Initial REMS Approval: 05/29/2008

Most Recent Modification: October/2013

NDA 21-775 ENTEREG (alvimopan)

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RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL

The goal of the E.A.S.E. ENTEREG REMS Program is to mitigate the potential risk of myocardial infarction by:

- Ensuring that ENTEREG (alvimopan) is used only for short-term use (no more than 15 doses) in a hospital inpatient setting
- Informing healthcare providers about the potential risk of myocardial infarction observed with long-term use of ENTEREG.

II. REMS ELEMENTS

A. Elements to Assure Safe Use

1. Cubist will ensure that ENTEREG will only be dispensed by hospital pharmacies that are specially certified.
    a. To become certified to dispense ENTEREG, each hospital pharmacy must enroll in the E.A.S.E. ENTEREG REMS Program.
    b. Each hospital pharmacy must designate an authorized representative to

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complete enrollment on behalf of the hospital pharmacy.

c. In order for the hospital pharmacy to be certified, the authorized representative must attest that:

   i. The E.A.S.E. ENTEREG REMS Program Kit has been received by the hospital and education on the benefits and risks of ENTEREG has been provided to the healthcare practitioners who are responsible for ordering, dispensing, or administering ENTEREG.

   ii. The representative understands the risks and benefits of ENTEREG and has read the materials in the E.A.S.E. ENTEREG REMS Program Kit

   iii. The certified hospital pharmacy has pharmacy systems, order sets, protocols, and/or other measures in place to limit the use of ENTEREG to no more than 15 doses per patient for administration in the hospital inpatient setting only.

   iv. The certified hospital pharmacy will not dispense ENTEREG for outpatient use and will not transfer ENTEREG to any hospital pharmacy not enrolled in the E.A.S.E. ENTEREG REMS Program.

d. The certified hospital pharmacy must train relevant staff (e.g., staff involved in prescribing, dispensing, or administering ENTEREG) on the safe use of ENTEREG, as described in the E.A.S.E. ENTEREG REMS Program Kit materials.

e. Cubist will ensure that, as part of the hospital pharmacy enrollment process, E.A.S.E ENTEREG REMS Program Kit contains the following materials:

   - **E.A.S.E. ENTEREG REMS Program Overview**, which provides an overview of the E.A.S.E program requirements and lists the materials included in the kit.
   - **Dear Healthcare Provider Letter**, which states that due to the potential risk of myocardial infarction observed with long-term use, ENTEREG is indicated only for short-term use (no more than 15 doses) in hospitalized patients, and provides details on how the E.A.S.E. ENTEREG REMS Program Kit can be accessed.
   - **Prescriber and Pharmacist Information Brochure**, which:
     - states that due to the potential risk of myocardial infarction observed with long-term use, ENTEREG is indicated only for short-term use (no more than 15 doses) in hospitalized patients
     - describes that enrollment in the E.A.S.E. program permits hospitals performing surgeries that include bowel

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resections to receive ENTEREG

  - describes the required pharmacy systems, order sets, protocols and/or other measures that must be in place to limit the use of ENTEREG to no more than 15 doses per hospitalized patient

- **Hospital Pharmacy Enrollment Form,** which specifically describes how a hospital pharmacy will enroll into the E.A.S.E. ENTEREG REMS Program.

f. Cubist will ensure that all materials listed in or appended to the E.A.S.E. ENTEREG REMS Program are available to hospital pharmacies in hard copy and online through the E.A.S.E. ENTEREG REMS Program website, www.ENTEREGREMS.COM.

Cubist will ensure that ENTEREG will only be dispensed in a hospital in patient setting that performs bowel resection surgery

B. Implementation System

The Implementation System includes the following:

1. Cubist will ensure that ENTEREG is distributed only to certified hospital pharmacies;
2. Cubist will maintain a database of all certified hospital pharmacies;
3. Cubist will monitor distribution to determine whether or not the drug is only distributed to certified hospital pharmacies and will conduct audits to verify;
4. Cubist will monitor dispensing of ENTEREG to ensure that it is dispensed only for inpatient use;
5. Cubist will monitor the duration of therapy to determine whether or not ENTEREG is being dispensed only to inpatients with evidence that the patient underwent bowel resection surgery and received no more than 15 doses;
6. Based on monitoring and evaluation of the elements to assure safe use, Cubist will take reasonable steps to work to improve implementation of these elements.

C. Timetable for Submission of Assessments

Cubist will submit REMS Assessments to FDA at 12 months following initial REMS approval (May 20, 2008), then annually, thereafter. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. Cubist will submit each assessment so that it will be received by the FDA on or before the due date.

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E.A.S.E.®

ENTEREG Access Support & Education Program

ENTEREG® REMS Program

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E.A.S.E. ENTEREG REMS Program Overview

What is the E.A.S.E.® ENTEREG REMS Program?

The **E.A.S.E.® ENTEREG REMS Program** was designed to allow hospitals that perform surgeries that include a bowel resection to receive ENTEREG. It is important that you understand this program in order to help your pharmacy order, stock, and dispense ENTEREG.

What are the E.A.S.E.® ENTEREG REMS Program Requirements?

- Educating healthcare practitioners who are responsible for ordering, dispensing, or administration of ENTEREG
- Ensuring the certified hospital pharmacy has pharmacy systems, order sets, protocols, and/or other measures in place to limit the use of ENTEREG to no more than 15 doses per patient for administration in the hospital inpatient setting only
- Ensuring the certified hospital pharmacy will not dispense ENTEREG for outpatient use and will not transfer ENTEREG to any hospital pharmacy not enrolled with the E.A.S.E. ENTEREG REMS Program

The enclosed E.A.S.E. ENTEREG REMS Program Kit contains all materials necessary to certify your inpatient hospital pharmacy:

- Program Overview
- Dear Healthcare Provider Letter
- Prescriber and Pharmacist Information Brochure
- Hospital Pharmacy Enrollment Form

The E.A.S.E. ENTEREG REMS Program Kit also includes a copy of the full ENTEREG Prescribing Information

For More Information:

In addition, all REMS materials are available on the E.A.S.E. ENTEREG REMS Program Website at www.ENTEREGREMS.com.

Adverse Event Reporting

To report suspected adverse reactions contact:

- Cubist Pharmaceuticals at 1-877-CUBIST-6 (1-877-282-4786)
- FDA at 1-800-FDA-1088 (1-800-332-1088) or at www.fda.gov/medwatch.

Please see accompanying complete Prescribing Information

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IMPORTANT DRUG WARNING

Subject: ENTEREG® is indicated only for short-term use (no more than 15 doses) in hospitalized patients

Dear Healthcare Provider:

ENTEREG, a peripherally acting μ-opioid receptor antagonist, is indicated to accelerate the time to upper and lower gastrointestinal (GI) recovery following surgeries that include partial bowel resection with primary anastomosis. **Cubist Pharmaceuticals, Inc. would like to inform/remind you that ENTEREG is indicated only for short-term use (no more than 15 doses) in hospitalized patients.**

The FDA has determined that a Risk Evaluation and Mitigation Strategy (REMS) is necessary to ensure that the benefits of ENTEREG outweigh the potential risk of:

- Myocardial Infarction observed with long-term use

The E.A.S.E.® ENTEREG REMS Program

In one long-term (12-month) clinical study of 0.5 mg 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.

ENTEREG is available only to hospitals that perform surgeries that include bowel resections and are enrolled in the E.A.S.E. ENTEREG REMS Program, and will not be dispensed for outpatient use.

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Dispensing by Certified Inpatient Hospitals

To become certified, your hospital pharmacy must be enrolled in the E.A.S.E. ENTEREG REMS Program before you can prescribe ENTEREG. This program requires that an authorized representative designated by the hospital pharmacy attests that:

- The E.A.S.E. ENTEREG REMS Program Kit been received by the hospital and education on the benefits and risks of ENTEREG has been provided to the healthcare practitioners who are responsible for ordering, dispensing, or administration of ENTEREG.
- The representative understands the risks and benefits of ENTEREG and has read the materials in the E.A.S.E. ENTEREG REMS Program Kit before ENTEREG is dispensed.
- The certified hospital pharmacy has pharmacy systems, order sets, protocols, and/or other measures in place to limit the use of ENTEREG to no more than 15 doses per patient for administration in the hospital inpatient setting only.
- The certified hospital pharmacy will not dispense ENTEREG for outpatient use and will not transfer ENTEREG to any hospital pharmacy not enrolled with the E.A.S.E. ENTEREG REMS Program.

For more information on the program, contact your Cubist account manager or visit www.ENTEREGREMS.com.

Adverse Event Reporting

To report suspected adverse reactions contact:

- Cubist Pharmaceuticals at 1-877-CUBIST-6 (1-877-282-4786)
- FDA at 1-800-FDA-1088 (1-800-332-1088) or at www.fda.gov/medwatch.

Please see accompanying complete Prescribing Information

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Prescriber and Pharmacist Information Brochure

ENTEREG® is a peripherally acting μ-opioid receptor antagonist indicated to accelerate the time to upper and lower gastrointestinal (GI) recovery following surgeries that include partial bowel resection with primary anastomosis. ENTEREG is approved for short-term use in the hospital in-patient setting

In one long-term (12-month) clinical study of 0.5 mg alvimopan in patients treated with opioids for chronic non-cancer pain, a numeric imbalance was seen in the incidence of ischemic cardiovascular events. As a result, the E.A.S.E ENTEREG REMS 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 and Boxed Warning on the reverse side.**

Enrollment in the E.A.S.E. ENTEREG REMS Program

ENTEREG is available only to hospitals that perform surgeries that include a bowel resection and dispensed by pharmacies that are enrolled in the E.A.S.E. ENTEREG REMS Program. This program is designed to ensure that ENTEREG is used in accordance with the FDA-approved label and requires that an authorized representative designated by the hospital pharmacy attests that:

- The E.A.S.E. ENTEREG REMS Program Kit has been received by the hospital and education on the benefits and risks of ENTEREG has been provided to the healthcare practitioners who are responsible for ordering, dispensing, or administration of ENTEREG
- The representative understands the risks and benefits of ENTEREG and has read the materials in the E.A.S.E. ENTEREG REMS Program Kit before ENTEREG is dispensed
- The certified hospital pharmacy has pharmacy systems, order sets, protocols, and/or other measures in place to limit the use of ENTEREG to no more than 15 doses per patient for administration in the hospital inpatient setting only
- The certified hospital pharmacy will not dispense ENTEREG for outpatient use and will not transfer ENTEREG to any hospital pharmacy not enrolled with the E.A.S.E. ENTEREG REMS Program

For more information on the program, contact your Cubist account manager or visit www.ENTEREGREMS.com.

How to Order

In order to receive ENTEREG, your hospital pharmacy must enroll in the E.A.S.E. ENTEREG REMS Program. Upon registration:

- ENTEREG can be ordered directly from wholesalers
- ENTEREG will be shipped directly to your inpatient hospital pharmacy by the distributor
- ENTEREG cannot be transferred from a certified to a non-certified hospital pharmacy

How supplied	Product code	Description
Actual size ENTEREG 12 mg	**NDC 67919-020-10**	Blue, hard gelatin capsules printed with "ADL2698" on both the body and the cap of the capsule

Store at 25°C (77°F); excursions permitted to 15°C–30°C (59°F–86°F) [see USP Controlled Room Temperature].

Important Safety Information for ENTEREG

WARNING: POTENTIAL RISK OF MYOCARDIAL INFARCTION WITH LONG-TERM USE:
FOR SHORT-TERM HOSPITAL USE ONLY
See full prescribing information for complete boxed warning.

- **Increased incidence of myocardial infarction was seen in a clinical trial of patients taking alvimopan for long-term use.**
- **ENTEREG is available only through a restricted program for short-term use (15 doses) called the ENTEREG Access Support and Education (E.A.S.E.) Program.**

ENTEREG Capsules are 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 non-cancer pain (alvimopan, n=538; placebo, n=267). 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 in patients treated with opioids for chronic pain nor in patients treated within the surgical setting, including patients undergoing surgeries that included bowel resection who received alvimopan 12 mg twice daily for up to 7 days (the indicated dose and patient population); (alvimopan 12 mg, n= 1,142; placebo, n= 1,120). A causal relationship with alvimopan with long-term use has not been established.

ENTEREG should be administered with caution to patients receiving more than 3 doses of an opioid within the week prior to surgery. These patients may be more sensitive to Entereg and may experience GI side effects (eg, abdominal pain, nausea and vomiting, diarrhea).

ENTEREG is not recommended for use in patients with severe hepatic impairment, end-stage renal disease, complete gastrointestinal obstruction, or pancreatic or gastric anastomosis, or in patients who have had surgery for correction of complete bowel obstruction.

Overall, the incidence of adverse reactions in short-term surgical clinical trials was similar between patients receiving either ENTEREG or placebo. The most common adverse reaction (incidence ≥1.5%) occurring with a higher frequency than placebo among Entereg treated patients undergoing surgeries that included a bowel resection was dyspepsia (ENTEREG, 1.5%; placebo, 0.8%).

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Dosing and administration	For hospital use only
The recommended adult dosage 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.	

Adverse Event Reporting

To report suspected adverse reactions contact Cubist Pharmaceuticals at 1-877-CUBIST-6 (1-877-282-4786) or FDA at 1-800-FDA-1088 (1-800-332-1088) or at www.fda.gov/medwatch

Please see accompanying complete Prescribing Information.

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HOSPITAL PHARMACY ENROLLMENT FORM

Enrollment in the E.A.S.E® ENTEREG REMS Program permits hospitals that perform surgeries that include a bowel resection to receive ENTEREG® for short-term, in-hospital use.

In one long-term (12-month) clinical study of 0.5 mg alvimopan in patients treated with opioids for chronic non-cancer pain, a numeric imbalance was seen in the incidence of ischemic cardiovascular events. As a result, the E.A.S.E ENTEREG REMS Program was developed to ensure that ENTEREG is administered only short-term in inpatient hospital settings and for no more than 15 doses.

This hospital pharmacy acknowledges that:

- ☐ The E.A.S.E. ENTEREG REMS Program Kit has been received by the hospital and education on the benefits and risks of ENTEREG has been provided to the healthcare practitioners who are responsible for ordering, dispensing, or administration of ENTEREG
- ☐ The representative understands the risks and benefits of ENTEREG and has read the materials in the E.A.S.E. ENTEREG REMS Program Kit before ENTEREG is dispensed
- ☐ The certified hospital pharmacy has pharmacy systems, order sets, protocols, and/or other measures in place to limit the use of ENTEREG to no more than 15 doses per patient for administration in the hospital inpatient setting only
- ☐ The certified hospital pharmacy will not dispense ENTEREG for outpatient use and will not transfer ENTEREG to any hospital pharmacy not enrolled with the E.A.S.E. ENTEREG REMS Program

*Hospital Name _____

*Hospital DEA# _____

Health Industry Number _____

*Authorized Signatory: First Name _____ *Last Name _____

*Title ☐ Hospital Pharmacist

☐ Representative of P&T Committee _____
(must check one) (insert title)

*E-mail Address _____

*Pharmacy Phone _____ *Pharmacy Fax _____

*Hospital Ship-to Address _____

*City _____ *State _____ *ZIP Code _____

Your Sales Representative for ENTEREG E-mail Address _____

Please check one: ☐ New Enrollment ☐ Update to Existing Enrollment

*Denotes mandatory fields to complete.

I confirm that the information above is correct.

I understand that this information will be used to enable Cubist to identify hospitals at which surgeries that include a bowel resection are performed that are eligible to receive shipments of ENTEREG. I also understand that this information may be shared with others working with Cubist, other hospitals enrolled in the E.A.S.E. ENTEREG REMS Program, and may be shared with government agencies.

Signature _____ Date _____

To submit via fax: Sign and fax to 1-800-278-1365.After verification of eligibility, a confirmation will be provided to you, **via e-mail**. If you have any questions, please contact Cubist Pharmaceuticals at 1-877-CUBIST-6 (1-877-282-4786) or visit www.ENTEREGREMS.com. **NOTE: If you have multiple shipping sites, please complete a separate E.A.S.E. registration for each ship site with an accompanying DEA number.**

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See Important Safety Information | View Prescribing Information

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E.A.S.E.® ENTEREG® REMS Program

E.A.S.E. Program Kit

- Program Overview
- Dear Healthcare Provider Letter
- Prescriber and Pharmacist Information Brochure
- Hospital Pharmacy Enrollment Form
- Prescribing Information

Program Overview

ENTEREG is available only to hospitals that perform surgeries that include a bowel resection and dispensed by pharmacies that are enrolled in the E.A.S.E. ENTEREG REMS 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. ENTEREG REMS Program Kit has been received by the hospital and education on the benefits and risks of ENTEREG has been provided to the healthcare practitioners who are responsible for ordering, dispensing, or administration of ENTEREG
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Adverse Event Reporting

Healthcare professionals should report all suspected adverse events associated with the use of ENTEREG.

To report suspected adverse reactions contact Cubist Pharmaceuticals at 1-877-CUBIST-6 (1-877-282-4786) or FDA at 1-800-FDA-1088 (1-800-332-1088) or at www.fda.gov/medwatch.

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/s/

JOYCE A KORVICK
10/18/2013