Use of lubiprostone in constipating disorders and its potential for opioid-induced bowel dysfunction

Lubiprostone is a novel medication, approved by the US FDA for the treatment of chronic idiopathic constipation in adults and constipation-predominant irritable bowel syndrome (IBS) in adult women. It is an activator of the CIC-2 chloride channel, indirectly making more water available in the lumen of the gastrointestinal tract. Secondary stretching of the gastrointestinal wall possibly causes increased small- and large-bowel transit, making it beneficial in constipation-based conditions, not only chronic idiopathic constipation and constipation-predominant irritable bowel syndrome, but also possibly opioid-induced bowel dysfunction. Lubiprostone has some preclinical data to support its use in this indication, confirmed by the preliminary efficacy and safety results of the two, very recently completed, randomized, double-blind, placebo-controlled studies.

**KEYWORDS:** chronic idiopathic constipation - constipation-predominant irritable-bowel syndrome - lubiprostone - opioid-induced bowel dysfunction

Lubiprostone is a novel medication that, in January 2006, was approved by the US FDA for the treatment of chronic idiopathic constipation in adults, and in April 2008, was approved for the treatment of constipation-predominant irritable bowel syndrome (IBS) in adult women. This review will discuss lubiprostone’s pharmacology, as well as its efficacy and safety in the approved indications; in addition the preclinical and preliminary clinical efficacy and safety data supporting its potential usefulness in the treatment of opioid-induced bowel dysfunction will be presented.

**Lubiprostone**

**Structure**
Lubiprostone (SPI-211/RU-211, Amitiza®) is a bicyclic fatty-acid derived from the 15-keto metabolite of prostaglandin E, (Figure 1). It is a member of a new class of compounds called prostones, a collective name for the 15-keto metabolites of natural prostaglandins and structurally similar compounds. The only other FDA-approved prostone is unoprostone, indicated for the lowering of intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

**Function**
Lubiprostone is an activator of the CIC-2 chloride channel, which is a transmembrane protein, located in the apical or luminal membrane of the epithelial cells lining the gastrointestinal tract (Figure 2). The protein allows the passage, in this case, of chloride ions, for which the lipid-bilayer cell membrane is not permeable. It facilitates diffusion down a concentration gradient, which is created by the uptake of chloride ions into the cell across the basolateral membrane through sodium–potassium–chloride cotransport activity. In simplified terms, there are four types of chloride channels: voltage-gated, calcium-gated, protein-kinase-gated and ligand-gated. The CIC-2 channel, the selective target of lubiprostone, is one of nine voltage-gated chloride channels. Activation of this channel results in an efflux of chloride ions from the epithelial intracellular space into the lumen of the gastrointestinal tract. The efflux of chloride ions is followed by a flow of sodium ions from the gastrointestinal extracellular space through paracellular pathways in between the epithelial cells, to maintain electroneutrality. The accumulation of sodium ions in the gastrointestinal lumen, in turn, draws extracellular water into the lumen to maintain osmotic balance.

**Metabolism**
As a fatty acid, lubiprostone is highly lipophilic, but its absorption is negligible due to rapid metabolism locally in the gastrointestinal tract, resulting in a bioavailability of less than 1%. Its main metabolite is M3 or 15-hydroxy-lubiprostone, which is pharmacologically active and does get absorbed. However, its systemic bioavailability is also low, and accounts for less than 10% of
the administered lubiprostone dose. It has a time to maximum plasma concentration and plasma-elimination half-life of approximately 1 h; its protein binding is 94%.

**Mode of action**

In healthy volunteers, lubiprostone has been shown to decrease gastric emptying and increase small-bowel and large-bowel transit [1], but not to increase colonic motor function [2]. The motility effects that occur with lubiprostone are secondary to the secretion of water it causes into the lumen of the gastrointestinal tract. The increased water, in turn, distends the gastrointestinal tract and causes mural stretching, delaying gastric emptying to facilitate digestion and accelerating bowel transit to facilitate stool evacuation. The latter makes the medication beneficial in constipation-based conditions, such as chronic idiopathic constipation, constipation-predominant IBS and, potentially, also opioid-induced bowel dysfunction. The slowing of gastric emptying, causing gastric distension, may account for its most common adverse event, nausea.

An important function of the colon is to extract water from the stool; with the increased transit the colon has less time to perform this function, resulting in softer stool, which, in turn, is easier to evacuate. A schematic of lubiprostone's mode of action in relieving constipation-based conditions is shown in Figure 3.

From a safety perspective, the studies in healthy volunteers have shown lubiprostone not to affect serum electrolytes and not to impact the electrocardiogram, which was also confirmed in the studies of lubiprostone in subjects with chronic constipation and constipation-predominant IBS reviewed below.

**Chronic idiopathic constipation**

**Definition**

Rome III refers to chronic idiopathic constipation as functional constipation that presents as persistently difficult, infrequent or seemingly incomplete defecation, not meeting IBS criteria [3]. It estimates constipation to occur in up to 27% of the population, affecting all ages, and to be most common in women and nonwhites.

The diagnostic criteria listed for functional constipation require them to be fulfilled for the last 3 months, with symptom onset at least 6 months prior to diagnosis:

- Must include two or more of the following:
  - Straining during at least 25% of defecations
  - Hard or lumpy stools in at least 25% of defecations
  - Sensation of incomplete evacuation for at least 25% of defecations
  - Sensation of anorectal obstruction or blockage for at least 25% of defecations
  - Manual maneuvers to facilitate in at least 25% of defecations
  - Fewer than three defecations per week

- Loose (mushy) or watery stools are rarely present without the use of laxatives
- There are insufficient criteria for IBS

In the above diagnostic criteria, hard or lumpy stools is defined as types 1 or 2 of the Bristol Stool Form Scale — that is, separate hard lumps like nuts (difficult to pass) or sausage shaped but lumpy; loose (mushy) or watery
stools are defined as types 6 or 7 on the Bristol Stool Form Scale – that is, fluffy pieces with ragged edges, a mushy or watery stool, no solid pieces or entirely liquid.

Lubiprostone

**Dose exploration**

A randomized, double-blind, placebo-controlled study evaluated lubiprostone in the treatment of chronic idiopathic constipation in doses of 24, 48 and 72 µg per day, administered as 24 µg once-daily, twice-daily and three-times daily, respectively, for 3 weeks [4]. The study randomized 129 adult subjects with a history of fewer than three spontaneous bowel movements per week, on average, for at least 6 months: 33 subjects were randomized to placebo, 30 subjects to 24-µg lubiprostone, 32 subjects to 48-µg lubiprostone and 34 subjects to 72-µg lubiprostone. A spontaneous bowel movement was defined as a bowel movement not preceded within 24 h by intake of rescue medication, consisting of a 10-mg bisacodyl suppository or a sodium-phosphate enema. The subjects also had to have abdominal bloating or discomfort and one or more of the following symptoms: (very) hard stool, subjectively incomplete evacuation and straining at defecation. The eligibility requirements were verified after a 14-day washout/baseline period during which the subjects discontinued all nonprescription and prescription laxatives and fiber supplements.
The primary end point was the average number of spontaneous bowel movements per week over the 3-week treatment period. The study was powered to detect a minimum difference of 2.5 spontaneous bowel movements per week ($\alpha = 0.05; \beta = 0.86$). Of the 129 randomized subjects, 127 subjects were in the intention-to-treat population, with two randomized subjects not having taken study medication. The primary end point was met for the 24 µg twice-daily treatment regimen. This treatment regimen also demonstrated significant differences versus placebo over the 3-week treatment period for straining, stool consistency, abdominal bloating, severity of constipation and subject rating of treatment effectiveness, but not for abdominal discomfort.

Effect confirmation
Two randomized, double-blind, placebo-controlled studies with lubiprostone 24 µg, twice-daily, provided confirmatory evidence of efficacy in the treatment of chronic idiopathic constipation, of which one was published in full [5]. This study randomized 244 adult subjects with a history of fewer than three spontaneous bowel movements per week, on average, for at least 6 months – 124 subjects to placebo and 120 subjects to lubiprostone. The subjects also had to have one or more of the following symptoms with at least 25% of the spontaneous bowel movements: (very) hard stool, subjectively incomplete evacuation and straining at defecation. The eligibility requirements were verified after a 14-day prospective baseline period, which was followed by a 4-week treatment period.

The primary end point was the number of spontaneous bowel movements during the first week of treatment, with spontaneous bowel movement defined as above, and the same rescue medications allowed. The study was powered to detect a minimum difference of two spontaneous bowel movements per week ($\alpha = 0.05; \beta = 0.90$). Of the 244 subjects, 242 were in the intention-to-treat population, with two randomized subjects discontinuing the study before receiving study medication. The primary end point was met, with 5.69 spontaneous bowel movements in the lubiprostone group and 3.46 in the placebo group ($p = 0.0001$). The differences in number of spontaneous bowel movements between lubiprostone and placebo were also significant for the subsequent three 1-week treatment periods. For week 1, the treatment regimen also demonstrated significant differences for stool consistency, straining and constipation severity, but not for abdominal bloating and abdominal discomfort.

Safety analysis
In the dose-ranging study, 75% of the subjects receiving lubiprostone, 24 µg twice-daily, reported adverse events, versus 40% of those receiving placebo ($p = 0.006$). The most common adverse event was nausea (43.8 vs 0.0%), followed by headache (12 vs 12%) and dizziness (9 vs 3%). In the confirmatory study, 70% of the subjects receiving lubiprostone, 24 µg twice-daily, reported adverse events versus 51% of those receiving placebo ($p = 0.003$). The most common adverse event was nausea (32 vs 3%; $p < 0.001$), followed by headache (12 vs 6%; $p = 0.115$), flatulence (6 vs 1%; $p = 0.035$) and dizziness (6 vs 1%; $p = 0.035$).

Constipation-predominant IBS

Definition
Rome III defines IBS as a functional bowel disorder in which abdominal discomfort or pain is associated with defecation or a change in bowel habit, and with features of disordered defecation [3]. It estimates that 10–20% of adolescents and adults have symptoms consistent with it; most studies find a female preponderance. IBS symptoms come and go over time, often overlap with other functional disorders, impair quality of life and result in high healthcare costs.

The diagnostic criteria listed for IBS require them to be fulfilled for the last 3 months, with symptom onset at least 6 months prior to diagnosis. Recurrent abdominal discomfort or pain, defined as an uncomfortable sensation not described as pain, must be present at least 3 days per month in the last 3 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

Supportive symptoms that are not part of the diagnostic criteria include:

- Abnormal stool frequency:
  - ≤3 bowel movements per week or
  - ≤3 bowel movements per day
- Abnormal stool form:
  - Lumpy/hard
  - Loose/watery
Abnormal stool passage:
- Defecation straining
- Urgency or also a feeling of incomplete bowel movement, passing mucus and bloating

Assuming no use of antidiarrheals or laxatives, the following system can be used to subtype IBS by predominant stool pattern:
- IBS with constipation (IBS-C) – hard or lumpy stools at least 25% and loose (mushy) or watery stools less than 25% of bowel movements
- IBS with diarrhea (IBS-D) – loose (mushy) or watery stools at least 25% and hard or lumpy stools less than 25% of bowel movements
- Mixed IBS (IBS-M) – hard or lumpy stools at least 25% and loose (mushy) or watery stools at least 25% of bowel movements
- Unsubtyped IBS – insufficient abnormality of stool consistency to meet criteria for IBS-C, -D or -M

In the above diagnostic criteria, hard or lumpy stools are defined as types 1 or 2 of the Bristol Stool Form Scale; loose (mushy) or watery stools are defined as types 6 or 7 of the Bristol Stool Form Scale.

### Lubiprostone

#### Dose exploration

A randomized, double-blind, placebo-controlled study evaluated lubiprostone in the treatment of constipation-predominant IBS in dosages of 16, 32 and 48 µg per day, administered in a twice-daily dosing regimen for 3 months (3 × 28 days) [6]. The study randomized 194 adult subjects meeting Rome II modular questionnaire criteria for constipation-predominant IBS: 48 subjects to placebo, 52 subjects to 16-µg lubiprostone, 49 subjects to 32-µg lubiprostone, and 45 subjects to 48-µg lubiprostone, with an average assessment of abdominal discomfort/pain of at least mild intensity, as well as any two of the following symptoms during a 4-week prospective baseline period:
- Fewer than three spontaneous bowel movements per week
- At least 25% of the spontaneous bowel movements accompanied by at least moderate straining
- At least 25% of the spontaneous bowel movements associated with a stool consistency rating of hard or very hard

Spontaneous bowel movement was defined as above with the same rescue medications allowed.

The primary end point was change from baseline in mean abdominal discomfort/pain score, rated on a 4-point scale (1 = mild; 2 = moderate; 3 = severe; 4 = very severe), during the first month of treatment. Of the 194 randomized subjects, 193 were in the intention-to-treat population, with one randomized subject not providing post-treatment assessments. The primary end point was met for the highest dose regimen, that is, 24 µg twice-daily (p = 0.023); significant differences versus placebo for all three dose regimens were observed for month 2. For month 1, the highest dose regimen also demonstrated significant differences versus placebo for abdominal bloating, degree of straining, severity of constipation, weekly rate of spontaneous bowel movements and stool consistency.

#### Effect confirmation

Two randomized, double-blind, placebo-controlled studies with lubiprostone, 8 µg twice-daily, analyzed as one, provided confirmatory evidence of efficacy in the treatment of constipation-predominant IBS [7]. In total, the two studies randomized 1171 adult subjects meeting the Rome II modular questionnaire criteria for constipation-predominant IBS and with an average assessment of abdominal discomfort/pain of at least mild intensity, as well as any two of the following symptoms during a 4-week prospective baseline period:
- Fewer than three spontaneous bowel movements per week at least 25% of the time
- At least 25% of the spontaneous bowel movements recorded a straining assessment of at least moderate
- At least 25% of the spontaneous bowel movements recorded a stool consistency assessment of hard or very hard

Spontaneous bowel movement was defined as above with the same rescue medications allowed.

The primary end point was calculated from the weekly assessments of symptom relief, based on the responses to the following questions: How would you rate your relief of IBS symptoms (abdominal discomfort/pain, bowel habits, and other IBS symptoms) over the past week compared with how you felt before you entered the study?
- 1. Significantly worse
- 2. Moderately worse
- 3. A little bit worse
Definition

“secretion. The direct effect is mediated through decreases gastrointestinal motility and intestinal tract. Related to the indirect effect, it has been shown that intrathecal administration of opioids directly through an effect on the gastrointestinal tract. Related to the indirect effect, it has been shown that intrathecal administration of opioids decreases gastrointestinal motility and intestinal secretion. The direct effect is mediated through µ-opioid receptors in the neuronal plexi, located between the longitudinal and circular muscle layers (myenteric plexus) and just underneath the mucosa (mucosal plexus). Under the influence of opioids on the myenteric plexus, the longitudinal smooth-muscle layer relaxes and the circular smooth-muscle layer increases in tone. These effects are thought to be mediated through inhibition of acetylcholine release and inhibition of the release of vasoactive intestinal polypeptide and nitric oxide, respectively. The result of this differential effect on the longitudinal and circular intestinal smooth muscles is an increase in segmental contraction and a decrease in peristaltic activity.

Normal peristalsis consists of sweeping movements in the small bowel, occurring every 90 min to move its luminal content from the duodenum to the ileum, and mass movements in the large bowel, occurring one- to three-times per day on average, moving its content over large distances. A secondary effect of the decrease in peristaltic activity is that food stays longer in the stomach and stool stays longer in the small and large bowel. The former effect causes gastric distension, resulting in nausea, and the latter contributes to the constipation by allowing more time for fluid absorption, a predominant function of the large bowel in particular. A decrease in bowel-movement frequency is the primary symptom of constipation, with secondary symptoms being hard stool, the need for straining with bowel movements, and a sense of incomplete evacuation afterwards. Tertiary symptoms are abdominal bloating/distension, discomfort, pain from stool or gas, borborygmi, flatulence, and dyspnea from interference of the abdominal stool and gas content with diaphragmatic contraction aiding inspiration.

Prevalence

A systematic review was performed of 11 randomized, double-blind, placebo-controlled studies of oral opioids in the treatment of chronic noncancer pain, given for periods ranging from 4 days to 8 weeks [8]. The opioids were morphine in five studies, morphine or methadone in one study, and oxycodone in four studies; all studies used inactive placebo, except two in which benztpine was given as active placebo. Of the 1025 subjects randomized, 674 completed the study they were in and 698 were evaluable. Adverse events and lack of efficacy were the most frequent reasons for discontinuation during both opioid and placebo treatment. The mean final daily dose of the oral opioids varied from 30 to 120 mg for morphine, and from 20 to 45 mg for

4. Unchanged
5. A little bit relieved
6. Moderately relieved
7. Significantly relieved

A weekly responder was defined as reporting either moderately (6) or significantly relieved (7) for that week. A monthly responder was defined as a moderate responder for all 4 weeks of the month, or a significant responder for at least 2 weeks of the month, without ratings of moderately (2) or significantly worse (1). An overall responder, the primary end point, was defined as a monthly responder for at least 2 of the 3 months of the study. The study was powered to detect a minimum relative increase in overall responders for lubiprostone, compared with placebo, of 70.6% (α = 0.05; β = 0.88).

Of the 1171 randomized subjects, 1154 were in the intention-to-treat population, with four randomized subjects not receiving study medication and 13 subjects not providing post-treatment assessments. The primary end point was met in both studies, with p-values of 0.009 and 0.031, respectively; in the two studies combined, the overall responder rate was 17.9% for lubiprostone and 10.1% for placebo (p = 0.001). In comparison with the nonresponders, the overall responders had a significantly greater decrease from baseline in abdominal discomfort/pain, bloating, constipation severity, stool consistency and straining.

Safety analysis

In the dose-ranging study, 67% of the subjects receiving lubiprostone, 8 µg twice-daily, reported adverse events, versus 58% of those receiving placebo. The most common adverse event was nausea (19 vs 13%), followed by diarrhea (14 vs 4%). In the confirmatory study, 50% of the subjects receiving lubiprostone, 8 µg twice-daily, reported adverse events, versus 51% of those receiving placebo. The most common, treatment-related adverse event was nausea (8 vs 4%), followed by diarrhea (6 vs 4%).

Opioid-induced bowel dysfunction

Definition

Opioids induce gastrointestinal dysfunction indirectly through an effect on the CNS and directly through an effect on the gastrointestinal tract. Related to the indirect effect, it has been shown that intrathecal administration of opioids decreases gastrointestinal motility and intestinal secretion. The direct effect is mediated through...
oxycodone (30–68.5 mg morphine equivalents); it was 15 mg for methadone (150 mg morphine equivalents).

Constipation was the most common adverse event in the opioid-treated subjects, reported by 41% of the subjects in comparison with 11% of those treated with placebo, followed by nausea (32 vs 12%). However, the actual occurrence of constipation with oral opioid treatment in the range of 30–150 mg morphine equivalents per day is probably higher because of the enriched nature of the studies, excluding subjects from randomization who did not tolerate the medication or who did not find it effective in relieving their pain. The subjects who were not randomized because of the latter reason would also have discontinued the medication in practice; however, the subjects who were not randomized because of tolerability reasons would possibly have continued the treatment if the adverse event was constipation and this was effectively treated. Of the adverse events reported in the systematic review – that is, constipation, nausea, somnolence/sedation, dizziness, vomiting, itching and dry mouth, constipation is the adverse event for which the most treatments are already available, although not necessarily specifically approved by the US FDA for opioid-induced bowel dysfunction.

### Available treatments

In April 2008, the US FDA approved the peripherally-acting µ-opioid receptor antagonist, methylaltrexone, for the treatment of opioid-induced constipation in patients with advanced illness who are receiving palliative care. Lubiprostone and tegaserod are US FDA-approved for the treatment of chronic idiopathic constipation in adults and can, of course, be used off-label for this condition as well. However, in March 2007, upon US FDA request, tegaserod was withdrawn from the market because of cardiovascular safety concerns. Lubiprostone products in general can also be used for opioid-induced bowel dysfunction, such as bulking agents (cellulose and psyllium), stool softeners (docusate), osmotic agents (lactulose, sorbitol, magnesium citrate and polyethylene glycol) and laxatives (senna or bisacodyl). A prokinetic medication could also be used, although not US FDA-approved for constipation. However, domperidone is not on the market in the USA, cisapride was withdrawn from the market because of long QT syndrome, and the long-term, daily use of metoclopramide is not recommended because of potential extrapyramidal side effects, particularly tardive dyskinesia. Misoprostol, a synthetic prostaglandin E1 analog, US FDA-approved for the prevention of nonsteroidal anti-inflammatory drug-induced gastric ulcers, also increases colonic transit and can be used off-label.

#### Drug development

Prior to its withdrawal from the market, tegaserod was being studied for opioid-induced bowel dysfunction. Another peripherally-acting µ-opioid receptor antagonist, alvimopan, was being studied as well, but cardiovascular safety concerns halted drug development. However, the US FDA approved the medication in May 2008 with a Risk Evaluation and Mitigation Strategy for the indication of accelerating the time to upper and lower gastrointestinal recovery following partial small- or large-bowel resection with primary anastomosis. The Risk Evaluation and Mitigation Strategy restricts the use of the medication to short-term (15 doses) treatment in hospitalized patients, and only in hospitals that have registered with the program and have met all the requirements.

### Lubiprostone

In relation to opioid-induced bowel dysfunction, lubiprostone was studied *in vivo* in mice [9] and *in vitro* in the human jejunum [10]. In mice, the administration of morphine hydrochloride, 5 mg/kg intraperitoneally, was followed by the oral administration of a graphite marker as well as lubiprostone 0.1, 1, 10 and 100 µg/kg or vehicle. The animals were sacrificed 150 min after administration of the marker, and were scored on the presence of marker in the rectum. Lubiprostone significantly increased the gastrointestinal transit of the marker in the morphine-treated animals, when compared with that of the morphine-treated control (vehicle) group (p < 0.01 at 1 µg/kg or higher). In addition, the effect of lubiprostone on morphine-induced analgesia was evaluated, but no changes were found.

In isolated human jejunum, morphine applied to the serosal side of the preparations significantly decreased basal short-circuit current, which is a reflection of chloride secretion. Lubiprostone, added 5 min later, reversed the inhibitory action of morphine as reflected by significant increases in short-circuit current. The results of both sets of experiments suggest that lubiprostone might also be effective in opioid-induced bowel dysfunction, confirmed...
by the preliminary efficacy and safety results of the two, very recently completed, randomized, double-blind, placebo-controlled studies [102].

The studies were identical Phase III trials in which a total of 875 subjects with opioid-induced bowel dysfunction were randomized to 12-week treatment with lubiprostone, 24 µg twice-daily. The subjects were taking opioid medications for chronic noncancer pain, including fentanyl, methadone, morphine and oxycodone, for at least 30 days prior to screening, and continued to take these medications for the duration of the study. During the 2-week baseline period before randomization, they were required to have fewer than three spontaneous bowel movements per week. The overall adverse-event rate for the combined studies was 54.9% for lubiprostone and 51.6% for placebo, with nausea being most common (15.0 vs 7.5%), followed by diarrhea (8.5 vs 3.7%).

The primary end point of the studies was the change from baseline in the frequency of spontaneous bowel movements at week 8 of treatment, which was met in one of the studies (OBD0631) but not in the other (OBD0632). The change from baseline in the frequency of spontaneous bowel movements in the first study was from 1.42 to 4.54 for lubiprostone and from 1.46 to 3.81 for placebo; in the second study, these changes were from 1.60 to 4.10 for lubiprostone and from 1.60 to 3.95 for placebo. An interesting post hoc subanalysis revealed that subjects taking methadone and randomized to lubiprostone experienced a lower increase in the frequency of spontaneous bowel movements than lubiprostone-treated subjects receiving other opioids.

**Future perspective**

The development of alvimopan and tegaserod for the treatment of opioid-induced bowel dysfunction was halted because of cardiovascular safety concerns. The US FDA recently approved methylnaltrexone for this indication, but in a very special population. Lubiprostone has been on the US market since 2006, approved for the treatment of chronic idiopathic constipation in adults and constipation-predominant IBS in adult women, with a good safety record. Extension of the indication to include opioid-induced bowel dysfunction would be a welcome addition to the treatment options available for this condition. Safe and effective treatment of opioid-induced bowel dysfunction will enhance the quality of life of those suffering from the condition, both directly as well as indirectly, by allowing less restricted dosing and, hence, better pain control.

**Financial & competing interests disclosure**

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Executive summary

- Lubiprostone is a novel medication, approved by the US FDA for the treatment of chronic idiopathic constipation in adults and constipation-predominant irritable bowel syndrome in adult women.
- It is an activator of the CIC-2 chloride channel, indirectly making more water available in the lumen of the gastrointestinal tract.
- Secondary stretching of the gastrointestinal wall causes increased small- and large-bowel transit.
- Lubiprostone has some preclinical data to support its potential use in opioid-induced bowel dysfunction, confirmed by the preliminary efficacy and safety results of the two, very recently completed, randomized, double-blind, placebo-controlled studies.

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