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Alvimopan

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Contents

Abstract

▲ Alvimopan, a trans-3,4-dimethyl-4-(3-hydroxyphenyl) piperidine, is a selective, peripherally acting μ-opioid receptor antagonist that is available for short-term use in hospitalized patients who have undergone bowel resection.

▲ The efficacy of alvimopan in the management of postoperative ileus has been evaluated in five phase III trials; four conducted in North America and one conducted in Europe/Australasia. Patients who had undergone partial large or small bowel resection surgery with primary anastomosis were randomized to receive alvimopan 12 mg or placebo as a single oral pre-operative dose followed by twice-daily administration for up to 7 days postoperatively.

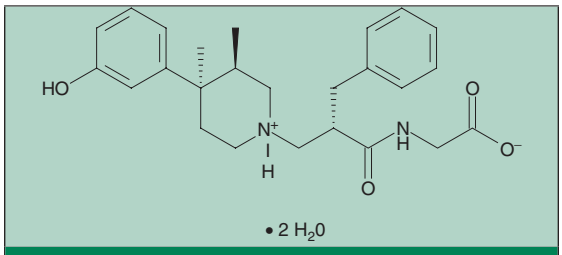
▲ In the five phase III trials, alvimopan was significantly more effective than placebo in reducing the time to recovery of upper and lower gastrointestinal (GI) function, as assessed using a two-component endpoint (GI2) comprising time to tolerance of solid food and first bowel movement. The mean time to reach the GI2 endpoint was 11–26 hours sooner with alvimopan than with placebo.

▲ In the phase III trials conducted in North America, the time to writing the hospital discharge order was 13–21 hours sooner with alvimopan than with placebo.

▲ Alvimopan did not reduce opioid-induced analgesia and/or increase the amount of opioids administered postoperatively.

▲ Short-term alvimopan was generally well tolerated in adults undergoing bowel resection.

Features and properties of alvimopan (Entereg®)	
Indication	
To accelerate the time to upper and lower gastrointestinal (GI) recovery following partial large or small bowel resection surgery with primary anastomosis	
Mechanism of action	
Selective antagonism of peripheral μ-opioid receptors, thereby blocking the adverse effects of opioids on GI motility without reversing central analgesia	
Dosage and administration	
Dosage preoperatively	Single 12 mg dose administered 30 min to 5 h prior to surgery
Dosage postoperatively	12 mg twice daily beginning on the day after surgery for a maximum of 7 days or until discharge (not to exceed 15 doses)
Route of administration	Oral
Pharmacokinetic profile (in healthy volunteers administered multiple oral doses of alvimopan 12 mg)	
Mean peak plasma concentration (C_{max})	10.98 ng/mL
Mean area under the plasma concentration-time curve from time 0 to 12 h	40.2 ng • h/mL
Time to C_{max}	≈2 h
Mean terminal phase elimination half-life	10–17 h
Absolute bioavailability	≈6%
Treatment-emergent adverse events in bowel resection patients treated with alvimopan	
Most frequent (incidence ≥3% and at least 1% greater than that with placebo)	Hypokalaemia, dyspepsia, anaemia, back pain, urinary retention



Alvimopan

Postoperative ileus is defined as a transient decrease in the motility of the gastrointestinal (GI) tract after intra-abdominal or non-abdominal surgery.[1] It affects all segments of the GI tract and commonly lasts 5–6 days. The signs and symptoms of postoperative ileus include nausea, vomiting, abdominal cramping and pain, abdominal distension and bloating, absence of bowel sounds, an inability to tolerate solid food and delayed passage of flatus or stools.[2] Postoperative ileus following surgery may delay recovery, prolong hospitalization and increase healthcare costs.[3]

The pathophysiology of postoperative ileus is multifactorial. However, it is thought that surgical trauma/bowel manipulation and postoperative administration of opioid analgesia leads to the disruption of normal hormonal, neural and local factor signalling, and results in abnormal electrophysiology and motility of the GI tract, with the consequent prolongation of postoperative ileus.[1,2] Each segment of the GI tract recovers motility at a different rate. Typically, motility returns first in the small intestine (generally 4–24 hours after surgery),[4] then in the stomach (usually 24–48 hours after surgery)[4] and finally in the colon (3–5 days after surgery).[5] Therefore, colonic dysfunction is typically the rate-limiting factor in the resolution of postoperative ileus.[1]

Until recently, a specific therapy for the management of postoperative ileus was not available. Management was generally multimodal and involved combining current practice approaches that were considered to be effective, including limiting the administration of opioids, combining continuous thoracic epidural with local anaesthetic, the use of NSAIDs as alternative analgesics, individualized use of nasogastric tubes, and early oral nutrition and ambulation.[1,2]

Selective, peripherally acting μ-opioid receptor antagonists, such as methylnaltrexone bromide and alvimopan (Entereg®),[1] have been investigated for their ability to block the adverse effects of opioid analgesics on the GI tract without affecting analgesia.[6]

Alvimopan, a trans-3,4-dimethyl-4-(3-hydroxyphenyl) piperidine, is the only μ-opioid receptor antagonist currently approved in the US (for short-term use in hospitalized patients only) to accelerate the time to upper and lower GI recovery following large or small bowel resection surgery with primary anastomosis.[7] This review focuses on the pharmacology and clinical profile of oral alvimopan in this indication. Medical literature referenced in this profile was identified using MEDLINE and EMBASE, supplemented by AdisBase (a proprietary database of Wolters Kluwer Health | Adis). Additional references were identified from the reference lists of published articles.

1. Pharmacodynamic Profile

Mechanism of Action

- Alvimopan has high affinity for μ-opioid receptors, with an apparent dissociation constant (K_i) of <1 nmol/L.[7-9] In radioligand-binding assays involving cloned human receptors, alvimopan had a higher affinity for μ-opioid than δ- and κ-opioid receptors (K_i 0.44 vs 10 and 100 nmol/L, respectively).[7,10]
- Alvimopan had no measurable opioid-agonist effects in standard pharmacological assays.[7]
- An amide hydrolysis compound of alvimopan (a product of intestinal flora metabolism; see section 2) is also a μ-opioid receptor antagonist, with a K_i of 0.8 nmol/L.[7]
- Alvimopan acts specifically at μ-opioid receptors and has no biologically relevant affinity for various

1 Use of trade names is for product identification purposes only and does not imply endorsement.

non-opioid receptors (adrenergic, dopaminergic, benzodiazepine, serotonin 5-HT_2, histaminic-1, GABA or muscarinic receptors) in studies using rat brain homogenates.[9]

Effects on Opioid-Induced Gastrointestinal Transit Delay

- Alvimopan reverses opioid-induced delays in GI transit without limiting central analgesia, according to data from randomized, double-blind, placebo-controlled, crossover[7,11,12] or parallel-group[13] studies in healthy volunteers.
- In 14 healthy volunteers, two doses of oral alvimopan 2 mg administered 90 minutes apart reversed prolonged GI transit time induced by intravenous morphine (0.05 mg/kg) from 103 to 76 minutes ($p = 0.004$ vs morphine plus oral placebo), restoring transit times to levels similar to those at baseline.[11] Morphine analgesia and pupil constriction were not affected by alvimopan.
- Oral alvimopan 3 mg three times daily for 4 days reversed the delay in GI transit (assessed using radio-opaque markers) associated with administration of morphine 30 mg twice daily in 11 healthy volunteers ($p < 0.01$ vs placebo).[7,12] Alvimopan did not antagonize morphine-associated pupil constriction.
- Oral alvimopan 12 mg twice daily reversed the delay in small bowel and colon transit time associated with administration of codeine 30 mg four times daily in 74 healthy volunteers ($p < 0.05$ vs placebo).[13] Small bowel and colonic transit were assessed by scintigraphy using a ^{99}Tc-labelled egg meal and ^{111}In-labelled charcoal delivered to the proximal colon via a delayed-release capsule.

2. Pharmacokinetic Profile

The pharmacokinetic properties of alvimopan have been investigated in healthy volunteers and patients with postoperative ileus.[7,14,15] Data in this section have largely been obtained from the manufacturer's prescribing information.[7]

- The pharmacokinetics of alvimopan were dose proportional with alvimopan 6–18 mg, but less than dose proportional with alvimopan 18–24 mg.[7,15]
- The mean peak plasma concentration (C_{max}) of alvimopan was 10.98 ng/mL and the mean area under the plasma concentration-time curve from time zero to 12 hours was 40.2 ng • h/mL after oral administration of alvimopan 12 mg twice daily for 5 days to healthy volunteers.[7] The time to C_{max} (t_{max}) was ≈2 hours. The extent of absorption was higher (≈1.9-fold) and the rate of absorption was slower in patients with postoperative ileus than in healthy volunteers.[7,10]
- Oral alvimopan has low absolute bioavailability (estimated to be 6%; range 1–19%), indicating poor absorption.[7]
- An amide hydrolysis compound (hereafter referred to as the 'metabolite'), which is found in the circulation of volunteers administered oral alvimopan, is considered to be a product of intestinal flora metabolism.[7,14] There was a delay in the appearance of the metabolite in the plasma, consistent with its formation in the gut.[14]
- Following a single dose of alvimopan, the median t_{max} of the metabolite was 36 hours. There was considerable intra- and inter-subject variability in plasma concentrations of the metabolite.[7] The metabolite accumulated after multiple doses, with a mean C_{max} of 35.73 ng/mL after administration of alvimopan 12 mg twice daily for 5 days.[7] Concentrations of the metabolite were ≈1.4-fold higher in postoperative ileus patients than in healthy volunteers.[7]
- Plasma concentrations of the metabolite were 81% lower in surgical patients treated with preoperative oral antibiotics (e.g. neomycin, erythromycin).[7,14] In healthy volunteers receiving alvimopan 6 mg twice daily, concomitant administration of a short course of ciprofloxacin (500 mg twice daily for 10 days) decreased the mean concentration of the metabolite by 99%.[16]
- The volume of distribution at steady state was estimated to be 30 L.[7] Mean plasma protein binding of alvimopan and the metabolite were 80% and 94%, with albumin being the protein involved.

Binding was independent of concentration over clinically observed ranges.

- Because alvimopan has a large molecular weight (461 Da), a zwitterionic structure and low lipophilicity, CNS penetration of either alvimopan or the metabolite is low.[8,17] P glycoprotein appears to play a very minor role in the CNS penetration of alvimopan or the metabolite.[18]
- The average plasma clearance of alvimopan was 402 mL/min.[7] Renal excretion accounted for ≈35% of the total clearance.
- After administration of multiple oral doses of alvimopan, the mean terminal phase elimination half-life of alvimopan was 10–17 hours and of the metabolite was 10–18 hours.[7] Alvimopan is primarily eliminated via biliary secretion, with the unabsorbed and unchanged drug being hydrolyzed to the metabolite by GI microflora. The metabolite is eliminated in the faeces and urine as the unchanged metabolite, the glucuronide conjugate of the metabolite and other minor metabolites.
- Age, race and sex did not have any clinically relevant effect on the pharmacokinetics of alvimopan or the metabolite.[7]
- An approximate 10-fold increase in C_{max} compared with that in healthy volunteers has been reported in a patient with severe hepatic impairment; administration of alvimopan to this group of patients is not recommended (section 5).[7]
- Following administration of multiple doses of alvimopan, there may be accumulation of alvimopan and the metabolite in patients with severe renal impairment.[7] The use of alvimopan has not been investigated in patients with end-stage renal disease, and this agent is not recommended in this group of patients (section 5).

3. Therapeutic Efficacy

The efficacy of oral alvimopan in the management of postoperative ileus has been evaluated in adults (aged ≥18 years) who have undergone abdominal surgery (including bowel resection) under general anaesthesia in randomized, double-blind, placebo-controlled, multicentre, phase III trials conducted in North America (studies 302 [n = 451 total patients enrolled],[19] 308 [n = 666],[20] 313 [n = 510][21] and 314 [n = 654][22]) or Europe/Australasia (study 001 [n = 911]).[23] Four of these trials also included patients who had undergone total abdominal hysterectomy under general anaesthesia;[19-21,23] however, the efficacy of alvimopan has not been established in this subgroup of abdominal surgery patients.[7,10] Consequently, this review will only focus on data from patients who underwent partial large or small bowel resection with primary anastomosis (approved indication) who received the approved dosage of alvimopan. Data from this patient population have also been presented in the manufacturer's prescribing information,[7] the report from the meeting of the US FDA's Gastrointestinal Drugs Advisory Committee (GIDAC) that evaluated the efficacy of alvimopan[10] and in *post hoc* pooled analyses of the studies.[24,25] Study 314 is available as an abstract.[22]

Across the five trials, 953 patients who underwent bowel resection were treated with alvimopan 12 mg (approved dosage) and 924 received placebo.[7,10] The mean age of these 1877 patients was 61 years, 88% were Caucasian and the proportion of male and female patients was equal.[7,25] Colon and rectal cancer and diverticular disease were the most common indications for bowel surgery.[7] Small bowel resection occurred in 7% of the patients and 93% underwent large bowel resection.[25]

Patients who had taken more than three doses of opioids during the 7 days prior to surgery or who were expected to receive intrathecal or epidural opioids or anaesthetics were excluded from the studies.[7,25] Other patients who were excluded from the trials included those with complete bowel obstruction,[19,21,23] or those scheduled for a total colectomy,[19,23] colostomy[19,21,23] or ileostomy.[19,21,23]

Alvimopan 12 mg or placebo was administered orally as a single dose at least 30 minutes and up to 5 hours prior to surgery, and subsequently twice daily beginning on the first day after surgery until a maximum of 7 days or hospital discharge.[7,19-23,25] In the North American studies, postoperative pain relief was provided by patient-controlled intravenous opioid analgesia.[19-22] In the trial conducted in

Europe/Australasia,[23] postoperative pain management with opioids was either intravenous patient-controlled or by staff-administered intravenous or intramuscular bolus injection. There was no restriction on the type of opioid used or the duration of intravenous patient-controlled opioid analgesia.[7] In the study conducted in Europe/Australasia, the average daily use of opioids postoperatively was 50% lower than that in the North American studies.[7] Non-opioid use in the first 48 hours postoperatively occurred in 69% of patients in the European/Australasian study compared with 4% in the North American study.[7]

Standardized accelerated postoperative care was used to facilitate GI recovery and included: early nasogastric tube removal (end of surgery); early ambulation (day 1 after surgery); and early diet advancement (liquid on day 1 and solid food on day 2 after surgery, as tolerated).[19-23]

The primary efficacy endpoint was the time to achieve resolution of postoperative ileus (i.e. recovery of both upper and lower GI tract function).[19-23] This involved either a three-component endpoint (GI3; time to toleration of solid food and either first flatus or first bowel movement)[19-21,23] or a two-component endpoint (GI2; time to toleration of solid food and first bowel movement).[22] However, because flatus is an unreliable measurement, GI3 has been considered a less objective and clinically relevant measurement of treatment response in this patient population.[7,10,25]

Other endpoints included the time from the end of surgery to readiness for hospital discharge based on surgeon assessed recovery of GI function (Ready) and the time from the end of surgery to when the discharge order was written (DOW).[10] Efficacy analyses were based on the modified intent-to-treat population (patients who received the protocol-specified surgery and had at least one efficacy evaluation).[19-23]

- In the five phase III studies, alvimopan 12 mg twice daily was significantly more effective than placebo ($p < 0.05$) in reducing the time to recovery of GI function in patients with bowel resection, as assessed by the GI2 endpoint.[19-23] The mean time to GI2 recovery ranged from 92.0–116.4 hours in recipients of alvimopan 12 mg twice daily and from 109.5–132.0 hours in recipients of placebo. The mean difference in the time to GI2 recovery between the two groups ranged from −10.7 to −26.1 hours.[7,10] The hazard ratio (HR) of time (hours) to the GI2 endpoint for alvimopan 12 mg twice daily compared with placebo ranged from 1.30 to 1.63 (see figure 1).[7]
- GI recovery began ≈48 hours after surgery and the proportion of alvimopan, compared with placebo, recipients who achieved the GI2 endpoint was higher at all timepoints throughout the study observation period, according to Kaplan-Meier estimates.[7]
- In study 314 (involving patients with bowel resection only),[7,10,22] the difference in the mean time to the pre-specified primary composite GI2 endpoint between recipients of alvimopan 12 mg twice daily (n = 317) and placebo recipients (n = 312) was −19.8 hours (HR 1.53; 95% CI 1.29, 1.82; $p < 0.001$).
- The reduction in time to the GI2 endpoint with alvimopan 12 mg twice daily compared with placebo was not affected by the co-variates of age, sex or race.[7,25]
- In patients who had undergone bowel resection and were enrolled in the five randomized, double-blind studies, the mean time to reach GI3 recovery was significantly shorter with alvimopan 12 mg twice daily than with placebo in studies 313 (HR 1.49; 95% CI 1.17, 1.91; $p = 0.001$),[10] 308 (HR 1.32; 95% CI 1.03, 1.69; $p = 0.029$) and 314 (HR 1.45; 95% CI 1.23, 1.71; $p < 0.001$),[10] but not studies 302 (HR 1.30; 95% CI 0.96, 1.74)[10] or 001 (HR 1.13; 95% CI 0.94, 1.37).[10,23]
- A *post hoc* analysis of data from all five trials reported that the mean time to GI2 (HR 1.44; $p < 0.001$) and GI3 (HR 1.32; $p < 0.001$) recovery was significantly shorter with alvimopan 12 mg twice daily than with placebo in bowel resection patients.[25]
- In the four trials conducted in North America, the mean time to Ready was significantly shorter in bowel resection patients treated with alvimopan

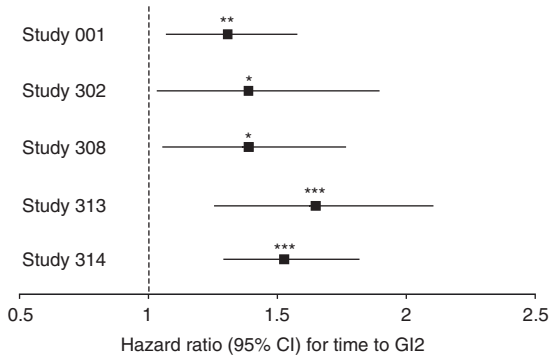


Fig. 1. Hazard ratio (95% CI) for the time (hours) to recovery of gastrointestinal (GI) function with alvimopan versus placebo.[10] Patients (n = 1877) who had undergone small or large bowel resection surgery with primary anastomosis were enrolled in five randomized, double-blind, placebo-controlled trials (302,[19] 308,[20] 313,[21] 314[22] and 001[23]), 953 of whom received single-dose alvimopan 12 mg at least 30 minutes and up to 5 hours prior to surgery, and then twice daily beginning on the first day after surgery until a maximum of 7 days or hospital discharge, and 924 of whom received placebo (modified intention-to-treat population). GI recovery was assessed according to a two-component endpoint (GI2; time to toleration of solid food and first bowel movement).[7,10] A hazard ratio >1 indicates a higher probability of achieving recovery of GI2 function during the study period with alvimopan than with placebo. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

12 mg twice daily than those treated with placebo (study 302 [HR 1.52; 95% CI 1.11, 2.09; $p = 0.01$], study 308 [HR 1.40; 95% CI 1.09, 1.78; $p = 0.008$], study 313 [HR 1.54; 95% CI 1.20, 1.96; $p < 0.001$] and study 314 [HR 1.38; 95% CI 1.17, 1.63; $p < 0.001$]).[10] In the study conducted in Europe/Australasia, there was no significant difference between patients who had undergone bowel resection treated with alvimopan 12 mg twice daily and those treated with placebo for the mean time to Ready (139.8 vs 146.1 hours; HR 1.11; 95% CI 0.92, 1.35).[23]

- In the four trials conducted in North America, the mean time to DOW with alvimopan 12 mg twice daily was approximately 13–21 hours shorter than with placebo in bowel resection patients,[7] with the between-group difference being significant in all but study 302 (see figure 2 for HRs).[10] In the study conducted in Europe/Australasia (where the discharge practices are different to those in North America), there was no significant difference for the time to DOW in bowel resection patients treated with alvimopan 12 mg twice daily versus placebo (see figure 2 for HR).[23]
- According to a pooled *post hoc* analysis of the four trials conducted in North America,[24] significantly fewer patients treated with alvimopan 12 mg twice daily than placebo experienced postoperative ileus-related morbidity (a composite endpoint of postoperative nasogastric tube insertion or complications of postoperative ileus) [7.6% vs 15.8%; odds ratio 0.44; 95% CI 0.30, 0.62; $p < 0.001$]. Significantly fewer alvimopan than placebo recipients required postoperative nasogastric tube insertion (6.6% vs 11.5%; $p = 0.001$) or experienced overall complications of postoperative ileus (2.9% vs 8.8%; $p \leq 0.001$).
- Alvimopan 12 mg twice daily did not reverse opioid analgesia, as measured by pain scores assessed on a visual analogue scale (0–100 mm) and/or postoperative opioid use.[7,19-24] For example, in the study conducted in Europe/Australasia, there

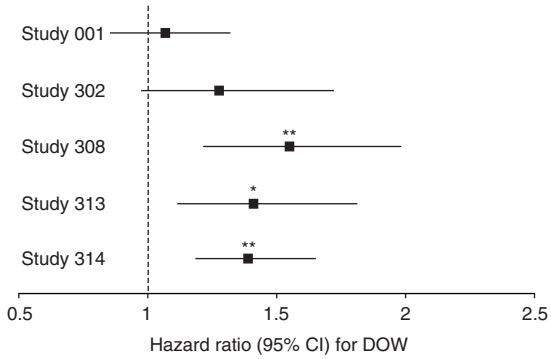


Fig. 2. Hazard ratio (95% CI) for mean time (days) to achieve discharge order written (DOW) in bowel resection patients treated with alvimopan or placebo.[10] Patients (n = 1877) who had undergone small or large bowel resection surgery with primary anastomosis were enrolled in five randomized, double-blind, placebo-controlled trials (302,[19] 308,[20] 313,[21] 314[22] and 001[23]); 953 of the patients received single-dose alvimopan 12 mg at least 30 minutes and up to 5 hours prior to surgery, and then twice daily beginning on the first day after surgery until a maximum of 7 days or hospital discharge, and 924 of the patients received placebo (modified intention-to-treat population). DOW was defined as the time from the end of surgery to the time that the hospital discharge order was written. A hazard ratio >1 indicates a higher probability of achieving DOW during the study period with alvimopan than with placebo. * $p < 0.01$, ** $p < 0.001$.

was no significant difference in the total postoperative opioid use during the study period between patients who had undergone bowel resection treated with alvimopan 12 mg twice daily and those treated with placebo (106.0 vs 103.8 mg morphine equivalents).[23]

- The incidence of anastomotic leak was 0.8% in recipients of alvimopan 12 mg twice daily and 1.1% in recipients of placebo.[7]

4. Tolerability

Tolerability data have been obtained from nine placebo-controlled clinical trials in surgical patients (reported in the manufacturer's prescribing information[7] and the US FDA GIDAC report[10]). Of the total 3975 surgical patients enrolled in the nine trials, 2610 patients had received alvimopan (1650 patients received the 12 mg dose). Alvimopan was administered as a single dose on the day of surgery followed by twice-daily administration starting on day 1 after surgery until discharge or a maximum of 7 days.[7,10]

- Short-term use of oral alvimopan 12 mg was generally well tolerated. Treatment-emergent adverse events that occurred in ≥3% of bowel resection patients (n = 999) or all surgical patients (n = 1650) treated with alvimopan and for which the incidence of adverse events was at least 1% greater than that with placebo are shown in figure 3).[7] In bowel resection patients treated with alvimopan 12 mg, the most common treatment-emergent adverse events were hypokalaemia, dyspepsia, anaemia, back pain and urinary retention.[7]
- In all surgical patients, the incidence of treatment-emergent adverse events causing discontinuation was 7.6% with alvimopan 12 mg and 11.9% with placebo.[10] In this patient group, non-fatal serious adverse events occurred in 11.6% of alvimopan 12 mg recipients and 18.3% of placebo recipients.[10]
- In a 12-month study in patients with chronic pain and opioid-induced bowel dysfunction, the incidence of myocardial infarction (MI) [1.3% vs 0%], neoplasms (2.8% vs 1.1%) and bone fracture (3.7% vs 1.1%) was numerically higher in recipients of alvimopan 0.5 mg twice daily (n = 538) than placebo (n = 267); the majority of MIs occurred 1–4 months after initiation of alvimopan.[7,10] However, between-group imbalances for these adverse events have not been reported in clinical studies in patients undergoing bowel resection surgery who received alvimopan 12 mg twice daily or placebo for up to 7 days.[7,10]

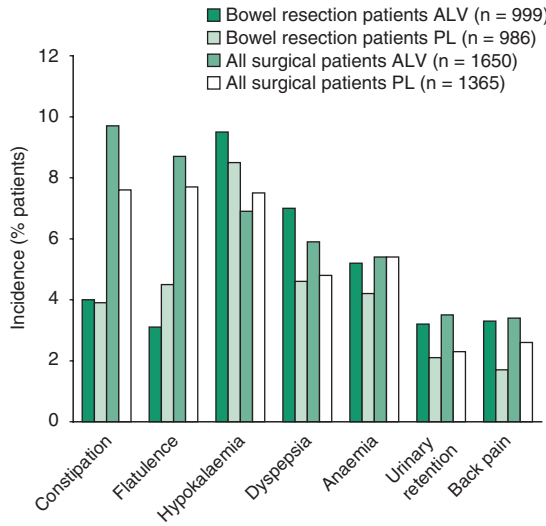


Fig. 3. Comparative tolerability of oral alvimopan (ALV) and placebo (PL) in the management of postoperative ileus in all surgical patients and in those undergoing bowel resection enrolled in nine placebo-controlled trials.[7] Patients received a single dose of ALV 12 mg or PL 30 minutes to 5 hours prior to surgery, and subsequently ALV 12 mg or PL was administered twice daily until discharge from hospital, or for a maximum of 7 days. Treatment-emergent adverse events that occurred in ≥3% of bowel resection patients or all surgical patients treated with ALV and for which the incidence of adverse events was ≥1% than that with PL are shown. Statistical evaluation was not reported.

5. Dosage and Administration

The recommended alvimopan dosage in adults who have undergone bowel resection surgery is 12 mg administered orally as a single dose 30 minutes to 5 hours before surgery and then 12 mg twice daily beginning the day after surgery for a maximum of 7 days or until discharge.[7] The maximum number of doses is 15.[7] Alvimopan 12 mg is only available for short-term use in hospitalized patients.

Alvimopan is contraindicated in patients who have received therapeutic doses of opioids for more than 7 days immediately prior to surgery. The use of alvimopan is not recommended in patients with severe hepatic impairment or with end-stage renal disease.[7]

Local prescribing information should be consulted for more detailed information, including warnings and precautions and use in special patient populations.

6. Alvimopan: Current Status

In five phase III trials, alvimopan accelerated the time to upper and lower GI2 recovery in patients who had undergone partial large or small bowel resection surgery with anastomosis. Short-term alvimopan was generally well tolerated. Alvimopan 12 mg is available in the US only for short-term (maximum of 15 doses) use in hospitalized patients. Hospitals must be registered in, and have met, all the requirements for the Entereg® Access Support and Education programme.[7]

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References

1. Behm B, Stollman N. Postoperative ileus: etiologies and interventions. Clin Gastroenterol Hepatol 2003 Apr; 1 (2): 71-80
2. Luckey A, Livingston E, Taché Y. Mechanisms and treatment of postoperative ileus. Arch Surg 2003 Mar; 138 (2): 206-14
3. Holte K, Kehlet H. Postoperative ileus: progress towards effective management. Drugs 2002; 62 (18): 2603-15
4. Kehlet H, Holte K. Review of postoperative ileus. Am J Surg 2001; 182 Suppl. 5A: 3-10S
5. Baig MK, Wexner SD. Postoperative ileus: a review. Dis Col Rectum 2004; 47 (4): 516-26
6. DeHaven-Hudkins D, DeHaven R, Little P, et al. The involvement of the mu-opioid receptor in gastrointestinal pathophysiology: therapeutic opportunities for antagonism at this receptor. Pharmacol Ther 2008; 117 (1): 162-87
7. Aldor Corporation, GlaxoSmithKline. Entereg® (alvimopan) capusules: US prescribing information [online]. Available from URL: http://www.entereg.com/pdf/entereg.pdf [Accessed 2008 Jun 6]
8. Zimmerman DM, Gidda JS, Cantrell BE, et al. Discovery of a potent, peripherally selective *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine opioid antagonist for the treatment of gastrointestinal motility disorders. J Med Chem 1994; 37: 2262-5
9. Zimmerman DM, Gidda JS, Cantrell BE, et al. LY246736 dihydrate: μ opioid receptor antagonist. Drugs Future 1994 Dec; 19 (12): 1078-83
10. FDA. FDA review documents for alvimopan (NDA 021775) [online]. Available from URL: http://www.fda.gov/cder/foi/nda/2008/021775_ENTEREGTOC.htm [Accessed 2008 Sep 1]
11. Liu SS, Hodgson PS, Carpenter RL, et al. ADL 8-2698, a trans-3,4-dimethyl-4-(3-hydroxyphenyl) piperidine, prevents gastrointestinal effects of intravenous morphine without affecting analgesia. Clin Pharmacol Ther 2001; 68 (1): 66-71
12. Barr W, Nguyen P, Slattery M, et al. ADL 8-2698 reverses opioid induced delay in colonic transit [abstract no. PI-7]. Clin Pharmacol Ther 2000 Feb; 67 (2): 91
13. Gonenne J, Camilleri M, Ferber I, et al. Effect of alvimopan and codeine on gastrointestinal transit: a randomized controlled study. Clin Gastroenterol Hepatol 2005 Aug; 3 (8): 784-91
14. Foss JF, Fisher DM, Schmith VD. Pharmacokinetics of alvimopan and its metabolite in healthy volunteers and patients in postoperative ileus trials. Clin Pharmacol Ther 2008 May; 83 (5): 770-6
15. Foss J, Schmith V, Wallin B. Alvimopan (Entereg™), a novel opioid antagonist, achieves active systemic concentrations [abstract no. PII-90]. Clin Pharmacol Ther 2005; 77: 74
16. Vasist L, Schmith D, Vearer D, et al. Effects of ciprofloxacin on the pharmacokinetics (PK) of alvimpoan (ALV) & its active metabolites (MET) [abstract no. PIII-80]. Clin Pharmacol Ther 2008; 83 Suppl. 1: S97
17. Schmidt WK. Alvimopan* (ADL 8-2698) is a novel peripheral opioid antagonist. Am J Surg 2001 Dec; 182 (5A Suppl.): 27-38S
18. Smart K, Churchill A, Boyle G, et al. Investigation of the CNS penetration of alvimopan and its active metabolite in mdr1a/b (-/-) knockout and control mice [abstract]. Annual Meeting of the American Association of Pharmaceutical Scientists; 2007 Nov 11-17; San Diego (CA)
19. Delaney CP, Weese JL, Hyman NH, et al. Phase III trial of alvimopan, a novel, peripherally acting, mu opioid antagonist, for postoperative ileus after major abdominal surgery. Dis Colon Rectum 2005 May 2; 48 (6): 1114-29
20. Viscusi ER, Goldstein S, Witkowski T, et al. Alvimopan, a peripherally acting mu-opioid receptor antagonist, compared with placebo in postoperative ileus after major abdominal surgery: results of a randomized, double-blind, controlled study. Surg Endosc 2006 Jan; 20 (1): 64-70
21. Wolff BG, Michelassi F, Gerkin TM, et al. Alvimopan, a novel, peripherally acting μ opioid antagonist: results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial of major abdominal surgery and postoperative ileus. Ann Surg 2004 Nov; 240 (4): 728-35
22. Ludwig KA, Enker WE, Delaney CP, et al. Accelerated gastrointestinal recovery and reduced length of stay following modi-

fied preoperative dose timing with alvimopan: results of a large randomized, placebo-controlled study in partial bowel resection [abstract]. American College of Surgeons 92nd Annual Clinical Congress; 2006 Oct 8-12; Chicago (IL)

23. Büchler MW, Seiler CM, Monson JRT, et al. Clinical trial: alvimopan for the management of postoperative ileus after abdominal surgery: results of an international randomised, double-blind, multicentre, placebo-controlled clinical study. Aliment Pharmacol Ther. Epub 2008 Mar 28
24. Wolff BG, Weese JL, Ludwig KA, et al. Postoperative ileus-related morbidity profile in patients treated with alvimopan after bowel resection. J Am Coll Surg 2007 Apr; 204 (4): 609-16
25. Senagore AJ, Bauer JJ, Du W, et al. Alvimopan accelerates gastrointestinal recovery after bowel resection regardless of age, gender, race, or concomitant medication use. Surgery 2007 Oct; 142 (4): 478-86

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