DOSAGES^{55,56,57,58,59}

Drug	Severe Diarrhea-Predominant Irritable Bowel Syndrome (IBS)	Availability
alosetron (Lotronex)	0.5 mg twice a day, may increase to 1 mg twice a day if well tolerated (discontinue if four weeks' treatment at this dose does not lead to adequate symptom control)	0.5 mg and 1 mg tablets

Drug	Chronic Idiopathic Constipation (CIC)	Irritable Bowel Syndrome with Constipation (IBS-C)	Availability
linaclotide (Linzess)	145 mcg once daily; at least 30 minutes prior to first meal*	290 mcg once daily; at least 30 minutes prior to first meal	145 mcg and 290 mcg capsules
lubiprostone (Amitiza)	Females: 24 mcg twice daily† Males: 24 mcg twice daily†	Females: 8 mcg twice daily Males: n/a**	8 mcg and 24 mcg capsules

Drug	Opioid-induced constipation (OIC) in adults with chronic non-cancer pain	Opioid-induced constipation (OIC) in adults with advanced illness	Availability
methylnaltrexone (Relistor) ***	12 mg subcutaneously once daily	Dosage based on body weight; one dose administered every other day, as needed; do not exceed one dose in a 24-hour period	Prefilled syringes: 8 mg/0.4 mL, 12 mg/0.6 mL Single-use vial: 12 mg/0.6 mL
naloxegol (Movantik)***	25 mg once daily; if not tolerated, reduce to 12.5 mg once daily (discontinue maintenance laxative therapy prior to treatment; may resume if OIC symptoms continue following three days of treatment) ††	--	12.5 mg and 25mg tablets

*In CIC, the 290 mcg linaclotide dose has not been shown to be more effective than the 145 mcg dose.

**Safety and efficacy have not been established for the use of lubiprostone in males for IBS-C.

***Shown to be efficacious in patients who have taken opioids for at least four weeks.

†Same dose used for treatment of opioid-induced constipation in adults with chronic, non-cancer pain and should be taken with food and water.

††Take on an empty stomach one hour prior to the first meal of the day, or two hours after the meal. Avoid consumption of grapefruit or grapefruit juice.

Note: methylnaltrexone and naloxegol should be discontinued along with opioid discontinuation.

CLINICAL TRIALS SEARCH STRATEGY

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class. Randomized, comparative, controlled trials comparing agents within this class for the approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance.

Due to the paucity of comparative trials, placebo-controlled studies are included.

alosetron (Lotronex) versus placebo

The efficacy and tolerability of alosetron in non-constipated female patients with IBS were evaluated in a double-blind, randomized, placebo-controlled trial. Patients received either 1 mg of alosetron (n=309) or placebo (n=317) twice daily for 12 weeks, followed by a 4-week post-treatment period.⁶⁰ Adequate relief of IBS pain and discomfort was the primary endpoint. Secondary endpoints included improvements in urgency, stool frequency, stool consistency, incomplete evacuation, and bloating. A total of 71% of patients were classified as having IBS-D. Forty-three percent of alosetron-treated patients with IBS-D reported adequate relief for all 3 months compared with 26% of placebo-treated patients (p<0.001; 95% confidence interval [CI], 8-25.4%). Improvement with alosetron compared with placebo was observed by the end of the fourth week of treatment and persisted throughout the remainder of treatment. Alosetron significantly decreased urgency and stool frequency and caused firmer stools within 1 week of starting therapy. Effects were sustained throughout treatment and symptoms returned following treatment cessation. No significant improvement in the percentage of days with sense of incomplete evacuation or bloating was observed compared with placebo during the first month of treatment. Constipation was the most commonly reported adverse event.

A randomized, double-blind, placebo-controlled study assessed long-term safety and efficacy of alosetron in women with severe, chronic IBS-D and in a subset having more frequent urgency (e.g., bowel urgency at least 10 of 14 days during screening).⁶¹ Patients received either alosetron 1 mg (n=351) or placebo (n=363) twice daily during a 48-week period. The primary endpoint was the 48-week average rate of adequate relief of IBS pain and discomfort. Secondary endpoints included 48-week average satisfactory control rates of urgency, stool frequency, stool consistency, and bloating. Other efficacy endpoints were average monthly adequate relief and urgency control rates and impact of provided rescue medication. Alosetron-treated patients had significantly greater 48-week average adequate relief (p=0.01) and urgency control (p<0.001) rates compared with placebo. Results in subjects with more frequent urgency were stronger than those in the overall population (p=0.005). Alosetron-treated patients had significantly greater adequate relief than placebo-treated patients (p<0.05) in 9 of 12 months and significantly greater urgency control (p<0.001) in all months. Adequate

relief and urgency control were maintained throughout the treatment. Adverse events and serious adverse events were similar between treatment groups, except for constipation. Neither ischemic colitis nor serious events related to bowel motor dysfunction was reported.

A randomized, placebo-controlled trial evaluated the effect of alosetron on bowel urgency and IBS global improvement in IBS-D.⁶² Women with a lack of satisfactory bowel urgency control at least 50% of the time during screening were randomized to receive alosetron 1 mg (n=246) or placebo (n=246) twice daily. The primary endpoint was the percentage of days with satisfactory control of bowel urgency. The response rate for the IBS global improvement scale (GIS) was a secondary endpoint. GIS responders were patients who recorded either moderate or substantial improvement in IBS symptoms relative to the way they felt before entering the study. Other endpoints included improvement in stool frequency, stool consistency, and percentage of days with incomplete evacuation. Further analyses were performed on a subset of patients who had at least 10 of 14 days during screening ($\geq 71\%$ of days) with a lack of satisfactory control of bowel urgency. Patients had severe chronic IBS symptoms, and 89% of patients had IBS-D. Alosetron resulted in a greater percentage of days with satisfactory control of urgency compared with placebo (69% versus 56%, respectively; $p < 0.001$). Greater percentages of alosetron-treated patients were GIS responders at 4, 8, and 12 weeks compared with placebo (59% versus 41%, 63% versus 41%, and 68% versus 46%, respectively; $p < 0.001$). Patients with more frequent urgency had similar results. Constipation occurred in 28% and 9% of subjects in the alosetron and placebo-treated groups, respectively. No cases of ischemic colitis were reported.

linaclotide (Linzess) versus placebo

The efficacy of linaclotide for the management of symptoms of IBS-C was established in 2 double-blind, placebo-controlled, randomized, multicenter trials in adult patients (trials 1 and 2).^{63,64,65} A total of 800 patients in trial 1 and 804 patients in trial 2 received treatment with linaclotide 290 mcg or placebo once daily. The trial designs were the same through the first 12 weeks. Trial 1 included a 4-week randomized withdrawal period after the initial 12 weeks, and trial 2 continued for 14 additional weeks (total of 26 weeks) of double-blind treatment. During the trials, patients were allowed to continue stable doses of bulk laxatives or stool softeners but were not allowed to take laxatives, bismuth, prokinetic agents, or other drugs to treat IBS-C or chronic constipation. There were 4 primary endpoints for these trials. Patients were considered an abdominal pain responder if they experienced at least a 30% reduction from baseline in mean abdominal pain. Patients were considered a complete spontaneous bowel movement (CSBM) weekly responder if they had at least 3 CSBMs and an increase of at least 1 CSBM from baseline all in the same week. The primary endpoint of CSBM weekly responders for at least 9 out of the 12 weeks of treatment with linaclotide versus placebo was 19.5% versus 16.3% (treatment difference 3.2%; 95% CI, 8.6 to 17.7%) in trial 1 and 18% versus 5% (treatment difference 13%; 95% CI, 8.7 to 17.3%) in trial 2. The primary endpoint of abdominal pain responder for at least 9 out of 12 weeks of treatment with linaclotide versus placebo was 34.3% versus 27.1% (treatment difference 7.2%; 95% CI, 0.9 to 13.65) in trial 1 and 38.9% versus 19.6% (treatment difference 19.3%; 95% CI, 13.2 to 25.4) in trial 2. The primary endpoint of combined CSBM weekly responder and abdominal pain responder for 9 out of 12 weeks of treatment with linaclotide versus placebo was 12.1% versus 5.1% (treatment difference seven%; 95% CI, 3.2 to 10.9%) in trial 1 and 12.7% versus 3% (treatment difference 9.7%; 95% CI, 6.1 to 13.4%) in trial 2. The primary endpoint of abdominal pain responders with an increase of at least 1 CSBM per week for at least 6 out of the 12 weeks of treatment with linaclotide versus placebo was 33.6% versus 21% (treatment difference

12.6%; 95% CI, 6.5 to 18.7%) in trial 1 and 33.7% versus 13.9% (treatment difference 19.8%; 95% CI, 14 to 25.55) in trial 2. During the 4-week randomized withdrawal period in trial 1, patients who received linaclotide during the 12-week treatment period were re-randomized to receive placebo or continue treatment on linaclotide 290 mcg. In linaclotide-treated patients re-randomized to placebo, CSBM frequency and abdominal-pain severity returned toward baseline within 1 week and did not result in worsening compared to baseline. Patients who continued on linaclotide maintained their response to therapy over the additional 4 weeks. Patients on placebo who were allocated to linaclotide had an increase in CSBM frequency and abdominal pain levels that were similar to the levels observed in patients taking linaclotide during the treatment period. The percentage of adverse reactions reported from both trials in at least 2% of the study patients and at an incidence greater than placebo included diarrhea (linaclotide 20 versus placebo 3), abdominal pain (7 versus 5), flatulence (4 versus 2), abdominal distension (2 versus 1), viral gastroenteritis (3 versus 1), and headache (4 versus 3).

The efficacy of linaclotide for the management of symptoms of CIC was established in 2 double-blind, placebo-controlled, randomized, multicenter clinical trials in adult patients (trials 3 and 4).^{66, 67} A total of 642 patients in trial 3 and 630 patients in trial 4 received treatment with linaclotide 145 mcg, 290 mcg, or placebo once daily. All patients included in the trial met criteria for functional constipation and were excluded if they met criteria for IBS-C or had fecal compaction. The trial designs were identical through the first 12 weeks. Trial 3 also included an additional 4-week randomized withdrawal period. During the trials, patients were allowed to continue stable doses of bulk laxatives or stool softeners but were not allowed to take laxatives, bismuth, prokinetic agents, or other drugs to treat chronic constipation. The primary endpoint 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 out of the 12 week period. In trial 3, the primary endpoint was achieved in 20.3% of patients taking linaclotide versus 3.3% of patients taking placebo (treatment difference 16.9%; 95% CI, 11 to 22.8%). In trial 4, the primary endpoint was achieved in 15.5% of patients taking linaclotide versus 5.6% of patients taking placebo (treatment difference 9.9%; 95% CI, 4.2 to 15.7%). Linaclotide 290 mcg did not consistently offer additional clinically meaningful treatment benefit over placebo than that observed with the 145 mcg dose. During the 4-week randomized withdrawal period in trial 3, patients who received linaclotide during the 12-week treatment period were re-randomized to receive placebo or continue treatment on the same dose taken during the treatment period. In linaclotide-treated patients re-randomized to placebo, CSBM and spontaneous bowel movement (SBM) frequency returned toward baseline within 1 week and did not result in worsening compared to baseline. Patients who continued on linaclotide maintained their response to therapy over the additional 4 weeks. Patients on placebo who were allocated to linaclotide had an increase in CSBM and SBM frequency similar to the levels observed in patients taking linaclotide during the treatment period. The percentage of adverse reactions reported from both trials in at least 2% of the study patients and at an incidence greater than placebo included diarrhea (linaclotide 16 versus placebo 5), abdominal pain (7 versus 6), flatulence (6 versus 5), abdominal distension (3 versus 2), upper respiratory tract infections (5 versus 4), and sinusitis (3 versus 2).

lubiprostone (Amitiza) versus placebo

In 2 double-blinded, placebo-controlled studies of identical design, lubiprostone was studied in patients with CIC.⁶⁸ A total of 479 were randomized and received Amitiza 24 mcg twice daily or placebo twice daily for 4 weeks. The primary endpoint of the studies was spontaneous bowel movement (SBM)

frequency. The change in SBMs frequency rate from baseline to week one for lubiprostone versus placebo was 4.3 versus 1.9 in study 1 and 4.5 versus 2.5 for placebo. The change in SBM frequency rate from baseline to week 4 for lubiprostone versus placebo was 3.9 versus 1.3 in study 1 and 4.1 versus 1.9 in study 2. The percentage of adverse effects occurring in at least 2% of lubiprostone-treated patients and that occurred more frequently than placebo include nausea (lubiprostone 29 versus placebo 3), diarrhea (12 versus 1), abdominal pain (8 versus 3), headache (11 versus 5), abdominal distension (6 versus 2), flatulence (6 versus 2), vomiting (3 versus 0), dizziness (3 versus <1), loose stools (3 versus 0), edema (3 versus <1), abdominal discomfort (2 versus <1), dyspepsia (2 versus <1), and fatigue (2 versus <1).

Two double-blinded, placebo-controlled studies of similar design were conducted studying lubiprostone in patients with IBS-C.⁶⁹ A total of 1,154 patients were randomized and received lubiprostone 8 mcg twice daily or placebo twice daily for 12 weeks. The primary efficacy endpoint was assessed weekly utilizing the patients' response to a questionnaire. The percentage of patients in study 1 qualifying as an "overall responder" was 13.8% in the group receiving lubiprostone compared to 7.8% of patients receiving placebo. In study 2, 12.1% of patients in the lubiprostone group were "overall responders" versus 5.7% of patients in the placebo group. In both studies, the treatment differences between the placebo and lubiprostone groups were statistically significant. There were not a sufficient number of men included in the studies to determine whether men respond differently to lubiprostone from women. The percentage of adverse effects occurring in at least 2% of lubiprostone-treated patients, and that occurred more frequently than placebo, include nausea (lubiprostone 8 versus placebo 4), diarrhea (7 versus 4), abdominal pain (5 versus 5), headache (11 versus 5), and abdominal distension (3 versus 2).

Three randomized, double-blind, placebo-controlled trials compared lubiprostone 24 mcg twice daily with placebo for 12 weeks in about 1,300 patients with chronic noncancerous pain and opioid-induced constipation (defined as less than 3 spontaneous bowel movements [SBMs] per week).⁷⁰ In 1 study in patients taking full-agonist opioids other than methadone, the primary efficacy endpoint of overall response (greater than or equal to 3 SBMs per week for at least 9 of the 12 weeks, and at least 1 more SBM per week than at baseline in every week for which data was available) was achieved in 27.1% of patients taking lubiprostone versus 18.9% of placebo (treatment difference = 8.2%; p=0.03). The other 2 studies did not exclude patients taking methadone; treatment with lubiprostone, compared to placebo, resulted in a significantly greater improvement from baseline in weekly SBM frequency at week 8 (the primary endpoint) in 1 study (3.3 versus 2.4, p=0.004) but not the other (2.7 versus 2.5, p=0.76); overall response rates in the 2 studies were 24.3% and 15.3% for lubiprostone versus 15.4% and 13% for placebo.

methylnaltrexone (Relistor) versus placebo

In a 4-week randomized, double-blinded, placebo controlled study (study 1), the safety and efficacy of subcutaneous methylnaltrexone 12 mg once daily versus placebo were evaluated for the treatment of OIC in patients with chronic non-cancer pain.⁷¹ A total of 312 patients (methylnaltrexone n=150; placebo n=162) were enrolled in the study and had previously received opioid therapy for pain for ≥1 month or greater (median daily baseline oral morphine equivalent dose = 161 mg) with a diagnosis of OIC (defined as less than 3 spontaneous bowel movements per week during the screening period). Patients were required to discontinue all previous laxative therapy and use only the study-permitted rescue laxative (bisacodyl tablets). Patients who did not experience a bowel movement for 3

consecutive days during the study, were allowed to use a rescue medication (up to 4 bisacodyl tablets taken orally once during a 24-hour period). Rescue laxatives were prohibited at least 4 hours after taking an injection of study medication. The primary endpoint was the proportion of patients with greater than 3 spontaneous bowel movements (SBMs), defined as a bowel movement that occurred without laxative use during the previous 24 hours, per week during the 4 week double-blind period. In the modified intent-to-treat (mITT) population, which included all randomized subjects who received at least 1 dose of the double-blind study medication, 59% of the participants in the methylnaltrexone group had greater than 3 SBMs per week compared to 38% in the placebo group during the entire study period.

In 2 (study 3 and 4) randomized, double-blinded, placebo controlled studies, the safety and efficacy were demonstrated in the treatment of OIC in adult patients with advanced illness who were additionally receiving palliative care (e.g., incurable cancer, end-stage COPD/emphysema, cardiovascular disease/heart failure, Alzheimer's disease/dementia, HIV/AIDS, and other advanced illnesses).⁷²

In study 3, a total of 154 patients (methylnaltrexone 0.15 mg/kg, n=47; methylnaltrexone 0.3 mg/kg, n=55; placebo, n=52) were enrolled in the study. The primary endpoint was the proportion of patients with a rescue-free laxation within 4 hours of the study medication. Methylnaltrexone-treated patients had a significantly higher rate of laxation within 4 hours of the double blind dose (62% for 0.15 mg/kg; 58% for 0.3 mg/kg) compared to placebo-treated patients [(14%); p < 0.0001] for each dose versus placebo.

In study 4, methylnaltrexone given every other day for 2 weeks versus placebo was evaluated in 133 (methylnaltrexone n=62; placebo n=71) patients.⁷³ Participants enrolled in the study had received opioid medication for greater than or equal to 2 weeks prior to receiving the study medication. During the first week (days 1, 3, 5, 7) patients received either 0.15 mg/kg methylnaltrexone or placebo. During the second week, the patient's assigned dose could be increased to 0.30 mg/kg if the patient had 2 or fewer rescue-free laxations up to day 8 and the patient's assigned dose could be reduced based on tolerability at any time during the study. The 2 primary endpoints included proportion of patients with a rescue-free laxation within 4 hours of the first dose of study medication and proportion of patients with a rescue-free laxation within 4 hours following at least 2 of the first 4 doses of study medication. A higher rate of laxation within 4 hours of the first dose was shown in the methylnaltrexone-treated patient (48%) compared to placebo-treated patients [16%; p<0.0001]. Additionally, the methylnaltrexone-treated patients exhibited significantly higher rates of laxation within 4 hours after at least 2 of the first 4 doses (52%) than did placebo-treated patients [9%, p<0.0001]. Both studies showed approximately 30% of patients reported laxation within 30 minutes of receiving a dose of methylnaltrexone.

naloxegol (Movantik) versus placebo

Naloxegol (Movantik) was evaluated in 2 randomized, double-blinded, placebo-controlled trials (study 1 and study 2) in patients with OIC and non-cancer related pain.^{74,75} A total of 652 patients in study 1 and 700 patients in study 2 were randomized in a 1:1:1 ratio to receive 12.5 mg or 25 mg of naloxegol or placebo once daily for 12 weeks. The mean age of the participants was 52 years of age. Inclusion criteria were opioid morphine equivalent daily dose between 30 mg and 1,000 mg (mean baseline opioid morphine equivalent daily dosage was 140 mg and 136 mg per day in study 1 and study 2,

respectively) for at least 4 weeks before enrollment and self-reported OIC (defined as less than 3 spontaneous bowel movements [SBMs] per week on average with at least 25% of the SBMs associated with of the following conditions: straining, hard and/or lumpy stools, and incomplete evacuation sensation). A SBM was defined as a bowel movement without rescue laxative taken within the past 24 hours. Participants were prevented from using laxatives (with the exception of bisacodyl rescue laxative if they had not had a bowel movement for 72 hours) and 1-time use of an enema (if no bowel movement after 3 doses of bisacodyl). The primary endpoint for both studies was three or more SBMs per week and a change from baseline of 1 or more SBM for at least 9 out of the 12 study weeks and 3 out of the last 4 weeks. A statistically significant difference in the 25 mg naloxegol treatment group versus placebo was exhibited for the primary endpoint in both studies (percentage of patients responding for naloxegol versus placebo study 1: 44% versus 29%, $p=0.001$; study 2: 40 versus 29%, $p=0.021$). Additionally, a significant difference was observed in the 12.5 mg treatment group versus placebo (41% versus 29% response, respectively; $p=0.015$) in study 1 but not in study 2 ($p=0.202$). A secondary endpoint in both studies was response in laxative users with OIC symptoms. Patients were identified using an investigator-administered questionnaire based on the use of a laxative at least 4 out of the past 14 days. Patients had to experience at least 1 of the following OIC symptoms of moderate, severe, or very severe intensity: incomplete bowel movements, hard stool, straining, or sensation of needing to pass a bowel movement without success. This subgroup of patients comprised 55% and 53% of the total patients in study 1 and study 2, respectively. A higher percentage of patients in the study 1 subgroup responded with 12.5 mg naloxegol compared to placebo (43% versus 29%; $p=0.03$) and 25 mg naloxegol compared to placebo (49% versus 29%; $p=0.002$). In study 2, a higher percentage of patients in this subgroup responded with naloxegol 25 mg compared to placebo (47% versus 31%, $p=0.01$). Time to first post-dose SBM was another secondary endpoint. In study 1, 61% and 58% of patients receiving naloxegol 25 mg and naloxegol 12.5 mg, respectively, experienced a SBM within 24 hours of the first dose. In study 2, 70% of patients receiving naloxegol 25 mg had a SBM within 24 hours of the first dose.

SUMMARY

Treatment for irritable bowel syndrome (IBS) focuses on management of symptoms and pharmacologic options should be considered as part of a multifocal approach to achieve relief. Alosetron (Lotronex) is limited to women with severe IBS-D who have not responded adequately to conventional therapy and have shown greater improvement of symptoms associated with IBS-D versus placebo. Alosetron (Lotronex) should only be prescribed by enrollees of the Prometheus Prescribing Program for Lotronex due to the possible risk of severe complications of constipation and ischemic colitis. Linaclotide (Linzess) and lubiprostone (Amitiza) are indicated for the treatment of chronic idiopathic constipation (CIC) and IBS with constipation (IBS-C), although lubiprostone (Amitiza) is not indicated for use in IBS-C for men. Lubiprostone (Amitiza) is also approved for the treatment of opioid-induced constipation (OIC) in adults with chronic, non-cancer pain. Despite a lack of comparative data between linaclotide (Linzess) and lubiprostone (Amitiza), both agents have been shown to be more effective than placebo in alleviating the symptoms associated with IBS-C; however, it is important that these medications not be used in patients with gastrointestinal (GI) obstruction. Diarrhea can occur with the use of both agents and, if severe, may require dosing interruption. The use of lubiprostone (Amitiza) has been associated with hypersensitivity reactions and nausea, which have not been reported with linaclotide (Linzess). Furthermore, linaclotide (Linzess) does not require dose adjustment for patients with hepatic

impairment and is dosed once daily versus twice daily administration with lubiprostone (Amitiza). The role of these agents in the treatment of IBS-C, IBS-D, and CIC continues to be determined given lack of comparative data and controlled data with long-term safety, remains to be established.

Constipation is a common adverse effect associated with opioid therapy. A variety of conventional options including lifestyle and dietary modifications and laxatives can improve bowel function. For refractory cases, in addition to oral lubiprostone (Amitiza), subcutaneous once daily methylnaltrexone (Relistor) and oral once daily naloxegol (Movantik) are also indicated for OIC in patients taking opioids for chronic non-cancer pain. Methylnaltrexone (Relistor) is additionally indicated for the treatment of OIC in adult patients with advanced illness who are receiving palliative care and response to laxative therapy has been insufficient. Methylnaltrexone (Relistor) and naloxegol (Movantik) have been studied in adults who have been taking opioid pain medicines for at least 4 weeks. However, the overall risk-benefit should be taken into account for both agents in patients with impaired integrity of the GI tract.

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