



# Alvimopan (Entereg), a Peripherally Acting mu-Opioid Receptor Antagonist For Postoperative Ileus

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## INTRODUCTION

In 2007, Goldstein et al. sought to determine the economic burden attributed to the management of postoperative ileus (POI) associated with abdominal surgery in the U.S. Their study revealed an annual national hospital cost of \$1.46 billion for both the index hospitalization and any readmissions within 30 days.<sup>1</sup> POI is one of the expected complications of major abdominal surgery. It can occur with other procedures, including extraperitoneal, gynecological, joint replacement, and cardiovascular surgeries,<sup>1,2</sup> and it is the most common cause of delayed hospital discharge after abdominal surgery.<sup>2,3</sup>

POI is the impairment of gastrointestinal (GI) motility after intra-abdominal surgery or other non-abdominal procedures. It affects all segments of the GI tract and may last from five to six days or even longer, and it has the potential to delay GI recovery and hospital discharge until its resolution.

POI is characterized by abdominal distention and bloating, nausea, vomiting, pain, accumulation of gas and fluids in the bowel, and delayed passage of flatus and defecation (Table 1). It is the result of a multifactorial process that includes inhibitory sympathetic input and the release of hormones, neurotransmitters, and other mediators (e.g., endogenous opioids).

A component of POI also results from

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an inflammatory reaction and the effects of opioid analgesics. Morphine and other mu-opioid receptor agonists are universally used for the treatment of acute post-surgical pain; however, they have an inhibitory effect on GI tract motility and may prolong the duration of POI.<sup>1-6</sup> These changes result in decreased motility and inhibition of propulsive motion.<sup>3,4</sup> Because opioid receptors are present in the GI tract, when opioids bind to these receptors, they can disrupt normal GI function, which allows for the passage of food through the GI tract. Consequently, POI can cause significant discomfort and pain.<sup>2</sup>

POI is associated with longer hospital stays and a high utilization of health care resources.<sup>1-3</sup> The duration of POI varies among patients and is associated with delayed enteral feeding, resulting in a negative impact on postoperative pain management and an increased risk of other postoperative morbidities.<sup>2,3</sup> Despite the consequences of the possible causative factors, the ensuing clinical injury associated with POI is characterized by abdominal distention and a delay in the return to normal bowel function.<sup>1,3</sup>

## INDICATION AND USAGE

In May 2008, the U.S. Food and Drug Administration (FDA) approved alvimopan (Entereg, Adolor/GlaxoSmith-Kline), a selective, quaternary, peripherally acting mu-opioid receptor (PAM-OR) antagonist, for accelerating upper and lower GI tract recovery after

partial large-bowel or small-bowel resection with primary anastomosis.<sup>3,6,7</sup> It is the first FDA-approved therapy for POI and is available for short-term use in hospitals. The drug is registered under the Entereg Access Support and Education (EASE) program.<sup>2</sup>

## CLINICAL PHARMACOLOGY

Alvimopan is a mu-opioid receptor antagonist with a considerably greater binding affinity for mu-opioid receptors than for delta- and kappa-opioid receptors. Following oral administration, the drug antagonizes the peripheral effects of opioids on GI motility and secretion by competitively binding to mu-opioid receptors in the GI tract. By working peripherally, alvimopan effectively antagonizes the GI motility effects of analgesics (such as morphine) without reversing central analgesic efficacy.

Alvimopan is a white to light beige powder with a molecular weight of 460.6. The empirical formula is  $C_{25}H_{32}N_2O_4 \cdot 2 H_2O$  (Figure 1). At physiological pH, alvimopan is zwitterionic, a property that contributes to its low solubility because of the ion's ability to carry a positive and negative charge at the same time.<sup>6,7</sup>

## PHARMACOKINETICS AND PHARMACODYNAMICS

In healthy subjects, the plasma concentration of alvimopan peaks approximately two hours after ingestion. The drug's oral bioavailability is approximately 6% (range, 1%–19%). Because of its

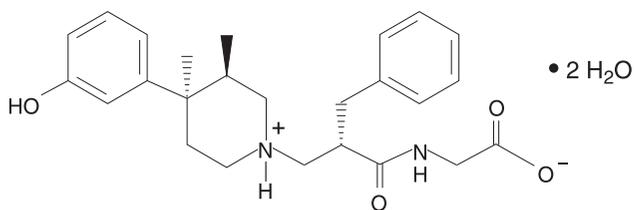
**Table 1 Clinical Features and Consequences of Postoperative Ileus**

Nausea	Patient discomfort
Vomiting	Delayed enteral feeding
Inability to eat	No flatus or bowel movement
Bowel distention	Cost: more than \$1 billion per year

Data from Wolff BG, Leslie JB, Saclarides TJ, et al. *Contemp Surgery* 2006(Suppl):1–24.<sup>3</sup>; Foss JF, Fisher DM, Schmith VD. *Clin Pharmacol Ther* 2008;83(5):770–776;<sup>4</sup> and Alvimopan (Entereg), package insert.<sup>6</sup>

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**Figure 1** Chemical structure of alvimopan (Entereg). (Data from package insert.<sup>6</sup>)

moderately large molecular weight and low lipophilicity, alvimopan does not cross the blood–brain barrier. Alvimopan has one major metabolite (ADL08-0011), and its terminal half-life ranges from 10 to 18 hours, similar to that of the parent drug.

This metabolite is a result of intestinal rather than hepatic metabolism. High-fat meals decrease the extent and rate of alvimopan absorption; however, the clinical significance is unknown.

The drug's pharmacokinetics is not affected by the patient's age or sex; therefore, no dosage adjustments are needed. Approximately 2% of the administered dose is excreted in the urine as the unchanged drug. Renal clearance of alvimopan accounts for approximately 30% of total plasma clearance. Biliary secretion is the primary pathway for alvimopan elimination; there is no evidence that hepatic metabolism plays a significant role in further elimination.

In a study designed to evaluate potential effects on cardiac conduction, alvimopan did not cause clinically significant prolongation of the corrected QT interval (QTc) at doses up to 24 mg twice daily for seven days. The potential for QTc effects at higher doses has not been studied.<sup>6,7</sup>

## CLINICAL TRIALS

### POI Studies<sup>8–12</sup>

The FDA's approval of alvimopan was based on the results of five multicenter, randomized, double-blind, parallel-group, placebo-controlled studies (four in the U.S. and one in Europe). The trials enrolled more than 2,000 adults undergoing partial large-bowel or small-bowel resection with primary anastomosis or total abdominal hysterectomy under general anesthesia. All five efficacy trials had the following common design features:

- Patients were randomly assigned to receive alvimopan oral capsules or placebo.
- The initial dose was administered preoperatively.
- Subsequent doses were given twice daily beginning on postoperative day seven or until hospital discharge.
- Patients who were taking preoperative chronic opioids or who were scheduled to have laparoscopic surgery or epidural anesthesia were excluded.

For all studies, the primary efficacy endpoint was the time to recovery of both upper and lower GI tract motility following surgery. In the four POI studies,<sup>8–11</sup> the time to recovery of the upper and lower GI tracts was a three-component composite endpoint called GI-3. GI-3 was defined as the time from the end of surgery to the time of recovery of the upper GI tract (toleration of solid food) and the lower GI tract (i.e., the first flatus or the first bowel movement, whichever occurred first). In the one POI efficacy study,<sup>12</sup> the time to recovery of the upper and lower GI tracts was a two-component composite endpoint called GI-2. GI-2 was defined as the time from the end of surgery to the time of recovery of the upper GI tract (i.e., toleration of solid food) and the lower GI tract (the first bowel movement).

Secondary efficacy endpoints included the following measurements of length of hospital stay (LOS):

- the discharge order written (DOW), defined as the time from the end of surgery to the time that the hospital discharge order was written
- ready, defined as the time from the end of surgery to the time ready for hospital discharge based solely on

recovery of GI function, as determined by the surgeon.

In all five studies, treatment with alvimopan significantly accelerated the time to recovery of GI function, compared with placebo, by 10.7 to 26.1 hours, as measured by a composite endpoint of toleration of solid food and first bowel movement. GI recovery began approximately 48 hours postoperatively. In addition, patients receiving alvimopan were discharged 13 to 21 hours sooner than those in the placebo group. The use of alvimopan did not reverse opioid analgesia in any of the studies.

Adverse events reported with alvimopan (n = 1,650), compared with placebo (n = 1,365), in nine placebo-controlled studies in surgical patients included constipation (9.7% vs. 7.6%), flatulence (8.7% vs. 7.7%), hypokalemia (6.9% vs. 7.5%), dyspepsia (5.9% vs. 4.8%), anemia (5.4% for both), urinary retention (3.5% vs. 2.3%), and back pain (3.4% vs. 2.6%, respectively).

## CHRONIC OPIOID-INDUCED BOWEL DYSFUNCTION

### Paulson et al.<sup>13</sup>

Paulson et al. reported results of a phase 3 randomized, placebo-controlled study involving 168 patients with opioid-induced bowel dysfunction, defined as fewer than three bowel movements per week. These patients had been receiving opioid analgesic therapy (the equivalent of at least 10 mg/day of oral morphine) for at least one month for nonmalignant pain or opioid dependence.

Patients were randomly assigned to receive a single daily dose of alvimopan 0.5 or 1 mg or placebo for 21 days. The average percentage of patients having at least one bowel movement within eight hours after receiving the study drug each day during the 21-day treatment period was significantly higher with alvimopan 1 mg (54%) and 0.5 mg (43%) than with placebo (29%) ( $P < 0.001$ ).

The effect of alvimopan appeared to be dose-related. The median time to the first bowel movement was significantly shorter after the first dose of alvimopan 1 mg compared with placebo (3 hours vs. 21 hours, respectively;  $P < 0.001$ ). The median time to the first bowel movement was also shorter after the first dose of alvimopan 0.5 mg (7 hours), but this dif-

ference was not statistically significant.

Alvimopan was well tolerated; 18 of 54 (33%) of patients in the placebo group, 22 of 58 (38%) of patients in the 0.5-mg group, and 27 of 56 (48%) of patients in the 1-mg group experienced at least one of the most common adverse effects, namely abdominal cramping, nausea, vomiting, diarrhea, and flatulence. Most of these effects were described as transient and mild to moderate in severity, resolving within one week. Alvimopan did not antagonize opioid-induced analgesia.

#### Webster et al.<sup>14</sup>

Webster et al. explored the efficacy and safety of alvimopan in subjects with non-cancer pain and opioid-induced bowel dysfunction (OBD) and sought to identify at least one treatment regimen that would improve OBD. Following a two-week baseline period, 522 subjects were enrolled who reported fewer than three spontaneous bowel movements per week (with 25% or more accompanied by a sensation of incomplete evacuation, straining, or lumpy hard stools) and who required analgesia equivalent to oral morphine 30 mg/day or more.

Patients were randomly assigned to receive alvimopan 0.5 mg twice daily, 1 mg once daily, 1 mg twice daily, or placebo for six weeks. Compared with placebo, alvimopan showed a statistically and clinically significant increase in the mean weekly frequency of spontaneous bowel movements over the initial three weeks of treatment (the primary endpoint) with 0.5 mg twice daily (+1.71 mean spontaneous bowel movements per week), 1 mg once daily (+1.64), and 1 mg twice daily (+2.52) ( $P < 0.001$  for all comparisons). The increased frequency of spontaneous bowel movements and additional treatment effects (less straining, incomplete evacuation, abdominal bloating or discomfort; more stool consistency; and better appetite) were sustained for more than six weeks.

The most commonly reported adverse events (abdominal pain, nausea, and diarrhea) occurred more often in those patients taking higher doses. The 0.5-mg twice-daily regimen demonstrated the best benefit-to-risk profile for managing OBD with alvimopan in this study population, with a side-effect profile similar to that of placebo. There was no evidence of

opioid analgesia antagonism. Competitive peripheral antagonism of opioids with alvimopan restored GI function and relieved OBD without compromising analgesia.

### ADVERSE DRUG REACTIONS

Patients tolerated alvimopan well. Commonly reported adverse effects included nausea, vomiting, and abdominal distention. The drug did not appear to reverse opioid analgesia at therapeutic doses.<sup>6</sup> However, in patients receiving chronic opioid therapy, the use of alvimopan may precipitate a dose-related, localized, gut-specific withdrawal.<sup>6,10</sup>

Three randomized, double-blind, placebo-controlled trials enrolled a total of 1,012 patients undergoing bowel resection or radical hysterectomy.<sup>10,12,15</sup> Patients were randomly assigned to receive alvimopan 6 mg or placebo two hours before surgery and then twice daily after surgery.

In trials by Delaney<sup>10</sup> and Wolff,<sup>12</sup> the most commonly observed treatment-emergent adverse events were nausea, vomiting, and hypotension. Nausea and vomiting occurred in a higher, but not statistically significant, percentage of patients receiving placebo than in those receiving alvimopan 6 mg. There was no difference between the groups in incidence of hypotension.

In the Wolff trial,<sup>12</sup> serious adverse events considered by the investigators to be related to the study drug were experienced by 1.2% of placebo patients and 3% of patients receiving alvimopan 6 mg. The percentage of patients who discontinued treatment because of adverse events was 2.4% for the alvimopan 6-mg group and 4.2% for the placebo group.

In the Taguchi trial,<sup>15</sup> nausea and vomiting occurred significantly less often with alvimopan 6 mg. No adverse events were considered to be related to the administration of alvimopan.

A phase 3, double-blind, placebo-controlled, 12-month study was designed to evaluate the long-term safety and tolerability of alvimopan 0.5 mg twice daily in patients taking opioids for chronic non-cancer pain and experiencing opioid-induced bowel dysfunction (OBD).<sup>16</sup> A total of 805 patients were randomly assigned, in a 2:1 fashion; 538 patients received alvimopan, and 267 received placebo.

A higher number of myocardial infarctions (MIs) occurred in patients treated with alvimopan (2.6%), compared with placebo patients (1.12%). Five of the MIs occurred at two investigational centers and did not appear to be related to the duration of alvimopan treatment.

In this study, most of the MIs occurred between one month and four months after initiation of treatment. This imbalance has not been observed in other studies of alvimopan, including studies in patients undergoing bowel-resection surgery who received alvimopan 12 mg twice daily for up to seven days, and a causal relationship with alvimopan has not been established.

The study also showed an imbalance in the incidence of neoplasms (2.8% for alvimopan vs. 0.7% for placebo) and in the rate of fractures reported for alvimopan compared with placebo.<sup>6</sup>

### USE IN SPECIAL POPULATIONS

Alvimopan is classified as a Pregnancy Category B agent.<sup>6</sup>

### DRUG INTERACTIONS

The concomitant administration of alvimopan with inducers or inhibitors of cytochrome P450 (CYP) enzymes is unlikely to alter its metabolism because it is not a substrate of CYP enzymes, according to *in vitro* data. The coadministration of alvimopan does not appear to alter the pharmacokinetics of morphine or its metabolite, morphine-6-glucuronide, when morphine is administered intravenously; dosage adjustments, therefore, are not necessary.<sup>6</sup>

### PRECAUTIONS AND CONTRAINDICATIONS

Alvimopan is not recommended for patients with severe hepatic impairment or end-stage renal disease or in patients undergoing surgery to correct complete bowel obstruction. Alvimopan is contraindicated in patients who have been receiving therapeutic doses of opioids for more than seven consecutive days.<sup>6</sup>

### DOSAGE AND ADMINISTRATION

As a tablet designed for oral administration, alvimopan should be used only in a hospital setting. The FDA has approved alvimopan with a Risk Evaluation and Mitigation Strategy (REMS) to ensure that the drug's benefits outweigh

the risks. Under REMS, the FDA has restricted the availability of alvimopan to hospitals that have enrolled in the EASE program. This restriction mandates that alvimopan is not to be dispensed to patients after hospital discharge.

To enroll in EASE, hospitals must acknowledge that the staff who prescribe, dispense, and administer alvimopan have been given educational materials about the need to restrict the use of alvimopan to inpatients only and to limit the dosage to 15 doses per patient.<sup>6</sup>

## FUTURE TRENDS AND ONGOING STUDIES<sup>16,17</sup>

Adolor plans to conduct two pediatric studies of alvimopan to assess GI recovery in (1) newborns zero to one month of age and (2) children one month of age and older, up to 16 years of age who are undergoing bowel resection. The studies will measure population pharmacokinetic parameters, safety, and time to the first tolerated feeding in hospitalized infants zero to one month of age. In patients older than one month of age up to 16 years, the study will measure the time to the first tolerated feeding, pharmacokinetic parameters, the proportion of postoperative days with stool passed while in the hospital, LOS, the need for postoperative nasogastric tube insertion for symptoms of POI, and safety.

In July 2008, the FDA lifted the clinical hold on the Investigational New Drug Application (IND) of alvimopan capsules for POI. Adolor and GlaxoSmithKline plan to begin a multicenter, double-blind, placebo-controlled, parallel-group clinical trial of alvimopan to treat POI in patients undergoing radical cystectomy, another population in whom POI is a significant burden, as part of a postmarketing commitment.<sup>16,17</sup>

As of September 2008, GlaxoSmithKline returned worldwide rights to Adolor related to Entereg for chronic OBD but is retaining the rights to Entereg for POI. The companies will continue to collaborate on developing and marketing Entereg for POI in the U.S.

## TRADITIONAL TREATMENT OPTIONS

Pharmacological agents for the treatment and prevention of POI include several FDA-approved drugs that have been used on an off-label basis. They

include prokinetic agents such as metoclopramide (Reglan, Schwarz) and intravenous (IV) erythromycin.<sup>18,19</sup> Introduced in the 1960s, metoclopramide accelerates gastric emptying and stimulates gastric, pyloric, and small-bowel motor activity, but it has little or no effect on the colon. Despite the drug's use in the management of POI, there are no data from randomized controlled trials to support this notion.

Cheape et al.,<sup>20</sup> in a prospectively randomized study, assessed metoclopramide in reducing the duration of ileus after colorectal surgery. One hundred consecutive patients who underwent elective abdominal colorectal surgery were assigned to receive or not to receive metoclopramide. IV metoclopramide was administered every eight hours from the completion of surgery until patients were able to tolerate a diet of solid food. Metoclopramide did not significantly alter the course of POI.

In a double-blind controlled study of 60 patients by Jepsen et al., metoclopramide had a negative effect upon the resolution of POI.<sup>21</sup> This drug can cause sedation, akathisia (feelings of motor restlessness), and other extrapyramidal reactions.<sup>19</sup>

Erythromycin, a motilin-receptor agonist, has been used in patients with POI, and some data suggest that it stimulates gastric emptying postoperatively. However, erythromycin lacks activity in the

colon.

Bonacini et al.<sup>22</sup> attempted to determine whether erythromycin shortened the period of POI in a prospective, double-blind, placebo-controlled study of 77 patients. Forty-one patients received IV erythromycin 250 mg every eight hours for nine doses upon admission to the recovery room; 36 patients received placebo. Recorded outcomes included the time (in hours) to the first passage of flatus, the first liquid meal, the first bowel movement, and total LOS. There was no significant difference between groups. The authors concluded that erythromycin did not seem to alter clinical parameters of GI motility after an abdominal operation.<sup>21</sup>

Other drugs such as propranolol (Inderal, Wyeth)<sup>23</sup> and neostigmine (Prostigmin, ICN)<sup>24</sup> have been used to treat POI; however, clinical data showing benefits in accelerating postoperative GI recovery are lacking.

Methylnaltrexone (Relistor, Wyeth/Progenics), another quaternary mu-opioid receptor antagonist, was approved in April 2008 for the treatment of opioid-induced constipation in palliative-care patients with insufficient response to laxative therapy. Preliminary results from the two phase 3 trials showed that methylnaltrexone did not achieve the primary endpoint of the study—a reduction in time to recovery of GI function (i.e., the time to the first bowel movement),

**Table 2 Therapy for Postoperative Ileus: Cost Comparison**

Drug	Dosing	Average Wholesale Price
Alvimopan (Entereg)	12 mg 30 minutes to 5 hours before surgery, followed by 12 mg twice daily for up to 7 days for a maximum of 15 doses	\$1,125 <sup>26</sup>
Metoclopramide (Reglan), generic	10 mg orally four times daily for 7 days	\$4.42 <sup>27</sup>
	10 mg IV four times daily for 7 days	\$11.80 <sup>27</sup>
Erythromycin	200 mg IV, then 250 mg orally three times daily for 7 days	\$15.79 <sup>27</sup>
	250 mg orally three times daily for 7 days	\$5.79 <sup>27</sup>

Data from University of Utah Hospitals & Clinics<sup>26</sup> and CardinalHealth.<sup>27</sup>

compared with placebo.<sup>19,25</sup>

At present, no head-to-head studies have compared alvimopan with other agents.

**COST**

Alvimopan 12-mg capsules are available in a unit package of 30. As of July 2008, the average wholesale price (AWP) for 30 tablets was \$2,250, or approximately \$75 per capsule. A full course of therapy, for up to seven days for a maximum of 15 doses, was \$1,125.<sup>26</sup> This cost may vary, depending on the acquisition cost for each hospital.

The AWP of other therapeutic options used for the management of POI are listed in Table 2 (see page 582).<sup>27</sup>

**CONCLUSION**

Alvimopan reverses opioid-induced slowing of GI transit time and constipation without antagonizing the analgesic effect of opioid analgesics or precipitating withdrawal in opioid-dependent patients. It has been studied in patients at high risk for POI and patients with OBD. With the recent FDA approval of alvimopan, many P&T committees will be impelled to evaluate it for inclusion on formularies. With the REMS and EASE programs in place, establishing criteria for the safe, appropriate, and cost-effective use of alvimopan will be imperative.

Criteria for use might call for restricting alvimopan use in patients undergoing abdominal surgeries associated with a higher risk of POI and for treating OBD in patients receiving chronic opioid therapy. The most important concern is the drug's safety profile. Because cardiovascular safety remains a concern, restrictions might apply to patients with cardiovascular disease. Although adding alvimopan might increase pharmacy budgets, substantial cost savings could be realized from the reductions in hospital LOS observed in some clinical trials.

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