CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-775

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-775

NDA APPROVAL

Adolor Corporation
Attention: Linda G. Young, R.Ph., J.D.
Vice President, Regulatory Affairs
700 Pennsylvania Drive
Exton, PA 19341-1127

Dear Ms. Young:

Please refer to your new drug application (NDA) dated August 9, 2007, received August 10, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Entereg (alvimopan) Capsules, 12 mg.

We acknowledge receipt of your submissions dated January 18, October 18, December 18 and 28, 2007, January 10, 17, 25, February 7, March 5 and 6, April 15, 17, 22, 29, and May 1, 2, 14, and 20, 2008.

The August 9, 2007 submission constituted a complete response to our November 3, 2006 action letter.

A meeting of FDA's Gastrointestinal Drugs Advisory Committee was held on January 23, 2008 to discuss the safety and effectiveness of Entereg.

This new drug application provides for the use of Entereg (alvimopan) Capsules, 12 mg, for the acceleration of time to gastrointestinal recovery following partial large or small bowel resection surgery with primary anastomosis.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

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 in pediatric patients unless this requirement is waived, deferred or inapplicable.

We are deferring submission of your pediatric studies for ages 0 months to 16 years until after the completion of your postmarketing required study, which is scheduled for completion

December 31, 2012, because this product is ready for approval in adults and additional safety data in adults are needed.

Your deferred pediatric studies required under section 505B(a) of the FDCA are required postmarketing studies. The status of these required postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. These required studies are listed below.

1. Conduct a study of Entereg for the acceleration of gastrointestinal recovery in pediatric patients age greater than 1 month up 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.

Protocol Submission:	December 2012
Study Start:	June 2013
Final Report Submission:	June 2016

2. Conduct a study of Entereg for the acceleration of gastrointestinal recovery in pediatric patients age 0 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.

Protocol Submission:	December 2016
Study Start:	June 2017
Final Report Submission:	June 2019

Submit all final study reports to your NDA. Use the following designator to prominently label all submissions:

Required Pediatric Assessment

POSTMARKETING REQUIREMENTS UNDER 505(o)

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amended 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 an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess 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.

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 therefore not sufficient to assess a serious risk.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess this signal of a serious risk of, and to monitor the incidence of, myocardial infarctions in Entereg-treated patients undergoing surgery compared to patients receiving a placebo.

Therefore, based on appropriate scientific data, FDA has determined that you are required, pursuant to section 505(o)(3) of the FDCA, to conduct a clinical trial.

You are required to conduct the following clinical trial:

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

The timetable you submitted on April 22, 2008 states you will conduct this trial according to the following timetable:

Protocol Submission:	June 2008
Trial Start:	March 2009
Final Report Submission:	June 2012

Submit the protocol to your IND 56,553 with a cross-reference letter to this NDA 21-775. Submit all final report(s) to your NDA. Use the following designators to prominently label all submissions, including supplements, relating to this postmarketing clinical trial as appropriate:

Required Postmarketing Protocol under 505(o)
Required Postmarketing Final Report under 505(o)
Required Postmarketing Correspondence under 505(o)

You are required to report periodically to FDA on the status of this postmarketing study pursuant to sections 505(o)(3)(E)(ii) and 506B of the FDCA, as well as 21 CFR 314.81. Under section 505(o)(3)(E)(ii), you are also required to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue associated with Entereg.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

Title IX, Subtitle A, Section 901 of FDAAA amended 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)). This provision took effect on March 25, 2008.

In accordance with 505-1 of the FDCA, we have determined that a REMS is necessary for Entereg (alvimopan) Capsules, 12 mg, to ensure that the benefits of the drug outweigh the risks of myocardial infarction. Pursuant to section 505-1(f)(1), we have also determined 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.

Your proposed REMS, submitted on May 14, 2008 and resubmitted May 20, 2008, and appended to this letter, is approved. The REMS consists of a communication plan, elements to assure safe use, an implementation system, a timetable for assessments, and assessments of the REMS.

Use the following designator to prominently label all submissions, including supplements, relating to this REMS:

Risk Evaluation and Mitigation Strategy (REMS) Submission

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the enclosed package insert. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "SPL for approved NDA 21-775."

CARTON AND IMMEDIATE CONTAINER LABELS

We acknowledge your May 1, 2008 submission containing final printed carton and container labels.

Marketing the product with FPL that is not identical to the approved labeling text and in the required format may render the product misbranded and an unapproved new drug.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see www.fda.gov/cder/ddmac.

Please submit one market package of the drug product when it is available.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
HFD-001, Suite 5100
5515 Security Lane
Rockville, MD 20852

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

We acknowledge your May 2, 2008 commitment to expedited reporting of ischemic cardiovascular events, defined as: acute myocardial infarction, new onset or unstable angina, congestive heart failure, congestive cardiac failure, cerebrovascular accident (CVA), transient ischemic attach (TIA), cardiac arrest, and sudden death.

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

If you have any questions, call Matthew Scherer, Regulatory Project Manager, at (301) 796-2307.

Sincerely,

{See appended electronic signature page}

Julie Beitz, M.D.
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosures

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Julie Beitz
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