CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-775

OFFICE DIRECTOR MEMO

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: May 16, 2008

FROM: Julie Beitz, MD

SUBJECT: Office Director Memo

TO: NDA 21-775 Entereg (alvimopan) Capsules, 12 mg
Adolor Corporation

Summary

Entereg (alvimopan) Capsules, 12 mg, is a peripherally acting μ-opioid receptor antagonist that has been evaluated in the postoperative setting for the management of ileus, a common cause of prolonged hospitalization. Entereg blocks the peripheral effects of opioids on gastrointestinal motility and secretion without reversing the central analgesic effects of μ-opioid receptor agonists. Currently there are no products approved for the treatment of postoperative ileus. This memo documents my concurrence with the Division of Gastroenterology Product's (DGP's) recommendation for the approval of Entereg to accelerate the time to upper and lower gastrointestinal recovery following partial large or small bowel resection surgery with primary anastomosis.

Dosing

Entereg will be approved for short-term hospital use only. Only hospitals that have enrolled in the EASE (Entereg Access Support and Education) program may dispense Entereg. The recommended adult dosage is 12 mg administered orally 30 minutes to 5 hours prior to surgery followed by 12 mg twice daily beginning the day after surgery for a maximum of 7 days. Patients should not receive more than 15 doses of Entereg.

Regulatory History

On June 25, 2004, Adolor Corporation submitted NDA 21-775 for alvimopan capsules. The current submission, dated August 9, 2007, represents a complete response to the Agency's second approvable letter issued on November 6, 2006. The safety and efficacy of Entereg were discussed in detail at an FDA advisory committee meeting on January 23, 2008.

Efficacy

The efficacy of Entereg in the management of postoperative ileus was evaluated in five multicenter, randomized, double-blind, parallel-group, placebo-controlled trials. A total of 1,096 patients received Entereg and 1,081 received placebo. The most common reasons for surgery were colon or rectal cancer and diverticular disease. The primary endpoint was defined as the time to achieve resolution of postoperative ileus using measures of both upper and lower gastrointestinal recovery. These measures were the time (in hours) from the end of surgery to toleration of solid food and time to first bowel movement.

Recovery times ranged from 10.7 to 26.1 hours shorter for Entereg-treated patients compared to placebo-treated patients in the five studies. Recovery began after approximately 48 hours postoperatively. In the four US studies, Entereg-treated patients had their discharge order written approximately 13 to 21 hours sooner compared to placebo-treated patients.

Safety

The safety of Entereg was assessed in a total of nine phase 2 and 3 postoperative ileus clinical trials enrolling 1650 patients on Entereg and 1365 on placebo. The most common treatment-emergent side effects reported were hypokalemia, anemia, or gastrointestinal in nature, including constipation, dyspepsia and flatulence. These events occurred with similar frequency in the Entereg and placebo treatment groups. Patients receiving more than 3 doses of an opioid within the week prior to surgery were not studied in the postoperative ileus clinical trials. Use of Entereg will be contraindicated in patients who have taken therapeutic doses of opioids for more than 7 consecutive days immediately prior to taking Entereg.

In the nine postoperative ileus trials, myocardial infarction was reported in 20 patients (13 on Entereg and 7 on placebo), corresponding to an event rate of 0.5% in each group. The relative risk of having a myocardial infarction on Entereg compared to placebo treatment was 0.97 (0.39, 2.43). Infarctions typically occurred within a week of the initiation of dosing. A blinded adjudication of case narratives by a Division of Cardiology Drugs consultant confirmed that the rate of possible or likely myocardial infarctions in the two treatment groups was similar. There were no differences in baseline cardiovascular risk factors between Entereg- and placebo-treated patients in these studies. DGP and the Division of Cardiology Drugs concluded, and I agree, that short-term Entereg treatment is not associated with an increased cardiovascular safety risk in patients treated for postoperative ileus.

On May 15, 2006, shortly after the submission of the complete response to the first approvable action, DGP received information about cardiovascular adverse events from a planned 6-month safety interim analysis of an ongoing clinical trial in patients with opioid-induced bowel dysfunction. Study SB767905/014 is a 12-month randomized clinical trial of 805 non-cancer patients on chronic opioid therapy comparing Entereg 0.5 mg bid to placebo treatment. The final report of this trial, along with an analysis of cardiovascular events across all opioid-induced bowel dysfunction trials, was submitted in response to the second approvable letter (November 6, 2006). In Study SB767905/014, seven myocardial infarctions were reported in Entereg-treated patients and none on placebo. The relative risk of having a myocardial infarction was 7.46 (0.4, 130) on Entereg compared to placebo. When the safety data from all non-cancer opioid-induced bowel dysfunction trials were pooled (including Study SB767905/014), there were eight myocardial infarctions reported in Entereg-treated patients and two on placebo. The relative risk of having a myocardial infarction was 1.83 (0.4, 8.6) on Entereg compared to placebo.

At the January 23, 2008 meeting of the Gastrointestinal Drugs Advisory Committee, the sponsor presented the findings of an independent data monitoring committee (IDMC) that was convened to adjudicate the cardiovascular adverse events in the pooled opioid-induced bowel dysfunction clinical trials. The IDMC concluded that the incidence of ischemic cardiac events was similar for Entereg- and placebo-treated patients (0.7% for each group). The incidence of other, non-ischemic, cardiovascular events was two-fold higher for Entereg-treated patients as compared to placebo (0.8% vs. 0.4%, respectively) although this difference was not statistically significant. The sponsor concluded that further opioid-induced bowel dysfunction trials should evaluate cardiovascular risk and that IDMC oversight should continue.

In summary, an excess number of myocardial infarctions were reported in a single clinical trial of opioid-induced bowel dysfunction that enrolled chronic opioid users with medium cardiovascular risk. This trial is the single longest duration trial (12 months) of Entereg. At this time, there is insufficient evidence in the literature to support either that opioids are cardioprotective or that opioid antagonists are cardiotoxic. Clinical experience with other approved opioid antagonists (naloxone and naltrexone) does not raise concerns about cardiovascular safety. From a pharmacokinetic standpoint, there is little accumulation of alvimopan with bid dosing, although an active degradant (ADL 08-0011) does appear to accumulate 6- to 9-fold after five days of dosing. Preclinical evaluation of alvimopan and this degradant did not raise any cardiovascular safety concerns. A detailed review by DGP revealed that there is no evidence that Entereg increases blood pressure compared to placebo in either the postoperative ileus or opioid-induced bowel dysfunction trials.

The Gastrointestinal Drugs Advisory Committee and DGP have both concluded, and I agree, that efficacy for Entereg Capsules,12 mg, for the acceleration of recovery of upper and lower gastrointestinal tract

motility following bowel resection surgery has been demonstrated. However, an excess number of myocardial infarctions were reported in a single long-term clinical trial for a different indication. Although it is possible that this finding may have occurred purely by chance, the serious nature of the risk prompted the Advisory Committee to recommend that Entereg be approved for postoperative ileus patients only if measures were implemented to restrict the use of the drug to short-term in-hospital use. In addition, the Advisory Committee recommended that the sponsor conduct a postmarketing clinical trial in patients undergoing surgery other than bowel resection in which cardiovascular safety would be prospectively monitored.

Tradename Review
The tradename "Entereg" is acceptable.

Required Pediatric Assessments

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred or inapplicable.

We are deferring the pediatric study requirement for ages 0 months up to 16 years because pediatric studies should be delayed until additional data from postmarketing studies in adults have been submitted.

The sponsor's deferred pediatric studies required under section 505B(a) of the Federal Food, Drug, and Cosmetic Act (FDCA) are required postmarketing studies and are listed below:

1. Conduct a study of Entereg for the acceleration of gastrointestinal recovery in pediatric patients ages greater than 1 month to 16 years undergoing bowel resection surgery. The study will measure the time to first tolerated feed, population pharmacokinetic parameters, the proportion of postoperative days with stool passed while in hospital, length of hospital stay, the need for postoperative nasogastric tube insertion for symptoms of postoperative ileus, and safety.

2. Conduct a study of Entereg for the acceleration of gastrointestinal recovery in pediatric patients ages 0 up to 1 month undergoing bowel resection surgery. The study will measure population pharmacokinetic parameters, safety, and time to first tolerated feed while in the hospital.

Postmarketing Requirements

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the FDCA to authorize FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A), 21 U.S.C. 355(o)(3)(A)). This provision took effect on March 25, 2008.

We have determined that Entereg is associated with a signal of a serious risk, that is, an imbalance in the number of myocardial infarctions in Entereg-treated patients receiving long-term treatment for opioid-induced bowel dysfunction.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess this signal of a serious risk. Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is thus not sufficient to assess this signal of a serious risk.
In addition, we 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.

Therefore, based on appropriate scientific data, we have determined that the sponsor is required, pursuant to section 505(o)(3) of the FDCA, to conduct the postmarketing clinical trial described below.

1. A multi-center, double-blind, placebo-controlled, parallel group clinical trial of Entereg for the management of postoperative ileus in subjects undergoing radical cystectomy.

Risk Evaluation and Mitigation Strategy (REMS) Requirements

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) if the Secretary determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)(1)). Section 505-1(a)(1) provides the following factors:

(A) The estimated size of the population likely to use the drug involved;
(B) The seriousness of the disease or condition that is to be treated with the drug;
(C) The expected benefit of the drug with respect to such disease or condition;
(D) The expected or actual duration of treatment with the drug;
(E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
(F) Whether the drug is a new molecular entity.

Entereg, a new molecular entity, has been shown to be effective to accelerate the time to upper and lower gastrointestinal recovery following partial small or large bowel resection surgery with primary anastomosis, procedures performed in about 343,000 patients in the U.S. annually. Patients receiving such procedures frequently experience postoperative ileus, a common cause of prolonged hospitalization. Entereg use has been associated with an increased number of myocardial infarctions in a single clinical trial evaluating longer-term use in patients with bowel dysfunction due to chronic opioid use.

Pursuant to section 505-1(a)(1), we have determined, after consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, that a REMS is necessary to ensure that the benefits of Entereg outweigh its risks. Pursuant to section 505-1(f)(1), we have also determined, after consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, that Entereg can be approved only if the elements necessary to assure safe use are required as part of a REMS to mitigate a specific serious risk, myocardial infarction, listed in the labeling of the drug. In reaching this determination, we considered the following:

A. Entereg will be approved for the acceleration of upper and lower gastrointestinal recovery following partial large or small bowel resection surgery with primary anastomosis. In the United States, about 343,000 patients have bowel resection surgery annually.[1] The degree to which Entereg will be used in patients who have bowel resection surgery is unknown.

B. Postoperative ileus is common following bowel resection surgery,[2] and can lead to longer hospital stay. Although not examined in the Entereg clinical development program, longer hospital stay can lead to iatrogenic complications (e.g., infection). In clinical trials, Entereg was shown to accelerate the time to upper and lower gastrointestinal recovery following bowel resection surgery. In addition, patients receiving Entereg had their hospital discharge order written approximately 13 to 21 hours sooner compared to patients receiving placebo.

C. In clinical trials submitted to NDA 21-775, patients treated with Entereg had a mean shorter time to recovery of bowel function of about 11 hours to 26 hours. See further discussion under Efficacy above.

D. Entereg will be approved for inpatient short-term use only; i.e., no more than 15 doses (7 days).

[1] See Healthcare Costs and Utilization Project (HCUP). 2005 National Statistics. Available at: http://www.ahrq.gov/HCUPnet. Accessed April 21, 2008.
[2] Livingston, EH, Passaro, EP, Jr. Postoperative ileus. Dig Dis Sci 1990;35:121-32.

E. An excess number of myocardial infarctions were noted in a single long-term clinical trial of Entereg for opioid-induced bowel dysfunction. In that trial, the majority of myocardial infarctions occurred between 1 and 4 months after initiation of treatment. An excess number of myocardial infarctions were not noted in postoperative ileus patients who received short-term treatment (up to 15 doses). See further discussion under Safety above.

F. Entereg (alvimopan) Capsules is a new molecular entity.

The elements of the REMS will be a communication plan, elements to assure safe use (including that hospitals that dispense the drug are specially certified, that the drug be dispensed to patients only in hospitals, and that the drug be dispensed to patients with evidence or other documentation of safe-use conditions), an implementation system, a timetable for submission of assessments, and assessments of the REMS. The sponsor's proposed REMS was submitted on May 14, 2008 and was found to be acceptable.

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/s/

Julie Beitz
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DIRECTOR