**Lubiprostone (Amitiza™)**

**Manufacturer:** Sucampo Pharmaceuticals, Inc. (marketed by Takeda Pharmaceuticals)

**Indication:** Lubiprostone is indicated for the treatment of chronic idiopathic constipation in adults. It is being investigated for use in patients with constipation-predominant irritable bowel syndrome and post-operative ileus (bowel obstruction).

**Current Regulatory Status:** Lubiprostone was approved by the US Food and Drug Administration (FDA) in January 2006 for the treatment of chronic constipation in adults, for which there is no known cause. Lubiprostone is not currently licensed for sale in Canada.

**Description:** Lubiprostone is a prostaglandin E1 metabolite analogue. It activates type 2 chloride (CIC-2) channels in the lining of the small intestine. This leads to an increase in intestinal fluid secretion and improves the passage of stool. The result is an alleviation of the symptoms due to constipation including abdominal discomfort, pain, and bloating. Lubiprostone is supplied in soft gelatine capsules containing 24 μg of active compound to be taken twice daily with food. Physicians and patients should periodically assess the need for continued therapy.

**Current Treatment:** Chronic idiopathic constipation may be defined as persistent difficulty in the evacuation of feces with <3 bowel movements per week for which there is no known cause. Signs and symptoms include abdominal pain or discomfort, bloating, straining, and hard or lumpy stools. An epidemiological survey conducted in Canada found that the prevalence of chronic idiopathic constipation, which varies according to the definition that is used, ranges from approximately 15% to 27%. It affects the young and elderly with similar frequency and about twice more women than men.

The standard treatments for constipation involve lifestyle modifications (increasing dietary fibre and exercise); and the use of bulk-forming laxatives (e.g., psyllium, methylcellulose), stool softeners (e.g., docusate sodium), lubricants (e.g., mineral oil), osmotic laxatives (e.g., magnesium citrate, lactulose), and rapid-acting stimulant laxatives (e.g., bisacodyl, senna). Other therapies, including behavioural approaches to retrain pelvic floor muscles and surgery, have been used with success for chronic constipation. Tegaserod (Zelnorm®), a serotonin 5-HT4 receptor agonist, is a prescription drug licensed by Health Canada for the treatment of chronic idiopathic constipation. Tegaserod is used after other agents have been ineffective or are poorly tolerated.

**Cost:** As lubiprostone is not currently licensed for sale in Canada, Canadian pricing is not available. In the US, the cost of treatment with lubiprostone for one month is approximately US$173, compared with US$188 for tegaserod. In Canada, tegaserod costs about C$2 per tablet.

**Evidence:** Clinical evidence for the safety and efficacy of lubiprostone comes from unpublished trials conducted by Johanson et al. Patients were included in these studies if they had <3 spontaneous bowel movements (SBMs) per week, and if they experienced symptoms of constipation for >6 months.
Lubiprostone

Two multi-centre, double-blind, placebo-controlled trials were conducted. These included 479 participants with chronic idiopathic constipation. After a two-week baseline washout period, participants were randomly assigned to receive active treatment with 24 μg of lubiprostone twice daily or placebo for four weeks. The primary endpoint for both trials was the frequency of SBMs during the first week. Secondary endpoints included SBM frequency during weeks 2, 3, and 4; SBMs within 24 hours; and weekly assessments of abdominal bloating, discomfort, stool consistency, and straining.

Trial data indicated that participants who were receiving lubiprostone rather than placebo experienced significantly more SBMs at the end of the first week (5.0 versus 3.5, p<0.0001) and (5.0 versus 3.0, p=0.0001). This was sustained throughout the four weeks of treatment.

In both trials, the percentages of patients who experienced SBMs within the first 24 hours after starting treatment with lubiprostone were higher when compared with those who received placebo (56.7% versus 36.9%, p=0.0024) and (61.3% versus 31.4%, p<0.0001). Lubiprostone led to statistically significant improvements in abdominal bloating, discomfort, stool consistency, and straining, when compared to placebo.

Most of the participants in these studies were female (89.2%) and Caucasian (81.6%). A minority (9.7%) of the study population were elderly (>65 years of age). Subpopulation analyses for gender, race, and age yielded clinically significant results that favoured lubiprostone.

Other studies have tried to extrapolate lubiprostone’s safety and efficacy in other populations. Ueno et al. compared subgroups of male and female participants by pooling results from previous trials. Results showed that males taking lubiprostone experienced twice as many SBMs per week as males receiving placebo. Compared with female participants, the weekly rates of SBMs were higher for males (4.99 to 5.75 versus 5.69 to 6.05 respectively). Ueno et al. also pooled results from previous trials to report that lubiprostone appeared efficacious and well-tolerated for long-term treatment in the elderly. The incidence rate of nausea was decreased in elderly (17.8%) compared with non-elderly participants (29.4%). Additional trials using larger, more representative populations are needed to confirm the generalizability of these results.

Relapse rates were assessed in a phase III study where 128 patients receiving lubiprostone for four weeks were then randomized to continue the regimen or receive placebo for an additional three weeks. Relapse was defined as <3 SBMs per week after previously experiencing >4 SBMs per week. The relapse rate was 18.2% in the lubiprostone group versus 44.4% in the placebo group (p=0.0223). Symptom severity continued to be better than baseline in the placebo group, indicating that symptoms do not worsen upon discontinuation. The authors concluded that no
Emerging Drug List
Lubiprostone

rebound effect was observed when the patients discontinued treatment with lubiprostone after four weeks.\textsuperscript{19}

Three unpublished open-label studies have been conducted to evaluate the long-term safety of lubiprostone.\textsuperscript{11,14} In the first study, 308 individuals were enrolled. They received 24 \(\mu\)g of lubiprostone twice daily for 24 weeks.\textsuperscript{11} Most of the participants reported statistically significant improvements in constipation severity, bloating, and abdominal symptoms (\(p<0.001\)) compared with baseline. Non-serious adverse events were recorded in 51.6\% of participants, 19.6\% of whom discontinued treatment. A further 16\% of patients discontinued treatment because of a lack of efficacy, and 10\% discontinued for other causes. The two other open-label studies were conducted over 48 weeks.\textsuperscript{14} Both studies reported persistent improvements compared with baseline in abdominal bloating, discomfort, and constipation (\(p<0.0001\)) during the treatment period.\textsuperscript{14}

There are no published studies comparing lubiprostone to other agents for constipation. Lubiprostone has not been studied in patients with kidney or liver impairment; and its safety in pregnant women, nursing mothers, and children has not been determined.

Adverse Effects:
The most common side effect reported in clinical trials was nausea, which occurred in approximately 31.1\% of patients receiving 24 \(\mu\)g of lubiprostone twice daily versus 5.1\% of those receiving placebo.\textsuperscript{1} The incidence of nausea was dose-dependent and decreased to 17.2\% when 24 \(\mu\)g of lubiprostone was taken once daily with food. Diarrhea occurred in approximately 13.2\% of patients taking lubiprostone versus 0.9\% for those receiving placebo. The incidence of diarrhea did not appear to be dose-dependent. Other side effects including headache (13.2\%), abdominal distension (7.1\%), abdominal pain (6.7\%), flatulence (6.1\%), sinusitis (4.9\%), vomiting (4.6\%), and loose stools (3.4\%) were also reported.\textsuperscript{1}

Commentary:
Lubiprostone offers clinicians another option for the treatment of chronic idiopathic constipation. Current evidence suggests that its unique mechanism of action, tolerability, and safety profile make it a useful additional option. FDA approval for lubiprostone use in patients \(\geq 65\) years of age may be a potential advantage when compared with tegaserod. The budget impact of lubiprostone should be similar to that of tegaserod because it is an alternative treatment option rather than a replacement. Comparative studies are needed to determine which treatment option is the most efficacious, safe, and cost effective. While lubiprostone has been shown to be effective in the management of chronic constipation, it should not be indicated as first-line therapy because current standard treatment options are less costly with fewer side effects. Until more evidence is available, lubiprostone should be reserved for patients with severe constipation who are refractory to other treatments.

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Emerging Drug List
Lubiprostone

References:


This series highlights medical technologies that are not yet in widespread use in Canada and that may have a significant impact on health care. The contents are based on information from early experience with the technology; however, further evidence may become available in the future. These summaries are not intended to replace professional medical advice. They are compiled as an information service for those involved in planning and providing health care in Canada.

These summaries have not been externally peer reviewed.

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