# *Therapeutic Class Overview*
# *Irritable Bowel Syndrome Agents*

**Therapeutic Class Overview/Summary:**
This review will focus on agents used for the treatment of Irritable Bowel Syndrome (IBS).[1-5] IBS is a gastrointestinal syndrome characterized primarily by non-specific chronic abdominal pain, usually described as a cramp-like sensation, and abnormal bowel habits, either constipation or diarrhea, in which there is no organic cause. Other common gastrointestinal symptoms may include gastroesophageal reflux, dysphagia, early satiety, intermittent dyspepsia and nausea. Patients may also experience a wide range of non-gastrointestinal symptoms. Some notable examples include sexual dysfunction, dysmenorrhea, dyspareunia, increased urinary frequency/urgency and fibromyalgia-like symptoms.[6] IBS is defined by one of four subtypes. IBS with constipation (IBS-C) is the presence of hard or lumpy stools with ≥25% of bowel movements and loose or watery stools with <25% of bowel movements. When IBS is associated with diarrhea (IBS-D) loose or watery stools are present with ≥25% of bowel movements and hard or lumpy stools are present with <25% of bowel movements. Mixed IBS (IBS-M) is defined as the presence of hard or lumpy stools with ≥25% and loose or water stools with ≥25% of bowel movements. Final subtype, or unsubtyped, is all other cases of IBS that do not fall into the other classes. Pharmacological therapy for IBS depends on subtype.[7]

While several over-the-counter or off-label prescription agents are used for the treatment of IBS, there are currently only two agents approved by the Food and Drug Administration (FDA) for the treatment of IBS-C and three agents approved by the FDA for IBS-D. Of note, each agent has a unique mechanism of action.[1-5] Agents used for the treatment of IBS-C include linaclotide (Linzess®) and lubiprostone (Amitiza®). Linaclotide is a guanylate cyclase-C (GC-C) agonist. It achieves improved gastrointestinal (GI) transit and reduced intestinal pain via activation of GC-C locally, on the luminal surface of the intestinal epithelium. Activation of GC-C stimulates the secretion of chloride and bicarbonate into the intestinal lumen while also decreasing the activity of pain-sensing nerves.[1] Lubiprostone is a locally acting chloride channel activator acting specifically at chloride channel-2 (CIC-2) receptors in the intestine. By increasing intestinal fluid secretion, lubiprostone increases motility in the intestine.[2] Agents used for the treatment of IBS-D include alosetron (Lotronex®), eluxadoline (Viberzi®) and rifaximin (Xifaxan®). Alosetron is a potent and selective serotonin-3 (5-$HT_3$) receptor antagonist. 5-HT3 receptors are ligand-gated cation channels that are extensively distributed on enteric neurons in the human gastrointestinal tract, as well as other peripheral and central locations. Activation of these channels and the resulting neuronal depolarization affect the regulation of visceral pain, colonic transit, and gastrointestinal secretions.[3] Eluxadoline (Viberzi®) is a μ-opioid receptor agonist/δ-opioid receptor antagonist/κ-receptor agonist. It is a locally active visceral analgesic, with low systemic absorption and bioavailability. The μ-opioid agonist activity works by inhibiting gastrointestinal (GI) motility and secretion and the δ-opioid receptor antagonism works by mitigating against the constipating effects of unopposed peripherally acting μ-opioid receptor agonist.[4] Rifaximin (Xifaxan®) is a semi-synthetic, non-systemic, broad-spectrum antibiotic and is a structural analog of rifampin. The proposed mechanism of action involves inhibition of bacterial RNA synthesis by binding to the beta-subunit of bacterial DNA-dependent RNA polymerase.[5]

**Table 1a. IBS-C Current Medications Available**[1-2]

| Generic (Trade Name) | Food and Drug Administration-Approved Indications | Dosage Form/Strength | Generic Availability |
|---|---|---|---|
| Linaclotide (Linzess®) | Chronic idiopathic constipation in adults, irritable bowel syndrome with constipation in adults | Capsule:<br>145 μg<br>290 μg | - |
| Lubiprostone (Amitiza®) | Chronic idiopathic constipation in adults, irritable bowel syndrome with constipation in adult women, opioid-induced constipation in adults with chronic non-cancer pain | Capsule:<br>8 μg<br>24 μg | - |

**Table 1b. IBS-D Current Medications Available**[3-5]

| Generic (Trade Name) | Food and Drug Administration-Approved Indications | Dosage Form/Strength | Generic Availability |
|---|---|---|---|
| Alosetron (Lotronex®*) | Irritable bowel syndrome with diarrhea in adult women | Tablet:<br>0.5 mg<br>1 mg | - |
| Eluxadoline (Viberzi®) | Irritable bowel syndrome with diarrhea in adults | Tablet:<br>75 mg<br>100 mg | - |
| Rifaximin (Xifaxan®) | Irritable bowel syndrome with diarrhea in adults, reduce the risk of recurrent overt hepatic encephalopathy in adults, travelers' diarrhea in adults and children 12 years of age or older | Tablet:<br>200 mg<br>550 mg | - |

*Generic available in at least one dosage form or strength.

**Evidence-based Medicine**

- Clinical trials have been shown to be safe and effective for the treatment of IBS-C or IBS-D.[1-5,8-16]
  - The FDA approval of linaclotide was based on four phase III, double-blind, placebo-controlled trials ranging from 12 to 26 weeks.[1] In the first trial (N=804) and the second trial (N=800), patients with IBS-C aged 18 and over were randomized to either linaclotide 290 µg or placebo. Treatment with linaclotide was associated with statistically significant changes in the proportion of patients who experienced ≥30% improvement in the daily worst abdominal pain score and increase of ≥1 in complete spontaneous bowel movement (CSBM) for at least 6 out of 12 weeks when compared to placebo. In addition, a greater proportion of patients treated with linaclotide were considered responders at 12 weeks in both trials.[1,8,9]
  - Safety and efficacy of lubiprostone in adult women with IBS-C was established in two similar double-blind, placebo-controlled studies of similar design. A mostly female study population (91.6%) of patients with IBS-C was randomized to receive lubiprostone 8 µg twice daily or matching placebo twice daily for 12 weeks. In a combined analysis, the percentage of patients in Study 1 qualifying as an "overall responder" was 18.2% in the group receiving lubiprostone 8 µg twice daily compared to 9.8% of patients receiving placebo twice daily (P=0.009). In Study 2, 17.7% of patients in the lubiprostone 8 µg group were "overall responders" versus 10.4% of patients in the placebo group (P=0.031).[10]
  - Several meta-analyses and systematic reviews evaluating alosetron and/or the 5-$HT_3$ antagonists as a class have been performed.[11-13]
    - An analysis by Andresen et al demonstrated that as a class, the 5-$HT_3$ antagonists significantly improve symptoms of non-constipating or diarrhea-predominant IBS in both men and women compared to placebo. These agents were also associated with a greater increase in the risk of becoming constipated compared to placebo.[11]
    - Cremonini et al demonstrated that alosetron treatment positively impacts global symptoms, and pain and discomfort in non-constipating IBS female patients. This analysis also showed an increased chance in developing constipation with alosetron compared to placebo.[12]
    - Ford et al evaluated all of the 5-$HT_3$ antagonists for the treatment of IBS. Results demonstrated that alosetron, along with others, are effective IBS treatments compared to placebo. Evaluation of 11 trials of patients receiving alosetron or cilansetron demonstrated that 49% of the active treatment group experienced persistent IBS symptoms after treatment cessation compared to 64% of the placebo group (P value not reported).[13]
  - The safety and efficacy of eluxadoline in the treatment of IBS-D was established in two identical randomized, multi-center, double-blind, placebo-controlled phase III clinical trials in

adults with IBS-D (IBS-3001 and IBS-3002). Both trials were 26 weeks long. Individuals were randomized to receive twice daily placebo, eluxadoline 75 mg or eluxadoline 100 mg.[14,15]
    - § For the IBS-3001 trial, the proportion of composite responders for the 75 mg and 100 mg treatment groups had a statistically greater response than placebo for weeks 1 to 12 (P<0.025) and weeks 1 to 26 for the 100 mg treatment group (P<0.001).
    - § In the IBS-3002 trial, the proportion of composite responders for the eluxadoline 75 mg and 100 mg groups had a statistically greater response than placebo for weeks 1 to 12 (P<0.001) and weeks 1 to 26 (P=0.001). The onset for response was noted to be within the first week of dosing in both trials.[14,15]
- o The safety and efficacy of rifaximin for the treatment of IBS-D was evaluated in three randomized, double-blind, placebo-controlled trials.
    - § Two studies, TARGET 1 and TARGET 2, evaluated rifaximin 550 mg three times a day for 14 days in adult patients. There were significantly more patients in the rifaximin group than in the placebo group that had adequate relief of global IBS symptoms for at least two of the first four weeks after treatment in both TARGET 1 (40.8% vs 31.2%; P=0.01) and TARGET 2 (40.6% vs 32.2%; P=0.03) as well as combined (40.7% vs 31.7%; P<0.001).[5,16]
    - § Another study, TARGET 3, evaluated retreatment with rifaximin 550 mg three times daily for 14 days who had previously responded to rifaximin, but who had experienced a recurrence of IBS-related symptoms (abdominal pain or mushy/watery stool). After the initial rifaximin treatment course, patients who were considered responders (N=1,257, 49%) were followed for 20 treatment free weeks. Overall, a numerically larger number of receiving rifaximin were month responders for both abdominal pain and stool consistency when compared to placebo (125 [38%] vs 97 [31%], respectively; no P value reported). The response rate difference was 7% (95% confidence interval, 1.2% to 11.6%, no P value reported).[5]

**Key Points within the Medication Class**

- According to Current Clinical Guidelines:
    - o Current clinical guidelines recommend the use of linaclotide, lubiprostone or other laxatives for the treatment of IBS-C.[18-20]
    - o Due to limited therapeutic options and efficacy data for the treatment of IBS-D, clinical guidelines have consistently provided only moderate or weak recommendations for the use of all agents, new and old.All current clinical guidelines suggest rifaximin, alosetron, TCAs, SSRIs, and antispasmodics as effective, but their place in therapy is not well defined and varies by guideline. Loperamide was granted a conditional recommendation by the American Gastrointestinal Association (AGA) due to its usefulness as a potential adjunctive therapy for the management of diarrhea, however the American College of Gastroenterology (ACG) and World Gastroenterology Organization Global Guidelines do not recommend its use due to no relief of the global symptoms of IBS-D. Only the World Gastroenterology Organization mentions the use of eluxadoline, but acknowledges that although it has been approved for use in the United States, its position in the management of IBS is difficult to define at this time.[18-20]

- Other Key Facts:
    - o There is a lack of head-to head data with these agents.
    - o Linaclotide is administered twice daily and lubiprostone is administered once daily.[1-2]
    - o Rifaximin is administered three times a day for 14 days. Other agents are administered twice daily.[3-5]
    - o Linaclotide is contraindicated in pediatric patients <6 years of age.[1]
    - o Alosetron and eluxadoline are contraindicated in patients with severe hepatic dysfunction (Child-Pugh class C).[3,4]

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**Overview/Summary**

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While several over-the-counter or off-label prescription agents are used for the treatment of IBS, there are currently only two agents approved by the Food and Drug Administration (FDA) for the treatment of IBS-C and three agents approved by the FDA for IBS-D. Of note, each agent has a unique mechanism of action.[1-5] Agents used for the treatment of IBS-C include linaclotide (Linzess®) and lubiprostone (Amitiza®). Linaclotide is a guanylate cyclase-C (GC-C) agonist. It achieves improved gastrointestinal (GI) transit and reduced intestinal pain via activation of GC-C locally, on the luminal surface of the intestinal epithelium. Activation of GC-C stimulates the secretion of chloride and bicarbonate into the intestinal lumen while also decreasing the activity of pain-sensing nerves.[1] Lubiprostone is a locally acting chloride channel activator acting specifically at chloride channel-2 (CIC-2) receptors in the intestine. By increasing intestinal fluid secretion, lubiprostone increases motility in the intestine.[2] Agents used for the treatment of IBS-D include alosetron (Lotronex®), eluxadoline (Viberzi®) and rifaximin (Xifaxan®). Alosetron is a potent and selective serotonin-3 ($5\text{-}HT_3$) receptor antagonist. 5-HT3 receptors are ligand-gated cation channels that are extensively distributed on enteric neurons in the human gastrointestinal tract, as well as other peripheral and central locations. Activation of these channels and the resulting neuronal depolarization affect the regulation of visceral pain, colonic transit, and gastrointestinal secretions.[3] Eluxadoline (Viberzi®) is a μ-opioid receptor agonist/δ-opioid receptor antagonist/κ-receptor agonist. It is a locally active visceral analgesic, with low systemic absorption and bioavailability. The μ-opioid agonist activity works by inhibiting gastrointestinal (GI) motility and secretion and the δ-opioid receptor antagonism works by mitigating against the constipating effects of unopposed peripherally acting μ-opioid receptor agonist.[4] Rifaximin (Xifaxan®) is a semi-synthetic, non-systemic, broad-spectrum antibiotic and is a structural analog of rifampin. The proposed mechanism of action involves inhibition of bacterial RNA synthesis by binding to the beta-subunit of bacterial DNA-dependent RNA polymerase.[5]

Clinical trials have been shown to be safe and effective for the treatment of IBS-C or IBS-D.[1-5,8-16] Current clinical guidelines recommend the use of linaclotide, lubiprostone or other laxatives for the treatment of IBS-C. However, due to limited therapeutic options and efficacy data for the treatment of IBS-D, clinical guidelines have consistently provided only moderate or weak recommendations for the use of all agents, new and old. All current clinical guidelines suggest rifaximin, alosetron, TCAs, SSRIs, and antispasmodics as effective, but their place in therapy is not well defined and varies by guideline. Loperamide was granted a conditional recommendation by the American Gastrointestinal Association (AGA) due to its usefulness as a potential adjunctive therapy for the management of diarrhea, however the American College of Gastroenterology (ACG) and World Gastroenterology Organization Global Guidelines do not recommend its use due to no relief of the global symptoms of IBS-D. Only the World Gastroenterology Organization mentions the use of eluxadoline, but acknowledges that although it has been approved for use in the United States, its position in the management of IBS is difficult to define at this time.[18-20]

## Medications

**Table 1a. Medications for IBS-C**[1-2]

| Generic Name (Trade name) | Medication Class | Generic Availability |
|---|---|---|
| Linaclotide (Linzess®) | Guanylate Cyclase-C (GC-C) agonist | - |
| Lubiprostone (Amitiza®) | Chloride Channel-2 (CIC-2) activator | - |

**Table 1b. Medications for IBS-D**[3-5]

| Generic Name (Trade name) | Medication Class | Generic Availability |
|---|---|---|
| Alosetron (Lotronex®*) | Serotonin-3 ($5\text{-}HT_3$) receptor antagonist | a |
| Eluxadoline (Viberzi®) | Mixed opioid agonist/antagonist | - |
| Rifaximin (Xifaxan®) | Antibiotic – Rifamycin | - |

*Generic available in at least one dosage form or strength.
†Eluxadoline is a μ-opioid receptor agonist, δ-opioid receptor antagonist and κ-opioid receptor agonist

## Indications

**Table 2a. IBS-C Agents – Food and Drug Administration Approved Indications**[1-2]

| Indications | Linaclotide | Lubiprostone |
|---|---|---|
| Chronic idiopathic constipation in adults | a | a |
| Irritable bowel syndrome with constipation in adults | a | |
| Irritable bowel syndrome with constipation in adult women | | a |
| Opioid-induced constipation in adults with chronic non-cancer pain | | a * |

IBS-C=irritable bowel syndrome-constipation predominant
*Efficacy of lubiprostone in the treatment of OIC in patients taking diphenylheptane opioids (e.g. methadone) has not been established

**Table 2b. IBS-D Agents – Food and Drug Administration Approved Indications**[3-5]

| Indications | Alosetron | Eluxadoline | Rifaximin |
|---|---|---|---|
| Irritable bowel syndrome with diarrhea in adults | | a | a |
| Irritable bowel syndrome with diarrhea in adult women | a * | | |
| Reduce the risk of recurrent overt hepatic encephalopathy in adults | | | a |
| Travelers' diarrhea in adults and children 12 years of age or older | | | a † |

IBS-D=irritable bowel syndrome-diarrhea predominant
*Indicated for chronic IBS-D (lasting six months or more) who had an anatomic or biochemical abnormality of the gastrointestinal tract ruled out, and not responded adequately to conventional therapy.
†Caused by noninvasive strains of *Escherichia coli*.

## Pharmacokinetics

**Table 3a. IBS-C Agents – Pharmacokinetics**[1-2]

| Generic Name | Absorption/ Bioavailability (%) | Renal Excretion (%) | Active Metabolites | Serum Half-Life (hours) |
|---|---|---|---|---|
| Linaclotide | Low* % Not reported | Not reported | Yes† | Unable to determine |
| Lubiprostone | Low* % Not reported | Not Reported | Not reported | Unable to determine |

*Following oral administration, concentrations in plasma are below the level of quantitation.
†Primary, active metabolite not named.

**Table 3b. IBS-D Agents – Pharmacokinetics**[3-5]

| Generic Name | Absorption/ Bioavailability (%) | Renal Excretion (%) | Active Metabolites | Serum Half-Life (hours) |
|---|---|---|---|---|
| Alosetron | Rapid<br>50 to 60 | 73<br>(6 unchanged) | Unlikely* | 1.5 |
| Eluxadoline | Not determined | <1 | Unknown† | 3.7 to 6 |
| Rifaximin | Limited | <1 | Not reported | 1.8 to 6.1 |

*Metabolites are not likely to contribute to the biological activity of alosetron.
†Metabolism of eluxadoline is not clearly established.

**Clinical Trials**

The safety and efficacy of agents used for the treatment of IBS have been established in a number of clinical trials.[1-5,8-17] Clinical trials for indications other than IBS will not be covered in this review.

The FDA approval of linaclotide was based on four phase III, double-blind, placebo-controlled trials ranging from 12 to 26 weeks.[1] In the first trial (N=804) and the second trial (N=800), patients with IBS-C aged 18 and over were randomized to either linaclotide 290 µg or placebo. Treatment with linaclotide was associated with statistically significant changes in the proportion of patients who experienced ≥30% improvement in the daily worst abdominal pain score and increase of ≥1 in complete spontaneous bowel movement (CSBM) for at least 6 out of 12 weeks when compared to placebo. In addition, a greater proportion of patients treated with linaclotide were considered responders at 12 weeks in both trials.[1,8,9]

Safety and efficacy of lubiprostone in adult women with IBS-C was established in two similar double-blind, placebo-controlled studies of similar design. A mostly female study population (91.6%) of patients with IBS-C was randomized to receive lubiprostone 8 µg twice daily or matching placebo twice daily for 12 weeks. The primary efficacy endpoint was overall response, which was based on patient response to a global-symptom relief question. Overall response was defined as a patient who was a monthly responder for at least two of the three study months. A monthly responder was a patient that was at least “significantly relieved” for final two weeks of the month or at least “moderately relieved” in all four weeks. Any patient that reported a “moderately worse” or “significantly worse” or required rescue medication was discontinued from the study and considered a non-responder. In a combined analysis (intention-to-treat and last observation carried forward), the percentage of patients in Study 1 qualifying as an "overall responder" was 18.2% in the group receiving lubiprostone 8 µg twice daily compared to 9.8% of patients receiving placebo twice daily (P=0.009). In Study 2, 17.7% of patients in the lubiprostone 8 µg group were "overall responders" versus 10.4% of patients in the placebo group (P=0.031).[10]

The safety and efficacy of alosetron for the treatment of IBS-D was established in five 12-week randomized, double-blind, placebo-controlled trials. Trials 1 and 2 evaluated alosetron 1 mg twice daily (N=633) in women with IBS that were not constipated. Trials 3 and 4 evaluated alosetron 1 mg twice daily (N=778) in women with severe IBS-D, defined as bowel urgency ≥50% of days. Study 5 evaluated alosetron 0.5 mg once daily (N=177), 1 mg once daily (N=175), and 1 mg twice daily (N=177) in women with serve IBS-D, defined as average pain ≥moderate, urgency ≥50% of days, and/or restriction of daily activities ≥25% of days. In addition, the long-term use of alosetron 1 mg twice daily (N=198) in women was evaluated in a 48-week double-blind, placebo-controlled trial. Alosetron provided a greater average rate of adequate relief of IBS pain and discomfort (52% vs 41%) and a greater average rate of satisfactory control of bowel urgency (60% vs 48%) compared with placebo for most of the 48-week treatment period with no evidence of tachyphylaxis (P values not reported).[3]

Several meta-analyses and systematic reviews evaluating alosetron and/or the 5-$HT_3$ antagonists as a class have been performed.[11-13] An analysis by Andresen et al demonstrated that as a class, the 5-$HT_3$ antagonists significantly improve symptoms of non-constipating or diarrhea-predominant IBS in both men and women compared to placebo. These agents were also associated with a greater increase in the risk of becoming constipated compared to placebo.[11] Cremonini et al demonstrated that alosetron treatment positively impacts global symptoms, and pain and discomfort in non-constipating IBS female patients. This analysis also showed an increased chance in developing constipation with alosetron compared to placebo.[12] Ford et al evaluated all of the

5-$HT_3$ antagonists for the treatment of IBS. Results demonstrated that alosetron, along with others, are effective IBS treatments compared to placebo. Evaluation of 11 trials of patients receiving alosetron or cilansetron demonstrated that 49% of the active treatment group experienced persistent IBS symptoms after treatment cessation compared to 64% of the placebo group (P value not reported).[13]

The safety and efficacy of eluxadoline in the treatment of IBS-D was established in two identical randomized, multi-center, double-blind, placebo-controlled phase III clinical trials in adults with IBS-D (IBS-3001 and IBS-3002). Both trials were 26 weeks long. Individuals were randomized to receive twice daily placebo, eluxadoline 75 mg or eluxadoline 100 mg. In Study IBS-3001, the double-blinded treatment period was continued for an additional 26 weeks to monitor long-term safety (total of 52 weeks of treatment), followed by a two-week follow-up. Study IBS-3002 included a four-week single-blinded, placebo-withdrawal period upon completion of the 26-week treatment period. During the double-blind treatment phase and the single-blinded placebo withdrawal phase, patients were allowed to take loperamide rescue medication for the acute treatment of uncontrolled diarrhea, but were not allowed to take any other antidiarrheal, antispasmodic agent or rifaximin for their diarrhea.[14,15]

Efficacy of eluxadoline was assessed in both trials using an overall composite responder primary endpoint. This was defined by patients meeting the daily response criteria (pain and stool consistency) for ≥ 50% of the days with diary entries for two criteria: daily pain response (improvement in worst abdominal pain [WAP] scores in the past 24 hours by ≥ 30% compared to baseline) and daily stool consistency (BSS score < five or the absence of a bowel movement if accompanied by ≥ 30% improvement in WAP compared to baseline pain). The primary endpoints for the IBS-3001 trial, showed that the proportion of composite responders for the 75 mg and 100 mg treatment groups had a statistically greater response than placebo for weeks 1 to 12 (P<0.025) and weeks 1 to 26 for the 100 mg treatment group (P<0.001). In the IBS-3002 trial, the proportion of composite responders for the eluxadoline 75 mg and 100 mg groups had a statistically greater response than placebo for weeks 1 to 12 (P<0.001) and weeks 1 to 26 (P=0.001). The onset for response was noted to be within the first week of dosing in both trials.[14,15]

The IBS-3002 trial also showed significant responses in the eluxadoline groups for several secondary endpoints. The proportion of stool consistency responders for the 75 mg and 100 mg eluxadoline treatment groups was statistically significant compared to placebo over weeks 1 to 12 and weeks 1 to 26 (P<0.001). A larger proportion of IBS-D global symptom responders for the 75 mg and 100 mg eluxadoline treatment groups had a statistically greater response than placebo over weeks 1 to 12 (P<0.001) and weeks 1 to 26 (P≤0.012). The proportion of IBS-adequate relief (AR) responders for the eluxadoline 75 mg and 100 mg treatment groups was also greater than placebo (P≤0.013) over weeks 1 to 12 and weeks 1 to 26.[14,15]

The safety and efficacy of rifaximin for the treatment of IBS-D was evaluated in three randomized, double-blind, placebo-controlled trials. Two studies, TARGET 1 and TARGET 2, evaluated rifaximin 550 mg three times a day for 14 days in adult patients. The primary endpoint for both trials was the proportion of patients who achieved "adequate relief" of IBS signs and symptoms, based on the patient's own perceived benefit, for at least two of four weeks during the month following 14 days of treatment. There were significantly more patients in the rifaximin group than in the placebo group that had adequate relief of global IBS symptoms for at least two of the first four weeks after treatment in both TARGET 1 (40.8% vs 31.2%; P=0.01) and TARGET 2 (40.6% vs 32.2%; P=0.03) as well as combined (40.7% vs 31.7%; P<0.001).[5,16] Another study, TARGET 3, evaluated retreatment with rifaximin 550 mg three times daily for 14 days who had previously responded to rifaximin, but who had experienced a recurrence of IBS-related symptoms (abdominal pain or mushy/watery stool). After the initial rifaximin treatment course, patients who were considered responders (N=1,257, 49%) were followed for 20 treatment free weeks. A total of 636 patients (51% of responders) subsequently had a recurrence of IBS-related abdominal pain or mushy/watery stool. The primary endpoint in the double-blind, placebo-controlled portion of the trial was the proportion of patients who were responders to repeat treatment in both IBS-related abdominal pain and stool consistency. Overall, a numerically larger number of receiving rifaximin were month responders for both abdominal pain and stool consistency when compared to placebo (125 [38%] vs 97 [31%], respectively; no P value reported). The response rate difference was 7% (95% confidence interval, 1.2% to 11.6%, no P value reported).[5]

**Table 4. Clinical Trials**

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| Irritable Bowel Syndrome with Constipation | | | | |
| Chey et al[8]<br><br>Linaclotide 290 µg QD at least 30 minutes before breakfast<br><br>vs<br><br>placebo | DB, MC, PC, PG, RCT<br><br>Men and women aged 18 years or older who met modified Rome II criteria for IBS-C, had < 3 SBM per week and ≥ 1 of the following symptoms: straining, hard stools, sensation of incomplete evacuation. Patients, during baseline period, reported an average score of ≥ 3 for daily abdominal pain. | N=804<br><br>26 weeks | Primary:<br>FDA's endpoint for IBS-C: (proportion of patients with ≥30% improvement from baseline in the average of the daily worst abdominal pain scores and an increase of ≥1 CSBM from baseline for ≥6 out of 12 weeks), proportion of patients with ≥30% improvement from baseline in the weekly average of the daily worst abdominal pain score for ≥9 out of 12 weeks, proportion of patients with ≥3 CSBMs and an increase of≥1 CSBM from baseline, and | Primary:<br>A greater proportion of patients treated with linaclotide were FDA end point responders compared to placebo at 12 weeks (33.7 vs 13.9%; difference, 19.8%; 95% CI, 14.0 to 25.5).<br><br>Compared to placebo, a greater proportion of patients treated with linaclotide experienced ≥30% improvement from baseline in abdominal pain (48.9 vs 34.5%; P<0.0001) and increase in weekly CSBM rate of ≥1 (47.6 vs 22.6%; P<0.0001) for at least 6 of 12 weeks.<br><br>A greater proportion of patients treated with linaclotide experienced ≥30% improvement from baseline in the average daily worst abdominal pain for at least 9 out of 12 weeks compared to placebo (38.9 vs 19.6%; difference, 19.3%; 95% CI, 13.2 to 25.4).<br><br>A greater proportion of patients treated with linaclotide experienced ≥3 CSBMs and an increase of ≥1 CSBM from baseline for at least 9 out of 12 weeks compared to placebo (18.0 vs 5.0%; difference, 13.0%; 95% CI, 8.7 to 17.3).<br><br>A greater proportion of patients treated with linaclotide met all endpoints (experienced ≥30% improvement from baseline in the average daily worst abdominal pain as well as ≥3 CSBMs and an increase of ≥1 CSBM from baseline) for at least 9 out of 12 weeks compared to placebo (12.7 vs 3.0%; difference, 9.7%; 95% CI, 6.1 to 13.4).<br><br>Secondary:<br>For at least 6 out of 12 weeks, a greater proportion of patients treated with linaclotide compared to placebo experienced from baseline ≥30% improvement in worst abdominal pain (48.9 vs 34.5%; P<0.0001), ≥30% improvement in abdominal discomfort (47.6 vs 30.8%; P<0.0001), ≥30% improvement in abdominal bloating (42.9 vs 23.8%; |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| | | | proportion of patients meeting all endpoints for ≥9 out of 12 weeks<br><br>Secondary:<br>12 and 26-week change-from-baseline in the following: worst abdominal pain, abdominal discomfort, abdominal bloating, stool frequency, stool consistency and severity of straining, abdominal fullness, abdominal cramping, IBS symptom severity, constipation severity, adequate relief of IBS-C symptoms, degree of relief of IBS symptoms and treatment satisfaction | P<0.0001), ≥30% improvement in abdominal bloating (42.4 vs 25.1%; P<0.0001), ≥1 CSBMs each week (47.6 vs 22.6%; P<0.0001), ≥2 SBMs each week (55.4 vs 27.8%; P<0.0001), BSFS ≥3 each week (80.3 vs 61.1% P<0.0001), and a mean weekly percent of SBM straining score ≤3 (82.4 vs 70.6% P<0.0001).<br><br>For at least 13 out of 26 weeks, a greater proportion of patients treated with linaclotide compared to placebo experienced from baseline ≥30% improvement in worst abdominal pain (49.1 vs 31.3%; P<0.0001), ≥30% improvement in abdominal discomfort (48.1 vs 28.8%; P<0.0001), ≥1 CSBMs each week (43.6 vs 18.6%; P<0.0001), ≥2 SBMs each week (49.6 vs 21.6%; P<0.0001) and mean weekly percent of SBM with BSFS ≥3 (81.0 vs 62.1% P<0.0001).<br><br>A greater proportion of patients treated with linaclotide experienced treatment satisfaction measured by 1 to 3 on relief scale[†] for 12 out of 12 weeks or 1 to 2 for 6 out of 12 weeks compared to placebo (45.4 vs 21.1%; P<0.001).<br><br>A greater proportion of patients treated with linaclotide experienced treatment satisfaction measured by 1 to 3 on relief scale[†] for 26 out of 26 weeks or 1 to 2 for 13 out of 26 weeks compared to placebo (37.9 vs 17.6%; P<0.0001). |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| Rao et al[9]<br><br>Linaclotide 290 µg QD at least 30 minutes before breakfast<br><br>vs.<br><br>placebo | DB, MC, PC, PG, RCT<br><br>Men and women aged 18 years or older who met modified Rome II criteria for IBS-C, had < 3 SBM per week and ≥ 1 of the following symptoms: straining, hard stools, sensation of incomplete evacuation. Patients, during baseline period, reported an average score of ≥ 3 for daily abdominal pain | 800<br><br>12-weeks | Primary:<br>FDA's endpoint for IBS-C: (proportion of patients with ≥30% improvement from baseline in the average of the daily worst abdominal pain scores and an increase of ≥1 CSBM from baseline for ≥6 out of 12 weeks), proportion of patients with ≥30% improvement from baseline in the weekly average of the daily worst abdominal pain score for ≥9 out of 12 weeks, proportion of patients with ≥3 CSBMs and an increase of≥1 CSBM from baseline, and proportion of patients meeting | Primary:<br>A greater proportion of patients treated with linaclotide were FDA endpoint responders compared to placebo from baseline for at least 6 out of 12 weeks (33.6 vs 21.0%; difference, 12.6%; 95% CI, 6.5 to 18.7).<br><br>Compared to placebo, a greater proportion of patients treated with linaclotide experienced ≥30% improvement from baseline in abdominal pain (50.1 vs 37.5%; P<0.0001) and increase in weekly CSBM rate of ≥1 (48.6 vs 29.6%; P<0.0001) for at least 6 of 12 weeks.<br><br>A greater proportion of patients treated with linaclotide experienced ≥30% improvement from baseline in the average daily worst abdominal pain for at least 9 out of 12 weeks compared to placebo (34.3 vs 27.1%; difference, 7.2%; 95% CI, 0.9 to 13.6).<br><br>A greater proportion of patients treated with linaclotide experienced ≥3 CSBMs and an increase of ≥1 CSBM from baseline for at least 9 out of 12 weeks compared to placebo (19.5 vs 6.3%; difference, 13.2%; 95% CI, 8.6 to 17.7).<br><br>A greater proportion of patients treated with linaclotide met all endpoints (experienced ≥30% improvement from baseline in the average daily worst abdominal pain as well as ≥3 CSBMs and an increase of ≥1 CSBM from baseline) for at least 9 out of 12 weeks compared to placebo (12.1 vs 5.1%; difference, 7.0%; 95% CI, 3.2 to 10.9).<br><br>Secondary:<br>For at least 6 out of 12 weeks, a greater proportion of patients treated with linaclotide compared to placebo experienced from baseline ≥30% improvement in abdominal pain (50.1 vs 37.5%; P=0.0003), ≥30% improvement in abdominal discomfort (48.1 vs 37.0%; P=0.0013), ≥30% improvement in abdominal bloating (43.5 vs 29.9%; P<0.0001), ≥1 CSBMs each week (48.6 vs 29.6%; P<0.0001), ≥2 SBMs each week |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| | | | all endpoints for ≥9 out of 12 weeks<br><br>Secondary:<br>12 and 26-week change-from-baseline in the following: worst abdominal pain, abdominal discomfort, abdominal bloating, stool frequency, stool consistency and severity of straining, abdominal fullness, abdominal cramping, IBS symptom severity, constipation severity, adequate relief of IBS-C symptoms, degree of relief of IBS symptoms and treatment satisfaction | (57.5 vs 29.4%; P<0.0001), a mean weekly percent of SBM with BSFS ≥3 (79.4 vs 60.7% P<0.0001) and a mean weekly percent of SBM straining score ≤3 (85.3 vs 71.7% P<0.0001).<br><br>A greater proportion of patients treated with linaclotide experienced treatment satisfaction measured by 1 to 3 on relief scale† for 12 out of 12 weeks or 1 to 2 for 6 out of 12 weeks compared to placebo (41.2 vs 24.3%; P<0.001). |
| Drossman et al[10]<br>(Study 0431 and 0432) | Two DB, MC, PC, PG, RCT | N=1,154 | Primary:<br>Overall | Primary:<br>A patient was considered an overall responder if they were monthly |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| Lubiprostone 8 µg BID<br><br>vs<br><br>placebo | Patients ≥18 years of age with a with a diagnosis of IBS-C, colonoscopy or sigmoidoscopy based on age | 12 weeks | responder status<br><br>Secondary: Monthly responder status, weekly responder rate, and symptom rating changes from baseline for abdominal discomfort/pain, bloating, BM and SBM frequency, stool consistency, degree of straining, constipation severity and symptom relief, safety | responders for at least two of the three months of the study. Monthly responders were defined as those who rated their IBS symptoms as being at least moderately relieved for all four weeks of the month or significantly relieved for at least 2 weeks of the month, with no ratings of moderately or severely worse. A weekly responder was defined as reporting either moderately or significantly relieved for that week.<br><br>In a combined (ITT with LOCF) analysis, the total number of overall responders in the lubiprostone group was significantly higher than that in the placebo group (17.9% vs 10.1% P=0.001).<br><br>Secondary:<br>When each study was evaluated independently, there was a significantly higher overall response rate in favor of lubiprostone compared to placebo for both trials (P=0.009 and P=0.031, respectively). There was a statistically significant difference in montly responder rates between treatment groups for Study 0431 month two (P=0.016) and Study 0432 month 3 (P=0.026).<br><br>The combined percentage of monthly responders using LOCF was significantly higher among those treated with lubiprostone compared with those treated with placebo at month two (18.3% vs 11.4%, P=0.003) and at month three (22.0% vs 14.5%, P=0.003). There was a trend towards a significance at month one (10.8% vs 7.5%, P=0.078).<br><br>For weekly responder rates, significant improvements were seen in the combined analysis with lubiprostone compared to placebo at weeks 2, 4, 5, 6, 10 and 12 (P≤0.030).<br><br>Mean improvement from baseline in abdominal discomfort/pain was significantly greater in lubiprostone-treated patients compared with placebo-treated patients at month two (−0.43 vs −0.35, P=0.039) and month three (−0.45 vs −0.36, P=0.028).<br><br>Mean improvement from baseline in the lubiprostone group was |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| | | | | significantly greater than the mean observed with placebo for abdominal bloating at month two (P=0.044).<br><br>Mean improvement from baseline in the lubiprostone group was significantly greater than the mean observed with placebo for BM frequency at month one (P=0.021).<br><br>Mean improvement from baseline in the lubiprostone group was significantly greater than the mean observed with placebo for stool consistency at months one, two and three, (P≤0.022).<br><br>Mean improvement from baseline in the lubiprostone group was significantly greater than the mean observed with placebo for degree of straining at months one and two (P≤0.013).<br><br>A total of 11 serious adverse events were reported during the trials, seven (1%) in the lubiprostone group and four (1%) in the placebo group. One serious adverse event was considered possibly related to lubiprostone. One patient randomized to the lubiprostone treatment arm died during the study. The investigator did not consider the patient's death as related to administration of lubiprostone given the patient's longstanding medical history.<br><br>No clinically significant differences between the two patient groups were detected in the analyses of laboratory values, vital signs or physical examination. |
| Irritable Bowel Syndrome with Diarrhea | | | | |
| Andresen et al[11]<br><br>Alosetron 1 mg BID or cilansetron* 2 mg TID<br><br>vs<br><br>placebo or mebeverine* | MA, SR of 14 RCTs<br><br>Trials evaluated alosetron or cilansetron on relief of abdominal pain | N=7,487<br><br>Duration varied | Primary:<br>Treatment efficacy and constipation rate<br><br>Secondary:<br>Not reported | Primary:<br>Treatment with alosetron or cilansetron was more effective than the comparators in achieving global improvement of IBS symptoms (pooled RR, 1.60; 95% CI, 1.49 to 1.72; P value not reported) and relief of abdominal pain and discomfort (pooled RR, 1.30; 95% CI, 1.22 to 1.39; P value not reported). Benefits were apparent in both male and female patients. |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| | and discomfort and global improvement of IBS symptoms in male and female patients with nonconstipated or diarrhea-predominant IBS | | | In a subgroup analysis regarding global improvement of IBS symptoms, there was a significant subgroup treatment interaction for the treatment duration with a higher RR for this efficacy end point in the 12 week subgroup compared with the 24 week subgroup (1.23; 95% CI, 1.05 to 1.44; P value not reported).<br><br>In a subgroup analysis regarding relief of abdominal pain and discomfort, there was a lower RR in the alosetron subgroup (1.23; 95% CI, 1.15 to 1.32; P value not reported) compared to the cilansetron subgroup (1.43; 95% CI, 1.29 to 1.59; P value not reported). In addition, there was a lower RR for studies including women only compared to studies including both sexes or men only (0.88; 95% CI, 0.76 to 0.98; P value not reported).<br><br>Alosetron and cilansetron were more likely to cause constipation (pooled RR, 4.28; 95% CI, 3.28 to 5.60; P value not reported) but less constipation was reported in patients with diarrhea-predominant IBS than in mixed IBS.<br><br>Nine (0.2%) patients administering alosetron or cilansetron had possible ischemic colitis vs none in the control group.<br><br>Secondary:<br>Not reported |
| Cremonini et al[12]<br><br>Alosetron 2 mg QD<br><br>vs<br><br>placebo or mebeverine* 135 mg TID | MA of 6 DB, MC, PG, RCTs<br><br>Trials assessed the effect of alosetron on symptoms of IBS in male and female patients with IBS | N=3,529<br><br>12 weeks | Primary:<br>Treatment effect on primary outcome measure and adverse effects<br><br>Secondary:<br>Not reported | Primary:<br>The pooled adjusted OR and 95% CI for a positive outcome from all studies was 1.81 and 1.57 to 2.10 (P<0.0001). All trials reported a disappearance of beneficial effects of alosetron compared to placebo after discontinuation of treatment.<br><br>Compared to placebo, patients treated with alosetron were 5.64 times more likely to report constipation (P<0.0001) and 1.7 times more likely to report any adverse event (P<0.0001). Other side-effects reported with a frequency >5% in patients treated with alosetron included nausea, abdominal pain, other gastrointestinal complaints (not |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| | | | | described), and headache.<br><br>Secondary:<br>Not reported |
| Ford et al[13]<br><br>Alosetron 0.1-8 mg BID, cilansetron* 3 mg BID, tegaserod* 0.5-12 mg BID, cisapride 5 TID, or renzapride* 1-4 mg QD<br><br>vs<br><br>placebo | MA, SR of 29 RCTs<br><br>Trials examined the effect of 5-$HT_3$ antagonists and 5-$HT_4$ agonists in male and females ≥16 years of age with IBS | N=17,501<br><br>Duration varied | Primary:<br>Global IBS symptoms or abdominal pain after cessation of therapy<br><br>Secondary:<br>Efficacy according to specific agents, IBS subtype according to predominant stool pattern, gender, and dose and duration of therapy; and adverse events | Primary:<br>Efficacy of 5-$HT_3$ antagonists:<br>Evaluation of 11 trials (N=7,216) demonstrated that symptoms persisted in 49% (2,118/4,330) of patients receiving alosetron or cilansetron compared to 64% (1,848/2,886) of patients receiving placebo after treatment was stopped (RR, 0.78; 95% CI, 0.71 to 0.86; P value not reported).<br><br>Efficacy of 5-$HT_4$ agonists:<br>Evaluation of 11 trials (N=9,242) demonstrated that symptoms persisted in 55.0% (3,301/6,041) of patients receiving tegaserod compared to 63.5% (2,032/3,201) of patients receiving placebo after treatment was stopped (RR, 0.85; 95% CI, 0.80 to 0.90; P value not reported).<br><br>Efficacy of mixed 5-$HT_3$ antagonists/5-$HT_4$ agonists:<br>Evaluation of seven trials (N=1,043) demonstrated that symptoms persisted in 64% (449/704) of patients receiving cisapride or renzapride compared to 57% (193/339) of patients receiving placebo after treatment was stopped (RR, 0.94; 95% CI, 0.76 to 1.17; P value not reported).<br><br>Secondary:<br>Efficacy of alosetron:<br>Evaluation of eight trials evaluating alosetron (N=4,987), demonstrated symptoms persisted in 49% (1,576/3,214) and 64% (1,127/1,773) of patients treated with alosetron and placebo (RR, 0.79; 95% CI, 0.69 to 0.90; P value not reported).<br><br>Efficacy of cilansetron:<br>Evaluation of three trials evaluating cilansetron (N=2,229), |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| | | | | demonstrated symptoms persisted in 49% (542/1,116) and 65% (721/1,113) of patients treated with cilansetron and placebo (RR, 0.75; 95% CI, 0.69 to 0.82; P value not reported).<br><br>Efficacy of cisapride:<br>Evaluation of four trials evaluating cisapride (N=317), demonstrated symptoms persisted in 43% (67/157) and 47% (75/160) of patients treated with cisapride and placebo (RR, 0.91, 95% CI, 0.58 to 1.43; P value not reported).<br><br>Efficacy of renzapride:<br>Evaluation of three trials evaluating renzapride (N=726), demonstrated that symptoms persisted in 70% (382/547) and 66% (118/179) of patients treated with renzapride and placebo (RR, 0.99, 95% CI, 0.79 to 1.23; P value not reported).<br><br>Efficacy according to IBS subtype according to predominant stool pattern:<br>Due to lack of evidence no analyses were possible for the treatment effect of alosetron or cilansetron according to predominant bowel habit.<br><br>Tegaserod results were very similar among patients with constipation-predominant IBS and an alternating stool pattern.<br><br>All trials evaluating cisapride had constipation-predominant IBS.<br><br>Sub-group analysis of the treatment effect of renzapride in constipation-predominant patients did not reveal any improvement.<br><br>Efficacy according to gender:<br>With regards to alosetron treatment, there was reduced heterogeneity in male patients, however in female patients; doses of 2 mg twice daily trended towards higher efficacy compared to males. The authors note this result may be due to a type II error and the difference was not statistically significant (P=0.39). |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| | | | | There were an insufficient number of trials to allow for sub-group analyses of cilansetron treatment by gender.<br><br>There was a greater treatment effect for tegaserod in male IBS patients, and the difference was statistically significant (P=0.03); although as there were only two studies used in this evaluation, no definite conclusions can be made.<br><br>Sub-group analysis of treatment effect of cisapride by gender was not reported.<br><br>Sub-group analysis according to gender did not reveal any improvement in the treatment effect of renzapride.<br><br>Efficacy according to dose and duration:<br>There were an insufficient number of trials to allow for any sub-group analysis of cilansetron treatment.<br><br>The dose of tegaserod used and duration of therapy had no significant effect on the RR of persisting symptoms.<br><br>All studies evaluating cisapride used the dose of 5 mg three times daily.<br><br>Sub-group analysis according to dose did not reveal any improvement in the treatment effect of renzapride.<br><br>Adverse events:<br>Evaluation of seven trials evaluating alosetron (N=4,607), demonstrated that adverse events were reported in 64% (1,877/2,915) and 55% (930/1,692) of patients treated with alosetron and placebo (RR, 1.19; 95% CI, 1.09 to 1.30; P value not reported).<br><br>None of the cilansetron studies reported adverse events. |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| | | | | Evaluation of three trials evaluating tegaserod (N=2,827), demonstrated that adverse events were reported in 51% (724/1,423) and 47% (662/1,404) of patients treated with tegaserod and placebo (RR, 1.07; 95% CI, 1.0 to 1.15; P value not reported).<br><br>None of the cisapride studies reported adverse events.<br><br>Only one of the trials evaluating renzapride provided total numbers of patients reporting adverse events (68% vs 67% with placebo; P value not reported). |
| Lembo et al[14,15]<br>IBS 3001<br><br>Eluxadoline 75 mg BID<br><br>vs<br><br>eluxadoline 100 mg BID<br><br>vs<br><br>placebo BID | DB, MC, PC, PG, RCT<br><br>Patients from 18 to 80 years of age with a documented diagnosis of IBS-D (by Rome III criteria), daily average WAP > 3.0 (on a 10-point scale), average BSS score of ≥ 5.5 and at least five days with a BSS score of ≥ 5 on BSS scale (on a 7-point scale), IBS-D global symptom score ≥ 2.0 (on a 4-point scale) | N=1,282<br><br>Treatment phase=52 weeks | Primary:<br>Evaluation of composite responders over the initial 12 weeks (for the FDA) and initial 26 weeks (for the EMA) of DB treatment (composite responders were defined as patients meeting the daily response criteria [pain and stool consistency] for ≥ 50% of the days with diary entries on the following two criteria: daily pain response [improvement in | Primary:<br>The proportion of composite responders for the eluxadoline 75 mg (23.9%; P=0.014) and 100 mg (25.1%; P=0.004) groups had a statistically greater response than placebo (17.1%) over weeks 1 to 12. In addition, the proportion of composite responders for the 100 mg group (29.3%, P<0.001) had a statistically greater response than placebo (19.0%) over weeks 1 to 26.<br><br>Secondary:<br>The proportion of pain responders was numerically higher in the eluxadoline 75 mg (43.2%; P=0.284) and 100 mg (42.4%; P=0.404) groups compared to placebo (39.6%) over weeks 1 to 12 but not statistically significant. This was the same for weeks 1 to 26.<br><br>The proportion of stool consistency responders was statistically significant in the eluxadoline 75 mg group (P=0.008) and 100 mg group (P<0.001) compared with placebo for weeks 1 to 12 and the eluxadoline 100 mg group only (P=0.001) during weeks 1 to 26.<br><br>The proportion of IBS-D global symptom responders was statistically significant compared with placebo for the 75 mg group (P=0.048) from weeks 1 to 12 and from weeks 21 to 24 (P=0.024).<br><br>The proportion of patients who reported adequate relief of their IBS symptoms was statistically significant for the eluxadoline 100 mg group |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| | | | WAP scores in the past 24 hours by ≥ 30% compared to baseline] and daily stool consistency response [BSS score < five or the absence of a bowel movement if accompanied by ≥ 30% improvement in WAP compared to baseline])<br><br>Secondary: Pain response and stool consistency response based on improvement from baseline in daily abdominal pain scores and stool consistency scores, IBS-D global symptom response (i.e., symptom score of 0 [none] or 1 [mild] or a daily IBS-D global symptom score | (P≤ 0.005) compared with placebo over weeks 1 to 12 and weeks 1 to 26. This was also apparent for the eluxadoline 75 mg group (P=0.008) compared to placebo over weeks 1 to 12.<br><br>The risks for frequency of bowel movements and urgency episodes were noted to be significantly lower for the eluxadoline 75 mg and 100 mg groups throughout week 26 compared to placebo using a longitudinal model. No P values were reported.<br><br>The proportion of IBS-QOL total score responders for the eluxadoline 100 mg group was higher than placebo at most weeks evaluated and significantly higher than placebo (P<0.05) at weeks 4 and 8. The proportion of IBS-QOL total score responders for the eluxadoline 75 mg group was numerically higher or similar to placebo but not significantly different.<br><br>The overall incidence of AEs was similar across treatment groups with most being mild to moderate in severity. GI symptoms were the most commonly reported AEs and included constipation, nausea, abdominal pain, distension, vomiting, flatulence and diarrhea. |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| | | | improved by ≥ 2.0 compared to the baseline average), IBS-QOL response (i.e., at least a 14-point improvement in IBS-QOL total score from baseline to the applicable visit), IBS-AR response (i.e., weekly response of 'yes' to adequate relief of their symptoms for ≥ 50% of the total weeks during the interval), abdominal bloating and discomfort, bowel function and QOL response with IBS-QOL | |
| Lembo et al[14,15]<br>IBS 3002<br><br>Eluxadoline 75 mg BID<br><br>vs | DB, MC, PC, PG, RCT<br><br>Patients from 18 to 80 years of age with a | N=1,145<br><br>Treatment phase=26 weeks | Primary:<br>Evaluation of composite responders over the initial 12 weeks (for the | Primary:<br>The proportion of composite responders for the eluxadoline 75 mg and 100 mg groups had a statistically greater response than placebo for weeks 1 to 12 (P<0.001) and weeks 1 to 26 (P=0.001). The onset of response for both eluxadoline treatment groups occurred within the first week of dosing. |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| eluxadoline 100 mg BID<br><br>vs<br><br>placebo BID | documented diagnosis of IBS-D (by Rome III criteria), daily average WAP > 3.0 (on a 10-point scale), average BSS score of ≥ 5.5 and at least five days with a BSS score of ≥ 5 on BSS scale (on a 7-point scale), IBS-D global symptom score ≥ 2.0 (on a 4-point scale) | | FDA) and initial 26 weeks (for the EMA) of DB treatment (composite responders were defined as patients meeting the daily response criteria [pain and stool consistency] for ≥ 50% of the days with diary entries on the following two criteria: daily pain response [improvement in WAP scores in the past 24 hours by ≥ 30% compared to baseline] and daily stool consistency response [BSS score < five or the absence of a bowel movement if accompanied by ≥ 30% improvement in WAP compared to baseline]) | Secondary:<br>The proportion of pain responders for the 75 mg and 100 mg treatment groups was numerically higher than placebo, but not statistically significant, over weeks 1 to12 and weeks 1 to 26.<br><br>The proportion of stool consistency responders for the 75 mg and 100 mg eluxadoline treatment groups was statistically significant (P<0.001) versus placebo over weeks 1 to 12 and weeks 1 to 26. The proportion of stool consistency responders was significantly higher than placebo for the 75 mg (P<0.05) and 100 mg eluxadoline groups (P<0.001) over each 4-week interval.<br><br>The proportion of IBS-D global symptom responders for the 75 mg and 100 mg eluxadoline treatment groups was statistically greater than that of placebo over weeks 1 to 12 (P<0.001) and weeks 1 to 26 (P≤0.012).<br><br>The proportion of IBS-AR responders for the 75 mg and 100 mg treatment groups was statistically greater compared to placebo (P≤ 0.013) over weeks 1 to 12 and weeks 1 to 26.<br><br>When analyzed over time using a longitudinal model, daily abdominal bloating scores were significantly lower than placebo for the 100 mg treatment group at weeks 16, 20, 24, and 26; daily abdominal discomfort scores were significantly lower than placebo for both eluxadoline treatment groups at each time point evaluated through week 26 (no P values reported).<br><br>When analyzed over time using a longitudinal model, the risks for frequency of bowel movements and urgency episodes were significantly lower than placebo for both eluxadoline treatment groups at each time point evaluated through week 26 (no P values reported).<br><br>Patients in both eluxadoline treatment groups had significantly better HRQOL than placebo patients at each time point assessed based on a |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| | | | Secondary: Pain response and stool consistency response based on improvement from baseline in daily abdominal pain scores and stool consistency scores, IBS-D global symptom response (i.e., symptom score of 0 [none] or 1 [mild] or a daily IBS-D global symptom score improved by ≥ 2.0 compared to the baseline average), IBS-QOL response (i.e., at least a 14-point improvement in IBS-QOL total score from baseline to the applicable visit), IBS-AR response (i.e., weekly response of 'yes' to | longitudinal analysis of IBS-QOL total scores.<br><br>GI AEs were the most commonly reported AEs and included constipation, nausea, vomiting, abdominal pain, distension, and flatulence. Constipation occurred in < 10% of patients in each treatment group, with most events being mild or moderate in severity.<br><br>Pooled data from IBS 3001 and IBS 3002 trials resulted in five cases out of 1,666 patients (0.3%) for pancreatitis and eight cases out of 1,666 patients (0.5%) for spasm of the sphincter of Oddi. No deaths were reported during these studies. |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| | | | adequate relief of their symptoms for ≥ 50% of the total weeks during the interval), abdominal bloating and discomfort, bowel function and QOL response with IBS-QOL | |
| Pimentel et al[16] (TARGET 1 & TARGET 2)<br><br>Rifaximin 550 mg TID<br><br>vs<br><br>placebo | DB, MC, PC, PG, RCT<br><br>Patients ≥18 years of age with a diagnosis of IBS and did not have adequate relief of global IBS symptoms of IBS-related bloating at both the time of screening and randomization | N=1,260<br><br>14 days | Primary:<br>Proportion of patients who had adequate relief of global IBS symptoms for at least two of the four weeks during the primary evaluation period (weeks three to six)<br><br>Secondary:<br>Proportion of patients who had adequate relief of IBS-related bloating during the primary evaluation | Primary:<br>Significantly more patients in the rifaximin group than in the placebo group met the criteria for the primary end point of adequate relief of global IBS symptoms for at least two of the first four weeks after treatment (0.8% vs 31.2%; P=0.01 in TARGET 1; 40.6% vs 32.2%; P=0.03 in TARGET 2; 40.7% vs 31.7%; P<0.001 in both combined).<br><br>Secondary:<br>Significantly more patients in the rifaximin group than in the placebo group met the criteria for the key secondary end point, adequate relief of IBS-related bloating for at least two of the first four weeks after treatment (39.5% vs 28.7%; P=0.005 in TARGET 1; 41.0% vs 31.9%; P=0.02 in TARGET 2; 40.2% vs 30.3%; P<0.001, in both combined).<br><br>On the basis of daily assessments of IBS-related bloating as rated on a 7-point scale during the same primary evaluation period, a significantly greater proportion of patients in the rifaximin group than in the placebo group had relief (39.2% vs 32.5%; P=0.05 in TARGET 1; 43.5% vs 30.9%; P<0.001 in TARGET 2; 41.3% vs 31.7%; P<0.001, in both combined)<br><br>On the basis of daily assessments of IBS symptoms, the proportion of |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| | | | period, proportion of patients who had relief was determined from the patients' daily assessments of IBS symptoms, bloating, and abdominal pain and discomfort | patients with a response to treatment during the primary evaluation period, was significantly greater in the rifaximin group than in the placebo group (42.7% vs 30.6%; P<0.001 in TARGET 1; 37.8% vs 28.4%; P=0.007 in TARGET 2; 40.2% vs 29.5%; P<0.001 in both combined).<br><br>A significantly greater proportion of patients in the rifaximin group than in the placebo group had relief of IBS-related abdominal pain and discomfort during the primary evaluation period (44.3% vs 36.3%; P=0.03 in TARGET 1; 42.9% vs 34.4%; P=0.02 in TARGET 2)<br><br>In an assessment of the composite end point of abdominal pain or discomfort and loose or watery stools, significantly more patients in the rifaximin group than in the placebo group had relief during the primary evaluation period (46.6% vs 38.5%; P=0.04 in TARGET 1; 46.7% vs 36.3%; P=0.008 in TARGET 2), and a significantly greater proportion of patients in the rifaximin group had relief with respect to the individual components of this end point (no P value reported). |

*Agent is not available for use in the United States.
Drug regimen abbreviations: BID=twice daily, QD=once daily, TID=three times a day
Study abbreviations: DB=double-blind, MA=meta-analysis, MC=multicenter, PC=placebo-controlled, PG=parallel-group, RCT=randomized controlled trial, SR=systematic review
Miscellaneous abbreviations: 5-HT=serotonin, AE=adverse event, BM=bowel movement, BSFS=Bristol Stool Form Scale, BSS= Bristol Stool Scale, CI=confidence interval, CSBM=complete spontaneous bowel movement, EMA=European Medicines Agency, FDA=Food and Drug Administration, GI=gastrointestinal, IBS=irritable bowel syndrome, IBS-AR=IBS-adequate relief, IBS-C=irritable bowel syndrome with constipation, IBS-D=irritable bowel syndrome with diarrhea, IBS-QOL=IBS-quality of life, IBS-SSS=IBS-Symptom Severity Score, ITT=intention-to-treat, LOCF=Last Observation Carried Forward, OR=odds ratio, QoL=quality of life, RR=relative risk, SBM=spontaneous bowel movement, WAP=worst abdominal pain

## Special Populations

**Table 5a. IBS-C Agents – Special Populations**[1-2]

| Generic Name | Population and Precaution | | | | |
|---|---|---|---|---|---|
| | Elderly/ Children | Renal Dysfunction | Hepatic Dysfunction | Pregnancy Category | Excreted in Breast Milk |
| Linaclotide | No dosage adjustment is required in the elderly.<br><br>Safety and effectiveness in pediatric patients have not been established.<br><br>Contraindicated in children <6 years of age. | No dosage adjustment is required. | No dosage adjustment is required. | C | Unknown; use with caution. |
| Lubiprostone | Clinical studies did not include sufficient numbers of patients aged 65 years and over to determine whether elderly patients respond differently from younger patients.<br><br>Safety and effectiveness in pediatric patients have not been established. | No dosage adjustment is required in patients with renal impairment | Starting dose should be reduced in patients with moderate or severe dysfunction (Child-Pugh class B or C).<br><br>No dose adjustment require for mild hepatic dysfunction (Child-Pugh class A). | C | Unknown; use with caution. |

**Table 5a. IBS-D Agents – Special Populations**[3-5]

| Generic Name | Population and Precaution | | | | |
|---|---|---|---|---|---|
| | Elderly/ Children | Renal Dysfunction | Hepatic Dysfunction | Pregnancy Category | Excreted in Breast Milk |
| Alosetron | Postmarketing experience suggests that elderly patients may be at greater risk for complications of constipation; appropriate caution and follow-up should be exercised<br><br>Safety and efficacy in the pediatric patients | No dosage adjustment required. | Use with caution in patients with mild or moderate hepatic impairment.<br><br>Use is contraindicated in patients with severe hepatic | B | Unknown; use with caution. |

| Generic Name | Population and Precaution | | | | |
|---|---|---|---|---|---|
| | Elderly/ Children | Renal Dysfunction | Hepatic Dysfunction | Pregnancy Category | Excreted in Breast Milk |
| | have not been established. | | impairment. | | |
| Eluxadoline | No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients.<br><br>Safety and efficacy in children have not been established | Not studied in renal dysfunction. | Increased concentration in mild or moderate impairment. Reduce dose to 75 mg twice daily in these patients.<br><br>Contraindicated in severe hepatic impairment. | Not studied in pregnancy | Unknown; use with caution |
| Rifaximin | No overall differences in safety or effectiveness were observed between elderly and younger subjects for a diagnosis of HE or IBS-D.<br><br>Clinical studies with did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently than younger subjects for a diagnosis of TD.<br><br>FDA approved for pediatric patients ≥12 years of age for a diagnosis of TD.<br><br>Safety and efficacy in pediatric patients have not been established for a diagnosis of HE or IBS-D. | Not studied in renal dysfunction. | No dosage adjustment is recommended for mild, moderate or severe hepatic dysfunction (Child-Pugh class A, B, or C) | Not studied in pregnancy | Unknown; use with caution |

HE=hepatic encephalopathy, IBS-D=irritable bowel syndrome with diarrhea, TD=traveler's diarrhea

## Adverse Drug Events

**Table 6a. IBS-C Agents – Adverse Drug Events**[1-2,20]

| Adverse Event (%) | Linaclotide | Lubiprostone |
|---|---|---|
| Abdominal pain (mild) | 7 | 4 to 8 |
| Chest pain, unspecified (moderate) | - | 2 |
| Diarrhea | 16 to 20 (mild) 2 (severe) | 7 to 12 |
| Dyspepsia (mild) | 1 to 1.9 | - |
| Dyspnea (moderate) | - | ≤3 |
| Dizziness (mild) | ≤4 | 1 to 3 |
| Fatigue (mild) | 1 to 1.9 | 2 |
| Flatulence (mild) | 4 to 6 | 4 to 6 |
| Gastroesophageal reflux (mild) | 1 to 1.9 | - |
| Headache (mild) | - | 2 to 11 |
| Infection (mild) | ≤5 | - |
| Nausea (mild) | - | 8 to 29 |
| Peripheral edema (moderate) | - | 3 |
| Sinusitis (mild) | ≤3 | - |
| Vomiting (mild) | 1 to 1.9 | ≤3 |

-Adverse event not reported or ≤1%

**Table 6b. IBS-D Agents – Adverse Drug Events**[3-5,20]

| Adverse Event (%) | Alosetron | Eluxadoline | Rifaximin |
|---|---|---|---|
| Abdominal pain (mild) | - | 6 to 7 | 6 to 9 |
| Anemia (moderate) | - | - | 8 |
| Arthralgia (mild) | - | - | 6 |
| Ascites (moderate) | - | - | 11 |
| Bronchospasm (severe) | - | 3 | - |
| Constipation (moderate) | 11 to 29 | 7 to 8 | - |
| Depression (moderate) | - | - | 7 |
| Dizziness (mild) | - | 3 | 13 |
| Dyspnea (moderate) | - | - | 6 |
| Elevated hepatic enzymes (moderate) | - | ≤3 | 2 |
| Fatigue (mild) | - | 3 | 12 |
| Fever (mild) | - | - | 6 |
| Gastroesophageal reflux (mild) | - | ≤3 | - |
| Headache (mild) | - | - | 10 |
| Infection (mild) | - | 3 to 5 | <5 |
| Nausea (mild) | - | 7 to 8 | 2 to 14 |
| Peripheral edema (moderate) | - | - | 15 |
| Pharyngitis (mild) | - | 3 | 7 |
| Proteinuria (severe) | - | - | <2 |
| Pruritus (mild) | - | - | 9 |
| Rash, unspecified (mild) | - | - | 5 |
| Tinnitus (mild) | - | - | <2 |
| Vertigo (mild) | - | - | <5 |
| Vomiting (mild) | - | 4 | - |
| Wheezing (moderate) | - | ≤2 | - |

-Adverse event not reported or ≤1%

## Contraindications

**Table 7a. IBS-C Agents – Contraindications**[1-2]

| Contraindications | Linaclotide | Lubiprostone |
|---|---|---|
| Hypersensitivity to the active drug or any excipient | a | a |
| Mechanical gastrointestinal obstruction, known or suspected | | a |
| Pediatric patients <6 years of age | a | |

**Table 7b. IBS-D Agents – Contraindications**[3-5]

| Contraindications | Alosetron | Eluxadoline | Rifaximin |
|---|---|---|---|
| Active constipation | a | | |
| Alcoholism | | a | |
| Concomitant use of Fluvoxamine | a | | |
| History of chronic, severe constipation or sequelae from constipation | a | a | |
| History of pancreatitis or structural diseases of the pancreas, including known or suspected pancreatic duct obstruction | | a | |
| History of severe bowel disorders (intestinal obstruction, stricture, toxic megacolon, GI perforation and/or adhesions, ischemic colitis, impaired intestinal circulation, thrombophlebitis, or hypercoagulable state, Crohn's Disease, Ulcerative Colitis, Diverticulitis) | a | | |
| History of severe hepatic impairment (Child-Pugh C) | a | a | |
| Hypersensitivity to the active drug or any excipient | a | a | a |
| Hypersensitivity to rifamycin antimicrobial agents | | | a |
| Known or suspected biliary duct obstruction; or sphincter of Oddi disease or dysfunction. | | a | |
| Known or suspected mechanical GI obstruction | | a | |

GI=gastrointestinal

## Warnings/Precautions

**Table 8a. IBS-C Agents – Warnings and Precautions**[1-2]

| Warnings/Precautions | Linaclotide | Lubiprostone |
|---|---|---|
| Confirm the absence of a mechanical gastrointestinal obstruction prior to initiating therapy | | a |
| Diarrhea has been reported; do not prescribe to patients that have severe diarrhea; use is not recommended in patients that experience severe diarrhea; discontinue use if severe diarrhea develops | a | a |
| Dyspnea has been reported; use with caution | | a |
| Nausea has been reported; take with food to reduce symptoms | | a |
| Pediatric risk; avoid use in patients 6 to 17 years of age; contraindicated in patients <6 years of age | a | |

**Table 8b. IBS-D Agents – Warnings and Precautions**[3-5]

| Warnings/Precautions | Alosetron | Eluxadoline | Rifaximin |
|---|---|---|---|
| *C. difficile*-associated diarrhea (CDAD) has been reported with use of all antibiotic agents and ranges from mild to fatal colitis; if CDAD is suspected or confirmed, non-C. difficile antibiotics may have to be discontinued. | | | a |
| Concomitant use with P-glycoprotein Inhibitors can increase the systemic exposure of drug; use caution when prescribing with a P-glycoprotein inhibitor. | | | a |
| Constipation and other serious complications, including obstruction, ileus, impaction, toxic megacolon, and secondary bowel ischemia have been reported; discontinue use if constipation develops. | a | | |
| Prescribing in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria. | | | a |
| Ischemic Colitis has been reported and may occur without warning; discontinue use in patients with signs of ischemic colitis; do not resume therapy if ischemic colitis has developed. | a | | |
| Pancreatitis, increased risk for development (independent of sphincter of Oddi Spasm); patients should avoid chronic or acute excessive alcohol; discontinue use if signs and symptoms for pancreatitis develop. | | a | |
| Severe (Child-Pugh C) Hepatic Impairment results in increased expose of drug; use caution in patients with severe impairment. | | | a |
| Sphincter of Oddi Spasm has occurred due to μ-opioid activation; potential to develop pancreatitis or hepatic enzyme elevation associated with acute abdominal pain; consider using another medication if the patient does not have a gallbladder; discontinue use with any signs of spasms; do not restart. | a | a | |
| Travelers' Diarrhea not cause by *E. coli*; medication has not been found to be effective in patients with diarrhea complicated by fever and/or blood in stool by other pathogens. | | | a |

**Blacked Warning for Linaclotide (Linzess®)**[1]

| WARNING |
|---|
| **WARNING: PEDIATRIC RISK**<br>LINZESS is contraindicated in pediatric patients up to 6 years of age; in nonclinical studies, administration of a single, clinically relevant adult oral dose of linaclotide caused deaths due to dehydration in young juvenile mice. Avoid use of LINZESS in pediatric patients 6 through 17 years of age. The safety and efficacy of LINZESS has not been established in pediatric patients less than 18 years of age. |

**Blacked Warning for Alosetron (Lotronex®)**[3]

| WARNING |
|---|
| **WARNING: SERIOUS GASTROINTESTINAL ADVERSE REACTIONS**<br>Infrequent but serious gastrointestinal adverse reactions have been reported with the use of LOTRONEX. These events, including ischemic colitis and serious complications of constipation, have resulted in hospitalization, and rarely, blood transfusion, surgery, and death.<br><br>LOTRONEX is indicated only for women with severe diarrhea-predominant irritable bowel syndrome (IBS) who have not responded adequately to conventional therapy.<br><br>LOTRONEX should be discontinued immediately in patients who develop constipation or symptoms of ischemic colitis. Patients should immediately report constipation or symptoms of ischemic colitis to their prescriber. LOTRONEX should not be resumed in patients who develop ischemic colitis. Patients who have constipation should immediately contact their prescriber if the constipation does not resolve after LOTRONEX is discontinued. Patients with resolved constipation should resume LOTRONEX only on the advice of their treating prescriber. |

**Drug Interactions**

Based on *in vivo* studies, no drug interactions have been reported with linaclotide. No *in vivo* studies have been conducted for lubiprostone, however, based on the results of *in vivo* human microsome studies, there is a low likelihood of pharmacokinetic drug-drug interactions.[1-2]

**Table 9. IBS-D Agents – Drug Interactions**[3-5]

| Generic Name | Interacting Medication or Disease | Potential Result |
|---|---|---|
| Alosetron | Fluvoxamine | Fluvoxamine was associated with a 6-fold increase in alosetron AUC. Concurrent use is contraindicated |
| Alosetron | Moderate CYP1A2 Inhibitors (e.g. quinolones, cimetidine) | Use has not been evaluated, but should be avoided unless clinically necessary due to the potential of an increased AUC for alosetron. |
| Alosetron | Moderate CYP3A4 Inhibitors (e.g. ketoconazole) | Increased AUC of alosetron; use caution with concurrent administration. |
| Alosetron | Strong CYP3A4 inhibitors (e.g. itraconazole) | Co-administration of strong CYP3A4 inhibitors have not been evaluated and should be used with additional caution. |
| Eluxadoline | OATP1B1 Inhibitors | Concurrent use may result in increased eluxadoline exposure; dose reduction for eluxadoline is recommended if concurrent administration is required. |
| Eluxadoline | Strong CYP Inhibitors | Due to incomplete metabolism information available for eluxadoline, it is recommended to monitor for potential increases in eluxadoline concentrations |
| Eluxadoline | Drugs that cause constipation (e.g. loperamide, alosetron) | Increased risk for constipation-related side effects and potential for constipation-related serious adverse effects; avoid use with other drugs that may cause constipation. |
| Rifaximin | Drugs that inhibit P-glycoprotein | Concurrent use may result in increased concentration of rifaximin; the clinical significance of this increase is unknown, but may increase risk for adverse effects. |

AUC=area under the curve, CYP=cytochrome P450

## Dosage and Administration

**Table 10a. IBS-C Agents – Dosing and Administration**[1-2]

| Generic Name | Adult Dose | Pediatric Dose | Availability |
|---|---|---|---|
| Linaclotide | Chronic idiopathic constipation:<br>Capsule: Initial, maintenance, maximum, 145 µg QD on an empty stomach at least 30 minutes prior to the first meal of the day<br><br>Irritable bowel syndrome with constipation in adults:<br>Capsule: Initial, maintenance, maximum, 290 µg QD on an empty stomach at least 30 minutes prior to the first meal of the day<br><br>Capsules may be opened and placed in applesauce or water and may be used via nasogastric or gastric feeding tubes with water. Consume first meal of the day 30 minutes after administration with applesauce. | Safety and effectiveness in pediatric patients have not been established.<br><br>Contraindicated in patients <6 years of age. | Capsule:<br>145 µg<br>290 µg |
| Lubiprostone | Chronic Idiopathic constipation; opioid-induced constipation in chronic non-cancer pain:<br>Capsule: 24 µg BID with food and water*<br><br>Irritable Bowel Syndrome with Constipation in adult women:<br>Capsule: Initial: 8 µg BID with food and water* | Safety and effectiveness in pediatric patients have not been established. | Capsule:<br>8 µg<br>24 µg |

Drug regimen abbreviations: BID=twice daily, QD=once daily
*Initial dose may be reduced in patients with impaired hepatic function.

**Table 10b. IBS-D Agents – Dosing and Administration**[3-5]

| Generic Name | Adult Dose | Pediatric Dose | Availability |
|---|---|---|---|
| Alosetron | Irritable bowel syndrome with diarrhea in adult women:<br>Tablet: initial, 0.5 mg BID; maintenance: 0.5 mg to 1 mg BID. Discontinue use after 4 weeks of treatment at 1 mg BID if control of symptoms has not been achieved. Patients who experience constipation at a dose of 0.5 mg BID may restart therapy at 0.5 mg QD after constipation has resolved. | Safety and efficacy have not been established in pediatric patients. | Tablet:<br>0.5 mg<br>1 mg |
| Eluxadoline | Irritable bowel syndrome with diarrhea in adults:<br>Tablet: Initial, maintenance, maximum, 100 mg BID with food. Use 75 mg BID with food when the patient has no gallbladder, unable to tolerate 100 mg, are receiving concomitant OATP1B1 inhibitors or have mild or moderate hepatic impairment. | Safety and efficacy have not been established in pediatric patients. | Tablet:<br>75 mg<br>100 mg |
| Rifaximin | Irritable bowel syndrome with diarrhea in adults:<br>Tablet: Initial, maintenance, maximum, 550 mg TID for 14 days. Patients who experience recurrence of symptoms may be retreated up | Travelers' diarrhea (12 years of age and older):<br>Tablet: see adult | Tablet:<br>200 mg<br>550 mg |

| Generic Name | Adult Dose | Pediatric Dose | Availability |
|---|---|---|---|
| | to two times with the same dosing regimen (total of 3 treatment courses of 14 days each).<br><br>Reduce the risk of recurrent overt hepatic encephalopathy in adults:<br>Tablet: Initial, maintenance, maximum, 550 mg BID<br><br>Travelers' diarrhea:<br>Tablet: 200 mg TID for 3 days | dosing.<br><br>Safety and efficacy in other diagnoses have not been established. | |

**Clinical Guidelines**

**Table 11. Clinical Guidelines**

| Clinical Guideline | Recommendations |
|---|---|
| American Gastroenterological Association (AGA) Institute: **Guideline on the Pharmacological Management of Irritable Bowel Syndrome (2014)**[17] | IBS-C<br>· The use of linaclotide is recommended. (Recommendation: strong; high quality evidence)<br>· The use of lubiprostone (over no drug treatment) is recommended. (Conditional recommendation; moderate-quality evidence)<br>· The use of laxatives (over no drug treatment) is suggested. (Conditional recommendation; low-quality evidence)<br><br>IBS-D<br>· The use of rifaximin (over no drug treatment) is suggested. (Conditional recommendation; moderate-quality evidence)<br>· The use of alosetron (over no drug treatment) is suggested. (Conditional recommendation; moderate evidence)<br>· The use of loperamide (over no drug treatment) is suggested. (Conditional recommendation; very low-quality evidence)<br><br>IBS<br>· The use of TCAs or SSRIs (over no drug treatment) is suggested. (Conditional recommendation; low-quality evidence)<br>· The use of antispasmodics (over no drug treatment) is suggested in patients with IBS. (Conditional recommendation; low-quality evidence) |
| American College of Gastroenterology (ACG): **Monograph on the Management of Irritable Bowel Syndrome and Chronic Idiopathic Constipation (2014)**[18] | Irritable bowel syndrome (IBS):<br>· Rome III criteria for diagnosing IBS:<br>o Recurrent abdominal pain or discomfort at least three days per month in the past three months associated with two or more of the following: improvement with defecation, onset associated with a change in frequency of stool, onset associated with a change in form (appearance) of stool<br>· Subtypes include IBS with constipation (IBS-C), IBS with diarrhea (IBS-D), mixed-type (IBS-M) and unclassified (IBS-U).<br>· Fiber provides overall symptom relief in IBS. (Recommendation: weak; quality of evidence: moderate)<br>· Probiotics improve global symptoms, bloating and flatulence in IBS. (Recommendation: weak; quality of evidence: low)<br>· Rifaximin has shown modest but consistent efficacy in non-constipated IBS and seems to be well tolerated and safe over the time periods evaluated.<br>· Antispasmodics (hyoscine and dicyclomine) provide symptomatic short-term |

| Clinical Guideline | Recommendations |
|---|---|
| | relief in IBS. (Recommendation: weak; quality of evidence: low).<br>· Peppermint oil is superior to placebo in improving IBS symptoms. (Recommendation: weak; quality of evidence: moderate).<br>· There is insufficient evidence to recommend loperamide for use in IBS. It is an effective antidiarrheal but there is no evidence to support its use for relief of global symptoms in IBS. (Recommendation strong, quality of evidence very low)<br>· Antidepressants (tricyclic antidepressants [TCAs] and selective serotonin reuptake inhibitors [SSRIs]) are effective in symptom relief in IBS. (Recommendation: weak; quality of evidence: high)<br>· Alosetron is effective in females with diarrhea-predominant IBS. (Recommendation: weak; quality of evidence: moderate)<br>· The prosecretory agents linaclotide and lubiprostone are effective in constipation-predominant IBS.<br>· There is no evidence that polyethylene glycol (PEG) improves overall symptoms and pain in patients with IBS. (Recommendation: weak; quality of evidence: very low) |
| World Gastroenterology Organisation Global Guidelines: **Irritable Bowel Syndrome: a Global Perspective (2015)**[19] | <u>Rome III subclassification criteria:</u><br>· IBS-D: loose stools>25% of time and hard stools< 25% of time, up to 1/3 of cases, more common in men<br>· IBS-C: hard stools > 25% of time and loose stools< 25% of time, up to 1/3 of cases, more common in women<br>· IBS-M: both hard and soft stools > 25% of time, 1/3 to 1/2 of cases<br>· Un-subtyped IBS: insufficient abnormality of stool consistency to meet criteria IBS-C or M.<br>· Patients commonly transition between subtypes.<br><br><u>Epidemiology:</u><br>· Prevalence of IBS in Europe and North America is estimated to be 10 to 15%.<br>· IBS mainly occurs between the ages of 15 and 65 years.<br>· Diagnosis is usually suspected on the basis of the patient's history and physical exam, without additional tests.<br><br><u>Management:</u><br>· Specialized diets may improve symptoms in some IBS patients (e.g., fiber-rich diet or bulk-former combine with sufficient fluids, low in fermentable oligo-, di-, and monosaccharides and polyols, wheat-free and gluten-free diets)<br>· Some probiotics give global relief of symptoms in IBS and others alleviate individual symptoms such as bloating and flatulence. The duration of benefits and the nature of the most effective species are not clear.<br>· There is insufficient evidence for a general recommendation of prebiotics or symbiotics in patients with IBS.<br><br><u>Overall symptoms- first-line therapy:</u><br>· Some antispasmodics (hyoscine, dicyclomine, otilonium [unavailable in U.S.], cimetropium [unavailable in U.S.], pinaverium [unavailable in U.S.], and mebeverine [unavailable in U.S.]) provide symptomatic short-term relief in IBS. |

| Clinical Guideline | Recommendations |
|---|---|
| | · Peppermint oil is superior to placebo in improving IBS symptoms.<br><br>Overall symptoms- second-line therapy:<br>· Laxatives<br>· Antidiarrheals<br>· TCAs and SSRIs are effective for symptom relief in IBS.<br>· SSRIs may be considered in resistant IBS-C, although it is not currently recommended that SSRIs be routinely prescribed for IBS in patients without comorbid psychiatric conditions due to conflicting and limited data on efficacy, safety and long-term outcomes.<br><br>Overall symptoms- other therapeutic options:<br>· Rifaximin is effective in reducing overall symptoms in IBS-D. It may be considered as second-line therapy but its efficacy and safety has not been established beyond 16 weeks. Older patients and women were found to have higher response rates.<br>· Alosetron is useful for second-line therapy of IBS-D. It has however been associated with an increased risk of ischemic colitis and may cause severe constipation.<br>· Lubiprostone is safe and effective for treatment of IBS-C.<br>· Linaclotide is safe and effective for treatment of IBS-C.<br>· There is insufficient evidence to recommend loperamide for use in IBS.<br>· Mixed 5-HT4 agonists/5-HT3 antagonists are no more effective than placebo at improving symptoms of IBS-C.<br>· Renzapride (unavailable in U.S.) and cisapride have no benefit in IBS.<br>· Evidence is lacking for the use of PEG for overall symptoms of IBS but it may relieve constipation.<br>· Ondansetron improves urgency, diarrhea and bloating in IBS-D, but did not help with pain. Ramosetron (unavailable in U.S.) should be considered as second-line therapy in IBS-D.<br><br>Specific symptoms-pain:<br>· If an analgesic is required, paracetamol (unavailable in U.S.) is preferable to nonsteroidal anti-inflammatory drugs (NSAIDs). Avoid opiates due to potential for dependence, addiction and undesirable side effects on the gastrointestinal tract.<br>· The probiotic strain *Bifidobacterium infantis* 35624 (one capsule per day) has been shown to reduce pain, bloating, and defecatory difficulty and to normalize stool habit in IBS patients, regardless of predominant bowel habit<br>· Antispasmodics, including peppermint oil, are still considered to represent a first-line treatment for abdominal pain in patients with IBS.<br>· TCAs (amitriptyline [starting dose: 10 mg/day, target dose 25 to 50 mg/day at bedtime], desipramine [target dose: 50 mg/day, target dose 100 to 150 mg/day at bedtime]). Avoid use in constipated patients.<br>· SSRIs (paroxetine 10 to 60 mg/day, citalopram 5 to 20 mg/day).<br>· Linaclotide reduces abdominal pain in IBS-C.<br><br>Specific symptoms- diarrhea:<br>· Loperamide (2 mg every morning or twice daily) is no more effective than placebo in reducing pain, bloating and global symptoms of IBS but it is an |

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| | effective agent for management of diarrhea, reducing stool frequency and improving stool consistency. However, there is insufficient evidence to recommend loperamide for use in IBS.<br>· Alosetron is indicated for women with severe IBS-D with symptoms > six months and no response to antidiarrheal agents.<br>· Eluxadoline and rifaximin have recently been approved in the U.S. for IBS-D. However, it is difficult to define their position in IBS management at this time. |

**Conclusions**

While several over-the-counter or off-label prescription agents are used for the treatment of IBS, there are currently only two agents approved by the Food and Drug Administration (FDA) for the treatment of IBS-C and three agents approved by the FDA for IBS-D.[1-5] Agents used for the treatment of IBS-C include linaclotide (Linzess®) and lubiprostone (Amitiza®). Both agents are limited to use in adults for IBS-C and the use of lubiprostone for IBS-C is further limited to use in adult women only. Both of these agents are also used for the management of chronic idiopathic constipation. Lubiprostone also carries another indication for opioid-induced constipation in chronic non-cancer pain.[1,2] Agents used for the treatment of IBS-D include alosetron (Lotronex®), eluxadoline (Viberzi®) and rifaximin (Xifaxan®). These agents are also limited to use in adults for the treatment of IBS-D with alosetron being further limited to use in adult women. Rifaximin carries additional indications for reducing the risk of recurrent hepatic encephalopathy in adults and the treatment of travelers' diarrhea in adults and children 12 years of age or older.[3-5]

Linaclotide is dosed once-daily for the treatment of IBS-C with lubiprostone dosed twice-daily. Alosetron and eluxadoline are dosed twice-daily for the treatment of IBS-D with rifaximin being dosed three times a day. These agents are generally prescribed chronically with the exception of rifaximin. The recommended treatment course for rifaximin in IBS-D is 14 days which should be repeated up to two additional times if there is a recurrence of symptoms and three days when used for travelers' diarrhea. Rifaximin should be administered chronically when used to reduce the risk of recurrent hepatic encephalopathy.[1-5]

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