CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-775

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Joyce Korvick, MD, MPH Deputy Director Division of Gastroenterology Products Office of New Drugs III Center for Drug Evaluation and Research
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	NDA 21-775
Applicant Name	Adolor Corporation
Date of Submission	Complete response August 9, 2007 (original application: June 25, 2004)
PDUFA Goal Date	May 10, 2008
Proprietary Name / **Established (USAN) Name**	Entereg™(alvimopan)
Therapeutic Class	Mu-opioid antagonist
Dosage Forms / Strength	Oral Capsule – 12 mg
Dosing and Administration	12 mg administered 30 minutes to 5 hours prior to surgery followed by 12 mg twice daily for up to 7 days for a maximum of 15 doses.
Proposed Indication(s)	Entereg is indicated to accelerate the time to upper and lower gastrointestinal recovery following partial large or small bowel resection surgery with primary anastomosis.
Action/Recommended Action:	**Approve**

1. Introduction

Entereg (alvimopan) is a peripherally-acting mu-opioid receptor (PAM-OR) antagonist.

Postoperative ileus is the impairment of gastrointestinal motility after intra-abdominal surgery or other non-abdominal surgeries. Postoperative ileus affects all segments of the gastrointestinal tract and may last from 5 to 6 days, or even longer. This may potentially delay gastrointestinal recovery and hospital discharge until its resolution. It 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. Postoperative ileus is the result of a multifactorial process that includes inhibitory sympathetic input, release of hormones, neurotransmitters, and other mediators (e.g., endogenous opioids). A component of postoperative ileus also results from 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 are known to have an inhibitory effect on gastrointestinal motility and may prolong the duration of postoperative ileus.

Following oral administration, alvimopan antagonizes the peripheral effects of opioids on gastrointestinal motility and secretion by competitively binding to gastrointestinal tract mu-opioid receptors. The antagonism produced by alvimopan at opioid receptors is evident in isolated guinea pig ileum preparations where alvimopan competitively antagonizes the effects of morphine on contractility. Alvimopan achieves this selective gastrointestinal opioid antagonism without reversing the central analgesic effects of mu-opioid agonists.

2. Background

This is the third review cycle for Entereg, this approval follows approvable actions taken for the previous 2 submissions.

In February, 2004 the Division of Gastroenterology Products granted the alvimopan development program for the treatment of post-operative ileus (POI) fast tract status. Adolor originally submitted the complete NDA on June 25, 2004, under the Pilot 1 Continuous Marketing Application program. Adolor changed their original proposed POI indication in the first-cycle to the indication which they are receiving approval, "to accelerate the time to upper and lower gastrointestinal (GI) recovery following partial large or small bowel resection with primary anastomosis." The review of this NDA resulted in an approvable letter requesting additional efficacy data, June 21, 2005.

A complete response was submitted to the FDA on May 9, 2006 initiating the second review cycle. On May 16, 2006, after a complete response (second cycle NDA) was submitted by Adolor, GlaxoSmithKline (GSK), a partner of Adolor in the development of alvimopan, informed the Division of Gastroenterology Products of a numerically higher incidence of serious cardiovascular events in an ongoing study. In a 12-month study of patients treated with opioids for chronic pain there were more reports of

myocardial infarctions in patients treated with alvimopan 0.5 mg twice daily compared with placebo-treated patients. In this study, the majority of myocardial infarctions occurred between 1 and 4 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 7 days. A causal relationship with alvimopan has not been established. Adolor received a second approvable letter on November 3, 2006.

On August 9, 2007, Adolor Corp submitted a complete response which included the final 12 month safety findings including analyses of severe cardiovascular events, a safety update and a risk management plan.

During the third cycle, an Advisory Committee meeting was held on January 23, 2008. The committee recommended approval (9 to 6 vote) with tighter risk management plan to prevent off-label use (>15 total doses), restricting use to in-hospital patients treated by surgeons performing bowel resections only, and the capture of clinical outcomes.

Due to late receipt of additional clinical dataset and statistical analyses which constitute a major amendment to the NDA, the PDUFA due date for this application was extended for 3 months to May 10, 2008.

3. Chemistry and Manufacturing

This is the summary recommendation of the Chemistry reviewers from the end of the second review cycle.

"The review of the original NDA found the [redacted] drug product can be approved from CMC point of view. The review of this amendment found that the sponsor provided improved manufacturing process for the drug substance with adequate process controls. The amendment review also found that the sponsor provided adequate information for composition of 12 mg dose strength of the drug product and the modified analytical methods. The updated stability data is adequate to support 24 months of expiring date. The GMP inspection of the manufacturing facilities has found that the facilities are adequate." The reviewers recommended minor changes to the labeling which were addressed in this review cycle.

I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the submission. There are no outstanding issues.

4. Nonclinical Pharmacology/Toxicology

Previous cycles found that there were no significant pharmacologic or toxicological concerns raised by the reviewers. The review of in vitro and in vivo cardiovascular safety pharmacology studies did not show any adverse effect of alvimopan. Alvimopan and ADL 08-001, the active metabolite of alvimopan, did not inhibit the cloned human cardiac potassium channel (hERG) at concentrations up to approximately 46 and 35 microM, respectively. Neither did the dog Purkinje fiber

assay at concentrations up to 100 microM. Alvimopan at intravenous doses of 0.05, 0.2 and 2.5 mg/kg showed no significant effect on the ECG or QTc in dogs.

Overall, they recommend that the preclinical data were adequate to support the approval of Alvimopan for the proposed use in post-operative patients.

In regard to the labeling, this cycle the reviewers provided comments on the review of the mouse carcinogenicity data and for the findings of rat carcinogenicity study as request by the Executive Carcinogenicity Advisory Committee. There were two specific conclusions: 1.) that "alvimopan caused statistically significant increase in the incidences of fibroma, fibrosarcoma and sarcoma in the skin/subcutis and osteoma/osteosarcoma in bones of female mice"; 2.) "upon reanalysis of the rat tumor data, we conclude that the rat study is negative".

The reviewers concluded that these findings "do not preclude approval, and the information is reflected in the labeling".

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

A summary of the review history is provided below, leading to the review activity from the current (3rd) cycle.

In the sponsor's complete response dated May 9, 2006 (Cycle 2), the sponsor indicated in the CMC section that they intended to seek approval of the 12 mg capsules. The sponsor also stated in the CMC section that they had conducted a BE study (Protocol 14CL130) comparing the two different strengths of capsules and the BE study report had been submitted to the IND. Upon receiving the above information in September 2006 from the reviewing chemist, the pharmacologists requested that the sponsor submit the BE study report to this NDA. The sponsor responded on September 15, 2006. Subsequently, it was determined that there was insufficient time to conduct a thorough review of the study by the Office of Clinical Pharmacology and the Division of Scientific Investigations before the action date. A cursory review of the BE study was conducted and an information request was made, which included a request for the electronic dataset. The Agency issued an approvable letter on November 3, 2006, indicating that the sponsor should submit the 12 month safety findings and develop a risk management plan. The sponsor responded to our information request on January 18, 2007, and submitted on August 9, 2007 (Cycle 3) a complete response to the Agency's approvable letter. The BE study is thus the subject of this review. Due to late receipt of additional clinical dataset and statistical analyses which constitute a major amendment to the NDA, the PDUFA due date for this application was extended for 3 months to May 10, 2008.

DSI inspection of the BE study revealed deficiencies.

"Following our evaluation of the inspectional findings, DSI concludes the following:

1. The alvimopan data (i.e., all period 1 data from subjects82,83, 84, 85 and 86) generated in batch 48 are not reliable. We recommend that these data be excluded from bioequivalence determination.
2. The data generation in the alvimopan freeze/thaw [redacted] stability study, long term frozen [redacted] stability study, and [redacted] stability study are not reliable."

The deficiencies cited in Form 483 were evaluated by the clinical pharmacology reviewers. For deficiencies that could result in biased outcome, the affected subjects were excluded from the dataset and reanalysis was performed by the reviewer using WINNONLIN. The reanalysis results showed that the 90% CI for Cmax and AUCt were within the 80-125% range but the 90% CI for $AUC_{0\text{-}inf}$ was 96.0-128.1% (table below). Nevertheless, they did not consider the findings for AUC0-inf would result in clinically significant difference between the two capsule strengths.

FDA reanalysis results:

Test/Reference Ratio and 90% CI (excluding Subjects #55-57 and #82–86)

Parameter	N	Ratio (T/R)	90% CI for Ratio
$AUC_{0\text{-}inf}$ (ng.hr/mL)	70	110.9	96.0-128.1
AUCt (ng.hr/mL)	79	102.2	84.7-123.3
Cmax (ng/mL)	79	102.0	84.1-123.8

The clinical pharmacology team made the following recommendation. "From a clinical pharmacology standpoint, the bioequivalence study has demonstrated that one 12 mg capsule is equivalent to two 6 mg capsules provided that the DSI inspection finds the conduct of the BE study (Protocol 14CL130) acceptable. Thus, the 12 mg capsules may be approved if all other disciplines find the NDA acceptable for approval."

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer regarding labeling and that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

NA- this is an oral formulation

7. Clinical/Statistical-Efficacy

The phase 3 clinical trials to support the efficacy of alvimopan in the treatment of post-operative ileus in the bowel resection surgery population included the following five POI trials with 1877 patients in the efficacy database [of which 953 (50.8%) and 924 (49.2%) patients received the 12 mg alvimopan dose and placebo, respectively].

The final analysis of these studies included only patients who were treated with the 12 mg alvimopan dose, and had bowel resection surgery. Early in the sponsor's development plan studies #2 - #5 (see table below) included patients with gynecologic

surgery as well as bowel resections. As the studies evolved the sponsor chose to limit the indication to bowel resection surgery patients. Patients with gynecologic surgery were removed from the analysis of these studies. Study #1 contributed the largest number of patients with bowel surgery to the overall analysis (312 placebo treated patients; 317 alvimopan treated patients). The table below (Table 2 from the approved label) represents these finalized analyses of the primary endpoint, GI2 (toleration of solid food and first bowel movement). A Hazard Ratio greater than 1 favors alvimopan.

Table 2. GI2 Recovery (Hours) in Bowel Resection Patients

Study No.	ENTEREG 12 mg Mean	Placebo Mean	Treatment Difference Mean	Hazard Ratio (95% CI)
1	92.0	111.8	19.8	1.533 (1.293, 1.816)
2	105.9	132.0	26.1	1.625 (1.256, 2.102)
3	116.4	130.3	14.0	1.365 (1.057, 1.764)
4	106.7	119.9	13.2	1.400 (1.035, 1.894)
5	98.8	109.5	10.7	1.299 (1.070, 1.575)

Across studies #1 through #4 patients receiving alvimopan had their discharge order written approximately 13 to 21 hours sooner compared to patients receiving placebo. This was felt to be an important secondary finding by the members of the GI Advisory Committee. Data from study #5, a study conducted outside of the US, did not show this difference, however, the practice of medicine may differ relative to the time discharge orders are written.

Overall, these data support the efficacy finding of Entereg for this patient population. It is a clinically meaningful difference as well as a statistically meaningful one. Prolonged hospitalization can lead to significant morbidity and mortality.
The clinical review team agrees that these data support the efficacy claim in the approved label (see approval letter). I agree.

8. Safety

The data described below reflect exposure to Entereg in 1,650 patients in 9 placebo-controlled studies worldwide. The population was 19 to 97 years old, 68% were female, and 83% were Caucasian; 61% were undergoing bowel resection surgery. The first dose of Entereg was administered 30 minutes to 5 hours before the scheduled start of surgery and then twice daily until hospital discharge (or for a maximum of 7 days of postoperative treatment).

The most frequent adverse reactions occurring more often in alvimopan than placebo in bowel resection patients were anemia, constipation, dyspepsia, hypokalemia, back pain and urinary retention.

Adverse events of interest included myocardial infarction, neoplasm and bone fracture. The Integrated Summary of Safety included reports of adverse reactions for short-term as well as long-term indications. This review revealed the 3 adverse reactions of interest outlined above. A brief review follows.

In a 12-month study of patients treated with opioids for chronic pain, there were more reports of myocardial infarctions in patients treated with alvimopan 0.5 mg twice daily compared with placebo-treated patients. In this study, the majority of myocardial infarctions occurred between 1 and 4 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 7 days. The Cardio-Renal Division was consulted regarding this safety issue and they concluded that for the short-term indication that there was no apparent signal for myocardial infarction. It was suggested that an additional study be conducted in post-operative surgical patients in order to prospectively collect specific information on cardiac status in these patients. This was recommended because specific tracking of this safety signal in the short-term protocols was collected in a passive way. This is the subject of the Post-Marketing Study Requirement (see section 12 below). A causal relationship with alvimopan has not been established in the short-term treatment population.

The number of neoplasms reported among 2610 patients treated for short term in the post operative ileus studies was similar to that of placebo patients (1365 placebo patients enrolled). The 5 events which occurred in the alvimopan treated group include chronic myelogenous leukemia (1), colon cancer metastatic (1), hepatic neoplasm (1), lymphoma (1), and thyroid neoplasm (1). The events which occurred in the placebo treated group were Burkitt's lymphoma (1), bladder neoplasm (1), carcinoma (1).

Long-term studies in patients receiving alvimopan were conducted in patients with cancer pain and non-cancer pain. There was an imbalance of neoplasms occurring in the alvimopan treated group, however, given the patient populations, imbalance in Karnofsky performance Scores, and other factors amongst the cancer-pain patients, no firm conclusions could be drawn. In the non-cancer treatment studies (study 014) there was an imbalance, whoever no obvious reason for the observed imbalance could be determined. There were 7 (1.3%) malignant neoplasms in the alvimopan treated group and 2 (0.7%) in the placebo treated group. The issue of neoplasm was discussed at the GI advisory committee, and it was determined that it was not a factor for the short term treatment indication.

There was only one reported case of rib fracture secondary to syncope after bowel resection surgery. In study 014 (short-term study), there was an imbalance in fractures (3.7% alvimopan treated; 1.1% placebo treated). The locations of the fractures were distributed amongst various bones, and were not typical of osteoporotic fractures, such

as hip and vertebrae. Most fractures reported were secondary to falls. The etiology of the imbalance in fracture rates is unclear. Again, the issue of fracture was not felt to be significant by the GI advisory committee for the short term indication.

The final conclusion of the medical team in consultation with the Safety team, Cardio-Renal review team and the Advisory Committee, was that for short-term treatment (15 doses) of post-operative bowel recovery in bowel resection patients, there was no evidence that there was an imbalance in safety signals compared to placebo. I agree with this conclusion.

- **Postmarketing data:**
  This product is not marketed in the US or the remainder of the world. Therefore, there exist no post-marketing data at this time.

- **Propiratary Name Review:** The division of Medication Error Prevention reviewed the name, Entereg, and found it acceptable. I agree with their conclusion.

- **Final labeling recommendations:**
  Some important highlights are outlined here (see full label for more detail).
  Black Box Warning – specific wording: Entereg is available only for short-term (15 doses) use in hospitalized patients. Only hospitals that have registered in and met all of the requirements for the Entereg Access Support and Education (EASE) program may use Entereg.
  Warning – In patients with severe hepatic impairment, there is a potential for 10-fold higher plasma levels of drug. Because of the limited data available, Entereg is not recommended for use in patients with severe hepatic impairment.
  -Entereg is not recommended for use in patients with end stage renal disease.
  -Use of Entereg in patients undergoing surgery for correction of complete bowel obstruction is not recommended.
  Opioid tolerance and GI Related Effects – Patients recently exposed to opioids are expected to be more sensitive to the effects of mu-opioid receptor antagonists. Increased sensitivity would likely be limited to the gastrointestinal tract resulting in abdominal pain, nausea and vomiting, and diarrhea. Patients receiving more than 3 doses of an opioid within the week prior to surgery were not studied in the postoperative ileus clinical trials; therefore, Entereg 12 mg capsules should be administered with caution to these patients.

- **REMS/RiskMAPs:**
  This application was submitted before March 25, 2008, pre-dating the Title IX, Subtitle A, Section 901 of FDAAA amends the FDCA to authorize FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) when such a strategy is necessary to ensure that the benefits of the drug outweigh the risks.

  This application was deemed to need a REMS for safe use.

  Accordingly, the current application contained a proposed RiskMAP (Risk Mitigation Action Plan) upon submission, which was reviewed by the DRISK, and discussed at

the Advisory Committee Meeting. This RiskMAP was converted to a REMS during this cycle.

The Sponsor's proposed RiskMAP attempts to limit the use of Entereg for short-term use in order to minimize the risk of cardiovascular events that have been observed only with longer-term use. The Sponsor proposed the following elements:

- Restriction to inpatient use in registered hospitals;
- Sale of Entereg only to registered hospitals;
- Hospital registration on attestation that the hospital
  - Has distributed educational materials to healthcare staff who participate in the prescribing, dispensing, or administration of Entereg,
  - Has established conditions of safe use; and
  - Will not divert alvimopan to outpatient use.

The amended RiskMAP now proposed by the Sponsor adequately responds to the questions that OSE posed to the Advisory Committee during its January 2008 meeting. Additional measures that were included in the amended RiskMAP include Sponsor control over who purchases the product (rather than wholesaler control), registration of hospitals after attestation of conditions of safe use, and education of healthcare personnel involved in using the product. Although cardiac safety data will not be collected within the RiskMAP, a post-marketing study will be required of the Sponsor to collect additional safety data.

The Division of Risk Management made the following comments. "The proposed RiskMAP can be converted to REMS comprised of a communication plan, elements to assure safe use, an implementation plan, and evaluation of elements to assure safe use." Adolor sumitted a formal REMS on May 14, 2008, which was reviewed by the DRISK and DGP. It was found to be acceptable, and will be incorporated into the action letter.

I concur with the REMS as it is outlined in the action letter.

- **Advisory Committee Meeting**
  An Advisory Committee meeting was held on January 23, 2008, during the third review cycle. The committee recommended approval (9 to 6 vote) with tighter risk management plan to prevent off-label use (15 total doses), restricting use to patients in hospitals treated by surgeons performing bowel resections only, and to capture the clinical outcomes.

9. Pediatrics

The sponsor is requesting a deferral of pediatric studies in pediatric patients aged 0 to 16 years. The reason given is the need for additional safety data collection in the adult population regarding cardiac events. This product was reviewed by the PERC committee and they agreed with this deferral. In addition, the pediatric planned studies were discussed and agreed upon.

The post marketing studies that are deferred are as follows:

1. Deferred pediatric study under PREA for the acceleration of gastrointestinal recovery in pediatric patients age greater than one month to 16 years undergoing bowel resection surgery to measure time to first tolerated feed, population pharmacokinetic parameters, proportion of postoperative days with stool passed while in hospital, length of hospital stay, need for postoperative NG tube insertion for symptoms of POI, and safety.

   Protocol Submission: 12/2012
   Study Start: 6/2013
   Final Report Submission: 6/2016

2. Deferred pediatric study under PREA for the acceleration of gastrointestinal recovery in pediatric patients age birth to one month to undergoing bowel resection surgery to measure population pharmacokinetic parameters, safety, and time to first tolerated feed while in the hospital.

   Protocol Submission: 12/2016
   Study Start: 6/2017
   Final Report Submission: 6/2019

I concur with the deferral recommendation.

10. Other Relevant Regulatory Issues

- **DSI Audits:** satisfactory for clinical sites. The analytical site for the clinical pharmacology bioequivalence study was issued Form FDA 483 with deficiencies. Review of these deficiencies and recommendations were made by the clinical pharmacology reviewer and team leader (see section 5 for further description).
- **Financial Disclosure:** form submitted and acceptable.
- **SEALD:** consult was obtained and essential elements of the PLR rule were made to the label and some additional editorial changes. Any changes to the Black Box Warning or other significant areas of the label which would impact the RiskMAP were deferred until submission of the REMS proposal.

There are no other unresolved relevant regulatory issues

11. Labeling

- **Physician labeling:** The approved labeling for Entereg will include a black box warning for short term hospital use only.
- **Carton and immediate container labels:** Comments from the DMEP reviewer were sent to the applicant, was agreed upon and satisfactorily addressed.
- **Patient labeling/Medication guide:**
  There is no Medication guide as this is a drug administered in a hospital by professional personnel. The risks are communicated to the patient in the E.A.S.E. (REMS) program.

12. Decision/Action/Risk Benefit Assessment

- **Regulatory Action:** I recommend approval of this supplement with the agreed upon labeling changes. This is agreement with review teams' recommendations.

- **Risk Benefit Assessment:**
  The benefit of bowel recovery post bowel-resection surgery was clearly demonstrated by the outcome measure used in the 4 pivotal studies. It was further agreed, by the GI advisory committee that this outcome measure (GI 2 and time to discharge order written) was clinically meaningful. Patients receiving Entereg had hospital discharge orders written approximately 13 to 21 hour sooner compared to patients receiving placebo. In addition, Entereg treated patients had a mean shorter time to recovery of bowel function of about 11 hours to 26 hours.

  In the United States, about 343,000 patients have bowel resection surgery annually.

  The imbalance in cardiovascular events, myocardial infarction, was seen in the chronic administration of alvimopan, on average at between 1 and 4 months of treatment. This imbalance was not seen in the patients receiving Entereg short-term (up to 15 doses). The GI advisory committee, the GI division and the Office of Surveillance and Epidemiology all recommended that approval and safe use of this drug be limited to 15 doses administered in the hospital under a RiskMAP converted to a REMS.

- **Recommendation for Postmarketing Risk Evaluation Mitigation Strategy (REMS) Activities:**
  The GI Division recommends a REMS. For complete details refer to approval letter (also, section 5 above outlines elements of E.A.S.E.).

- **Recommendation for other Postmarketing Study Requirements:**

  We (GDP, ODE III, OSE) have determined that only a clinical trial will be sufficient (rather than an observational study) to monitor for and assess the incidence of myocardial infarctions in Entereg-treated patients undergoing surgery compared to patients receiving a placebo.

  Adolor Corp. submitted letter dated April 22, 2008 outlining a draft protocol, "A multi-center, double-blind, placebo-controlled, parallel group clinical trial of Entereg for the management of postoperative ileus in subjects undergoing radical cystectomy." This will be the required post marketing study to fulfill the above stated goal.

Material Reviewed/Consulted: OND Action Package	**Reviewer**
Medical Officer Review	M. Dannis (2/27/08)
Medical Team Leader Review	R. He (4/25/08)
Statistical Review	S. Castillo (4/15/08)
Pharmacology Toxicology Review	T. Chakraborti (2/11/2008)
Clinical Pharmacology Review	S. Lee (5/8/08)
CMC Review	Z. Ge (10/18/2006)
DSI Inspection BE studies	X. Chen (5/5/08)
OSE/ Epidemiology	S. Bezabeh (5/5/08)
OSE/Division of Risk Management Review	J. Weaver, C. Karwoski (see advice letters, final review 5/2/08)
OSE/Division of Medication Error Prevention Review	K. Arnwine (4/22/2008)

OND=Office of New Drugs
OSE= Office of Surveillance and Epidemiology
SEALD=Study Endpoints and Label Development Division
Note that the review material noted above relates to this current cycle. In addition, material prepared for the FDA Backgrounder for the Advisory Committee has been reviewed. I have consulted materials from cycle 1 and 2 in my prior reviews.

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/s/

Joyce Korvick
5/16/2008 02:31:49 PM
MEDICAL OFFICER