Therapeutic Class Overview
Irritable Bowel Syndrome and Constipation Agents

INTRODUCTION

- Irritable bowel syndrome (IBS) is a gastrointestinal disorder that most commonly manifests as chronic abdominal pain and altered bowel habits in the absence of any organic disorder (Wald, 2017).
- IBS may consist of diarrhea-predominant (IBS-D), constipation-predominant (IBS-C), IBS with a mixed symptomatology (IBS-M), or unclassified IBS (IBS-U). Switching between the subtypes of IBS is also possible (Ford et al, 2014).
- IBS is a functional disorder of the gastrointestinal tract characterized by abdominal pain, discomfort, and bloating, as well as disturbed bowel habit. The exact pathogenesis of the disorder is unknown; however, it is believed that altered gastrointestinal tract motility, visceral hypersensitivity, autonomic dysfunction, and psychological factors indicate disturbances within the enteric nervous system, which controls the gastrointestinal system (Ford, 2009; Andresen, 2008).
- Prevalence estimates of IBS range from 5% to 15%, and it typically occurs in young adulthood (Ford et al, 2014). IBS-D is more common in men, and IBS-C is more common in women (World Gastroenterology Organization [WGO], 2015).
- Symptoms of IBS often interfere with daily life and social functioning (WGO, 2015).
- The general goals of therapy are to alleviate the patient's symptoms and to target any specific exacerbating factors (e.g., medications, dietary changes), concerns about serious illness, stressors, or potential psychiatric comorbidities that may exist.
- Non-pharmacological interventions to combat IBS symptoms include dietary modifications such as exclusion of gas-producing foods (e.g., beans, prunes, brussel sprouts, bagels, etc.), trials of gluten avoidance, consumption of probiotics, as well as psychosocial therapies (e.g., hypnosis, biofeedback, etc.) (Ford et al, 2014).
- Depending upon the clinical presentation of an individual's IBS condition, a number of therapies exist to help alleviate the constellation of disease symptoms. Commonly used agents that are often initiated for disease control include poorly absorbable antibiotics such as rifaximin; laxative agents, including stimulant laxatives (bisacodyl, etc.) and osmotic laxatives (polyethylene glycol [PEG], lactulose, etc.); antispasmodics (e.g., dicyclomine, hyoscine, etc.); selective chloride channel activators (e.g. lubiprostone); serotonin-3 receptor antagonists (e.g., alosetron); guanylate cyclase-c agonists (e.g., linaclotide); antidepressants such as tricyclic antidepressants and selective serotonin reuptake inhibitors; select probiotics; and peppermint oil (Ford et al, 2014).
- In addition to treatment of IBS-C, AMITIZA® (lubiprostone), LINZESS® (linaclotide), and TRULANCE™ (plecanatide) are indicated for the treatment of chronic idiopathic constipation (CIC). Symptoms of constipation are common with a prevalence of approximately 16% in adults overall and 33% in adults >60 years of age. Constipation is defined as fewer than three bowel movements (BMs) per week with symptoms that may include hard stools, a feeling of incomplete evacuation, abdominal discomfort, bloating, and distention. Initial treatment typically includes osmotic laxatives, stimulant laxatives, and increased fiber intake (American Gastroenterological Association [AGA] Medical Position Statement, 2013; Bharucha et al, 2013).
- AMITIZA (lubiprostone) is also Food and Drug Administration (FDA)-approved for the treatment of opioid-induced constipation (OIC) in adults with chronic, non-cancer related pain. OIC is a frequent adverse event of opioid therapy. Opioids exert their action on the enteric nervous system causing dysmotility, decreased fluid secretion and sphincter dysfunction. Laxatives are typically prescribed but often are inadequate to completely relieve constipation (Brock et al, 2012).
- Three other products are approved for use in OIC:
  - RELISTOR® (methylnatrexone) injection is an opioid receptor antagonist indicated for treatment of OIC in adults with chronic non-cancer pain and in patients with advanced illness who are receiving palliative care, when response to laxative therapy has not been sufficient. RELISTOR has also been FDA-approved in a tablet formulation, which is indicated for the treatment of OIC in adults with chronic non-cancer pain.
  - MOVANTIK® (naloxegol) and SYMPROIC® (naldemedine) are once-daily oral peripherally acting mu-opioid receptor antagonists (PAMORA) indicated for the treatment of OIC in adult patients with chronic non-cancer pain.

- LOTRONEX® (alosetron) is FDA-approved with restrictions for the treatment of women who exhibit severe IBS-D and have failed conventional therapy.

- ZELNORM® (tegaserod) was approved in July 2002 for short-term treatment of IBS-C in women and in August 2004 for treatment of CIC in men and women <65 years of age. In March 2007, the FDA requested the manufacturer to discontinue the marketing of ZELNORM due to safety concerns related to increased rate of heart attack, stroke, and worsening heart-related chest pain. In July 2007, ZELNORM became available for use as a treatment investigational new drug (IND) protocol for IBS-C and CIC in women < 55 years of age meeting specific guidelines; however, in April 2008, the manufacturer discontinued the availability as a treatment IND. ZELNORM is currently available for use only in emergency situations with FDA authorization (Clinical Pharmacology, 2016).
- IBS-D is an IBS subtype characterized mainly by loose or watery stools at least 25% of the time. In May 2015, two new treatments with different mechanisms of action were approved for use in the treatment of IBS-D, VIBERZI® (eluxadoline) and XIFAXAN® (rifaximin). VIBERZI is a mu-opioid receptor agonist, and XIFAXAN is a rifamycin antibacterial (FDA News Release, 2015). VIBERZI is a schedule IV controlled substance.
- The scope of this review will focus upon AMITIZA (lubiprostone), LINZESS (linaclotide), LOTRONEX (alosetron), MOVANTIK (naloxegol), RELISTOR (methylnaltrexone bromide), SYMPROIC (naldemedine), TRULANCE (plecanatide), VIBERZI (eluxadoline), and XIFAXAN (rifaximin) for their respective FDA-approved indications, which are outlined in Table 2.
- Medispan Classes: Agents for CIC (TRULANCE); Gastrointestinal Chloride Channel Activators (AMITIZA); IBS Agents (LOTRONEX, LINZESS, VIBERZI); Peripheral Opioid Receptor Antagonists (MOVANTIK, RELISTOR, SYMPROIC); Anti-infective Agents – Misc (XIFAXAN)

Table 1. Medications Included Within Class Review

Drug	Manufacturer	FDA Approval Date	Generic Availability
AMITIZA (lubiprostone)	Sucampo Pharmaceuticals, Inc./Takeda	01/31/2006	-
LINZESS (linaclotide)	Ironwood Pharmaceuticals/ Forest Pharmaceuticals	08/30/2012 (145 and 290 mcg capsules) 1/25/2017 (72 mcg capsule)	-
LOTRONEX (alosetron)	Prometheus Laboratories, Inc.	02/09/2000	✔
MOVANTIK (naloxegol)	AstraZeneca	09/16/2014	-
RELISTOR (methylnaltrexone bromide)	Salix Pharmaceuticals	04/24/2008 (injection) 07/19/2016 (tablet)	-
SYMPROIC® (naldemedine)	Shionogi Inc.	3/23/2017	-
TRULANCE (plecanatide)	Synergy Pharmaceuticals Inc.	1/19/2017	-
VIBERZI (eluxadoline)	Patheon Pharmaceuticals/Forest Pharmaceuticals (now Actavis)	05/27/2015	-
XIFAXAN (rifaximin)	Salix Pharmaceuticals	05/25/2004 (200 mg tablet) 03/24/2010 (550 mg tablet)	-

(Drugs@FDA, 2017; Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, 2017)

INDICATIONS

Table 2. FDA Approved Indications

Indication	AMITIZA (lubiprostone)	LINZESS (linaclotide)	LOTRONEX (alosetron)	MOVANTIK (naloxegol)	RELISTOR (methylnaltrexone bromide)	SYMPROIC (naldemedine)	TRULANCE (plecanatide)	VIBERZI (eluxadoline)	XIFAXAN (rifaximin)
Treatment of CIC in adults	✔	✔					✔		
Treatment of OIC in adults with chronic, non-cancer pain	✔*			✔	✔	✔			
Treatment of OIC in patients with chronic pain related to prior cancer or its treatment who do not require frequent (e.g., weekly) opioid dosage escalation.	✔			✔	✔	✔			
Treatment of OIC in patients with advanced illness who are receiving palliative care, when response to laxative therapy has not been sufficient or pain caused by active cancer which requires opioid dosage escalation for palliative care					✔†				
Treatment of IBS-C in women ≥18 years of age	✔								
Treatment of IBS-C in adults		✔							
Treatment of IBS-D in adults								✔	✔‡
Women with severe IBS-D who have: • chronic IBS symptoms (generally lasting six months or longer) • had anatomic or biochemical abnormalities of the gastrointestinal tract excluded, and not responded adequately to conventional therapy§			✔						

*Effectiveness of AMITIZA in the treatment of opioid-induced constipation in patients taking diphenylheptane opioids such as methadone has not been established.

†Injection formulation only. Use of RELISTOR beyond four months in treatment of OIC in patients with advanced illness has not been studied.

‡XIFAXAN has additional indications for treatment of traveler's diarrhea (TD) caused by noninvasive strains of *Escherichia coli* in adult and pediatric patients 12 years of age and older, and reduction in risk of overt hepatic encephalopathy (HE) recurrence in adults. Do not use XIFAXAN in patients with TD complicated by fever or blood in the stool or diarrhea due to pathogens other than *E. coli*.

§IBS-D is severe if it includes diarrhea and one or more of the following: frequent and severe abdominal pain/discomfort, frequent bowel urgency or fecal incontinence, disability or restriction of daily activities due to IBS.

(Prescribing information: AMITIZA, 2017; LINZESS, 2017; LOTRONEX, 2016; MOVANTIK, 2017; RELISTOR, 2017; SYMPROIC 2017; TRULANCE, 2017; VIBERZI, 2017; XIFAXAN, 2017)

- LOTRONEX was approved by the FDA in February of 2000 and was later withdrawn from the market due to numerous reports of serious and fatal gastrointestinal adverse events. Approval of a supplemental New Drug Application (sNDA) was accepted in July 2002 by the FDA to allow restricted marketing of LOTRONEX to treat only women with severe IBS-D. Physicians are required to complete training before prescribing alosetron to ensure that the benefits and risks of the agent are considered before administering it to patients (LOTRONEX FDA press release, 2016).

- Information on indications, mechanism of action, pharmacokinetics, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- There are currently no head-to-head trials comparing the available agents used in the treatment of CIC, OIC, IBS-C, and IBS-D.

CIC

- A network meta-analysis demonstrated linaclotide and lubiprostone to be superior to placebo for the treatment of CIC. Treatment with linaclotide resulted in a significant increase in the proportion of patients with ≥3 complete spontaneous bowel movements (CSBMs)/week compared with placebo with a relative risk (RR) of 1.96 (95% confidence interval [CI], 1.12 to 3.44), and was superior vs placebo with an increase over baseline by ≥1 CSBM/week (RR 1.72; 95% CI, 1.18 to 2.52). For change from baseline in the number of SBMs/week, the weighted mean difference (WMD) with lubiprostone was 1.91 (95% CI, 1.41 to 2.41) and WMD with linaclotide was 2.11 (95% CI, 1.68 to 2.54) (Nelson et al, 2017).
- A meta-analysis demonstrated the total pooled treatment effect of spontaneous bowel movements (SBMs)/week in patients with CIC or IBS-C was greater in lubiprostone-treated patients compared with placebo (combined standardized difference in means, 0.419; 95% CI, 0.088 to 0.750; P<0.001) (Li et al, 2016).
- In another meta-analysis, treatment with linaclotide 145 mcg demonstrated significant improvements in the weekly frequency of CSBMs from baseline compared with placebo in patients with CIC (RR, 3.80; 95% CI, 2.20 to 6.55). Results were similar for abdominal discomfort or bloating responders for linaclotide 145 mg vs placebo, with pooled RRs of 1.57 (95% CI, 1.26 to 1.97) and 1.97 (95% CI, 1.44 to 2.69), respectively (Videlock et al, 2013).
- Results from a long-term safety study illustrated that overall lubiprostone was well tolerated. The most commonly reported events were diarrhea, nausea, urinary tract infection, sinusitis, abdominal distension, and headache. Significant changes from baseline in hematology, laboratory values, vital signs, weight, body mass index and physical examination were not seen over the study duration (Chey et al, 2012).
- For the recently approved linaclotide 72 mcg, a double-blind, placebo-controlled, multicenter, randomized controlled trial demonstrated that linaclotide improved the weekly frequency of CSBMs compared with placebo, with 13% of linaclotide-treated patients meeting responder requirements compared with 9% in the placebo group (95% CI, 4.8% to 12.5%) (LINZESS prescribing information, 2017).
- Two double-blind, placebo-controlled, multicenter, randomized controlled trials demonstrated that treatment with plecanatide 3 mg significantly increased weekly CSBM frequency as measured by the overall CSBM responder rate vs placebo (Study 1: 21.0% vs 10.2%; P<0.001; Study 2: 20.1% vs 12.8%; P=0.004) (Miner et al [abstract], 2016; Miner et al, 2017).

IBS

- In 2 meta-analyses, linaclotide demonstrated significant improvements in the FDA-defined composite endpoint of improvement in both daily worst abdominal pain scores and CSBM frequency from baseline compared to placebo after 12 weeks and demonstrated a similar result when compared over 26 weeks (Atluri et al, 2014; Videlock et al, 2013). More patients in the placebo treatment arm failed to achieve the FDA endpoint compared with patients treated with linaclotide (82.6% vs 66%; RR of failure to respond 0.80; 95% CI, 0.76 to 0.85).
- For the treatment of IBS-C, placebo-controlled trials demonstrated that lubiprostone had a significantly higher percentage of overall responders (Drossman et al, 2007; Drossman et al, 2009; Johanson et al, 2008b). In multiple 12-week studies, lubiprostone-treated patients reported significant improvements in abdominal pain/discomfort, stool consistency, straining, constipation severity, and quality of life (Drossman et al, 2007; Drossman et al, 2009; Johanson et al, 2008b).
- Treatment with alosetron is associated with a significantly greater proportion of patients reporting adequate relief of IBS pain and discomfort, and improvements in bowel function compared to placebo (Camilleri et al, 2000; Camilleri et al, 2001; Chey et al, 2004; Lembo et al, 2001; Lembo et al, 2004; Rahimi et al, 2008; Watson et al, 2001).
- A meta-analysis concluded that the 5-HT3 antagonists as a class significantly improve symptoms of non-constipating or IBS-D in both men and women compared to placebo; however, these agents were also associated with a greater increase in the risk of causing constipation compared to placebo (Andresen et al, 2008).
- Alosetron treatment has been shown to positively impact global symptoms, as well as pain and discomfort in non-constipated females with IBS. This analysis further supports the increased chance of developing constipation with alosetron compared to placebo (Cremonini et al, 2003).
- The safety and efficacy of eluxadoline for treatment of IBS-D were established in two randomized, multicenter, multinational, double-blind, placebo-controlled, phase 3 clinical trials in which 2,427 patients with IBS-D (meeting Rome III criteria), average abdominal pain scores greater than 3 on a 0 to 10 scale during the week prior to randomization, and

a Bristol Stool Scale (BSS) of 5.5 or greater with at least five days of BSS of 5 or more during the week prior to randomization. Patients were randomly assigned to receive eluxadoline 75 mg, 100 mg, or placebo twice daily. The primary endpoint was defined by the simultaneous improvement in the daily worst abdominal pain score by 30% or more compared to the baseline weekly average and a reduction in the BSS to 5 or less on at least 50% of the days within a 12-week or 26-week time interval. From weeks 1 through 12, the primary endpoint was achieved by 23.9% of patients in the 75 mg group (P=0.01) and 25.1% of patients in the 100 mg group (P=0.004) versus 17.1% of patients in the placebo group. From weeks 1 through 26, 23.4% in the 75 mg group (P=0.11) and 29.3% in the 100 mg group (P<0.001) achieved the primary endpoint compared to 19% in the placebo group (Lembo et al, 2016).

- The safety and effectiveness of rifaximin for treatment of IBS-D were established in three double-blind, placebo-controlled trials.
  - In the first two trials, 1,258 patients with IBS-D (Rome II criteria) were randomly assigned to receive rifaximin 550 mg three times daily (n=624) or placebo (n=634) for 14 days, and then followed for a 10-week treatment-free period. The primary endpoint for both trials was the proportion of patients who achieved adequate relief of IBS signs and symptoms for at least two of four weeks during the month following 14 days of treatment. More rifaximin-treated patients reported improvements in abdominal pain and stool consistency than those on placebo (Trial 1: 47% vs 39%; P<0.05; Trial 2: 47% vs 36%; P<0.01 in rifaximin and placebo groups, respectively).
  - TARGET3 was the third trial, which evaluated repeat courses of rifaximin in adult patients with IBS-D (Rome III criteria) for up to 46 weeks. During a 14-day open-label phase, 1,074 patients responded to rifaximin and were evaluated over 22 weeks for continued response or recurrence of IBS symptoms. A total of 636 patients who developed recurrent signs and symptoms after a single treatment course of rifaximin were randomized to receive either rifaximin 550 mg three times daily (n=328) or placebo (n=308) for two additional 14-day courses separated by 10 weeks. More patients treated with rifaximin than placebo were responders in abdominal pain and stool consistency in this phase of the study (38% vs 31% in rifaximin and placebo groups, respectively; P<0.05) (ClinicalTrials.gov NCT01543178, 2016).

OIC

- Two randomized, double-blind, placebo-controlled trials, COMPOSE-1 and COMPOSE-2, were conducted in adult patients with chronic non-cancer pain and OIC to assess the efficacy and safety of naldemedine. The primary endpoint was the proportion of responders, where response was defined as at ≥3 SBMs per week. Patients in COMPOSE-1 and COMPOSE-2 were randomized to receive naldemedine 0.2 mg (n=274; n=277) or placebo (n=273; n=276) once daily for 12 weeks. Results from both COMPOSE-1 and COMPOSE-2 showed that participants receiving naldemedine 0.2mg experienced a significantly higher response compared to patients receiving placebo in both studies(COMPOSE-1 responders: 47.6% vs 34.6%; P=0.002 and COMPOSE-2 responders: 52.5% vs 33.6%; P<0.0001, respectively). Treatment-related adverse events due to gastrointestinal disorders were more common with naldemedine than with placebo in both studies (15% vs 7% and 16% and 7%, respectively) (Hale et al, 2017).
- A total of 1,300 patients were enrolled in three, double-blind, randomized controlled trials evaluating lubiprostone compared to placebo in patients with chronic, non-cancer related pain on stable opioid therapy and constipation. In Study 1, overall responder rate, the primary outcome, was defined as ≥1 SBM improvement over baseline for all treatment weeks and ≥3 SBMs per week for at least nine of the 12-week study period. Lubiprostone (27.1%) had a significantly higher “overall responder rate” than placebo (18.9%; P=0.03) (Jamal et al, 2015). Primary outcome parameter for Study 2 and 3 was the mean change from baseline in SBM frequency at week eight. In Study 2, lubiprostone significantly increased the mean change from baseline in SBM frequency compared to placebo (P=0.004). In Study 3, the difference was not statistically significant; however, Study 3 was the only study, which enrolled patients who received diphenylheptane opioids such as methadone. Studies 2 and 3 have not been published in a peer-reviewed journal at this time.
- A prospective, randomized, double-blind, placebo-controlled trial was conducted to evaluate the efficacy and safety of lubiprostone for relieving symptoms of OIC in adult patients with chronic non-cancer pain. OIC was defined as less than three SBMs per week. Patients were randomized to receive lubiprostone 24 mcg (n=210) or placebo (n=218) twice daily for 12 weeks. The primary endpoint was change from baseline in SBM frequency at week eight. Changes from baseline in SBM frequency rates were significantly higher at week eight (P=0.005) and overall (P=0.004) in patients treated with lubiprostone compared with placebo. The most common treatment-related adverse events with lubiprostone and placebo were nausea (16.8% vs 5.8%, respectively), diarrhea (9.6% vs 2.9%, respectively), and abdominal distention (8.2% vs 2.4%, respectively). No lubiprostone-related serious adverse events occurred (Cryer et al, 2014).
- A 2013 systematic review evaluated pharmacological therapies for the treatment of OIC. A total of 14 randomized clinical trials of mu-opioid receptor antagonists were included. All treatments including methylnaltrexone, naloxone, and

alvimopan, were superior to placebo for the treatment of OIC. Lubiprostone was included in the review; however, the reporting of data precluded meta-analysis (Ford et al, 2013).

- In 2014, another systematic review of 21 randomized clinical trials evaluated seven pharmacological treatments of OIC. Efficacy assessment was based on objective outcome measures (OOMs): BM frequency, BM within four hours, and time to first BM. Methylnatrexone showed improvements in all three OOMs. Randomized control trials in naloxone and alvimopan tended to be effective for BM frequency measures. Naloxegol (≥ 12.5 mg) improved all OOMs. Though effectiveness of lubiprostone was demonstrated for all OOMs, group differences were small to moderate. Although not FDA-approved, CB-5945 and prucalopride tended to increase BM frequency, especially for 0.1 mg twice daily and 4 mg daily, respectively. Besides nausea and diarrhea, abdominal pain was the most frequent adverse event for all drugs except for alvimopan. Treatment-related serious adverse events were slightly higher for alvimopan (cardiac events) and prucalopride (severe abdominal pain, headache) (Siemens et al, 2015).
- The efficacy of naloxegol has been established in K4 and K5, two replicate Phase 3 clinical trials with a total of 1,352 participants with OIC who had taken opioids for at least four weeks for non-cancer related pain. Participants were randomly assigned to receive oral naloxegol 12.5 mg or 25 mg or placebo once daily for 12 weeks. The trials were designed to measure a response rate, defined as ≥3 SBMs per week and an increase of ≥1 SBM from baseline.
  - Results from K4 showed that participants receiving naloxegol 25 mg or naloxegol 12.5 mg both experienced a significantly higher response rate compared to participants receiving placebo (P=0.001 and P=0.02, respectively). Results from K5 also showed significantly higher response rates in participants receiving naloxegol 25 mg vs placebo (P=0.02) but did not show a significant difference in response rate in patients receiving naloxegol 12.5 mg vs placebo (P=0.2) (Chey et al, 2014).
  - In K4, patients with an inadequate response to laxatives achieved a significantly higher response with naloxegol 25 mg vs placebo (P=0.002) and with naloxegol 12.5 mg vs placebo (P=0.03). In K5, patients receiving naloxegol 25 mg achieved a significantly higher response rate vs placebo (P=0.01); however, patients receiving naloxegol 12.5 mg did not have a significantly higher response rate.
  - Median time to first SBM was significantly shorter with both naloxegol 12.5 mg and 25 mg compared to placebo in K4 and was significantly shorter with naloxegol 25 mg in K5 (P<0.001 for all comparisons).
  - Average pain scores and opioid use remained relatively stable in both studies for patients receiving naloxegol; thus, supporting the preservation of centrally mediated analgesia.
- Clinical trials of methylnaltrexone injection in patients with advanced illness have shown response over several months with most patients reporting laxation effects similar to SBMs and predictable timing (Bull et al, 2015; Thomas et al, 2008). Similar findings have been reported in patients with OIC with chronic non-cancer pain (Michna et al, 2011, Webster et al, 2017).
- The efficacy of methylnaltrexone tablets was demonstrated in a randomized, double-blind, placebo-controlled study in patients using opioids for chronic non-cancer pain. Patients were randomized to methylnaltrexone (150 mg, 300 mg, or 450 mg) or placebo once daily for a period of four weeks followed by as-needed dosing for 8 weeks. A responder to methylnaltrexone treatment was defined as a patient with three or more SBMs per week, with an increase of one or more SBMs per week over baseline, for at least three weeks in the four-week treatment period. The percentage of patients classified as responders was 42.8%, 49.3% (P=0.03 vs placebo), 51.5% (P=0.005 vs placebo), and 38.3% in the methylnaltrexone 150 mg, 300 mg, 450 mg and placebo groups, respectively (Rauck et al, 2017).
- A systematic review and network analysis compared the efficacy and safety of agents for the treatment of OIC, including lubriprostone, naldemedine, naloxegol, subcutaneous and oral methylnaltrexone, and 2 agents, alvimopan and prucalopride, not approved for OIC in the U.S. (Sridharan & Sivaramakrishan, 2017). Observations from 16 RCTs with 4,048 patients demonstrated lubriprostone, naldemedine, naloxegol, and subcutaneous and oral methyl naltrexone to perform better vs. placebo in terms of rescue-free bowel movements (RFBM). Based on the odds ratios from direct and indirect pooled estimates, treatment with subcutaneous methyl naltrexone resulted in significantly improved RFBMs vs. lubiprostone, naloxegol, and oral methyl naltrexone. Lubiprostone and naldemedine were associated with increased risks of adverse events, while subcutaneous methylnaltrexone did not significantly affect the analgesia due to background opioid use. Of note, the quality of evidence for the comparisons was either low or very low.

IBS and CIC

- An updated systematic review on IBS and CIC was commissioned by the American College of Gastroenterology to assess the efficacy of available therapies in treating IBS and CIC compared with placebo or no treatment. The secondary objectives included assessing the efficacy of available therapies in treating IBS according to predominant stool pattern reported (IBS-C, IBS-D, and IBS-M), as well as assessing adverse events with therapies for both IBS and CIC. Parallel-group, randomized controlled trials comparing active interventions with either placebo or no therapy were evaluated. Crossover trials were eligible for inclusion if extractable data were provided at the end of the first treatment period, before crossover. The following were identified as "strong" recommendations for IBS and CIC treatments:
  - IBS
    - There is insufficient evidence to recommend loperamide for use in IBS. Quality of evidence is very low.
    - Mixed 5-HT 4 agonists/5-HT 3 antagonists are not more effective than placebo at improving symptoms of IBS-C. Quality of evidence is low.
    - Linaclotide is superior to placebo for the treatment of IBS-C. Quality of evidence is high.
    - Lubiprostone is superior to placebo for the treatment of IBS-C. Quality of evidence is moderate.
  - CIC
    - Some medicinal and dietary fiber supplements increase stool frequency in patients with CIC. Quality of evidence is low.
    - PEG is effective in improving symptoms of CIC. Quality of evidence is high.
    - Lactulose is effective in improving symptoms of CIC. Quality of evidence is low.
    - Sodium picosulfate and bisacodyl are effective in CIC. Quality of evidence is moderate.
    - Prucalopride is more effective than placebo in improving symptoms of CIC. Quality of evidence is moderate.
    - Linaclotide is effective in CIC. It is generally safe, with the main adverse event being diarrhea. Quality of evidence is high.
    - Lubiprostone is effective in the treatment of CIC. Quality of evidence is high (Ford et al, 2014).

CLINICAL GUIDELINES

- Guidelines on management of constipation suggest increased fiber intake and osmotic laxatives. Stimulant laxatives are to be used as needed or as "rescue agents". Lubiprostone and linaclotide can be considered when symptoms of constipation do not respond to laxatives (AGA, 2013; Bharucha et al, 2013; Lindberg et al, 2010).
- The American College of Gastroenterology monograph on the management of IBS and CIC makes the following statements (reported with the strength of recommendation and quality of evidence, respectively) (Ford et al, 2014):
  - Rifaximin is effective in reducing total IBS symptoms and bloating in IBS-D (weak; moderate)
  - Alosetron is effective in females with IBS-D (weak; moderate)
  - Linaclotide is superior to placebo for the treatment of IBS-C (strong; high)
  - Linaclotide is effective in CIC (strong; high)
  - Lubiprostone is superior to placebo for the treatment of IBS-C (strong; moderate)
  - Lubiprostone is effective in the treatment of CIC (strong; high)
- The AGA guideline on management of IBS makes the following statements (reported with strength of recommendation and quality of evidence, respectively) (Weinberg et al, 2014):
  - Recommends using linaclotide (over no drug treatment) in patients with IBS-C (strong; high)
  - Suggests using lubiprostone (over no drug treatment) in patients with IBS-C (conditional; moderate)
  - Suggests using rifaximin (over no drug treatment) in patients with IBS-D (conditional; moderate)
  - Suggests using alosetron (over no drug treatment) in patients with IBS-D to improve global symptoms (conditional; moderate)
- The 2015 WGO guideline on IBS lists rifaximin and alosetron as second-line therapies for IBS-D, although it notes a risk of ischemic colitis and constipation with alosetron. Lubiprostone and linaclotide are noted to be safe and effective for the treatment of IBS-C (WGO, 2015).
- In the 2014 Technical Review of the Pharmacological Management of Irritable Bowel Syndrome, the AGA Institute reviewed and graded the evidence for pharmacological interventions (linaclotide, lubiprostone, PEG laxative, rifaximin, alosetron, loperamide, tricyclic antidepressants [TCAs], selective serotonin reuptake inhibitors (SSRIs), and antispasmodics) for treatment of IBS. Review of the evidence for these pharmacological treatments showed that across all outcomes, evidence was high for linaclotide; moderate for lubiprostone, rifaximin, and alosetron; low for TCAs, SSRIs, and PEG; and very low for loperamide and antispasmodics (Chang et al, 2014).

SAFETY SUMMARY

- AMITIZA is contraindicated with known or suspected mechanical gastrointestinal obstruction. LOTRONEX is associated with several contraindications, including history of chronic or severe constipation or sequelae from constipation; intestinal obstruction, stricture, toxic megacolon, gastrointestinal perforation, and/or adhesions; ischemic colitis; impaired intestinal circulation, thrombophlebitis, or hypercoagulable state; Crohn's disease or ulcerative colitis; diverticulitis; severe hepatic impairment. LINZESS and TRULANCE are contraindicated in patients age 6 years or younger and in patients with known or suspected mechanical obstruction. MOVANTIK is contraindicated in patients with known or suspected gastrointestinal obstruction and at increased risk of recurrent obstruction, in patients with concomitant use of strong CYP3A4 inhibitors (e.g., clarithromycin, ketoconazole), and when there is a known serious or severe hypersensitivity reaction to the drug or any of its excipients. RELISTOR is contraindicated in patients with known or suspected mechanical gastrointestinal obstruction and at increased risk of recurrent obstruction. SYMPROIC is contraindicated in patients with known or suspected gastrointestinal obstruction or at increased risk of recurrent obstruction, and when there is a known serious or severe hypersensitivity reaction to the drug or any of its excipients. VIBERZI has several contraindications, including use in patients with the following conditions: known or suspected biliary duct obstruction or sphincter of Oddi disease or dysfunction; alcoholism, alcohol abuse, alcohol addiction, or more than three alcoholic beverages daily; history of pancreatitis or structural diseases of the pancreas including known or suspected hepatic duct obstruction; severe hepatic impairment; severe constipation or sequelae from constipation; known or suspected mechanical gastrointestinal obstruction; or use in patients without a gallbladder. XIFAXAN is contraindicated in patients with a hypersensitivity to rifaximin, any of the rifamycin antimicrobial agents, or any of the components in XIFAXAN.
  - On March 15, 2017, an FDA Drug Safety Communication was released warning that VIBERZI should not be used in patients who do not have a gallbladder. The safety announcement was based on an FDA review that found these patients have an increased risk of developing serious pancreatitis that could result in hospitalization or death (FDA Drug Safety Communication, 2017). A contraindication was added to the prescribing label for patients without a gallbladder due to an increased risk of developing serious pancreatitis. Pancreatitis was reported in patients taking either the 75 mg or 100 mg dose with most of the cases of serious pancreatitis occurring within a week of starting treatment.
- LINZESS and TRULANCE have a Boxed Warning regarding the contraindication in pediatric patients 6 years of age and younger due to the risk of serious dehydration; use should be avoided in children 6 to 17 years of age.
- LOTRONEX has a Boxed Warning regarding serious gastrointestinal adverse reactions such as ischemic colitis and serious complications of constipation that may lead to hospitalization, blood transfusion, surgery, and/or death. If patients develop constipation or ischemic colitis, LOTRONEX should be discontinued. The agent should be used only in female patients with severe IBS-D who have not benefited from usual therapies (Lotronex – FDA MedWatch, 2016).
- LOTRONEX also has a Risk Evaluation and Mitigation Strategy (REMS) that distributes education to providers about the risks for ischemic colitis and serious complications of constipation (Drugs@FDA, 2017).
- There are no known drug interactions with LINZESS. Diphenylheptane opioids such as methadone may interfere with the efficacy of AMITIZA. Clinically significant drug interactions associated with LOTRONEX include cytochrome P450 (CYP) 1A2 moderate inhibitors, CYP3A4 inhibitors, drugs that decrease gastrointestinal motility, and fluvoxamine.
- Concomitant use of MOVANTIK should be avoided with the following drug classes: moderate CYP3A4 inhibitors (e.g., diltiazem, erythromycin, verapamil) due to increased naloxegol concentrations, strong CYP3A4 inducers (e.g., rifampin) due to decreased naloxegol concentrations, and other opioid antagonists due to potentially additive effects that may increase risk of opioid withdrawal. In the event concomitant use with moderate CYP3A4 inhibitors is unavoidable, a dose reduction of MOVANTIK is warranted.
- Concomitant use of RELISTOR with other opioid antagonists should be avoided due to potentially additive effects that may increase risk of opioid withdrawal.
- Concomitant use of SYMPROIC should be avoided with strong CYP3A inducers (e.g., rifampin, carbamazepine, phenytoin, St. John's Wort) due to a significant decrease in naldemedine concentrations, and other opioid antagonists due to potentially additive effect of opioid receptor antagonism that may increase the risk of opioid withdrawal. Moderate CYP3A inhibitors (e.g., fluconazole, atazanavir, aprepitant, diltiazem, erythromycin), strong CYP3A inhibitors (itraconazole, ketoconazole, clarithromycin, ritonavir, saquinavir), and P-glycoprotein inhibitors (e.g., amiodarone, captopril, cyclosporine, quercetin, quinidine, verapamil) can increase SYMPROIC concentrations.
- A clinically important drug interaction with VIBERZI which potentially may result in clinically relevant interactions may occur with concomitant use of the following drug classes: OATP1B1 inhibitors (e.g., cyclosporine, gemfibrozil, antiretrovirals, rifampin, eltrombopag, etc.), strong CYP inhibitors (e.g., ciprofloxacin, fluconazole, clarithromycin,

paroxetine, bupropion, etc.), constipation-inducing drugs (e.g., alosetron, anticholinergics, opioids, etc.), OATP1Bi and BCRP substrate (rosuvastatin), and CYP3A substrates (e.g., alfentanil, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, and tacrolimus).

- Concomitant administration of drugs that are P-glycoprotein inhibitors with XIFAXAN can substantially increase the systemic exposure to rifaximin. Caution should be exercised when concomitant use of XIFAXAN and a P-glycoprotein inhibitor such as cyclosporine is needed.
- The IBS agents are most commonly associated with gastrointestinal-related adverse events.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Dosage Form: Strength	Usual Recommended Dose	Administration Considerations
AMITIZA (lubiprostone)	Capsule: 8 mcg 24 mcg	Treatment of CIC in adults and OIC: Capsule: 24 mcg twice daily by mouth Treatment of IBS-C in women ≥18 years of age: Capsule: 8 mcg twice daily Adjust dosing in moderate and severe hepatic impairment.	Take with food and water.
LINZESS (linaclotide)	Capsule: 72 mcg, 145 mcg, 290 mcg	IBS-C: 290 mcg once daily CIC: 145 mcg once daily. A dosage of 72 mcg once daily may be used based on individual presentation or tolerability.	Take on an empty stomach at least 30 minutes before the first meal of the day. Swallow capsules whole; do not crush or chew. If unable to swallow, administer contents of capsule with applesauce or water. No titration
LOTRONEX (alosetron)	Tablet: 0.5 mg 1 mg	Women with severe IBS-D: Tablet: 0.5 mg twice daily for four weeks; if dosage is well tolerated but does not adequately control IBS symptoms after four weeks, the dose may be increased to up to 1 mg twice daily	Take with or without food. Discontinue treatment in patients who have not had adequate control of IBS symptoms after four weeks of treatment with 1 mg twice daily.

Drug	Dosage Form: Strength	Usual Recommended Dose	Administration Considerations
MOVANTIK (naloxegol)	Tablets: 12.5 mg 25 mg	OIC in chronic non-cancer pain: 25 mg once daily; if not tolerated, may reduce to 12.5 mg once daily • Renal Impairment (CrCl <60 mL/min): 12.5 mg once daily; if tolerated, may increase to 25 mg once daily	Discontinue maintenance laxative therapy prior to initiating therapy with MOVANTIK. Take on an empty stomach at least one hour before or two hours after the first meal of the day. For patients who are unable to swallow the tablet whole, the tablet can be crushed to a powder, mixed with 4 ounces of water, and drunk immediately. The glass should be refilled with an additional 4 ounces of water and drunk immediately. Crushed MOVANTIK can also be administered via a nasogastric tube. Avoid ingestion of grapefruit or grapefruit juice. Discontinue MOVANTIK when opioid pain medication is discontinued.
RELISTOR (methylnaltrex-one)	Single-use vial: 12 mg/0.6 mL solution for use with a 27 gauge x 0.5 inch needle and 1 mL syringe Single-use pre-filled syringe: 8 mg/0.4 mL 12 mg/0.6 mL Tablet: 150 mg	OIC in chronic non-cancer pain: Injection: 12 mg subcutaneously once daily Tablets: 450 mg orally once daily in the morning • Moderate to severe renal impairment (CrCl <60 mL/min): reduce subcutaneous dose to 6 mg once daily (one-half usual dose); reduce oral dose to 150 mg once daily • Hepatic impairment: for RELISTOR tablets in patients with moderate or severe hepatic impairment: 150 mg once daily. When considering dose adjustment of RELISTOR injection in patients with severe hepatic impairment, follow reduced weight-based dosing: o Weight <38 kg: 0.075 mg/kg o Weight 38 kg to <62 kg: 4 mg o Weight 62 kg to 114 kg: 6 mg o >114 kg: 0.075 mg/kg OIC in advanced illness (injection; subcutaneous dosing): weight-based dosing once every other day, as needed (max of once daily):	Inject subcutaneously in the upper arm, abdomen, or thigh. Rotate injection sites. Be within close proximity to toilet facilities after administration. Discontinue maintenance laxative therapy prior to initiating therapy with RELISTOR. Discontinue RELISTOR when opioid pain medication is discontinued. Pre-filled syringes only should be used for patients taking 8 mg or 12 mg dose. Take RELISTOR tablets with water on an empty stomach at least 30 minutes before the first meal of the day.

Drug	Dosage Form: Strength	Usual Recommended Dose	Administration Considerations
		• Weight <38 kg: 0.15 mg/kg • Weight 38 kg to <62 kg: 8 mg • Weight 62 kg to 114 kg: 12 mg • >114 kg: 0.15 mg/kg • Moderate to severe renal impairment (CrCl <60 mL/min): reduce to one subcutaneous dose every other day based on weight, as needed o Weight <38 kg: 0.075 mg/kg o Weight 38 kg to <62 kg: 4 mg o Weight 62 kg to 114 kg: 6 mg o >114 kg: 0.075 mg/kg	
SYMPROIC (naldemedine)	Tablet: 0.2 mg	OIC in chronic non-cancer pain: 0.2 mg once daily	Take with or without food. Patients taking opioids < 4 weeks may be less responsive to treatment. Discontinue SYMPROIC when opioid pain medication is discontinued.
TRULANCE (plecanatide)	Tablet: 3 mg	CIC: 3 mg once daily	Take with or without food. For adult patients with swallowing difficulties, can be crushed and administered orally either in applesauce or with water or administered with water via a nasogastric or gastric feeding tube.
VIBERZI (eluxadoline)	Tablet: 75 mg 100 mg	Treatment of IBS-D in adults: 100 mg twice daily 75 mg twice daily in select patients who: • do not have a gallbladder • are unable to tolerate the 100 mg dose • are receiving concomitant OATP1B1 inhibitors • have mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment	Take with food Discontinue treatment in patients who develop severe constipation for more than four days.
XIFAXAN (rifaximin)	Tablet: 200 mg 550 mg	TD: 200 mg three times daily for three days Hepatic encephalopathy: 550 mg twice daily IBS-D: 550 mg three times daily for 14 days	Take with or without food. Patients with IBS-D who experience recurrence may be retreated up to two times with the same regimen. Do not use in patients with TD complicated by fever or blood in the stool or diarrhea due to pathogens other than *E. coli*.

SPECIAL POPULATIONS

Table 4. Special Populations

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
AMITIZA (lubiprostone)	The efficacy among those ≥65 years was consistent with the overall study population of CIC. Clinical trials of OIC had insufficient numbers of older patients to determine if differences exist. Safety profile among those ≥65 years was consistent with the overall study population of IBS-C.	Safety and efficacy have not been established.	No dosage adjustment required.	CIC or OIC with moderate impairment (Child-Pugh Class B): recommended dose is 16 mcg twice daily† CIC or OIC with severe impairment (Child-Pugh Class D): recommended dose is 8 mcg twice daily† IBS-C with severe impairment (Child-Pugh Class C): recommended dose is 8 mcg once daily†	Pregnancy Category C Unknown whether excreted in breast milk; use with caution.
LINZESS (linaclotide)	Clinical studies did not include sufficient numbers of patients ≥65 years to determine whether they respond differently from younger patients.	Contra-indicated in <6 years. Boxed Warning to avoid use in children ages 6 to <18 years.	No dosage adjustment required.	No dosage adjustment required.	Not categorized‡ Unknown whether excreted in breast milk; use with caution.
LOTRONEX (alosetron)	Use with caution in patients ≥65 years due to risk for constipation.	Safety and efficacy have not been established.	No dosage adjustment required.	Use with caution in mild or moderate impairment; avoid use in severe impairment.	Pregnancy category B Unknown whether excreted in breast milk; use with caution.
MOVANTIK (naloxegol)	No overall differences in effectiveness were observed between patients at least 65 years of age and younger patients. No dosage adjustments are required in older patients.	Safety and efficacy have not been established.	Reduce starting dose to 12.5 once daily in patients with CrCl <60 mL/min. No dose adjustments are required for mild renal impairment.	Avoid use in patients with severe hepatic impairment (Child-Pugh Class C). No dose adjustments are required for mild or moderate hepatic impairment.	Pregnancy Category C Unknown whether excreted in breast milk; discontinue nursing or discontinue the drug.
RELISTOR (methylnal-	No overall differences in effectiveness were observed between patients	Safety and efficacy have	Reduce dose in patients with CrCl <60	Reduce dose in patients with OIC in chronic non-cancer	Not categorized‡

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
trexone bromide)	at least 65 years of age and younger patients. No dosage adjustments are required in older patients.	not been established.	mL/min (See Table 3). No dose adjustments are required for mild renal impairment.	pain and moderate or severe hepatic impairment (see Table 3). No dose adjustments are required for mild hepatic impairment.	Unknown whether excreted in breast milk; breastfeeding not recommended during treatment.
SYMPROIC (naldemedine)	No overall differences in safety or effectiveness between patients at least 65 years of age and younger patients were observed, but greater sensitivity of some older individuals cannot be ruled out.	Safety and efficacy have not been established.	No dosing adjustments necessary.	Avoid use in patients with severe hepatic impairment (Child-Pugh Class C). No dose adjustments are required for mild or moderate hepatic impairment.	Not categorized‡ Unknown whether excreted in breast milk; discontinue nursing or discontinue the drug. If drug is discontinued, breastfeeding can be resumed 3 days after the final dose.
TRULANCE (plecanatide)	Clinical studies did not include sufficient numbers of patients ≥65 years to determine whether they respond differently from younger patients.	Contra-indicated in <6 years. Boxed Warning to avoid use in children ages 6 to 17 years.	No dosing adjustments necessary.	No dosing adjustments necessary.	Not categorized‡ Unknown whether excreted in breast milk; use with caution.
VIBERZI (eluxadoline)	No overall differences in effectiveness were observed between patients at least 65 years of age and younger patients.	Safety and efficacy have not been established.	No information available.	Reduce the dose to 75 mg twice daily with mild (Child-Pugh Class A) and moderate (Child-Pugh Class B) hepatic impairment. Do not use in patients with severe hepatic impairment (Child-Pugh Class C).	No studies in pregnant women. Unknown whether excreted in breast milk; use with caution.
XIFAXAN (rifaximin)	No overall differences in effectiveness were observed between patients at least 65 years of age and younger patients.	Safety and efficacy have not been established in pediatric patients less	Studies in patients with renal impairment have not	No dose adjustment is recommended in patients with mild, moderate, or severe hepatic impairment.	No studies in pregnant women. Unknown whether

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
	Clinical studies with XIFAXAN for TD did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently than younger subjects.	than 12 years of age with TD or in patients less than 18 years of age for HE and IBS-D.	been conducted.		excreted in breast milk, effects on breastfed infant, or effects on milk production; use with caution.

*Pregnancy Category B = No evidence of risk in humans, but there remains a remote possibility. Animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women. Pregnancy Category C = Risk cannot be ruled out. Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
†If this dose is tolerated and an adequate response has not been obtained after an appropriate interval, doses can then be escalated to full dosing with appropriate monitoring of response.
‡In accordance with the FDA's Pregnancy and Lactation Labeling Rule (PLLR), this product is not currently assigned a Pregnancy Category. Consult product prescribing information for details.

CONCLUSION

- Irritable Bowel Syndrome (IBS) is a gastrointestinal disorder with symptoms of abdominal pain, discomfort and bloating, and abnormal bowel habits with bouts of diarrhea and/or constipation (WGO, 2015; Quigley et al, 2012).
- Irritable Bowel Syndrome has four subtypes depending on the change in bowel habits – Irritable Bowel Syndrome-Diarrhea (IBS-D), Irritable Bowel Syndrome-Constipation (IBS-C), mixed type having diarrhea and constipation (IBS-M), or unspecified (IBS-U). IBS-C symptoms include abdominal pain and bloating, less than three bowel movements per week, straining, and feeling of incomplete evacuation of bowels.
- Most patients with mild disease are managed with disease state education and support, coupled with lifestyle modifications, including diet changes and stress reduction and, when possible, symptom control (Andresen et al, 2008; Ford et al, 2009).
- There are currently no head-to-head trials comparing the available agents used in the treatment of CIC, OIC, IBS-C, and IBS-D.
- Guidelines on management of constipation suggest increased fiber intake and osmotic laxatives. Stimulant laxatives are to be used as needed or as "rescue agents." Lubiprostone and linaclotide can be considered when symptoms of constipation do not respond to laxatives (AGA, 2013; Bharucha et al, 2013; Chang et al, 2014; Lindberg et al, 2010).
- The American College of Gastroenterology monograph on the management of IBS and CIC notes that rifaximin is effective in reducing IBS symptoms and bloating in IBS-D; alosetron is effective in females with IBS-D; and linaclotide and lubiprostone are each superior to placebo for the treatment of IBS-C. In addition, linaclotide and lubiprostone are each effective for the treatment of CIC (Ford et al, 2014).
- AMITIZA (lubiprostone) is currently the only chloride channel activator commercially available. It selectively activates intestinal chloride channels, increasing intestinal fluid secretion and delaying gastric emptying.
- In clinical trials, AMITIZA has demonstrated efficacy in the treatment of CIC as well as IBS-C in women, with improvement in SBMs, straining, constipation severity, stool consistency, and global assessment of constipation (Drossman et al, 2007; Drossman et al, 2009; Johanson et al, 2004; Johanson et al, 2005; Johanson et al, 2007; Johanson et al, 2008a; Johanson et al, 2008b).
- LINZESS (linaclotide) is a guanylate cyclase-C agonist. LINZESS acts locally in the intestine to accelerate intestinal transit, increase intestinal secretions and reduce intestinal pain. LINZESS has been shown in placebo-controlled studies to be effective in improving constipation related to IBS-C and CIC (Li et al, 2016; Nelson et al, 2017; Videlock et al, 2013).
- TRULANCE (plecanatide) is approved by the FDA for treatment of CIC. Similar to LINZESS, it is a guanylate cyclase-C agonist. In two randomized control trials, TRULANCE 3 mg demonstrated a significantly increased weekly CSBM frequency as measured by the overall CSBM responder rate vs placebo (Miner et al [abstract], 2016; Miner et al, 2017).
- Agents approved for use in OIC include MOVANTIK (naloxegol), SYMPROIC (naldemedine), and RELISTOR (methylnaltrexone) in patients with chronic non-cancer pain. RELISTOR is also approved in patients with advanced illness (including cancer) receiving palliative care and unresponsive to laxative therapy. SYMPROIC, RELISTOR,

MOVANTIK and AMITIZA, are also indicated in patients with chronic pain related to prior cancer or its treatment in those who do not require frequent (e.g., weekly) opioid dosage escalation.

- LOTRONEX (alosetron), a 5-HT receptor antagonist, has been shown to reduce pain, abdominal discomfort, urgency, and diarrhea in patients with IBS as demonstrated in several placebo-controlled trials (Andresen et al, 2008; Bardhan et al, 2000; Camilleri et al, 2000; Camilleri et al, 2001; Chey et al, 2004; Cremonini et al, 2003; Ford et al, 2009; Lembo et al, 2001; Lembo et al, 2004; Krause et al, 2007; Rahimi et al, 2008; Watson et al, 2001).
- Use of LOTRONEX is limited to female patients with chronic, severe IBS-D who have not responded to conventional therapy. Due to serious safety concerns, a boxed warning regarding gastrointestinal adverse events has been added to the alosetron prescribing information. The medication also has an approved REMS program.

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