Alvimopan (Entereg) for the Management Of Postoperative Ileus in Patients Undergoing Bowel Resection
Michael Kraft, PharmD, BCNSP; Robert MacLaren, PharmD; Wei Du, PhD; and Gay Owens, PharmD

ABSTRACT
Postoperative ileus (POI) after open abdominal surgery and bowel resection can lead to significant patient discomfort, morbidity, and prolonged length of stay in the hospital. Several factors have been implicated in the pathophysiology of POI, including surgical manipulation of the bowel, inflammation, inhibitory neural reflexes, and endogenous and exogenous opioids. Alvimopan (Entereg), approved by the FDA to accelerate upper and lower gastrointestinal (GI) recovery following partial large-bowel or small-bowel resection with primary anastomosis, represents a potential advance in the care of these patients. In five randomized, double-blind, placebo-controlled, phase 3 clinical trials, alvimopan, compared with placebo, accelerated the time to GI recovery and hospital discharge status after bowel resection. In this article, we review the formulary details of alvimopan for in-hospital management of POI following this procedure.

INTRODUCTION
Postoperative ileus (POI) is a transient cessation of coordinated bowel motility that occurs universally after bowel resection and prevents effective transit of intestinal contents or tolerance of dietary intake.1 POI is also characterized by pain and abdominal distention, nausea, vomiting, and accumulation of gas or fluids in the bowel.2 The causes of POI are multifactorial and include surgical manipulation, inflammatory response, inhibitory neural reflexes, secretion of endogenous opioids, and exogenous opioids used to manage pain.2–4 Moreover, POI is associated with a greater incidence of postoperative morbidity and is a common reason for an increased hospital length of stay (LOS) or readmission.5–7 An analysis of a large national database revealed that patients with coded POI had a higher health care costs (an additional $9,417) per hospital stay or tolerance of dietary intake.1 POI is also characterized by pain and abdominal distention, nausea, vomiting, and accumulation of gas or fluids in the bowel.1 The causes of POI are multifactorial and include surgical manipulation, inflammatory response, inhibitory neural reflexes, secretion of endogenous opioids, and exogenous opioids used to manage pain.2–4 Moreover, POI is associated with a greater incidence of postoperative morbidity and is a common reason for an increased hospital length of stay (LOS) or readmission.5–7 An analysis of a large national database revealed that patients with coded POI had a higher health care costs (an additional $9,417) per hospital stay compared with patients without coded POI.8
OPD

Pharmacology
Alvimopan is a trans-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine mu-opioid receptor antagonist (Figure 1).12 At clinically relevant concentrations, its passage from the systemic circulation to the central nervous system (CNS) is limited as a consequence of its large molecular size, zwitterionic form, and high polarity.20 Because the site of action at clinically relevant concentrations is primarily in the periphery, alvimopan does not interfere with the analgesic activity mediated by mu-opioid receptors in the CNS.13–15,18

As in vitro radioligand binding has shown, alvimopan binds with high affinity to mu-opioid receptors (with an inhibition constant [Kᵢ] of 0.4 nM), but it has no significant activity toward delta-opioid (Kᵢ = 4.4 nM) or kappa-opioid (Kᵢ = 40 nM) receptors.21,22 Furthermore, alvimopan has low affinity for non-opioid (adrenergic, dopaminergic, serotonergic, and peptidergic) receptor types.22

The drug’s slow rate of dissociation from the mu-opioid

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Various strategies have been implemented in attempts to reduce the duration of POI, including:8–11

• epidural anesthesia.
• a less invasive surgical procedure, such as laparoscopy.
• accelerated postoperative care pathways (e.g., multimodal approaches, including epidural local anesthetics, early removal of a nasogastric tube, early ambulation, early oral intake, and the use of laxatives or other prokinetic agents).

Despite the implementation of accelerated GI recovery protocols, patients undergoing bowel resection via laparotomy who are receiving opioid-based intravenous patient-controlled analgesia (IV–PCA) may still experience delayed GI recovery and considerable postoperative morbidity.7

Alvimopan (Entereg, Adolor), an oral, peripherally acting mu-opioid receptor (PAM-OR) antagonist, was approved by the FDA in May 2008. In four North American phase 3 multicenter trials and a single European phase 3 trial, alvimopan accelerated GI recovery in patients undergoing laparotomy for bowel resection.12–18 Following are the relevant formulary considerations for alvimopan and updates of recent findings regarding the management of POI in these patients.19

PHARMACOLOGY

Alvimopan is a trans-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine mu-opioid receptor antagonist (Figure 1).12 At clinically relevant concentrations, its passage from the systemic circulation to the central nervous system (CNS) is limited as a consequence of its large molecular size, zwitterionic form, and high polarity.20 Because the site of action at clinically relevant concentrations is primarily in the periphery, alvimopan does not interfere with the analgesic activity mediated by mu-opioid receptors in the CNS.13–15,18

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The drug’s slow rate of dissociation from the mu-opioid

Disclosure. Dr. Kraft has participated in educational symposia sponsored by, and has served as a consultant for, Adolor Corporation and GlaxoSmithKline. Dr. MacLaren has served as a consultant for Adolor Corporation. Dr. Du is a former employee of Adolor Corporation, and Dr. Owens is currently an employee of Adolor Corporation.
that alvimopan 12 mg significantly accelerated GI recovery when it was given 30 to 90 minutes preoperatively and twice daily postoperatively.18

Because alvimopan does not alter the pharmacokinetic properties of opioids, it can be administered with opioids without loss of analgesic efficacy.16,20,28 In addition, alvimopan does not alter pain scores or opioid consumption in phase 2 and 3 studies; this suggests that at clinically relevant doses, alvimopan and its metabolite have limited access to the CNS.12–15,17,18,20 Moreover, no other drug interactions have been identified.12,16 No data are available to determine whether it is possible or appropriate to open the capsules or to dissolve the drug into a solution.

CLINICAL TRIALS

The POI clinical development program initially included multiple alvimopan doses of 6 or 12 mg and mixed patient populations who were undergoing bowel resection or total abdominal hysterectomy.12 However, phase 3 clinical trial results demonstrated a consistent and robust treatment effect of alvimopan 12 mg after bowel resection (the approved indication for this agent).12,16 These results are the primary focus of this section.

Phase 2 Trials

Phase 2 studies investigated the safety and preliminary efficacy of alvimopan in various settings. In a randomized, double-blind, parallel, phase 2 study (n = 45), pain scores after dental extraction were comparable for patients receiving alvimopan 4 mg and morphine and for patients receiving morphine alone.20 Therefore, alvimopan did not appear to affect centrally mediated opioid analgesia.

Taguchi et al.29 examined the preliminary efficacy of alvimopan for accelerating GI recovery in 79 patients undergoing bowel resection (n = 15) or total abdominal hysterectomy (n = 63) in a phase 2 randomized trial. Alvimopan 6 mg significantly accelerated median times to the first bowel movement by 41 hours and readiness for hospital discharge by 23 hours without compromising opioid-based analgesia, as assessed by opioid consumption and Visual Analogue Scale (VAS) scores.29

Phase 3 Trials

To date, four randomized, double-blind, placebo-controlled, parallel-group, phase 3 trials conducted in the U.S. and Canada (14CL302, 14CL308, 14CL313, and 14CL314)13–15,18 and a single phase 3 trial conducted in Europe (SB-767905/001)17 have examined the efficacy and safety of alvimopan for the management of POI after laparotomy. Patients underwent major abdominal surgery via laparotomy and were scheduled to receive opioid-based IV-PCA. In trial SB-767905/001, however, patients were not required to use opioid-based IV-PCA; nonsteroidal anti-inflammatory drugs (NSAIDs) and other non-opioid analgesics were allowed.17 In each trial, a multimodal standardized accelerated care pathway was used to facilitate GI recovery, consistent with best care practices, for all patients in placebo and alvimopan groups. These measures involved nasogastric tube removal no later than noon the day after surgery, encouragement of liquids and ambulation (when possible) starting on postoperative day 1, and encouragement of solid food on postoperative day 2.
Table 1  Kaplan–Meier Mean Times to Recovery of Gastrointestinal Function and Incidence of Postoperative Ileus–Related Morbidity for Patients Undergoing Bowel Resection (Modified Intent-to-Treat Population)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Placebo</th>
<th>Alvimopan 12 mg</th>
<th>Placebo</th>
<th>Alvimopan 12 mg</th>
<th>Placebo</th>
<th>Alvimopan 12 mg</th>
<th>Placebo</th>
<th>Alvimopan 12 mg</th>
<th>Placebo</th>
<th>Alvimopan 12 mg</th>
<th>Placebo</th>
<th>Alvimopan 12 mg</th>
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<tbody>
<tr>
<td>GI-2, mean hours</td>
<td>119.9</td>
<td>106.7</td>
<td>130.3</td>
<td>116.4</td>
<td>132</td>
<td>105.9</td>
<td>111.8</td>
<td>92</td>
<td>108.8</td>
<td>92</td>
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<tr>
<td>(95% CI)</td>
<td>(110.8,129.1)</td>
<td>(98.9,114.5)</td>
<td>(120.5,140.1)</td>
<td>(107.5,125.3)</td>
<td>(105.7,118.0)</td>
<td>(87.2,196.9)</td>
<td>(102.6,115.1)</td>
<td>(93.3,130.1)</td>
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<tr>
<td>Difference, Pbo–Alv (HR)</td>
<td>13.2 (1.4)^a</td>
<td>14.0 (1.4)^a</td>
<td>26.1 (1.6)^a</td>
<td>19.8 (1.5)^a</td>
<td>10.6 (1.3)^a</td>
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<tr>
<td>GI-3, mean hours</td>
<td>113.9</td>
<td>103.6</td>
<td>122.1</td>
<td>109.7</td>
<td>119.2</td>
<td>99</td>
<td>97.8</td>
<td>82</td>
<td>92.1</td>
<td>87.3</td>
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<tr>
<td>(95% CI)</td>
<td>(104.9,122.8)</td>
<td>(95.6,111.5)</td>
<td>(113.0,131.1)</td>
<td>(101.3,118.1)</td>
<td>(108.3,130.0)</td>
<td>(92.3,105.7)</td>
<td>(77.9,86.1)</td>
<td>(86.5,97.7)</td>
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<tr>
<td>Difference, Pbo–Alv (HR)</td>
<td>10.3 (1.3)</td>
<td>12.4 (1.3)^a</td>
<td>20.2 (1.5)^a</td>
<td>15.8 (1.5)^a</td>
<td>4.8 (1.1)</td>
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<tr>
<td>BM, mean hours</td>
<td>104.7</td>
<td>86.4</td>
<td>107.9</td>
<td>90.6</td>
<td>103.3</td>
<td>84.1</td>
<td>96.2</td>
<td>80.6</td>
<td>89.2</td>
<td>77.5</td>
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<tr>
<td>(95% CI)</td>
<td>(95.5,114.0)</td>
<td>(87.5,107.0)</td>
<td>(109.2,128.0)</td>
<td>(99.0,116.1)</td>
<td>(100.6,123.7)</td>
<td>(85.1,99.6)</td>
<td>(75.7,87.7)</td>
<td>(68.2,76.9)</td>
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<tr>
<td>Difference, Pbo–Alv (HR)</td>
<td>6.4 (1.2)</td>
<td>7.3 (1.5)^a</td>
<td>16.2 (1.4)^a</td>
<td>15.6 (1.5)^a</td>
<td>11.8 (1.4)^a</td>
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<td>Solid food, mean hours</td>
<td>104.7</td>
<td>98.3</td>
<td>118.6</td>
<td>107.6</td>
<td>112.2</td>
<td>92.3</td>
<td>81.7</td>
<td>72.6</td>
<td>83</td>
<td>81.6</td>
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<tr>
<td>(95% CI)</td>
<td>(95.5,114.0)</td>
<td>(87.5,107.0)</td>
<td>(109.2,128.0)</td>
<td>(99.0,116.1)</td>
<td>(100.6,123.7)</td>
<td>(85.1,99.6)</td>
<td>(75.7,87.7)</td>
<td>(68.2,76.9)</td>
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<tr>
<td>Difference, Pbo–Alv (HR)</td>
<td>6.4 (1.2)</td>
<td>11.0 (1.3)^a</td>
<td>19.8 (1.4)^a</td>
<td>9.1 (1.2)^a</td>
<td>1.5 (1.0)</td>
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<td>DCO written, mean hours</td>
<td>143.2</td>
<td>130.3</td>
<td>149.1</td>
<td>127.8</td>
<td>147</td>
<td>127.8</td>
<td>138.1</td>
<td>120.5</td>
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<tr>
<td>(95% CI)</td>
<td>(133.9,152.5)</td>
<td>(121.7,138.9)</td>
<td>(140.6,157.6)</td>
<td>(120.6,135.0)</td>
<td>(136.6,157.5)</td>
<td>(120.2,135.4)</td>
<td>(131.8,144.3)</td>
<td>(115.2,125.7)</td>
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<tr>
<td>Difference, Pbo–Alv (HR)</td>
<td>12.9 (1.3)</td>
<td>21.3 (1.6)^a</td>
<td>19.3 (1.4)^a</td>
<td>17.6 (1.4)^a</td>
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<td>Postoperative LOS, mean days</td>
<td>6.4</td>
<td>6.1</td>
<td>6.6</td>
<td>5.7</td>
<td>7.4</td>
<td>6.1</td>
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<tr>
<td>Difference, Pbo–Alv (HR)</td>
<td>0.3</td>
<td>0.9</td>
<td>1.3</td>
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<tr>
<td>POI-related morbidity</td>
<td>10.1</td>
<td>10.2</td>
<td>12</td>
<td>7.2</td>
<td>14.8</td>
<td>5</td>
<td>10.3</td>
<td>6.0</td>
<td>7.9</td>
<td>4.6</td>
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<td>NGT insertion, %</td>
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<tr>
<td>Difference, Pbo–Alv</td>
<td>–0.1</td>
<td>4.8</td>
<td>9.8</td>
<td>4.3</td>
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<tr>
<td>Prolonged stay, %</td>
<td>5.1</td>
<td>0</td>
<td>7</td>
<td>4.3</td>
<td>8.5</td>
<td>3.1</td>
<td>6.4</td>
<td>1.3</td>
<td>0.9</td>
<td>0</td>
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<tr>
<td>Difference, Pbo–Alv</td>
<td>5.1</td>
<td>2.7</td>
<td>5.4</td>
<td>5.1^a</td>
<td>0.9</td>
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<tr>
<td>Readmission, %</td>
<td>3</td>
<td>1</td>
<td>1.4</td>
<td>0.7</td>
<td>2.1</td>
<td>1.3</td>
<td>1.9</td>
<td>0.9</td>
<td>1.3</td>
<td>0</td>
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<tr>
<td>Difference, Pbo–Alv</td>
<td>2</td>
<td>0.7</td>
<td>0.8</td>
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</table>

BM = bowel movement; BR = bowel resection; CI = confidence interval; DCO = discharge order; GI = gastrointestinal; GI-2 = time to first toleration of solid food and first bowel movement; GI-3 = time to first toleration of solid food, and first flatus or first bowel movement; HR = hazard ratio; LOS = length of hospital stay; NGT = nasogastric tube; Pbo–Alv = placebo–alvimopan; POI = postoperative ileus.

*P < 0.05, calculated from Wald chi-square tests for pair-wise comparisons from the Cox proportional hazards model.

*^P < 0.05, calculated from Wald chi-square tests for pair-wise comparisons from the Cox proportional hazards model.

*P < 0.05, calculated from an ANOVA model that included treatment only.

*^P < 0.001, calculated from an ANOVA model that included treatment only.

*P < 0.05, calculated from Fisher’s exact test.

*^P < 0.001, calculated from Fisher’s exact test.

Time to hospital discharge order written and postoperative length of stay in the European trial (SB-767905/001) are not comparable to the North American trials because of cultural differences in criteria used for discharge decisions (see text for details).

Data on file from Adolor Corp.; the FDA, and references 13–15, 17, and 18 (Delaney, Viscusi, Wolff, Buchler, and Ludwig).
About 10% of patients in both the alvimopan and placebo groups received concomitant treatment with laxatives. Patients received alvimopan or placebo before surgery and then twice daily until hospital discharge or for a maximum of seven postoperative days, or a maximum of 15 in-hospital doses. Patients in each study received a median of eight to 14 doses. The primary endpoint in all trials (except 14CL314) was the time to GI-3 recovery, a composite measurement including upper GI tract recovery (toleration of solid food), and lower GI tract recovery (first flatus or first bowel movement). The endpoint of GI-2 recovery (first toleration of solid food and first bowel movement) was also evaluated in all trials and was the primary endpoint in the most recent study (14CL314). The time to GI-2 recovery may be a more objective measure of upper and lower bowel function because it does not rely on the reporting of flatus. Other endpoints included the time to first bowel movement, the time to the first toleration of solid food, and the time to the written hospital discharge order (DCO).

For all studies, postoperative LOS (a supportive analysis based on the time to the written DCO) was defined as the number of days from the calendar day after surgery to the calendar day of the written DCO. Postoperative LOS and the time to the written DCO for the European trial (SB-767905/001) were not comparable to the North American trials because of differences in social and financial pressures contributing to discharge decisions. GI tract recovery is not a primary determinant of hospital discharge in these regions. As an example, a comparison of the placebo groups in the five trials comparing alvimopan and placebo indicated that the time to the written DCO was, on average, three to four days longer in the European trial than in the North American trials. Morbidity related to POI was defined as postoperative nasogastric tube insertion or POI resulting in a prolonged hospital stay or readmission seven days or less after initial hospital discharge.

Opioid use and VAS pain scores were recorded. Safety was monitored by adverse-event reporting. Alvimopan was administered 2 to 5 hours before surgery in four of the trials (14CL302, 14CL308, 14CL313, and SB-767905/001) and 30 to 90 minutes preoperatively in the fifth trial (14CL314). The modified intent-to-treat population included all randomized patients who were undergoing laparoscopic surgery, taking therapeutic doses of opioids for more than one week before surgery, and who had at least one on-treatment evaluation for flatus, bowel movement, or solid food.

In the phase 3 North American trials, patients undergoing bowel resection who received alvimopan 12 mg experienced an accelerated mean time to recovery of upper and lower GI function, as assessed by GI-2 (13 to 26 hours sooner; P < 0.05 for all) or GI-3 (10 to 20 hours sooner) versus placebo. The mean time to the written DCO was also accelerated (13 to 21 hours sooner; P < 0.05 for all but one trial) versus placebo. Moreover, the mean proportion of patients needing postoperative nasogastric tube insertion was lower with alvimopan (4.3% to 9.8%) than with placebo in most trials. In trial 14CL302, however, no difference was observed (see Table 1). These findings mirrored the lower incidences of nausea, vomiting, and abdominal bloating and distention in the alvimopan patients within the same time frame, as shown in individual studies and pooled analyses.

In the European trial (SB-767905/001), patients receiving alvimopan 12 mg had an accelerated mean time to GI-2 recovery (11 hours sooner) and GI-3 recovery (5 hours sooner) than those receiving placebo (Table 1). In this trial, 69% of patients received non-opioid analgesics, including NSAIDs, in the first 48 hours after surgery. However, a post hoc analysis of patients who received opioid-based IV-PCA revealed a 15-hour acceleration in time to GI-2 recovery for alvimopan patients when compared with placebo patients (P < 0.05). Thus, in this subset of patients receiving opioid-based IV-PCA, alvimopan 12 mg resulted in an accelerated time to GI-2 recovery, similar to data reported in the North American trials.

Phase 3 Study Limitations

The phase 3 trials were associated with several limitations. Patients who were undergoing laparoscopic surgery, taking therapeutic doses of opioids for more than one week before surgery, or unable to swallow capsules were excluded from enrollment. Although the approved indication for alvimopan does not preclude its use after laparoscopic bowel resection, no published data are available on its use in these patients. Therefore, further studies are warranted for this population and other patient groups. Moreover, comparisons of LOS cannot be made between the North American and European trials because of cultural differences in criteria used for hospital discharge. Patients in the North American trials (all of whom received opioid-based IV-PCA per protocol) and the patients in the European trials who received opioid-based IV-PCA appeared to benefit the most from alvimopan. It is unclear whether a similar benefit would be achieved in patients receiving non-PCA analgesia.

Finally, these trials were conducted with the background of a standardized accelerated postoperative care pathway intended to facilitate GI recovery in both the placebo and the treatment groups. In clinical practice, GI postoperative care can vary substantially. However, the benefits of alvimopan on GI-3, GI-2, and written DCOs were seen above and beyond the standardized postoperative care pathway.

**DOSAGE RECOMMENDATIONS**

Alvimopan 12 mg should be given from 30 minutes to 5 hours before surgery, then twice daily for up to seven days, for a maximum of 15 doses in the hospital. According to the FDA-approved label, no dose adjustments are necessary for elderly patients or for patients with mild-to-moderate hepatic impairment or mild-to-severe renal impairment; however, these patients should be monitored for adverse drug effects. Alvimopan is not recommended for patients with severe hepatic impairment or end-stage renal disease. It is contraindicated if patients have taken therapeutic doses of opioids for more than seven consecutive days immediately before taking alvimopan.

**ADVERSE EFFECTS**

Alvimopan was generally well tolerated, and the overall incidence of treatment-emergent adverse events was similar between groups. In worldwide population studies of bowel resection, treatment-emergent adverse events occurring more often (at a rate of 1% or higher) in patients receiving alvimopan than placebo included anemia, GI disorders (constipation, dyspepsia, and flatulence), hypokalemia, back pain, and urinary retention.
Alvimopan (Entereg) for Postoperative Ileus in Bowel Resection

In a long-term safety study of twice-daily alvimopan 0.5 mg for opioid-induced bowel dysfunction (OBD) (a chronic indication for alvimopan) in patients with chronic non-cancer pain, preliminary results demonstrated a higher number of reports of myocardial infarction (MI) in alvimopan-treated patients, leading to a clinical hold on the OBD trials. In contrast, no imbalance in severe events was observed in worldwide population data from the trials of POI (the acute indication for alvimopan), but the duration of follow-up was limited to less than two weeks after hospital discharge for more than 95% of these patients.12

Although these studies were not prospectively designed to evaluate the rate of cardiovascular (CV) events in this patient population, fewer CV events were reported with alvimopan—50 of 2,610 patients (2%), compared with 39 of 1,365 placebo patients (3%).12 Patients who experienced a CV event were older (generally 65 years of age or older) or had established CV disease, and rates of both of these traits were higher in the alvimopan group than in the placebo group.12 The FDA lifted the clinical hold in July 2008.16 32 Ongoing surveillance of patients who receive alvimopan is essential to assess any potential risks or further adverse effects.

WARNINGS AND SAFETY

Because of the higher number of MIs observed in patients receiving alvimopan in the OBD studies and new rules established by the FDA Amendments Act of 2007, a Risk Evaluation and Mitigation Strategy (REMS) was implemented to ensure the safe use of alvimopan. A boxed warning in the prescribing information states that alvimopan is indicated for short-term in-hospital use only.16 Hospitals performing bowel resection must enroll in the Entereg Access Support and Education (E.A.S.E.) program for their pharmacies to be able to order, stock, and dispense alvimopan.18 Authorized representatives (a P&T committee member, surgeon, or pharmacist) at hospitals enrolled in the E.A.S.E. program must confirm that (1) educational materials have been provided to health care professionals responsible for ordering, dispensing, or administering alvimopan; (2) measures are in place to limit alvimopan use to a maximum of 15 doses per patient for in-hospital use only; and (3) alvimopan will not be transferred to a non-registered hospital.34 REMS assessments are to be submitted to the FDA quarterly for the first 18 months after approval and annually thereafter to determine whether the program is meeting its goals and whether additional alterations are needed.35

THERAPEUTIC CONSIDERATIONS

POI is an unavoidable response to surgery, especially abdominal procedures, and provides no known clinical benefit to patients. Recovery of GI function is the primary determinant of readiness for patient discharge after bowel resection and, therefore, is directly related to hospital LOS.32 Several studies have suggested that POI increases LOS by two to eight days and results in an increase in average hospital costs of $4,000 to $9,000 per patient.8,36–38 The overall annual cost to the health care system is approximately $1.47 billion.8

GI recovery after bowel resection may be facilitated by the implementation of multimodal standardized accelerated care pathways. Alvimopan 12 mg, in conjunction with a standardized accelerated care pathway, speeds the time to GI recovery after bowel resection.12–15,18 This medication has also been associated with a lower incidence of POI-related morbidity and GI-related adverse events and reduced LOS without an increased risk of morbidity or a reversal of the benefits derived from opioid analgesia.12–15,18

Patients most likely to benefit from alvimopan are those undergoing bowel resection who will receive systemic opioids for analgesia. Hospitals should consider taking appropriate measures to ensure that alvimopan is used appropriately to achieve the maximum potential benefit. In addition to enrollment in the E.A.S.E. program, these measures may include:16

- • limiting prescribing to physicians who perform bowel resection or surgical services for patients undergoing this procedure.
- • incorporating alvimopan into existing standardized accelerated care pathways or establishing such pathways.
- • limiting the use of alvimopan to patients undergoing open abdominal surgery who are receiving systemic opioids for analgesia.
- • ensuring that patients receive the preoperative dose.
- • restricting the maximum number of in-hospital doses to 15, as described in the package insert.

Alvimopan has not been extensively studied in patients receiving epidural analgesia or laparoscopic bowel resection, although the approved indication does not preclude its use in these patients. However, opioid consumption is typically lower and LOS is shorter after laparoscopy than after laparotomy; therefore, it is not clear whether alvimopan would benefit these patients. Further investigation is necessary to assess the efficacy of alvimopan in patients who receive epidural analgesia (i.e., no systemic opioid therapy) or in patients undergoing laparoscopy. Additional research is also needed to determine the appropriate use of alvimopan in other patient populations, such as those taking therapeutic doses of opioids for more than one week before surgery, those who cannot swallow capsules, and those who do not receive a preoperative dose.

COST CONSIDERATIONS

In an economic analysis of the four phase 3 North American efficacy trials, mean estimated hospital costs were $879 to $977 lower with the use of alvimopan than with placebo.30 The published wholesale price of alvimopan is $62.50 per 12-mg capsule, resulting in a cost of $362.50 to $625 for nine to 10 doses (the median number of doses in the North American phase 3 clinical trials), or a cost of $937.50 for a total of 15 doses. Therefore, if a reduction in LOS can be achieved, this could result in a cost-neutral to cost-saving benefit to the hospital, depending on payer mix and reimbursement, institution capacity, and census. Further economic analysis in clinical practice is needed.30

CONCLUSION

In patients undergoing bowel resection who received opioid-based IV–PCA and were treated with a standardized accelerated care pathway, alvimopan 12 mg significantly accelerated GI recovery and time to the written hospital DCO; it was associated with reduced POI-related morbidity, fewer GI-related
adverse events, and a shorter hospital LOS.12–15,17,18 Alvimopan represents a potentially important advance in the management of POI in patients undergoing bowel resection.

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