

## NDA 21-775 Entereg (alvimopan)

### RISK EVALUATION AND MITIGATION STRATEGY (REMS)

#### I. GOAL

To reduce the risk of myocardial infarction observed with longer use, Entereg (alvimopan) will be used only for short-term use (not to exceed 15 doses) in inpatient settings.

#### II. REMS ELEMENTS

##### A. Communication Plan

Adolor will implement a communication plan to healthcare providers to support implementation of this REMS.

Adolor will provide educational materials for distribution to healthcare professionals involved in the prescribing, dispensing, or administration of Entereg. This includes surgeons who perform bowel resection surgery, hospitalists, anesthesiologists, nurse anesthetists, pharmacists, nurses, and physicians assistants.

##### Healthcare Professional Education

- **Dear Hospital Pharmacist Letter**

The Dear Hospital Pharmacist Letter, to be distributed on product launch, will state that Entereg can be used for no more than 15 doses in inpatients, and that Entereg is not available for outpatient use. Additionally, the letter will provide a description of and directions on how to enroll in the E.A.S.E. program, the program that incorporates elements for safe use as shown in the appended [Dear Hospital Pharmacist Letter](#).

- **Entereg Access Support and Education (E.A.S.E.) educational materials**

Adolor will use the E.A.S.E. educational materials (available in printed form as part of the E.A.S.E. Program Kit Folder [a print-based registration package], and on-line as part of the web-based registration system), to educate all hospital-based healthcare professionals that are involved in the prescribing, dispensing, or administration of Entereg.

The E.A.S.E. printed materials include:

- E.A.S.E. Program Overview
- E.A.S.E. Hospital Brochure
- E.A.S.E. Kit Folder
- Program Overview

- Registration Form
- Hospital Brochure
- Prescribing Information Brochure

Additional educational materials include:

- Dear Hospital Pharmacist Letter
- Professional Labeling

The educational materials will prominently feature the safety-related message that because of the risk of myocardial infarction observed with longer use, Entereg can be used for no more than 15 doses in inpatients, and Entereg cannot be prescribed for outpatients as shown in the appended [printed material and web shots](#).

## **B. Elements to Assure Safe Use**

### **1. Drug Dispensed Only in Hospitals**

Entereg will be dispensed to patients only in hospitals. The hospital will not dispense Entereg for outpatient use.

### **2. Drug Dispensed in Specially Certified Hospitals**

Entereg will be dispensed only in hospitals that perform bowel resection surgery and that are specially certified by enrollment in the E.A.S.E. program. The specially certified hospital will not transfer Entereg to any hospital not registered with the E.A.S.E. Program. To register in the E.A.S.E. program, responsible hospital personnel must attest that:

- E.A.S.E. educational materials have been received by the hospital and distributed to healthcare professionals who are responsible for the ordering, prescribing, dispensing, or administering of Entereg;
- The hospital has systems, order sets, protocols, or other measures in place to ensure that Entereg is dispensed only to patients with evidence of safe use conditions. Please see [Hospital Registration](#) form.

Entereg will be distributed to registered hospitals via a drop-ship program through which Adolor retains direct control over who purchases Entereg. Hospitals that are registered in the E.A.S.E. Program may purchase Entereg utilizing the drop-ship program. The registered hospitals may order Entereg through their usual wholesalers; the wholesalers transmit the order through Adolor's distributor. This distributor sends Entereg only to registered hospitals. Please see the appended [Drop Shipment Procedure](#).

### **3. Drug Dispensed Only to Patients with Evidence of Safe-Use Conditions**

Entereg will be dispensed only to patients in hospitals performing bowel resections; each patient will receive no more than 15 doses of the drug.

### **C. Implementation System**

The Implementation System includes the following:

- Adolor will maintain a database of all specially certified hospitals;
- Adolor will monitor distribution to determine whether the drug is only drop-shipped to certified hospitals and will conduct audits to verify;
- Adolor will monitor dispensing of Entereg to ensure that it is dispensed only for inpatient use;
- Adolor will monitor the duration of therapy to determine whether Entereg is being dispensed to patients with evidence that the patient is hospitalized for bowel resection surgery and has received no more than 15 doses;
- Based on monitoring and evaluation of the elements to assure safe use, Adolor will take reasonable steps to work to improve implementation of these elements.

### **D. Timetable for Submissions of Assessments**

REMS Assessments (see III below for content) will be submitted to FDA quarterly for the first 18 months following approval, then annually (from approval date) thereafter.

## **III. INFORMATION NEEDED FOR ASSESSMENTS**

REMS Assessments will include the following:

- An assessment of use data establishing the circumstances of use of Entereg:
  - the extent of outpatient use;
  - the extent of inpatient use;
  - the extent of use > 15 doses within hospitals;
  - the extent of use in bowel resection procedures;
  - the extent of use in non-bowel resection procedures;
  - the extent of use for other (not associated with bowel resection or non-bowel resection procedures) reasons;
  - the extent of use by specially certified hospitals; and
  - the extent of use by hospitals that are not specially certified.
- A description of the investigation of use deviations and corrective actions taken.

- An assessment of healthcare professional understanding regarding the safe use of Entereg; i.e., the results of surveys administered to hospital pharmacists and surgeons 12 and 18 months following the launch of Entereg, and every 12 months thereafter if sufficient understanding is not displayed. Please see the appended [Survey Program](#).
- A narrative summary and analysis of myocardial infarctions reported with use of Entereg.
- Based on the information provided, an assessment and conclusion of whether the REMS is meeting its goals, and whether modifications to the REMS are needed.

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## Dear Hospital Pharmacist Letter



GlaxoSmithKline  
Three Franklin Plaza  
1600 Vine Street  
Philadelphia, PA 19102



700 Pennsylvania Drive  
Exton, PA 19341-1127

May 1, 2008

Dear Hospital Pharmacist:

Adolor and GlaxoSmithKline are pleased to introduce you to ENTEREG® (alvimopan) and the ENTEREG Access Support & Education (E.A.S.E.™) Program.

ENTEREG, a peripherally acting  $\mu$ -opioid receptor antagonist, is indicated to accelerate the time to upper and lower gastrointestinal (GI) recovery following partial large or small bowel resection with primary anastomosis.

ENTEREG is approved for short-term use in the hospital setting. Enrollment in the E.A.S.E. Program permits hospitals performing bowel resection surgeries to receive ENTEREG. It is important that you understand this program in order to help your pharmacy order, stock, and dispense ENTEREG.

### Efficacy in clinical trials in the management of postoperative ileus following bowel resection

#### ENTEREG:

- Accelerated time to upper and lower GI recovery
- Reduced the length of hospital stay

In clinical trials, ENTEREG did not reverse opioid analgesia.

### Enrollment in the E.A.S.E. Program

In one long-term (12-month) clinical study of alvimopan in patients treated with opioids for chronic pain, a numeric imbalance was seen in the incidence of ischemic cardiovascular events. As a result, the E.A.S.E. Program was developed to ensure that ENTEREG is administered only short-term in inpatient hospital settings and for no more than 15 doses. See Important Safety Information.

ENTEREG is available only to hospitals that perform bowel resections and are enrolled in the E.A.S.E. Program. This program is designed to ensure that ENTEREG is used in accordance with the FDA-approved label and requires that:

- The E.A.S.E. Program Educational Materials have been received by the hospital and provided to the healthcare practitioners who are responsible for the ordering, dispensing, or administration of ENTEREG
- The hospital has systems, order sets, protocols, or other measures in place to limit the use of ENTEREG to no more than 15 doses per patient for administration in the hospital only
- The hospital will not dispense ENTEREG for outpatient use and will not transfer ENTEREG to any hospital not registered with the E.A.S.E. Program

For more information on the program, contact your Adolor/GlaxoSmithKline account manager or visit [www.entereg.com](http://www.entereg.com).

### Ordering Information

After hospitals have enrolled in the E.A.S.E. Program, ENTEREG can be ordered from wholesalers and will be shipped directly to your inpatient hospital pharmacy by the distributor. ENTEREG cannot be transferred from an enrolled to a nonenrolled hospital.



### Dosing With ENTEREG

ENTEREG is for hospital use only. The recommended adult dose of ENTEREG is 12 mg administered 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 or until discharge. Patients should not receive more than 15 doses of ENTEREG.

### Important Safety Information

ENTEREG® (alvimopan) is contraindicated in patients who have taken therapeutic doses of opioids for more than 7 consecutive days immediately prior to taking ENTEREG.

There were more reports of myocardial infarctions in patients treated with alvimopan 0.5 mg twice daily compared with placebo-treated patients in a 12-month study of patients treated with opioids for chronic pain. 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 of 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.

Overall, the incidence of adverse reactions in short-term surgical clinical trials was similar between patients receiving either ENTEREG or placebo. Most common adverse reactions (incidence  $\geq 3\%$  and  $\geq 1\%$  placebo) in patients undergoing bowel resection were anemia, dyspepsia, hypokalemia, back pain, and urinary retention.

### Adverse Event Reporting

Healthcare professionals should report all suspected adverse events associated with the use of ENTEREG. Please contact Adolor Corporation at 700 Pennsylvania Drive, Exton, PA 19341 or 1-866-4ADOLOR (1-866-423-6567), or the GSK Response Center at 1-888-825-5249.

Alternatively, this information may be reported to the FDA MedWatch Reporting System by phone at 1-800-FDA-1088 (1-800-332-1088) or by mail using Form 3500 at [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

If you have any questions, please contact Adolor Corporation at 1-866-4ADOLOR (1-866-423-6567) or visit [www.entereg.com](http://www.entereg.com).

Please see accompanying complete Prescribing Information.

Sincerely,

(Signature)

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Source: ENTEREG (prescribing information), Exton, PA: Adolor Corporation; 2008.  
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