CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-775

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-775

Adolor Corporation
Attention: Linda Y. Harver, R.Ph., J.D.
700 Pennsylvania Drive
Exton, PA 19341

Dear Ms. Harver:

Please refer to your new drug application (NDA) dated May 9, 2006, received May 9, 2006, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ENTEREG® (alvimopan) Capsules.

We acknowledge receipt of your submissions dated June 7, July 12, August 17, September 13, September 15, September 21, September 27, and October 4, 2006.

The May 9, 2006 submission constituted a complete response to our July 21, 2005 action letter.

We completed our review of this application, as amended, and it is approvable. Before the application may be approved, however, it will be necessary for you to:

- Submit the 12 month safety findings (including analyses of myocardial infarction, unstable angina, and other serious cardiovascular events) from Study SB767905/014 for review when they become available; and
- Develop a risk management plan that includes elements to a) communicate the possible cardiovascular risk of longer-term alvimopan exposure and b) minimize off-label use. This plan could include appropriate labeling for prescribers and patients, and restriction of alvimopan use to hospital settings.

In addition, we recommend you collect blood samples to assess levels of alvimopan and its active degradant (i.e., ADL 08-0011) in patients experiencing cardiovascular adverse events enrolled in ongoing alvimopan studies, if this is not already being done.

Product labeling remains unresolved at this time. Please include revised draft product labeling with submission of your NDA amendment.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
   - Present tabulations of the new safety data combined with the original NDA data.
   - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

7. Provide English translations of current approved foreign labeling not previously submitted.

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with this division to discuss what steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call Tanya Clayton, Regulatory Project Manager, at (301) 796-0871.

Sincerely,

{See appended electronic signature page}

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

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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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-775

Adolor Corporation
Attention: Linda Y. Harver, R.Ph., J.D.
700 Pennsylvania Drive
Exton, PA 19341

Dear Ms. Harver:

Please refer to your new drug application (NDA) dated June 25, 2004, received June 25, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Entereg (alvimopan) Capsules, [redacted].

We acknowledge receipt of your submissions dated May 4, 14, and 27, June 25, August 11 and 12, September 15 and 24, October 15, 22, and 25, December 2, 2004, January 20, 26, and 28, February 14, April 8 and 21, May 19 and 26, June 1 and 7, and July 14, 2005.

This new drug application provides for the use of Entereg (alvimopan) Capsules for acceleration of time to recovery of gastrointestinal function following bowel resection surgery.

We completed our review of this application, as amended, and it is approvable. Before the application may be approved, however, it will be necessary for you to resolve the following:

Insufficient proof of efficacy to support your proposed indication of acceleration of time to recovery of gastrointestinal function following bowel resection surgery. In Study 14CL302, the 6 mg alvimopan dose, but not the 12 mg dose, was statistically superior to placebo treatment in time to recovery of gastrointestinal motility as measured by GI^3. In contrast, the 12 mg alvimopan dose in Study 14CL313 was statistically superior to placebo treatment while the 6 mg dose was not. Two additional studies (14CL308 and SB767905/001) failed to show statistical superiority for either dose compared to placebo treatment. When both doses are considered together, time to gastrointestinal recovery when assessed at 108 hours post-surgery ranged from one hour longer to 17 hours shorter relative to placebo treatment.

- The following are our recommendations for resolution of your above cited deficiency:

  1. Provide at least one additional adequate and well-controlled study (in patients scheduled to have partial small or partial large bowel resection) that demonstrates statistically significant superiority of the proposed dosing regimen relative to placebo treatment. Your ongoing Study 14CL314 could address this deficiency if statistically superior results for the 12 mg alvimopan dose relative to placebo treatment are demonstrated.

2. Justify your conclusion that the median reduction in time to gastrointestinal recovery relative to placebo treatment would be clinically meaningful to patients undergoing bowel resection surgery, e.g., in terms of shortened hospital stay or other factors.

Product labeling remains unresolved at this time. Please include revised draft product labeling with submission of your NDA amendment.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
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3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

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5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

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Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request an informal meeting or telephone conference with this division to discuss what steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, please call Melissa Hancock Furness, Regulatory Health Project Manager, at (301)-827-7450.

Sincerely,

{See appended electronic signature page}

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

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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