Amitiza (Lubiprostone): The First Oral Treatment Approved by the FDA for Opioid-Induced Constipation

By Loretta Fala, Medical Writer

The opioid class of analgesic agents is sometimes used to treat pain in patients with noncancer pain, including chronic nociceptive or neuropathic pain. Careful consideration and monitoring are required with long-term opioid therapy, because of the adverse effects associated with these agents, the potential to develop tolerance to the opioid’s analgesic effect, and the potential for abuse or diversion.

One of the most common adverse effects of long-term opioid therapy is opioid-induced constipation (OIC). OIC occurs because the opioids bind to peripheral opioid receptors in the gastrointestinal (GI) tract, causing the absorption of electrolytes (ie, chloride), subsequently reducing the volume of fluid in the small intestine and resulting in abnormal gut motility. Constipation may range from discomfort to severe enough to warrant discontinuation of opioid treatment.

Based on data from the National Health and Wellness Survey of patients receiving opioids, patients with OIC reported significantly more physician visits (mean difference, 3.84 visits; \( P < .05 \)) than patients without OIC. Moreover, patients with OIC reported more missed time from work, more impairment at work and in daily activities, and a significantly lower health-related quality of life than patients without OIC (\( P < .05 \)).

A cost analysis based on 197 patients receiving strong opioids during a 6-month period showed that the total cost per patient per month was significantly higher for patients with severe constipation than for patients with mild, moderate, or no constipation. The authors concluded that OIC causes considerable patient discomfort, impacts quality of life, and can limit effective pain treatment.

In addition to behavioral or lifestyle changes, such as increasing dietary fiber, increasing fluid intake, and increasing physical activity, OIC treatment may require additional medications. These medications may include osmotic laxatives, cathartics (ie, lubricant, bulk, or stimulant), prostaglandins or prokinetic drugs, or others. In some cases, rectal interventions (ie, suppositories, enemas, or colonic irrigation) may be recommended.

Methylaltrexone bromide, an opioid receptor antagonist administered subcutaneously, is US Food and Drug Administration (FDA)-approved to treat OIC in patients with advanced illness (ie, cancer, chronic obstructive pulmonary disorder, Alzheimer’s disease) who are receiving palliative care when response to laxative therapy is not sufficient.

First Oral Option for Opioid-Induced Constipation

In April 2013, the FDA approved a supplemental indication for lubiprostone (Amitiza; Sucampo Pharmaceuticals/Takeda Pharmaceuticals USA), a volume-activated chloride channel (CIC-2) activator, for the treatment of OIC in adults with chronic noncancer pain. Lubiprostone is the first oral therapy to receive FDA approval for this indication.

Lubiprostone was first approved by the FDA in 2006 for the treatment of chronic idiopathic constipation. In 2008, lubiprostone received FDA approval for another indication—the treatment of irritable bowel syndrome (IBS) with constipation in women aged \( \geq 18 \) years—making it the first drug available in the United States for IBS with constipation.

Mechanism of Action

Lubiprostone is a locally acting chloride channel activator that enhances a chloride-rich intestinal fluid secretion without altering sodium and potassium concentrations in the serum. Lubiprostone specifically activates CIC-2, a normal constituent of the apical membrane of the human intestine, in a protein kinase A–independent fashion.

By increasing intestinal fluid secretion, lubiprostone increases motility in the intestine, thereby facilitating the passage of stool and alleviating symptoms associated with chronic idiopathic constipation. Through its activation of apical CIC-2 channels in intestinal epithelial cells, lubiprostone bypasses the antisecretory action of opiates that results from suppression of secretomotor neuron excitability. The activation of CIC-2 by lubiprostone has also been shown to stimulate recovery of mucosal barrier function and reduce intestinal permeability via the restoration of tight junction protein complexes in ex vivo studies of ischemic porcine intestine.
Dosing

The recommended dose of lubiprostone for the treatment of OIC is 24 mcg taken orally twice daily with food and water. The dosage should be reduced in patients with moderate and severe hepatic impairment.10

Clinical Trials

The efficacy of lubiprostone was evaluated in 3 randomized, double-blind, placebo-controlled studies in patients with documented constipation at baseline. Patients received stable opioid therapy for at least 30 days before screening, and the treatment continued throughout the 12-week period. Laxative use was discontinued at the beginning of the screening period and throughout the study. At baseline and monthly during the treatment period, patients were administered the Brief Pain Inventory–Short Form questionnaire to assess pain control.10

Lubiprostone was evaluated in 3 randomized, double-blind, placebo-controlled studies in patients with documented OIC. Lubiprostone achieved the overall efficacy end points in Studies 1 and 2, but not in Study 3.10

Study 1

In Study 1, at baseline, the mean oral morphine equivalent daily doses were 99 mg for the placebo-treated group and 130 mg for the lubiprostone-treated group. The median weekly spontaneous bowel movement frequencies at baseline were 1.5 for the placebo arm and 1.0 for the lubiprostone arm. Except for the 48-hour period before first dose and for at least 72 hours after the first dose, the use of rescue medication was allowed in cases where no bowel movement had occurred over a 3-day period.10

In this study, 431 patients receiving nondiphenylheptane (eg, nonmethadone) opioids were randomized to receive placebo or lubiprostone twice daily for 12 weeks. The primary efficacy analysis was a comparison of the proportion of overall responders in each treatment group. In Study 1, the proportion of overall responders was 8.2% greater with lubiprostone compared with placebo (P = .03) in patients with OIC (Table 1).10

Study 2

In Study 2, the baseline mean oral morphine equivalent daily doses were 237 mg for the placebo-treated group and 265 mg for the lubiprostone-treated group. The median weekly spontaneous bowel movement frequencies at baseline were 1.5 for both treatment groups. With the exception of the 48-hour period before the first dose and for at least 1 week after the first dose, the use of rescue medication was allowed in cases where no bowel movement had occurred in a 3-day period.10

The 418 patients receiving opioids were randomized to receive placebo or lubiprostone twice daily for 12 weeks. This study did not exclude patients receiving diphenylheptane opioids (eg, methadone). Results for the primary efficacy end point—the mean change from baseline in spontaneous bowel movement frequency at week 8—were a 0.9 greater mean change from baseline (P = .004) with lubiprostone compared with placebo (Table 2).10

Study 3

In Study 3, the baseline mean oral morphine equivalent daily doses were 330 mg for the placebo-treated group and 373 mg for the lubiprostone-treated group. The median weekly spontaneous bowel movement frequencies at baseline were 1.5 for both treatment groups. Except for the 48-hour period before the first dose and for at least 1 week after the first dose, the use of rescue medication was allowed in cases where no bowel movement had occurred in a 3-day period.10

Table 1

Study 1: Lubiprostone versus Placebo; Proportion of Overall Respondersa in Patients with OIC

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Proportion of overall responders</th>
<th>Treatment difference, %</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo twice daily, % (N = 217)</td>
<td>18.9</td>
<td>8.2</td>
<td>.03</td>
</tr>
<tr>
<td>Lubiprostone 24 mcg twice daily, % (N = 214)</td>
<td>27.1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NOTE: Examination of gender and race subgroups did not identify differences in response to lubiprostone in these subgroups. There were too few patients aged ≥65 years to adequately assess differences in effects in the elderly population. OIC indicates opioid-induced constipation.

Source: Amitiza (lubiprostone) capsules prescribing information; 2013.

Table 2

Study 2: Lubiprostone versus Placebo: Mean Change from Baseline in SBM Frequency in Patients with OIC

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean change from baseline in SBM frequency at week 8</th>
<th>Treatment difference</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo twice daily, % (N = 208)</td>
<td>2.4</td>
<td>0.9</td>
<td>.004</td>
</tr>
<tr>
<td>Lubiprostone 24 mcg twice daily, % (N = 210)</td>
<td>3.3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NOTE: Examination of gender and race subgroups did not identify differences in response to lubiprostone in these subgroups. There were too few patients aged ≥65 years to adequately assess differences in effects in the elderly population. OIC indicates opioid-induced constipation; SBM, spontaneous bowel movement.

Source: Amitiza (lubiprostone) capsules prescribing information; 2013.
Patients receiving opioids (N = 451) were randomized to receive placebo or lubiprostone 24 mcg twice daily for 12 weeks. This study, too, did not exclude patients receiving diphenylheptane opioids (eg, methadone). The findings for the primary efficacy end point—the mean change from baseline in spontaneous bowel movement frequency at week 8—were a 0.2 greater mean change from baseline in spontaneous bowel movement frequency in the lubiprostone group (P = .76) compared with placebo (Table 3).10

**Safety**

The most common adverse reactions (incidence >4%) reported in patients receiving lubiprostone for the treatment of OIC are nausea and diarrhea. Adverse reactions that occurred in at least 1% of patients who received lubiprostone 24 mcg twice daily and that occurred more frequently with lubiprostone than with placebo are listed in Table 4.10

**Contraindications**

Lubiprostone is contraindicated in patients with known or suspected mechanical GI obstruction.10

**Warnings and Precautions**

**Nausea.** Patients taking lubiprostone may experience nausea. Concomitant administration of food may reduce the symptoms of nausea.10

**Diarrhea.** Lubiprostone should not be prescribed to patients who have severe diarrhea. Patients should be made aware of the potential for diarrhea during treatment, and they should be instructed to discontinue lubiprostone and inform their physician if severe diarrhea occurs.10

**Dyspnea.** Patients taking lubiprostone may experience dyspnea within 1 hour of the first dose. This symptom generally resolves within 3 hours, but may recur with repeat dosing.10

**Bowel obstruction.** Patients with symptoms suggestive of mechanical GI obstruction should be evaluated before initiating treatment with lubiprostone.10

**Drug interactions.** The concomitant use of diphenylheptane opioids (eg, methadone) may interfere with the efficacy of lubiprostone.10

**Use in Specific Populations**

**Pregnancy.** Lubiprostone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.10

**Nursing mothers.** Caution should be exercised when administering lubiprostone to a nursing woman.10

**Conclusion**

Lubiprostone, an oral chloride channel activator treatment, became the first oral treatment to treat OIC in adults with chronic, noncancer pain, when it received FDA approval for this supplemental indication in April 2013. This approval provides a new and convenient

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**Table 3**

<table>
<thead>
<tr>
<th>Mean change from baseline in SBM frequency at week 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo twice daily (N = 216)</td>
</tr>
<tr>
<td>2.5</td>
</tr>
</tbody>
</table>

*a This study did not demonstrate a statistically significant improvement in SBM frequency at week 8.

**NOTE:** Examination of gender and race subgroups did not identify differences in response to lubiprostone in these subgroups. There were too few patients aged ≥65 years to adequately assess differences in effects in the elderly population.

OIC indicates opioid-induced constipation; SBM, spontaneous bowel movement.

Source: Amitiza (lubiprostone) capsules prescribing information; 2013.

**Table 4**

<table>
<thead>
<tr>
<th>System/adverse reaction</th>
<th>Percentage of patients with adverse reactions</th>
<th>Placebo, % (N = 632)</th>
<th>Lubiprostone 24 mcg twice daily, % (N = 860)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>5</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>1</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Flatulence</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Abdominal distension</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Abdominal discomfortb</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>General disorders and site administration conditions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>&lt;1</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

*a Includes only those events associated with treatment (possibly, probably, or definitely related, as assessed by the investigator).

b This term combines abdominal tenderness, abdominal rigidity, gastrointestinal discomfort, stomach discomfort, and abdominal discomfort.

OIC indicates opioid-induced constipation.

Source: Amitiza (lubiprostone) capsules prescribing information; 2013.
treatment option for patients with OIC who prefer to use an oral rather than a subcutaneous therapy. Two other indications were previously approved by the FDA for lubiprostone—for the treatment of chronic idiopathic constipation, and the treatment of IBS with constipation in women aged ≥18 years.

Lubiprostone was evaluated in 3 randomized, double-blind, placebo-controlled studies in patients with documented OIC. Lubiprostone achieved the overall efficacy end points in Studies 1 and 2, but not in Study 3. The most common adverse reactions (incidence >4%) reported in patients treated with lubiprostone for OIC are nausea and diarrhea.

**References**

10. Amitiza (lubiprostone) capsules [prescribing information]. Bethesda, MD: Sucampo Pharma Americas, LLC; and Deerfield, IL: Takeda Pharmaceuticals America, Inc; April 2013.