TITLE: Alvimopan for Surgical Patients: A Review of the Clinical and Cost-Effectiveness

DATE: 06 February 2009

CONTEXT AND POLICY ISSUES:

Post-operative ileus (POI) is a condition that affects all patients undergoing abdominal surgeries\(^1\) including bowel resections.\(^2\) POI refers to the delayed recovery of bowel function following abdominal surgeries\(^3\) and is characterized by abdominal pain, nausea, vomiting, abdominal distension and bloating, or delayed passage of flatus and stool.\(^4\) POI can also delay the progress to normal fluid and food intake which can impede healing and patient recovery.\(^1\) POI is associated with increased post-operative morbidity and prolonged hospital stay\(^2\) and consequently, increased health care resource utilization.\(^5\) Patient discharge is often delayed until POI is resolved,\(^6\) therefore interventions to manage POI effectively may improve not only patient morbidity, but may also decrease the costs associated with POI.\(^6\) The pathophysiology of POI is multi-factorial, but it is believed that surgical trauma/bowel manipulation\(^1\) as well as peri-operative administration of opioid analgesia contributes to a disruption in the normal physiology of the gastrointestinal (GI) tract and impairs motility.\(^7\)

Opioid analgesics, including morphine and its analogues are used to control post-operative pain and limiting their use with the intent of improving POI may compromise pain relief.\(^1\) Alvimopan (Entereg®) is a peripherally-acting mu-opioid receptor antagonist that was recently approved in the US for the indication of POI.\(^8\) Mu-opioid receptors in the GI tract play a role in mediating reduced GI motility.\(^9\) Alvimopan does not cross the blood brain barrier and therefore, it does not block the centrally-mediated analgesic effect of opioids for pain control.\(^9\) Antagonizing the mu-opioid receptor with alvimopan will reduce the opioid-induced disruption of GI function.

Alvimopan has yet to be approved by Health Canada,\(^10\) however, it can be accessed through the special access program in some jurisdictions. Given the likely frequency of abdominal surgeries across Canada, and therefore the incidence of POI, there is a need to review the effectiveness of alvimopan. This report with review the clinical and cost-effectiveness of alvimopan for the management of POI.

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RESEARCH QUESTIONS:

1. What is the clinical effectiveness of alvimopan for adult surgical patients?
2. What is the cost-effectiveness of alvimopan for adult surgical patients?

METHODS:

A limited literature search was conducted on key health technology assessment resources, including PubMed, OVID’s Embase, the Cochrane Library (Issue 4, 2008), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, EuroScan, international HTA agencies, and a focused Internet search. Results include articles published between 2004 and January 2009, and are limited to English language publications only. No filters were applied to limit the retrieval by study type.

HTIS reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews, and meta-analyses are presented first. These are followed by randomized controlled trials (RCTs) and economic evaluations. This review included studies that assessed the effectiveness of the mu-opioid antagonist alvimopan for the treatment of POI. Additional studies evaluating the use of alvimopan for other indications, including opioid-induced constipation, and additional articles that may be of interest have been included in the appendix.

SUMMARY OF FINDINGS:

This report included studies that assessed the effectiveness of the mu-opioid antagonist alvimopan for the treatment of POI. The literature search identified four systematic reviews. Two additional RCTs that were not included in the four systematic reviews were also identified. No health technology assessments or economic evaluations were identified.

Health technology assessments
No health technology assessments were identified.

Systematic reviews and meta-analyses

A systematic review by McNicol et al. (2008) compared the efficacy and safety of traditional and peripherally active opioid antagonists versus conventional treatment options for opioid-induced bowel dysfunction (OBD), including POI. For inclusion, studies had to be RCTs involving mu-opioid antagonists for the treatment of OBD. Twenty-three studies met inclusion criteria. A systematic review addressing the same research questions was published previously by the same group. The older systematic review included 22 studies, all of which were reviewed in the group’s more recent review, therefore only the data from the more recent review will be discussed in this report. Five studies addressing the effectiveness of alvimopan for the management of POI (following bowel resection, hysterectomy, and gastrectomy) were included with a total of 2,225 patients treated with alvimopan. The outcomes of interest varied between trials and were grouped for analysis as follows: 1) time to complete (upper and lower) GI tract recovery [GI-3: defined by time to tolerance of solid food and time to either first bowel movement (BM) or first flatus, 2) time to complete (upper and lower) GI tract recovery [GI-2: defined by time to tolerance of solid food and time to first BM, 3) time to first BM, 4) time to tolerance of solid food, 5) time to hospital discharge order being written, and 6) time to readiness for hospital discharge based on GI recovery. The trials reported outcomes as hazard
ratios (HR). The authors conducted a meta-analysis of HRs for all outcomes and reported combined HR at doses of six and 12 mg. A HR greater than 1.00 represented a benefit in recovery of GI function favouring alvimopan, while a HR less than 1.00 represented a benefit favouring the placebo group. Results are reported in Table 1.

**Table 1. Combined hazard ratios for trials of alvimopan for the treatment of POI. (adapted from McNicol et al.)**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Dose of alvimopan</th>
<th>Combined HR compared to placebo (95% CI)</th>
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<tbody>
<tr>
<td></td>
<td>6 mg</td>
<td>12 mg</td>
</tr>
<tr>
<td>Time to GI-3 recovery</td>
<td>1.29 (1.13-1.48)</td>
<td>1.29 (1.15-1.45)</td>
</tr>
<tr>
<td>Time to GI-2 recovery</td>
<td>1.40 (1.20-1.62)</td>
<td>1.60 (1.25-2.06)</td>
</tr>
<tr>
<td>Time to first BM</td>
<td>1.57 (1.33-1.87)</td>
<td>1.72 (1.27-2.34)</td>
</tr>
<tr>
<td>Time to first tolerance of solid food</td>
<td>1.41 (1.00-2.00)</td>
<td>1.14 (1.00-1.29)</td>
</tr>
<tr>
<td>Time to hospital discharge order written</td>
<td>1.53 (1.19-1.95)</td>
<td>1.25 (1.12-1.39)</td>
</tr>
<tr>
<td>Readiness for hospital discharge based on GI recovery</td>
<td>1.41 (1.22-1.66)</td>
<td>1.36 (1.15-1.60)</td>
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</table>

HR = hazard ratio; CI = confidence interval; GI = gastrointestinal; BM = bowel movement; GI-3 = a composite measure of the time to recovery of both upper and lower gastrointestinal function as defined by time to tolerance of solid food and time to flatus or bowel movement; GI-2 = a composite measure of the time to recovery of both upper and lower gastrointestinal function as defined by time to tolerance of solid food and time to first bowel movement.

The authors concluded from the combined outcomes analysis that alvimopan is superior to placebo for all outcomes except for tolerance of solid food. Adverse events including treatment-related withdrawal, serious adverse events, re-hospitalization, and death were either lower in the treatment group or in the case of death, showed no difference between the alvimopan and placebo group. The authors also noted that both the intervention and placebo arms of the trials were performed in conjunction with an accelerated post-operative care program that included early ambulation, oral feeding, and post-operative nasogastric tube removal; which have become a standard-of-care at many institutions. None of the studies of alvimopan involved treatment beyond 35 days, which is sufficient for management of POI, although may not be appropriate for the treatment of other OBD conditions including constipation. Authors of the systematic review noted that the manufacturer of alvimopan suspended the development of the drug for use in opioid-induced constipation after a higher risk of cardiovascular events, fractures, and skin cancers was reported. The only approved indication for alvimopan is for the treatment of POI.

Traut et al. (2008) conducted a systematic review to evaluate the clinical effectiveness of systemically-acting prokinetic drugs (including alvimopan) for the treatment of POI with or without peri- or post-operative epidural anesthesia or analgesia in patients undergoing open or laparoscopic abdominal surgery. To be considered for inclusion, studies had to be RCTs or quasi-randomized trials comparing prokinetic drugs to placebo or no intervention. After applying inclusion/exclusion criteria, 39 RCTs were included and six of these trials compared alvimopan to placebo. Data from the six studies will be discussed in this report. Authors of the systematic review noted deficiencies in the methodology reported for five of the six studies. The alvimopan 12 mg dose versus placebo comparison had a total of 2,181 participants and the 6 mg dose versus placebo comparison had a total of 1,034 participants. The authors conducted a meta-analysis of HRs for all outcomes and reported pooled hazard ratios at doses of six and 12 mg. Results are reported in Table 2.
Table 2. Pooled hazard ratios for trials of alvimopan for the treatment of POI. Traut et al. (2008)³

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Dose of alvimopan</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pooled HR compared to placebo (95% CI)</td>
<td>6 mg</td>
<td>12 mg</td>
</tr>
<tr>
<td>Time to GI-3 recovery</td>
<td>1.31 (1.15-1.50)</td>
<td>1.30 (1.16-1.46)</td>
<td></td>
</tr>
<tr>
<td>Time to GI-2 recovery</td>
<td>1.41 (1.22-1.63)</td>
<td>1.59 (1.33-1.90)</td>
<td></td>
</tr>
<tr>
<td>Time to first BM</td>
<td>1.60 (1.32-1.92)</td>
<td>1.74 (1.29-2.34)</td>
<td></td>
</tr>
<tr>
<td>Time to first tolerance of solid food</td>
<td>1.57 (1.04-2.37)</td>
<td>1.14 (1.00-1.29)</td>
<td></td>
</tr>
<tr>
<td>Length of hospital stay</td>
<td>1.38 (1.22-1.57)</td>
<td>1.31 (1.20-1.43)</td>
<td></td>
</tr>
</tbody>
</table>

HR = hazard ratio; CI = confidence interval; GI = gastrointestinal; BM = bowel movement; GI-3 = a composite measure of the time to recovery of both upper and lower gastrointestinal function as defined by time to tolerance of solid food and time to flatus or bowel movement; GI-2 = a composite measure of the time to recovery of both upper and lower gastrointestinal function as defined by time to tolerance of solid food and time to first bowel movement

Authors noted that there was large variability in adverse event reporting in the studies. Alvimopan was associated with a non-significant increase risk of headache. Authors concluded that results from six studies of moderate methodological quality demonstrated that alvimopan may reduce the time to recovery of bowel function in patients undergoing abdominal surgery. The authors also highlighted that two of the studies received funding from the pharmaceutical company that developed the drug and all six of the studies had co-authors that were employees of the funding sponsors.

A pooled analysis of three phase III trials involving alvimopan in the treatment of POI following bowel resection (BR) was conducted by Delaney et al. (2007).¹³ All three trials were randomized, double-blind, placebo-controlled multi-centre studies that investigated the safety and efficacy of alvimopan following BR. Patients received either alvimopan 6 mg (n=397), 12 mg (n=413), or placebo (n=402) at least two hours prior to surgery and twice daily until discharge (maximum treatment of seven days). The primary outcome of interest was complete recovery of upper and lower GI function, GI-3 (defined by time to first toleration of solid food and either the time to first flatus or time to first BM), and secondary outcomes were GI-2 recovery (defined by time to first toleration of solid food or first BM, whichever occurred last), hospital discharge based on GI recovery, and time to hospital discharge order being written. Mean time to recovery of GI function endpoints at doses of six and 12 mg are reported in Table 3.

Table 3. Mean time to recovery of GI function and hospital discharge following BR. Delaney et al. (2008)¹³

<table>
<thead>
<tr>
<th>Event/outcome</th>
<th>Placebo: time to event (hour) (mean±SEM)</th>
<th>Alvimopan (6 mg) versus placebo: difference in time to event (hour) (95% CI)</th>
<th>Alvimopan (12 mg) versus placebo: difference in time to event (hour) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to GI-3 recovery</td>
<td>118.8 ± 2.90</td>
<td>-12.4 (-19.7, -5.2)</td>
<td>-14.8 (-22.1, -7.6)</td>
</tr>
<tr>
<td>Time to GI-2 recovery</td>
<td>128.1 ± 3.09</td>
<td>-15.0 (-22.6, -7.3)</td>
<td>-18.3 (-26.0, -10.7)</td>
</tr>
<tr>
<td>Ready for hospital discharge</td>
<td>126.3 ± 2.87</td>
<td>-14.2 (-21.3, -7.1)</td>
<td>-17.6 (-24.7, -10.6)</td>
</tr>
<tr>
<td>Discharge order written</td>
<td>146.8 ± 2.82</td>
<td>-16.0 (-23.1, -8.8)</td>
<td>-18.4 (-25.6, -11.3)</td>
</tr>
</tbody>
</table>

SEM = standard error of the mean; CI = confidence interval; GI = gastrointestinal; BM = bowel movement; GI-3 = a composite measure of the time to recovery of both upper and lower gastrointestinal function as defined by time to tolerance of solid food and time to flatus or bowel movement; GI-2 = a composite measure of the time to recovery of both upper and lower gastrointestinal function as defined by time to tolerance of solid food and time to first bowel movement

Alvimopan for Surgical Patients
Differences in endpoints between studies were considered statistically significant if \( p < 0.05 \). The authors reported that alvimopan (6 or 12 mg) significantly accelerated GI recovery (GI-3) (hazard ratio 1.28 and 1.38, respectively; \( p \leq 0.001 \) for both doses). Time to hospital discharge orders being written were also significantly reduced for patients treated with either dose of alvimopan (\( p \leq 0.001 \) for both doses) as was incidence of nasogastric tube insertion (\( p=0.011 \) and 0.009 for 6 and 12 mg, respectively), prolonged hospital stay (\( p=0.024 \) and 0.002 for 6 and 12 mg, respectively), and incidence of serious adverse events (\( p \leq 0.001 \) for both doses). Authors noted a greater benefit of alvimopan at a dose of 12 mg for GI recovery as well as other outcomes. The higher dose also demonstrated a greater benefit in female patients and in patients over the age of 65 years.

Tan et al. (2006)\(^{14} \) conducted a meta-analysis of RCTs of alvimopan versus placebo for the treatment of POI following BR or total abdominal hysterectomy. Five trials reporting on 2,195 participants were included in the meta-analysis. A total of 1,521 participants were treated with alvimopan and 674 with placebo. The outcomes of interest were recovery of GI function (GI-3 and GI-2) and return to normal GI activities. The combined HR for these outcomes are reported in Table 4. Data were considered statistically significant at the \( p < 0.05 \) level, if the 95% CI did not include the value one.

**Table 4. Combined hazard ratios for trials of alvimopan for the treatment of POI.** (adapted from Tan et al. (2006)\(^{14} \))

<table>
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<tr>
<td></td>
<td>Combined HR compared to placebo (95% CI)</td>
</tr>
<tr>
<td></td>
<td>6 mg</td>
</tr>
<tr>
<td>Time to GI-3 recovery</td>
<td>1.50 (1.14-1.96); ( p=0.003 )</td>
</tr>
<tr>
<td>Time to GI-2 recovery</td>
<td>1.58 (1.22-2.04); ( p&lt;0.001 )</td>
</tr>
<tr>
<td>Time to first BM</td>
<td>1.60 (1.32-1.93); ( p&lt;0.001 )</td>
</tr>
<tr>
<td>Time to first tolerance of solid food</td>
<td>1.41 (1.00-2.00); ( p=0.03 )</td>
</tr>
<tr>
<td>Readiness for hospital discharge</td>
<td>1.58 (1.04-2.38); ( p&lt;0.001 )</td>
</tr>
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HR = hazard ratio; CI = confidence interval; GI = gastrointestinal; BM = bowel movement; GI-3 = a composite measure of the time to recovery of both upper and lower gastrointestinal function as defined by time to tolerance of solid food and time to flatus or bowel movement; GI-2 = a composite measure of the time to recovery of both upper and lower gastrointestinal function as defined by time to tolerance of solid food and time to first bowel movement

Treatment with alvimopan (at either 6 or 12 mg dose), resulted in significant improvements for all outcomes reported. No significant differences were reported for the incidence of treatment related adverse events (both GI-related and non-GI-related). The authors concluded that alvimopan showed significant advantage over placebo in terms of GI recovery and reduced the time to discharge following abdominal surgery. Alvimopan also had an acceptable side-effect profile.

**Randomized controlled trials**

A RCT was conducted by Büchler et al. (2008)\(^{15} \) to evaluate the effect of alvimopan on POI in patients undergoing abdominal surgery. A total of 911 patients were treated; results were presented for 705 of the participants that underwent bowel resection and completed the study. A total of 229 patients received placebo, 237 received alvimopan (6 mg), and 239 received alvimopan (12 mg). The primary endpoint of recovery of GI function (GI-3) was reduced by 8.5...
hours in the 6 mg dose group compared to placebo (p=0.042) and by 4.5 hours in the 12 mg dose group compared to placebo (p<0.20). Time to GI-2 recovery was also reduced by alvimopan treatment compared to placebo (6 mg: reduction of 14.3 hours, p<0.001; 12 mg: reduction of 10.7 hours, p=0.008). Post-hoc analysis of sub-groups of revealed that patients who received post-operative pain management with opioids via patient-controlled analgesia had enhanced GI recovery. This study was funded by the manufacturers of alvimopan and the majority of the authors have received funds from or were employees of the company.

Ludwig et al. (2008)\textsuperscript{16} evaluated the effect of alvimopan at a dose of 12 mg given pre- and post-operatively in combination with an accelerated care pathway for the management of POI following BR. A total of 654 patients were randomized to receive either alvimopan (n=329) or placebo (n=325). Twenty-two participants in each arm did not complete the study either due to adverse events, protocol violation, a withdrawn consent, or at the request of the principal investigator of study sponsor. Alvimopan significantly reduced the time to GI-2 recovery (HR: 1.50; 95% CI, 1.29-1.82; p<0.001) from 112 hours (4.7 days) in the placebo group to 92 hours (3.8 days) in the alvimopan group. The time to GI-3 recovery was also accelerated: (HR: 1.50; 95% CI, 1.23-1.71; p<0.001) from 98 hours in the placebo group to 82 hours in the alvimopan group. Alvimopan-treated groups compared to placebo-treated groups demonstrated a reduction in time to tolerance of solid food (9 hours), first BM (16 hours), first flatus (10 hours), and hospital discharge (17 hours). Authors concluded that alvimopan accelerates GI recovery and results in reduced length of stay (LOS) in hospital. This study was funded by the manufacturers of alvimopan and the majority of the authors have received funds from or were employees of the company.

**Economic evaluations**

No economic evaluations were identified.

**Limitations**

No HTAs were identified that examined the clinical and cost-effectiveness of alvimopan for the treatment of POI following abdominal surgery; however, a number of systematic reviews and RCTs were identified by our literature search. Several of the RCTs included in this report and discussed within the systematic reviews were funded by industry and all but one of the included studies had co-authors that had received funding from the manufacturers of alvimopan. In addition, several of the trials included in the systematic reviews and in this report were conducted by the same research group. The majority of the studies reported that the patient populations were heterogeneous and typically involved patients undergoing very different surgeries, and patients who had varying exposure to opioid analgesia pre-operatively for the management of pain. Quality assessments performed by one of the systematic reviews assessed the methodological quality only as moderate. Very few of the included studies gave complete explanations for the number of patients who did not complete the trial and all analyzed a modified intended to treat population rather than an intended to treat population.

Most of the studies assessed GI recovery using the composite end-points of GI-2 or GI-3. The GI-3 end-point that measures upper (toleration of solid food) and lower (passages of flatus or a BM) GI tract recovery was used as a primary end-point in earlier trials; however, more recent trials suggest that the time to first flatus may be less objective since it is patient-reported and the patient must be conscious and willing to report the information. Only one study discussed in detail the timing of alvimopan treatment pre-operatively.\textsuperscript{16}

No economic evaluations regarding the cost-effectiveness of alvimopan were identified.
CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING:

All of the studies included in this report found that alvimopan was effective for the treatment of POI. Alvimopan treatment accelerated the time to GI recovery and has some effect on reducing the time to hospital discharge. The majority of the studies included in this report had some association to industry funding, although with the approval of alvimopan by the FDA in the US, additional non-industry-funded RCTs may be expected in the future.

The most effective dosage of alvimopan was not clear from the results of the study; however one study reported that the 12 mg dose was more effective in females and in older patients. There were no significant differences in pain control in alvimopan versus placebo-treated patients, nor were there significant differences in rates of nasogastric tube re-insertion.

Alvimopan is not yet approved by Health Canada, but was recently approved for the treatment of POI in the US. A US-based study reported that total annual costs attributed to managing POI were $1.46 billion. In Canada, the management of POI likely represents a significant burden to the health care system. Clearly, interventions that effectively treat POI and allow for shorter hospital stays and fewer post-operative complications are critical to reducing health care costs.

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APPENDIX: Additional studies (not meeting inclusion criteria) about alvimopan that may be of interest

**Systematic reviews**


**Randomized controlled trials**


**Economic reviews**