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

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FDA-APPROVED INDICATIONS

Drug	Manufacturer	Indication(s)
alosetron (Lotronex®)[1]	generic, Sebela	▪ Treatment of severe, diarrhea-predominant irritable bowel syndrome (IBS-D) in women who have chronic IBS symptoms and have failed conventional therapy
eluxadoline* (Viberzi®)[2]	Allergan	▪ Treatment of irritable bowel syndrome with diarrhea (IBS-D) in adult patients
linaclotide (Linzess®)[3]	Allergan	▪ Treatment of chronic idiopathic constipation (CIC) ▪ Treatment of irritable bowel syndrome with constipation (IBS-C)
lubiprostone (Amitiza®)[4]	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, including patients with chronic pain related to prior cancer or its treatment who do not require frequent (e.g., weekly) opioid dosage escalation†
methylnaltrexone‡ (Relistor®)[5]	Salix	▪ Treatment of opiate-induced constipation (OIC) in adult patients with advanced illness or pain caused by active cancer who require opioid dosage escalation for palliative care (injection only)§ ▪ Treatment of OIC in patients taking opioids for chronic non-cancer pain, including patients with chronic pain related to prior cancer or its treatment who do not require frequent (e.g., weekly) opioid dosage escalation (tablet and injection formulations)
naldemedine (Symproic®)[6]	Shionogi	▪ Treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain, including patients with chronic pain related to prior cancer or its treatment who do not require frequent (e.g., weekly) opioid dosage escalation
naloxegol (Movantik®)[7]	AstraZeneca	▪ Treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain, including patients with chronic pain related to prior cancer or its treatment who do not require frequent (e.g., weekly) opioid dosage escalation
plecanatide (Trulance®)[8]	Synergy/Bausch	▪ Treatment of chronic idiopathic constipation (CIC) in adult patients ▪ Treatment of irritable bowel syndrome with constipation (IBS-C)
prucalopride (Motegrity™)[9]	Shire	▪ Treatment of chronic idiopathic constipation (CIC) in adults

* Eluxadoline (Viberzi) is considered a Schedule IV controlled substance, while naldemedine (Symproic) has been descheduled and is no longer classified as a controlled substance. Other agents in this review are non-controlled prescription products.

† Effectiveness of lubiprostone for 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 patients with advanced illness.

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.[10] Chronic idiopathic constipation (CIC) is diagnosed if there are < 3 spontaneous bowel movements (SBMs) per week with symptoms occurring for ≥ 6 months and at least 2 of the previously mentioned bowel symptoms.

Irritable bowel syndrome (IBS) is a functional bowel disorder which can be chronic, relapsing, and often life long.[11,12,13] 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 consistency, abnormal stool passage, and/or bloating or abdominal distension, which may or may not be relieved by defecation, ≥ 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.[14,15,16] 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 2018, the American College of Gastroenterology (ACG) provided a monograph on the management of IBS as an update to their 2014 monograph on IBS and CIC.[17] Based on available data, strong recommendations for symptom improvement are provided for the use of soluble fiber, psyllium, and tricyclic antidepressants (TCAs). Loperamide is an effective antidiarrheal; however, there is no evidence to support the use of loperamide for relief of symptoms in IBS. The osmotic laxative polyethylene glycol (PEG) has shown to be effective in chronic constipation, but its efficacy in IBS-C is less certain. No recommendations of other laxatives are provided. They suggest the non-absorbable antibiotic rifaximin (Xifaxan®) for reduction in global IBS symptoms as well as bloating in non-constipated IBS patients (weak recommendation). Linaclotide (Linzess), lubiprostone (Amitiza), and plecanatide (Trulance) are all effective in IBS-C (Strong recommendations for all; linaclotide, high level of evidence [LOE]; others, moderate LOE). Alosetron (Lotronex, generic) and eluxadoline (Viberzi) are indicated for IBS-D; the ACG suggests use of these agents for overall symptom improvement based on low and moderate LOE, respectively. This monograph does not address CIC.

The 2014 AGA guidelines recommend laxatives as well as 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, generic) over no drug treatment in patients with IBS-D.[18] The guidelines do not address eluxadoline, as it was not available at the time of publication. 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.[19,20,21] 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, 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 (Xifaxan) 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.[22,23,24,25] No data exist as to the role in mixed or alternating IBS, and recommendations regarding use as first- or second-line treatments need to be determined based on issues of efficacy, safety, and cost. Alosetron (Lotronex) was voluntarily withdrawn from the US market in 2000 due to ischemic colitis and serious complications of severe constipation.[26] In 2002, it returned to market but with tight restrictions.[27]

The AGA 2013 position statement on constipation suggests a gradual increase in fiber intake and an osmotic laxative (e.g., polyethylene glycol) as a first step.[28] A stimulant laxative (e.g., bisacodyl, glycerol suppository) may be added if needed. When symptoms do not abate, consider use of linaclotide (Linzess), lubiprostone (Amitiza), or prucalopride (Motegrity; prucalopride was available in countries other than the US was at the time these guidelines were published). Similarly, the 2016 American Society of Colon and Rectal Surgeons guideline for the evaluation and management of constipation recommends increased fiber and fluid update for constipation.[29] Osmotic laxatives are effective and safe for chronic constipation and stimulant laxatives (e.g., bisacodyl) are reasonable for short-term as second-line treatment. If constipation has not resolved, the society recommends linaclotide or lubiprostone; no recommendations are provided for prucalopride since it was not FDA-approved at the time of guideline publication.

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.[30] The 2017 American Society of Interventional Pain Physicians (ASIPP) guidelines for responsible opioid prescribing in chronic noncancer pain recommend that prescribers initiate a prophylactic bowel regimen (e.g., increased fluid and fiber intake, stool softeners, laxatives) even before the development of constipation and definitely after its development.[31] The 2019 AGA guideline on the medical management of opioid-induced constipation recommends use of traditional laxatives as first-line agents (strong recommendation, moderate quality of evidence).[32] However, in patients with laxative refractory OIC, it is recommended that peripherally acting mu-opioid receptor antagonists (PAMORAs), such as naldemedine and naloxegol, are utilized over no treatment (strong, high [naldemedine] and moderate [naloxegol]). Methylnaltrexone (Relistor) is suggested over no treatment, but this was given a conditional recommendation due to low quality of evidence. Additionally, the guidelines makes no recommendations for intestinal secretagogues (e.g., lubiprostone [Amitiza]) or 5-HT agonists (e.g. prucalopride [Motegrity]) due to limited consistent evidence to support their use.

PHARMACOLOGY[33,34,35,36,37,38,39,40,41]

Alosetron (Lotronex, generic) is a selective serotonin 5-HT_3 receptor antagonist. The 5-HT_3 receptors are ligand-gated cation channels 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-HT_3 receptor antagonists inhibit the activation of these channels resulting in modulation of the GI tract.

Eluxadoline (Viberzi) is a mu and kappa opioid receptor agonist and a delta opioid receptor antagonist. When eluxadoline interacts with receptors located in the GI tract, stomach, pancreas, and biliary tract secretions are decreased. Thus, the combination effects of opiate agonists on the GI tract results in constipation and delayed digestion.

Both linaclotide (Linzess) and plecanatide (Trulance) are guanylate cyclase-C (GC-C) agonists. Both agents and their active metabolites 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 GI transit. In animal models, linaclotide and plecanatide have both been shown to 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. In an animal model of visceral pain, plecanatide reduced abdominal muscle contractions, which is considered a measure of intestinal pain; however, this mechanism was not evaluated.

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. 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 limited 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.

Naldemedine (Symproic) functions as a peripherally-acting mu-opioid receptor antagonist in tissues such as the GI tract, thereby decreasing the constipating effects of opioids.

Prucalopride (Motegrity) is a selective serotonin-4 (5-HT_4) receptor agonist which acts as a GI prokinetic agent to stimulate colonic peristalsis (high-amplitude propagating contractions) and increase bowel motility.

PHARMACOKINETICS[42,43,44,45,46,47,48,49,50]

Drug	Bioavailability (%)	Half-Life (hr)	Metabolism	Excretion (%)
alosetron (Lotronex)	50–60	1.5	Predominately metabolized by cytochrome P450 enzymes 2C9, 3A4, and 1A2	Urine: 74 Feces: 11
eluxadoline (Viberzi)	nr	3.7 to 6	Not established; evidence suggests it undergoes glucuronidation resulting in an acyl glucuronide metabolite	Urine: < 1 Feces: 82.2
linaclotide (Linzess)	n/a*	n/a*	Proteolytically degraded in the lumen to smaller peptides and naturally occurring amino acids	Feces
lubiprostone (Amitiza)	n/a*	n/a*	Rapidly and extensively metabolized by carbonyl reductase mediated oxidation and reduction	Feces
methylnaltrexone (Relistor)	nr	8	Primarily metabolized to methyl-6-naltrexol isomers and methylnaltrexone sulfate	Urine: 53.6 Feces: 17.3
naldemedine (Symproic)	nr	11	Naldemedine is primarily metabolized by CYP3A to nor-naldemedine, with minor contribution from UGT1A3 to form naldemedine 3-G.	Urine: 57 Feces: 35
naloxegol (Movantik)	nr	6 to 11	Primarily metabolized by the CYP3A enzyme system	Urine: 16 Feces: 68
plecanatide (Trulance)	nr	nr	Metabolized in the GI tract; both plecanatide and metabolite proteolytically degraded in the lumen to smaller peptides and naturally occurring amino acids	nr†
prucalopride (Motegrity)	> 90%	24	CYP3A4 substrate *in vitro*	Urine: 84.2 Fecal: 13.3

nr = not reported; n/a = not applicable

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

† Plecanatide is minimally absorbed, with little systemic availability following oral administration; thus, many pharmacokinetic variables were unable to be calculated in pharmacokinetics studies.

CONTRAINDICATIONS/WARNINGS[51,52,53,54,55,56,57,58,59,60]

Alosetron (Lotronex, generic) is contraindicated in patients with a history of severe bowel disorders (e.g., GI obstruction/perforation, stricture, toxic megacolon, GI adhesions) and in patients with impaired intestinal circulation, diverticulitis, Crohn's disease, thrombophlebitis, hypercoagulable state, or ischemic or ulcerative colitis is also contraindicated. Similarly, prucalopride (Motegrity) is contraindicated in patients with intestinal perforation or obstruction due to structural or functional disorder of the gut wall, obstructive ileus, or severe inflammatory conditions of the intestinal tract (e.g., Crohn disease, ulcerative colitis, or toxic megacolon). Eluxadoline (Viberzi), linaclotide (Linzess), lubiprostone (Amitiza), and plecanatide (Trulance) are contraindicated in patients with known or suspected mechanical GI obstruction. Methylnaltrexone (Relistor), naldemedine (Symproic), 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.

Alosetron (Lotronex, generic) and eluxadoline (Viberzi) should not be initiated in patients with constipation; severe cases with development of intestinal obstruction, intestinal perforation, and fecal impaction, requiring intervention, have been reported. If constipation develops, alosetron and eluxadoline should be stopped immediately. Alosetron labeling also carries boxed warnings advising of serious GI adverse reactions, including ischemic colitis.

Cases of GI perforation have been reported with administration of a peripherally-acting opioid antagonist other than naloxegol (Movantik) or naldemedine (Symproic) in patients with medical conditions associated with reduced GI tract wall structural integrity (e.g., peptic ulcer disease, Ogilvie's syndrome, diverticular disease, infiltrative GI tract malignancies, peritoneal metastases). Therefore, the overall risk-benefit profile should be assessed in patients administered naloxegol (Movantik) and naldemedine (Symproic). 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. Additionally, reports of severe abdominal pain and/or diarrhea have been reported in patients taking naloxegol (Movantik). In some cases, this resulted in hospitalization. Most cases of severe abdominal pain were reported in patients utilizing the 25 mg dosage. Symptoms generally occurred within a few days of starting the drug. Patients should be monitored for development of abdominal pain and/or diarrhea with naloxegol and discontinue therapy if severe symptoms occur. Patients may be re-started on therapy with the 12.5 mg dose if deemed necessary. Severe diarrhea has also been reported in patients using linaclotide (Linzess), lubiprostone (Amitiza), methylnaltrexone (Relistor), and plecanatide (Trulance); if this occurs, dosing should be suspended and the patient should be rehydrated. Children < 6 years of age are at greater risk of severe diarrhea and serious dehydration; therefore, use of linaclotide (Linzess) and plecanatide (Trulance) is contraindicated in children < 6 years of age and boxed warnings for these products carries advise to avoid use in patients < 18 years of age.

Alosetron (Lotronex, generic) and eluxadoline (Viberzi) are contraindicated in patients with severe hepatic impairment; a history of pancreatitis; structural diseases of the pancreas, including known or suspected pancreatic/biliary duct obstruction; or sphincter of Oddi disease/dysfunction. Additionally, eluxadoline is contraindicated in patients with alcohol abuse (> 3 alcoholic beverages per day). In 2017, the FDA issued a Drug Safety Communication warning of an increased risk of serious pancreatitis, potentially leading to hospitalizations or death, with eluxadoline (Viberzi) use in patients without a gallbladder.[61] Thus, use of eluxadoline is contraindicated in patient without a gallbladder.

Patients taking lubiprostone (Amitiza) may experience nausea; taking with food may reduce symptoms of nausea. Syncope and hypotension, some cases requiring hospitalization, have been reported with lubiprostone postmarketing. Dyspnea has also been reported with lubiprostone 24 mg doses in the postmarketing setting; symptoms generally resolve within a few hours of taking the dose and can recur with subsequent doses.

Eluxadoline (Viberzi), naldemedine (Symproic), and prucalopride (Motegrity) are contraindicated in patients with hypersensitivity to the active ingredient. Reactions reported with naldemedine include bronchospasm and rash. Dyspnea, rash, pruritus, urticaria, and facial edema have been reported with prucalopride. Postmarketing experience of eluxadoline has demonstrated serious hypersensitivities reactions, including anaphylaxis; with some cases occurring after the first 1 or 2 doses. Use of naloxegol is contraindicated in patients who have experienced a severe reaction to naloxegol or any of the excipients contained in the drug, and postmarketing reactions, including rash, urticaria, and angioedema. Hypersensitivity reactions (rash, swelling, throat tightness) have been reported postmarketing with lubiprostone (Amitiza) .

Opioid withdrawal symptoms (e.g., increased sweating, chills, lacrimation, flushing, pyrexia, abdominal pain, diarrhea, nausea, vomiting) have been reported in patients treated with methylnaltrexone (Relistor), naldemedine (Symproic), or naloxegol (Movantik). 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.

Alosetron (Lotronex, generic) is contraindicated in patients taking concomitant fluvoxamine.

Suicide, suicide attempts, and suicide ideation have been reported with prucalopride (Motegrity); however, no causal association has been established. Patients should be monitored for persistent worsening depression or development of suicidal thoughts.

Risk Evaluation and Mitigation Strategy (REMS)[62]

Alosetron (Lotronex, generic) is subject to a REMS program consisting of healthcare provider training to ensure safe use and prescriber awareness of the risk of ischemic colitis and complications of constipation associated with alosetron. The Patient Education Sheet is the primary educational tool used by the prescriber to counsel the patient on safety risks of alosetron.

DRUG INTERACTIONS[63,64,65,66,67,68,69,70,71]

Based on data from *in vivo* studies, alosetron (Lotronex, generic) 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.

Eluxadoline (Viberzi) is a substrate of the organic anion-transporting peptide (OATP1B1) and when coadministered with OATP1B1 inhibitors (e.g., cyclosporine, gemfibrozil, antiretrovirals, rifampin), an increased plasma concentration of eluxadoline may occur; therefore, it is recommended that the dosage of eluxadoline should be decreased to 75 mg twice daily. Other established drug interactions with eluxadoline include drugs that cause constipation (e.g., anticholinergics, opioids, alosetron) and strong CYP inhibitors (e.g., ciprofloxacin, gemfibrozil, fluconazole, clarithromycin, paroxetine,

bupropion), which may impair a patient's mental and physical abilities. Thus, patients should be monitored to avoid these adverse events.

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 nor lubiprostone 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.

Methylnaltrexone (Relistor) and naloxegol (Movantik) 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.

Naldemedine (Symproic) and naloxegol (Movantik) are primarily metabolized by the cytochrome P450 3A4 enzyme system. Administration with moderate CYP3A4 inhibitors (e.g., diltiazem, erythromycin, verapamil) may increase concentrations of both naldemedine and naloxegol; therefore, concomitant use of these agents with CYP3A4 inhibitors are not recommended. However, if concomitant use is unavoidable, the dosage of naloxegol (Movantik) and naldemedine (Symproic) may need to be decreased and the patient should be monitored for adverse effects. Use of naloxegol or naldemedine with strong CYP3A4 inducers (e.g., rifampin) is not recommended as well due to a decrease in drug concentrations.

Increased plasma concentrations of naldemedine can also occur when given with P-gp inhibitors (e.g., amiodarone, captopril, cyclosporine) and patients should be monitored for naldemedine-related adverse reactions.

There are no reported or known drug interactions associated with plecanatide (Trulance).

In vitro, prucalopride (Motegrity) is a CYP3A4 substrate and is primarily excreted renally; however, clinical drug interaction studies have not indicated strong CYP3A4 inhibitors (e.g., ketoconazole) cause clinically relevant drug interactions. *In vitro* data does demonstrate a low potential for prucalopride to inhibit CYP enzymes (1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4) and transporters (P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, MATE1, MATE2-K, BSEP, and MRP2 transporters) or induce CYP enzymes (1A2, 2B6, and 3A4) to clinically relevant concentrations.

ADVERSE EFFECTS[72,73,74,75,76,77,78,79,80]

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
eluxadoline (Viberzi) n=1,839 (150 to 200 mg/day)	7–8 (2)	nr	7–8 (5)	6–7 (4)	3 (2)	3 (2)	1–3 (2)	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
naldemedine (Symproic)	nr	7 (2)	4 (2)	8 (2)	nr	nr	2 (1)	nr	nr
naloxegol (Movantik) n=446 (25 mg dose)	nr	9 (5)	8 (5)	21 (7)	6 (3)	nr	nr	4 (3)	nr
plecanatide (Trulance) n=1,733 (CIC)	nr	5 (1)	nr	nr	< 2 (nr)	< 2 (nr)	nr	nr	nr
n=1,449 (IBS-C)	nr	4.3 (1)	< 2 (0.4)	nr	nr	nr	nr	nr	nr
prucalopride (Motegrity) n=1,251 (CIC)	nr	13 (5)	14 (7)	16 (11)	3 (2)	5 (4)	nr	19 (9)	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, generic) and the most frequently reported adverse effect in clinical trials. Constipation associated with alosetron 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. Patients who are elderly, debilitated, or taking other medications that decrease GI

motility may be at greater risk for constipation complications. Alosetron should be discontinued immediately in any patient experiencing constipation.

In clinical trials with eluxadoline (Viberzi), constipation was the most commonly reported adverse reaction. Approximately 50% of the constipation events happened within the initial 2 weeks of treatment. While the remaining constipation events occurred within the first 3 months.

Severe diarrhea was reported in approximately 2% of the patients taking linaclotide (Linzess) and lubiprostone (Amitiza) and in < 1% of those treated with plecanatide (Trulance). If severe diarrhea occurs, the patient should be instructed to contact their physician and dosing of the drug may need to be interrupted or suspended. Cases of higher than normal readings in liver biochemical tests (e.g., alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) have been reported in patient taking plecanatide. Also, in clinical trials with prucalopride (Motegrity), severe diarrhea was reported in 1.8% of the patients treated with prucalopride 2 mg versus 1% in the placebo group; however, the onset and duration of diarrhea was similar overall in the trial.

The most common adverse effect associated with lubiprostone is nausea. The incidence of nausea increases in a dose-dependent manner with the highest percentage being reported in patients receiving 24 mcg twice daily. It is recommended that lubiprostone be given with food and water, which has shown to decrease reported nausea. Additionally, syncope and hypotension have also been reported with lubiprostone which resulted in hospitalization in a few reported cases. This adverse event occurred primarily in patients taking 24 mcg twice daily and within an hour after taking the first dose or subsequent doses of lubiprostone. Some patients had concomitant diarrhea or vomiting prior to developing this adverse reaction. Syncope and hypotension generally resolved following discontinuation.

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 a breath, these symptoms generally resolve within 3 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, prescribers should consider the overall risk: benefit of naloxegol and methylnaltrexone (Relistor) 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. Postmarketing reports indicate that naloxegol (Movantik) can also cause angioedema, rash, and urticaria.

SPECIAL POPULATIONS[81,82,83,84,85,86,87,88,89]

Pediatrics

Safety and effectiveness have not been established in pediatric patients for alosetron (Lotronex, generic), eluxadoline (Viberzi), linaclotide (Linzess), lubiprostone (Amitiza), methylnaltrexone (Relistor), naldemedine (Symproic), naloxegol (Movantik), plecanatide (Trulance), or prucalopride (Motegrity).

Linaclotide (Linzess) is contraindicated in pediatric patients < 6 years of age and should be avoided in patients 6 years through 17 years of age.

Pregnancy

The labeling for alosetron (Lotronex, generic) was updated in compliance with the Pregnancy and Lactation Labeling Rule (PLLR) to say, the available data with Alosetron (Lotronex) use in pregnant women are insufficient to draw conclusions about any drug-associated risks for major birth defects, miscarriage, or adverse maternal or fetal outcomes. Previously, alosetron was assigned Pregnancy Category B.

Methylnaltrexone (Relistor) 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. Previously, lubiprostone (Amitiza), methylnaltrexone (Relistor), naloxegol (Movantik), and linaclotide (Linzess) were assigned Pregnancy Category C; however, their labeling was updated in compliance with the PLLR. Linaclotide is negligibly absorbed systemically, and maternal use is not expected to result in fetal exposure to the drug; however, data are not sufficient to inform any drug-associated risk for major birth defects and miscarriage. The limited available data with lubiprostone, methylnaltrexone, and naloxegol in pregnant women are not sufficient to inform of a drug-associated risk for major birth defects and miscarriages. If used during pregnancy, naloxegol may precipitate opioid withdrawal in both pregnant women and the fetus.

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

There are no well-controlled studies in pregnant women as it relates to naldemedine (Symproic). However, the use of naldemedine during pregnancy may precipitate opioid withdrawal in a fetus due to the immature fetal blood brain barrier.

The potential for eluxadoline (Viberzi) and plecanatide (Trulance) to cause adverse effects on a fetus or reproductive system is unknown as studies have not been conducted in pregnant women. It should be noted, however, that plecanatide and its active metabolite have shown negligible systemic absorption following oral administration and use in pregnancy is not anticipated to result in fetal exposure or harm.

Renal Impairment

No dose adjustment is necessary based on renal function for alosetron (Lotronex, generic), linaclotide (Linzess), lubiprostone (Amitiza), or naldemedine (Symproic).

Methylnaltrexone (Relistor) requires dose adjustment in patients with moderate to severe renal impairment (CrCl < 60 mL/min).

A reduced dose of naloxegol (Movantik) is recommended for patients with moderate, severe, or end-stage renal impairment (creatinine clearance [CrCl] < 60 mL/min).

Plecanatide (Trulance) labeling does not report any studies in patients with renal impairment.

Given prucalopride (Motegrity) is extensively excreted by the kidney, a decreased dose is recommended in patients with severe renal impairment (CrCl < 30 mL/min) and its use should be avoided in patients with end-stage renal disease (ESRD) requiring dialysis.

Use of eluxadoline (Viberzi) in patients with renal impairment is not addressed in the product labeling.

Hepatic Impairment

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

Eluxadoline (Viberzi) is contraindicated in patients with severe hepatic impairment (Child-Pugh Class C) as plasma concentrations increase significantly (16-fold). In patients with Child-Pugh Class A (mild) or Child-Pugh Class B (moderate) hepatic impairment, plasma concentrations of eluxadoline are increased to a lesser extent (6- and 4-fold, respectively). For patients with mild or moderate hepatic impairment, a reduced dose should be administered.

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

For the treatment of IBS-C, there is no dose adjustment of lubiprostone (Amitiza) needed for patients with moderately impaired hepatic function (Child-Pugh Class B). Dosage reductions are recommended for patients with severely impaired hepatic function (Child-Pugh Class C). If tolerated, the dose can be escalated to full dosing with appropriate monitoring of patient response. For the treatment of CIC with lubiprostone, the recommended dose is reduced in patients with moderately (Child-Pugh Class B) and severely impaired hepatic function (Child-Pugh Class C). If tolerated, the dose can be escalated to full dosing with appropriate monitoring of patient response.

The effect of severe hepatic impairment (Child-Pugh Class C) on the pharmacokinetics of naldemedine (Symproic) has not been evaluated. Thus, use of naldemedine should be avoided in patients with severe hepatic impairment. A dose adjustment of naldemedine is not required in patients with mild or moderate hepatic impairment.

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

In patients with moderate to severe hepatic impairment (Child-Pugh Class B or C), a dose adjustment is required for methylnaltrexone (Relistor) tablets. When utilizing the injection formulation, a dose adjustment is required in severe hepatic impairment.

Plecanatide (Trulance) labeling does not report any studies in patients with hepatic impairment.

Prucalopride (Motegrity) pharmacokinetic studies suggest differences in drug exposure in patients with moderate or severe hepatic impairment (Child-Pugh B or C) are not clinically significant from individuals with normal hepatic function.

DOSAGES[90,91,92,93,94,95,96,97,98]

Drug	IBS-D	IBS-C	CIC	OIC in adults with chronic non-cancer pain	OIC in adults with advanced illness	Availability
alosetron (Lotronex)	Females only: 0.5 mg twice a day, may increase to 1 mg twice a day if well tolerated (discontinue if 4 weeks' treatment at this dose does not lead to adequate symptom control)	--	--	--	--	0.5 mg and 1 mg tablets
eluxadoline* (Viberzi)	100 mg twice a day with food; 75 mg twice daily with food in patients unable to tolerate 100 mg dose, receiving concomitant OATP1B1 inhibitors, or mild or moderate hepatic impairment*	--	--	--	--	75 mg and 100 mg tablets
linaclotide (Linzess)	--	290 mcg once daily at least 30 minutes prior to first meal	145 mcg once daily at least 30 minutes prior to first meal†	--	--	72 mcg, 145 mcg, and 290 mcg capsules

CIC = chronic idiopathic constipation; IBS-C = irritable bowel syndrome with constipation; IBS-D = irritable bowel syndrome with diarrhea; OIC = opioid-induced constipation

* Discontinue eluxadoline in patients who develop severe constipation for > 4 days. Do not take > 2 doses at once; if dose is missed, take the next dose at the regular time. The current labeling for eluxadoline also recommends a dose of 75 mg in those without a gallbladder; however, a FDA Drug Safety Communication issued in 2017 no longer recommends use of eluxadoline in patients without a gallbladder due to the increased risk of pancreatitis. For patients with mild or moderate hepatic impairment, a reduced dose of 75 mg twice daily should be administered.

† In CIC, the 290 mcg linaclotide dose has not been shown to be more effective than the 145 mcg dose. A dosage of 72 mcg once daily may be used based on the patient's tolerability. Linaclotide may be administered with applesauce or water for patients who have difficulty swallowing capsules or those with a nasogastric or gastrostomy tube.

Dosages (continued)

Drug	IBS-D	IBS-C	CIC	OIC in adults with chronic non-cancer pain	OIC in adults with advanced illness	Availability
lubiprostone‡ (Amitiza)	--	Females: 8 mcg twice daily§	Females: 24 mcg twice daily Males: 24 mcg twice daily¶	Females: 24 mcg twice daily Males: 24 mcg twice daily	--	8 mcg and 24 mcg capsules
methylnaltrexone‖,†† (Relistor)	--	--	--	12 mg subcutaneously once daily OR 450 mg (three 150 mg tablets) orally once daily ≥ 30 minutes before the first meal of the day**	Dosage based on body weight; one dose administered every other day, as needed; do not exceed 1 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 Tablets: 150 mg
naldemedine‖ (Symproic)	--	--	--	0.2 mg orally once daily with or without food	--	0.2 mg tablets

CIC = chronic idiopathic constipation; IBS-C = irritable bowel syndrome with constipation; IBS-D = irritable bowel syndrome with diarrhea; OIC = opioid-induced constipation

‡ Should be taken with food and water.

§ Safety and efficacy have not been established for the use of lubiprostone in males for IBS-C. 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 CIC, the recommended dose of lubiprostone 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.

‖ Methylnaltrexone and naldemedine were shown to be efficacious in patients who have taken opioids for at least 4 weeks. Discontinue along with opioid discontinuation. Re-evaluate continued need for methylnaltrexone when opioid regimen is changed.

**In OIC in adult patients with chronic non-cancer pain with moderate to severe renal and hepatic impairment (Child Pugh Class B or C), the dosing for methylnaltrexone (Relistor) tablets is 150 mg once daily in the morning or 6 mg SC once daily (moderate to severe renal impairment only). See prescribing information for detailed weight-based injection dosing in patients with advanced illness and severe renal or hepatic impairment as well as patients with OIC in adult patients with chronic non-cancer pain and severe hepatic impairment.

†† Methylnaltrexone (Relistor) injection may be administered subcutaneously by the patient or caregiver with proper training.

Dosages (continued)

Drug	IBS-D	IBS-C	CIC	OIC in adults with chronic non-cancer pain	OIC in adults with advanced illness	Availability
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 3 days of treatment) **,††	--	12.5 and 25 mg tablets
plecanatide (Trulance)	--	3 mg once daily‡‡	3 mg once daily‡‡	--	--	3 mg tablets
prucalopride (Motegrity)	--	--	2 mg orally once daily with or without food§§	--	--	1 and 2 mg tablets--

CIC = chronic idiopathic constipation; IBS-C = irritable bowel syndrome with constipation; IBS-D = irritable bowel syndrome with diarrhea; OIC = opioid-induced constipation

‖ Naloxegol was shown to be efficacious in patients who have taken opioids for at least 4 weeks. Discontinue along with opioid discontinuation.

** In patients with CrCl < 60 mL/min, initial dose of naloxegol is 12.5 mg once daily; if well tolerated and OIC symptoms continue may increase to 25 mg once daily. If concurrent use of a moderate CYP3A4 inhibitor is unavoidable, reduce dose of naloxegol to 12.5 mg once daily.

†† Take on an empty stomach 1 hour prior to the first meal of the day, or 2 hours after the meal. Avoid consumption of grapefruit or grapefruit juice. For patients unable to swallow the naloxegol tablet whole, the tablet can be crushed and mixed with water then given orally or administered via nasogastric tube.

‡‡ Patients who have difficulty swallowing plecanatide tablets may place crushed tablets in either applesauce or water. Patients with a nasogastric or gastric feeding tube may crush the tablets and administer in water.

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

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.[99] 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 to 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).[100] 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.[101] 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 (≥ 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.

eluxadoline (Viberzi) versus placebo

The efficacy and safety of eluxadoline was evaluated in 2 randomized, multicenter, multinational, double-blind, placebo-controlled trials.[102] The two 26 week trials (trial 1 [n=1,281] and trial 2 [n=1,145]) evaluated twice daily dosing of 75 mg or 100 mg. Patients were required to meet Rome III criteria for IBS-D and were also required to meet both of the following: an average of worst abdominal pain scores in the past 24 hours of $>$ 3 (scale 0 to 10 over the week prior to randomization and an average daily stool consistency score (Bristol Stool Scale [BSS]) of ≥ 5.5 and at least 5 days with a BSS score of ≥ 5 (scale 1 to 7 over the week prior to randomization). Trial 1 was continued for an additional 26 weeks, double-blinded, for long-term safety, followed by a 2 week follow up. Trial 2 included a 4 week single-blind, placebo withdrawal period. An overall composite responder primary endpoint was used to assess the efficacy of eluxadoline in both trials. Patients were allowed to take loperamide rescue medication for acute treatment of uncontrolled diarrhea and aspirin-containing medications or nonsteroidal anti-inflammatories (NSAIDs) for abdominal pain; however, no other therapy was allowed to treat these conditions during the double-blind and single-blind phases. The primary endpoint was simultaneous improvement in the daily worst abdominal pain score (by at least 30%) and a reduction in the BSS (stool consistency scores) to < 5% on at least 50% of the days within a 12-week time interval compared to the weekly baseline average. An improvement in daily worst abdominal pain in the absence of a concurrent bowel movement was also evaluated. In both trials, the proportion of patients who were responders to eluxadoline was statistically higher than placebo for both doses (23% to 33% versus 19% to 20%, respectively) after 26 weeks. The percentage of patients with an abdominal pain response improvement of ≥ 30% over 12 weeks was also higher in patients treated with eluxadoline compared to placebo (42% to 51% versus 40% to 45%, respectively). The BSS $<$ 5 response over 12

weeks was higher in patients treated with eluxadoline versus placebo, as well (30% to 37% versus 21% to 22%, respectively).

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).[103,104,105] 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 7%; 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 3%, respectively), abdominal pain (7% versus 5%, respectively), flatulence (4% versus 2%, respectively), abdominal distension (2% versus 1%, respectively), viral gastroenteritis (3% versus 1%, respectively), and headache (4% versus 3%, respectively).

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).[106,107] 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 verses 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 5%, respectively), abdominal pain (7% versus 6%, respectively), flatulence (6% versus 5%, respectively), abdominal distension (3% versus 2%, respectively), upper respiratory tract infections (5% versus 4%, respectively), and sinusitis (3% versus 2%, respectively).

lubiprostone (Amitiza) versus placebo

In 2 double-blinded, placebo-controlled studies of identical design, lubiprostone was studied in patients with CIC.[108] A total of 479 patients were randomized and received lubiprostone 24 mcg twice daily or placebo twice daily for 4 weeks. The primary endpoint of the studies was SBM frequency. The change in SBMs frequency rate from baseline to week 1 for lubiprostone versus placebo was 4.3 versus 1.9 in study 1 and 4.5 versus 2.5 in study 2. 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, respectively. The percentage of adverse effects occurring in at least 2% of lubiprostone-treated patients and that occurred more frequently than placebo included nausea (29% versus 3%, respectively), diarrhea (12% versus 1%, respectively), abdominal pain (8% versus 3%, respectively), headache (11% versus 5%, respectively), abdominal distension (6% versus 2%, respectively), flatulence (6% versus 2%, respectively), vomiting (3% versus 0%, respectively), dizziness (3% versus < 1%, respectively), loose stools (3% versus 0%, respectively), edema (3% versus < 1%, respectively), abdominal discomfort (2% versus < 1%, respectively), dyspepsia (2% versus < 1%, respectively), and fatigue (2% versus < 1%, respectively).

Two double-blinded, placebo-controlled studies of similar design were conducted studying lubiprostone in patients with IBS-C.[109] 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 than women. The percentage of adverse effects occurring in at least 2% of lubiprostone-treated patients compared to placebo include nausea (8% versus 4%, respectively), diarrhea (7% versus 4%, respectively), abdominal pain (5% in both groups), headache (11% versus 5%, respectively), and abdominal distension (3% versus 2%, respectively).

Three randomized, double-blind, placebo-controlled trials compared lubiprostone 24 mcg twice daily to placebo for 12 weeks in approximately 1,300 patients with chronic noncancerous pain and opioid-induced constipation (defined as < 3 SBMs per week).[110] In 1 study with patients taking full-agonist opioids other than methadone, the primary efficacy endpoint of overall response (≥ 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 treated patients (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, respectively; p=0.004) but not the other study (2.7 versus 2.5, respectively; 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, respectively.

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.[111] 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 (median daily baseline oral morphine equivalent dose = 161 mg) with a diagnosis of OIC (defined as < 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 > 3 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 > 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/AID, other advanced illnesses).[112] 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.[113] Participants enrolled in the study had received opioid medication for ≥ 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 0.3 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.

naldemedine (Symproic) versus placebo

Two replicate, 12-week, randomized, double-blind, placebo-controlled, phase 3 trials, COMPOSE 1 and COMPOSE 2, evaluated the safety and efficacy of naldemedine for the treatment of OIC in patients 18 to 80 years of age with chronic non-cancer pain.[114] In COMPOSE 1, 547 patients were randomized 1:1 to naldemedine 0.2 mg or placebo daily. In COMPOSE 2, 553 subjects were randomized 1:1 to daily naldemedine 0.2 mg or placebo. Patients were required to either not be using laxatives or willing to discontinue laxative use prior to study enrollment. During the treatment period, bisacodyl was allowed as a rescue laxative if patients did not have a bowel movement (BM) for 72 hours. In addition, subjects were allowed 1-time use of an enema if after 24 hours of taking bisacodyl there was not a BM. The primary endpoint was assessed using a responder analysis. A responder was defined as a patient who had at least 3 spontaneous bowel movements (SBMs) per week and a change from baseline of at least 1 SBM per week for at least 9 out of the 12 study weeks and 3 out of the last 4 weeks. Primary outcome data were available from 273 patients randomized to naldemedine and 272 patients randomized to placebo in COMPOSE 1 and 276 patients randomized to naldemedine and 274 patients randomized to placebo in COMPOSE 2. In both studies, a significantly greater proportion of patients responded to naldemedine versus placebo (COMPOSE 1: 47.6% versus 34.6%, respectively, $p=0.002$; COMPOSE 2: 52.5% versus 33.6%, $p<0.0001$). Abdominal pain (8% versus 2%), diarrhea (7% versus 2%), nausea (4% versus 2%), and gastroenteritis (2% versus 1%) were reported with naldemedine versus placebo use, respectively.

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.[115,116] 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 was an 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 < 3 SBMs per week on average with at least 25% of the SBMs associated with 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 the patient had not had a bowel movement for 72 hours and 1-time use of an enema was allowed if no bowel movement after 3 doses of bisacodyl). The primary endpoint for both studies was ≥ 3 SBMs per week and a change from baseline of ≥ 1 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.

plecanatide (Trulance) versus placebo

The efficacy of plecanatide for the management of symptoms of CIC was established in two 12-week, double-blind, placebo-controlled, randomized, multicenter clinical studies in adult patients, designated as Study 1 and Study 2.[117] A total of 905 patients were enrolled in Study 1 and 870 patients entered into Study 2. All patients were randomized 1:1 to either placebo or plecanatide 3 mg, given once daily without respect to food. The overall mean age of the participants was 45 years and ranged from 18 to 80 years. Patients were required to meet modified Rome III functional constipation criteria of at least 3 months before the initial screening visit and with an onset of symptoms occurring at least 6 months prior to their diagnosis. The modified Rome III criteria required patients to report < 3 SBMs a week, rarely have a loose stool without the use of laxatives, avoid using manual maneuvers to facilitate defecations, and participants could not meet IBS-C criteria. Additionally, potential participants were required to report at least 2 of the following symptoms with at least 25% of all defecations: straining; lumpy or hard stools; the sensation of incomplete evacuations; and the sensation of anorectal obstruction/blockage. Patients who met the initial screening criteria were further required to demonstrate the following during the final 2 weeks of the screening process: < 3 CSBMs (a SBM associated with a sense of complete evacuation) in each of the 2 weeks and a Bristol Stool Form Scale (BSFS) of 6 or 7 in < 25% of SBMs (a bowel movement occurring in the absence of laxative use). Also,

prospective patients had to meet 1 out of the following 3 conditions: a BSFS of 1 or 2 in at least 25% of all defecations; a straining value recorded on at least 25% of days when a BM was reported; and at least 25% of all BMs resulting in a feeling of incomplete bowel evacuation. A responder analysis was utilized to evaluate the efficacy of plecanatide and the change-from-baseline-screening data in regards to CSBM and SBM endpoints. The primary endpoint for both Study 1 and Study 2 was defined as a patient who had a least 3 CSBMs in a given week and an increase of at least 1 CSBM from baseline in the same week for at least 9 weeks out of the 12 week treatment period as well as at least 3 of the last 4 weeks of the active study timeframe. As early as week 1, patients in the active medication arm saw improvements in the frequency of CSBMs per week and improvements were maintained through week 12. The difference in activity reported between the plecanatide group and the placebo group resulted in a 1.1 mean change of CSBMs per week frequency from the baseline numbers to week 12 of the study. During the 12-week active treatment period, improvements were seen by patients in stool frequency (number of CSBMs per week and SBMs per week) and/or stool consistency (as measured by the BSFS), and/or in the amount of straining with bowel movements (amount of time pushing or physical effort to pass stool) in the plecanatide group compared to the results seen in the placebo group. Data collected 2 weeks after the active study period, demonstrated patients in the plecanatide treatment arm generally returned to their baseline activity levels. In both Studies 1 and 2, a third randomized treatment arm was established with patients taking plecanatide 6 mg once daily. Patients in the higher-dose arm did not demonstrate additional treatment benefit and experienced greater incidences of adverse reactions than patients in the plecanatide 3 mg once daily group. As a result, the 6 mg daily dose is not recommended for the treatment of CIC.

The efficacy of plecanatide for IBS-C was studied in two, 12-week, double-blind, placebo-controlled trials in a total of over 1,461 adult patients with IBS-C who met the Rome III IBS-C criteria regarding abdominal pain and stool changes.[118] Both trials included a 2-week pre-treatment baseline period, a 12-week treatment period, and a 2-week post-treatment follow-up period. Patients were randomized to once-daily plecanatide 3 mg or placebo; the study also included a plecanatide 6 mg arm that is not reported here since this dose was not submitted to the FDA for approval. Response (primary endpoint) was defined as meeting both abdominal pain intensity (≥ 30% reduction in worst abdominal pain and an increase of ≥ 1 CSBM per week from baseline in the same week, for ≥ 6 of the 12 treatment weeks). In the intent-to-treat (ITT) populations in both studies, significantly more patients in the plecanatide group were considered to be responders compared to the placebo group (Study 1: 30% versus 18%, $p<0.001$; Study 2: 21% versus 14%, $p=0.009$). The most common adverse effect associated with plecanatide was diarrhea (4.3% versus 1% with placebo). The most common reason for study discontinuation was diarrhea (1.2% with plecanatide and 0% with placebo).

prucalopride (Motegrity) versus placebo

Six, multicenter, randomized, double-blind, placebo-controlled clinical trials evaluated the efficacy and safety of prucalopride in the treatment of 2,484 adult patients with CIC (Study 1, n=501; Study 2, n=358; Study 3, n=476; Study 4, n=383; Study 5, n=426; Study 6, n=340). Five of the studies consisted of 12 weeks of treatment while the sixth trial lasted for 24 weeks. Patients included in the trials were required to have a history of CIC, defined as ≤ 3 SBMs per week that result in a feeling of complete evacuation (CSBMs), and ≥ 1 of the select symptoms (lumpy or hard stools, sensation of incomplete evacuation, or straining at defecation) for > 25% of the bowel movements in the prior 3 months, with the onset of symptoms > 6 months prior to the screening. In Study 1, sensation of anorectal

obstruction or blockade or the need for digital manipulation were also eligible select symptoms.[119,120,121,122] In Studies 1, 2, and 6, only 2 mg doses were included for most adults, while in Studies 3, 4, and 5, patients were randomized to either 2 or 4 mg daily. Notably, Studies 2 and 6 initiated geriatric patients on 1 mg and the dose could be increased to 2 mg after a few weeks if the response was inadequate (dose was increased in 88% of these patients). Results discussed here include data for placebo and 1 or 2 mg. Study 2 included only males; however, the majority of patients across all trials were female (76%). Baseline demographics included 76% Caucasians, a mean age of 47 years (range, 17 to 95 years), and the mean duration of constipation of 16 (± 15 years) years. The primary efficacy endpoint in all studies was response, defined as those with an average of ≥ 3 CSBMs/week over the 12-week treatment period, assessed using patient-reported diary entries. Proportion of patients who met the primary endpoint of response in the 6 studies (prucalopride versus placebo, respectively) is as follows: Study 1: 33% versus 10% (difference, 23%; 95% CI, 16 to 30; p<0.001); Study 2: 39% versus 18% (difference, 20%; 95% CI, 11 to 29; p=0.002); Study 3: 19% versus 10% (difference, 10%; 95% CI, 4 to 16; p<0.001); Study 4: 29% versus 13% (difference, 16%; 95% CI, 8 to 24; p<0.001); Study 5: 24% versus 12% (difference, 12%; 95% CI, 4 to 19; p<0.001); and Study 6: 25% versus 20% (difference, 5%; 95% CI, -4 to 14; p=0.341). A statistically significant difference in response was found in all studies favoring treatment with prucalopride versus placebo, with the exception of Study 6. An alternative definition (endpoint) of response, defined as those with ≥ 3 CSBMs/week and an increase of ≥ 1 CSBMs from baseline for ≥ 9 weeks of the 12-week treatment period and ≥ 3 of the last 4 weeks of treatment, was also assessed. The data demonstrated the following results (prucalopride versus placebo, respectively; p-values not reported): Study 1: 26% versus 9% (difference, 17%; 95% CI, 11 to 24); Study 2: 32% versus 14% (difference, 18%; 95% CI, 10 to 27); Study 3: 13% versus 5% (difference, 8%; 95% CI, 2 to 12); Study 4: 19% versus 8% (difference, 11%; 95% CI, 5 to 18); Study 5: 16% versus 5% (difference, 11%; 95% CI, 5 to 16); and Study 6: 17% versus 13% (difference, 4%; 95% CI, -4 to 12).

SUMMARY

Treatment for irritable bowel syndrome (IBS) and constipation focuses on management of symptoms, and should be considered a multifocal approach to achieve relief, including nonpharmacologic (dietary and lifestyle modifications) and pharmacologic therapies.

Alosetron (Lotronex, generics) and eluxadoline (Viberzi) are indicated for diarrhea-predominant IBS (IBS-D); however, alosetron is limited to women with severe IBS-D who have not responded adequately to conventional therapy. Eluxadoline (Viberzi) is a Scheduled IV controlled substance.

Linaclotide (Linzess), lubiprostone (Amitiza), and plecanatide (Trulance) are indicated for the treatment of IBS with constipation (IBS-C) and chronic idiopathic constipation (CIC). Lubiprostone's indicated for IBS-C is limited to use only in women. Prucalopride (Motegrity) was also recently approved for the treatment of CIC.

Constipation is a common adverse effect associated with opioid therapy. A variety of conventional options including lifestyle, dietary modifications, and laxatives can improve bowel function. For refractory cases, oral twice daily, lubiprostone (Amitiza), subcutaneous or oral once-daily methylnaltrexone (Relistor), oral once-daily naloxegol (Movantik), and oral once daily naldemedine (Symproic) are indicated for OIC in patients taking opioids for chronic non-cancer pain. Subcutaneous methylnaltrexone (Relistor) is also indicated for the treatment of OIC in patients with advanced illness or pain caused by active cancer who require opioid dosage escalation for palliative care.

Several contraindications are listed for agents in this review. All are contraindicated in patients with gastrointestinal (GI) obstruction and various disorders of the GI or digestive (hepatic, pancreas, biliary) tracts. Diarrhea has been reported with linaclotide (Linzess), lubiprostone (Amitiza), methylnaltrexone (Relistor), naloxegol (Movantik), and plecanatide (Trulance) and, if severe, may require dosing interruption. Dose adjustments are recommended various agents in patients with renal or hepatic impairment. Hypersensitivity reactions have been reported with eluxadoline (Viberzi), lubiprostone (Amitiza), naldemedine (Symproic), naloxegol (Movantik), and prucalopride (Motegrity) in clinical trials and/or postmarketing.

Opioid withdrawal symptoms have been reported in patients treated with the mu-opioid antagonists, methylnaltrexone (Relistor), naldemedine (Symproic), and naloxegol (Movantik).

The agents in this review are effective via various mechanisms of action. All are administered orally; methylnaltrexone (Relistor) is also available in a subcutaneous formulation than can be administered by the patient or caregiver with proper training. Currently, there are no comparative trials among these agents for their respective indications.

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