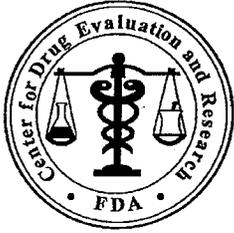


**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-775**

**PROPRIETARY NAME REVIEW(S)**



**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: April 22, 2008

To: Donna Griebel, M.D., Director  
Division of Gastrointestinal Products

Through: Denise Toyer, Pharm.D., Deputy Director  
Carol Holquist, R.Ph., Director  
Division of Medication Error Prevention, HFD-420

From: Kristina Arnwine, PharmD, Acting Team Leader  
Division of Medication Error Prevention, HFD-420

Subject: Proprietary Name, Label, and Labeling Review

Drug Name(s): Entereg (Alvimopan) Capsules 12 mg

Application Type/Number: NDA # 21-775

Applicant/sponsor: Adolor Corp.

OSE RCM #: 2008-353

**\*\*\* This document contains proprietary and confidential information that should not be released to the public.\*\*\***

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## **EXECUTIVE SUMMARY**

The results of the Proprietary Name Risk Assessment found that the proposed name, Entereg, has some similarity to other proprietary and established drug names, but the findings of the FMEA indicates that the proposed name does not appear to be vulnerable to name confusion that could lead to medication errors. Thus, we do not object to the use of the proprietary name Entereg for this product.

The results of the Label and Labeling Risk Assessment found that the presentation of information and design of the proposed container labels and carton labeling appear to be vulnerable to confusion that could lead to medication errors. Specifically, we are concerned with redundancy and clutter on the [REDACTED], and a lack of appropriate prominence of important information on the carton labeling. We believe the risks can be addressed and mitigated prior to drug approval, and provide recommendations in Section 6 that aim at reducing the risk of medication errors.

However; if any of the proposed product characteristics as stated in this review are altered prior to approval of the product, we rescind this Risk Assessment finding, and recommend that the name be resubmitted for review. Additionally, if the product approval is delayed beyond 90 days from the date of this review, the proposed name must be resubmitted for evaluation.

## **1 BACKGROUND**

### **1.1 INTRODUCTION**

This review is in response to a request from the Division of Gastrointestinal Products for re-assessment of the proprietary name, Entereg, regarding potential name confusion with other proprietary or established drug names and for its potential to contribute to medication errors.

Additionally, the container labels, carton and insert labeling were provided for evaluation to identify areas that could lead to medication errors.

### **1.2 REGULATORY HISTORY**

We originally reviewed the proprietary name, container labels, and insert labeling on January 23, 2003 (ODS Review 03-0034) with no objection to the name, but provided recommendation to revise the label and labeling.

The name Entereg was also reviewed on July 12, 2005 (ODS Review 03-0034-1) and August 15, 2006 (OSE Consult 03-0031-2); again with no objections to the name.

### **1.3 PRODUCT INFORMATION**

Entereg is indicated to accelerate recovery time of gastrointestinal function following partial large or small bowel resection with primary anastomosis. Entereg is for inpatient use only. Patients will not be discharged on this medication. The recommended dosage 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 the patient is discharged from the hospital.

## **2 METHODS AND MATERIALS**

This section consists of two sections which describe the methods and materials used by the Division of Medication Error and Prevention's medication error staff conducting a proprietary name risk assessment (see 2.1 Proprietary Name Risk Assessment) and label, labeling, and/or packaging risk assessment (see 2.2 Container, Carton Label, and Insert Label Risk Assessment).

The primary focus for both of the assessments is to identify and remedy potential sources of medication error prior to drug approval. The Division defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer.<sup>1</sup>

## 2.1 PROPRIETARY NAME RISK ASSESSMENT

FDA's Proprietary Name Risk Assessment considers the potential for confusion between the proposed proprietary name, Entereg, and the proprietary and established names of drug products existing in the marketplace and those pending IND, NDA, and ANDA products currently under review by the Agency.

For the proprietary name, Entereg, the Medication Error Staff search a standard set of databases and information sources to identify names with orthographic and phonetic similarity (see Sections 2.1.1 for detail) and held an CDER Expert Panel discussion to gather professional opinions on the safety of the proposed proprietary name (see 2.1.1.2). We normally conduct internal CDER prescription analysis studies and, when provided, external prescription analysis studies results are considered and incorporated into the overall risk assessment. However, since this name was previously evaluated, CDER prescription analysis studies were not conducted upon re-review of Entereg.

The Safety Evaluator assigned to the Proprietary Name Risk Assessment is responsible for considering the collective findings, and provides an overall risk assessment of the proposed proprietary name (see detail 2.1.2). The overall risk assessment is based on the findings of a Failure Modes and Effects Analysis (FMEA) of the proprietary name, and is focused on the avoidance of medication errors. FMEA is a systematic tool for evaluating a process and identifying where and how it might fail.<sup>2</sup> FMEA is used to analyze whether the drug names identified with look- or sound-alike similarity to the proposed name could cause confusion that subsequently leads to medication errors in the clinical setting. We use the clinical expertise of the medication error staff to anticipate the conditions of the clinical setting that the product is likely to be used in based on the characteristics of the proposed product.

In addition, the product characteristics provide the context for the verbal and written communication of the drug names and can interact with the orthographic and phonetic attributes of the names to increase the risk of confusion when there is overlap, or, in some instances, decrease the risk of confusion by helping to differentiate the products through dissimilarity. As such, the Staff considers the product characteristics associated with the proposed drug throughout the risk assessment, since the product characteristics of the proposed may provide a context for communication of the drug name and ultimately determine the use of the product in the *usual* clinical practice setting.

Typical product characteristics considered when identifying drug names that could potentially be confused with the proposed drug name include, but are not limited to established name of the proposed product, the proposed indication, dosage form, route of administration, strength, unit of measure, dosage units, recommended dose, typical quantity or volume, frequency of administration, product packaging, storage conditions, patient population, and prescriber population. Because drug name confusion can occur at any point in the medication use process, we consider the potential for confusion throughout the entire U.S. medication use process,

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<sup>1</sup> National Coordinating Council for Medication Error Reporting and Prevention.  
<http://www.nccmerp.org/aboutMedErrors.html>.

<sup>2</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

including drug procurement, prescribing and ordering, dispensing, administration, and monitoring the impact of the medication.<sup>3</sup>

### **2.1.1 Search Criteria**

The Medication Error Prevention Staff considers the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted as outlined in Appendix A.

For this review, particular consideration was given to drug names beginning with the letter 'E' when searching to identify potentially similar drug names, as 75% of the confused drug names reported by the USP-ISMP Medication Error Reporting Program involve pairs beginning with the same letter.<sup>4,5</sup>

To identify drug names that may look similar to Entereg, the Staff also consider the orthographic appearance of the name on lined and unlined orders. Specific attributes taken into consideration include the length of the name (seven letters), upstrokes (two, capital letter 'E' and lower case letter 't'), downstrokes (one, lower case letter 'g'), cross-strokes (two, capital letter 'E' and lower case 't') and dotted letters (none). Additionally, several letters in Entereg may be vulnerable to ambiguity when scripted, including the capital letter 'E' may appear as capital 'I'; lower case 'e' may look like lower case 'l' and 'i'; lower case 'n' may look like lower case 'r', 'u', 'h', 's' or 'x'; lower case letter 't' may appear as lower case 'x', 'r' or 'f'; lower case 'e' may appear as lower case 'l' or an un dotted 'i'; lower case 'r' may appear as lower case 'n' and 's'; and lower case 'g' may appear as lower case 'z', 's', or 'y'. As such, the Staff also considers these alternate appearances when identifying drug names that may look similar to Entereg.

When searching to identify potential names that may sound similar to Entereg, the Medication Error Staff search for names with similar number of syllables (3), stresses (en-TER-reg, en-ter-REG or EN-ter-reg), and placement of vowel and consonant sounds. In addition, several letters in Entereg may be subject to interpretation when spoken, including the letters 'EN' may be interpreted as 'IN' the letter 't' may be interpreted as 'pt' or 'd'. The Sponsor's intended pronunciation of the proprietary name could not be expressly taken into consideration, as this was not provided with the proposed name submission.

The Staff also consider the product characteristics associated with the proposed drug throughout the identification of similar drug names, since the product characteristics of the proposed drug ultimately determine the use of the product in the clinical practice setting. For this review, the Medication Error Staff were provided with the following information about the proposed product: the proposed proprietary name (Entereg) the established name (alvimopan), proposed indication (accelerate the time to upper and lower gastrointestinal recovery following bowel resection surgery), strength (12 mg), dose (12 mg), frequency of administration (one dose prior to surgery then twice daily for 7 days), route (oral), and dosage form (capsule). Appendix A provides a more detailed listing of the product characteristics the Medication Error Staff generally take into consideration.

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<sup>3</sup> Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006.

<sup>4</sup> Institute for Safe Medication Practices. Confused Drug name List (1996-2006). Available at <http://www.ismp.org/Tools/confuseddrugnames.pdf>

<sup>5</sup> Kondrack, G and Dorr, B. Automatic Identification of Confusable Drug Names. Artificial Intelligence in Medicine (2005)

Lastly, the Medication Error Staff also consider the potential for the proposed name to inadvertently function as a source of error for reasons other than name confusion. Post-marketing experience has demonstrated that proprietary names (or components of the proprietary name) can be a source of error in a variety of ways. As such, these broader safety implications of the name are considered and evaluated throughout this assessment and the Medication Error Staff provide additional comments related to the safety of the proposed name or product based on their professional experience with medication errors.

#### **2.1.1.1 Database and information sources**

The proposed proprietary name, Entereg, was provided to the medication error staff to conduct a search of the internet, several standard published drug product reference texts, and FDA databases to identify existing and proposed drug names that may sound-alike or look-alike to Entereg using the criteria outlined in 2.1.1. A standard description of the databases used in the searches is provided in Section 7. To complement the process, the Medication Error Staff use a computerized method of identifying phonetic and orthographic similarity between medication names. The program, Phonetic and Orthographic Computer Analysis (POCA), uses complex algorithms to select a list of names from a database that have some similarity (phonetic, orthographic, or both) to the trademark being evaluated. Lastly, the Medication Error Staff review the USAN stem list to determine if any USAN stems are present within the proprietary name. The findings of the individual Safety Evaluators were then pooled and presented to the Expert Panel.

#### **2.1.1.2 CDER Expert Panel Discussion**

An Expert Panel Discussion is held by The Medication Error and Prevention Staff to gather CDER professional opinions on the safety of the product and the proprietary name, Entereg. Potential concerns regarding drug marketing and promotion related to the proposed names are also discussed. This group is composed of Medication Errors Prevention Staff and representatives from the Division of Drug Marketing, Advertising, and Communications (DDMAC).

The pooled results of the medication error staff were presented to the Expert Panel for consideration. Based on the clinical and professional experiences of the Expert Panel members, the Panel may recommend the addition of names, additional searches by the Safety Evaluator to supplement the pooled results, or general advice to consider when reviewing the proposed proprietary name.

#### **2.1.2 Safety Evaluator Risk Assessment of the Proposed Proprietary Name**

Based on the criteria set forth in Section 2.1, the Safety Evaluator Risk Assessment applies their individual expertise gained from evaluating medication errors reported to FDA to conduct a Failure Modes and Effects Analysis and provide an overall risk of name confusion. Failure Mode and Effects Analysis (FMEA) is a systematic tool for evaluating a process and identifying where and how it might fail.<sup>6</sup> When applying FMEA to assess the risk of a proposed proprietary name, the Division seeks to evaluate the potential for a proposed name to be confused with another drug name as a result of the name confusion and cause errors to occur in the medication use system. FMEA capitalizes on the predictable and preventable nature of medication errors associated with drug name confusion. FMEA allows the Agency to identify the potential for medication errors due to look- or sound-alike drug names prior to approval, where actions to

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<sup>6</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

overcome these issues are easier and more effective than remedies available in the post-approval phase.

In order to perform an FMEA of the proposed name, the Safety Evaluator must analyze the use of the product at all points in the medication use system. Because the proposed product is not yet marketed, the Safety Evaluator anticipates the use of the product in the usual practice settings by considering the clinical and product characteristics listed in Appendix A. The Safety Evaluator then analyzes the proposed proprietary name in the context of the usual practice setting and works to identify potential failure modes and the effects associated with the failure modes.

In the initial stage of the Risk Assessment, the Safety Evaluator compares the proposed proprietary name to all of the names gathered from the above searches, expert panel evaluation, and studies, and identifies potential failure modes by asking: "Is the name Entereg convincingly similar to another drug name, which may cause practitioners to become confused at any point in the usual practice setting?" An affirmative answer indicates a failure mode and represents a potential for Entereg to be confused with another proprietary or established drug name because of look- or sound-alike similarity. If the answer to the question is no, the Safety Evaluator is not convinced that the names possess similarity that would cause confusion at any point in the medication use system and the name is eliminated from further review.

In the second stage of the Risk Assessment, all potential failure modes are evaluated to determine the likely *effect* of the drug name confusion, by asking "Could the confusion of the drug names conceivably result in medication errors in the usual practice setting?" The answer to this question is a central component of the Safety Evaluator's overall risk assessment of the proprietary name. If the Safety Evaluator determines through FMEA that the name similarity would ultimately not be a source of medication errors in the usual practice setting, the name is eliminated from further analysis. However, if the Safety Evaluator determines through FMEA that the name similarity could ultimately cause medication errors in the usual practice setting, the Safety Evaluator will then recommend that an alternate proprietary name be used. In rare instances, the FMEA findings may provide other risk-reduction strategies, such as product reformulation to avoid an overlap in strength or an alternate modifier designation may be recommended as a means of reducing the risk of medication errors resulting from drug name confusion.

We will object to the use of proposed proprietary name when one or more of the following conditions are identified in the Safety Evaluator's Risk Assessment:

1. DDMAC finds the proposed proprietary name misleading from a promotional perspective, and the review Division concurs with DDMAC's findings. The Federal Food, Drug, and Cosmetic Act provides that labeling or advertising can misbrand a product if misleading representations are made or suggested by statement, word, design, device, or any combination thereof, whether through a trade name or otherwise. [21 U.S.C 321(n); see also 21 U.S.C. 352(a) & (n)].
2. We identify that the proposed proprietary name is misleading because of similarity in spelling or pronunciation to another proprietary or established name of a different drug or ingredient [CFR 201.10.(C)(5)].
3. FMEA identifies potential for confusion between the proposed proprietary name and other proprietary or established drug names, and demonstrates that medication errors are likely to result from the drug name confusion under the conditions of usual clinical practice.
4. The proposed proprietary name contains an USAN stem, particularly in a manner that is contradictory to the USAN Council's definition.

5. Medication Error Staff identify a potential source of medication error within the proposed proprietary name. The proprietary name may be misleading; or inadvertently introduce ambiguity and confusion that leads to errors. Such errors may not necessarily involve confusion between the proposed drug and another drug product.

In the event that we object to the use of the proposed proprietary name, based upon the potential for confusion with another proposed (but not yet approved) proprietary name, we will provide a contingency objection based on the date of approval: whichever product is awarded approval first has the right to the use the name, while we will recommend that the second product to reach approval seek an alternative name.

If none of these conditions are met, then we will not object to the use of the proprietary name. If any of these conditions are met, then we will object to the use of the proprietary name. The threshold set for objection to the proposed proprietary name may seem low to the Sponsor; however, the safety concerns set forth in criteria 1 through 5 are supported either by FDA Regulation or by external healthcare authorities, including the IOM, WHO, JCAHO, and ISMP, who have examined medication errors resulting from look- or sound-alike drug names and called for Regulatory Authorities to address the issue prior to approval.

Furthermore, we contend that the threshold set for the Proprietary Name Risk Assessment is reasonable because proprietary drug name confusion is a predictable and preventable source of medication error that, in many instances, can be identified and remedied prior to approval to avoid patient harm.

Additionally, post-marketing experience has demonstrated that medication errors resulting from drug name confusion are notoriously difficult to remedy post-approval. Educational efforts and so on are low-leverage strategies that have proven to have limited effectiveness at alleviating the medication errors involving drug name confusion. Higher-leverage strategies, such as drug name changes, have been undertaken in the past; but at great financial cost to the Sponsor, and at the expense of the public welfare, not to mention the Agency's credibility as the authority responsible for the approving the error-prone proprietary name. Moreover, even after Sponsor's have changed a product's proprietary name in the post-approval phase, it is difficult to eradicate the original proprietary name from practitioner's vocabulary, and as such, the Agency has continued to receive reports of drug name confusion long after a name change in some instances. Therefore, we believe that post-approval efforts at reducing name confusion errors should be reserved for those cases in which the potential for name confusion could not be predicted prior to approval (see limitations of the process).

If we object to a proposed proprietary name on the basis that drug name confusion could lead to medication errors, the FMEA process is used to identify strategies to reduce the risk of medication errors. We are likely to recommend that the Sponsor select an alternative proprietary name and submit the alternate name to the Agency for us to review. However, in rare instances FMEA may identify plausible strategies that could reduce the risk of medication error of the currently proposed name, and so we may be able to provide the Sponsor with recommendations that reduce or eliminate the potential for error would render the proposed name acceptable.

## **2.2 LABEL AND LABELING RISK ASSESSMENT**

The label and labeling of a drug product are the primary means by which practitioners and patients (depending on configuration) interact with the pharmaceutical product. The container labels and carton labeling communicate critical information including proprietary and established name, strength, form, container quantity, expiration, and so on. The insert labeling is intended to communicate to practitioners all information relevant to the approved uses of the drug, including the correct dosing and administration.

Given the critical role that the label and labeling has in the safe use of drug products, it is not surprising that 33 percent of medication errors reported to the USP-ISMP Medication Error Reporting Program may be attributed to the packaging and labeling of drug products, including 30 percent of fatal errors.<sup>7</sup>

Because the Medication Error Prevention staff analyzes reported misuse of drugs, the staff are able to use this experience to identify potential errors with all medication similarly packaged, labeled or prescribed. We use FMEA and the principles of human factors to identify potential sources of error with the proposed product labels and insert labeling, and provided recommendations that aim at reducing the risk of medication errors.

For this product the Sponsor submitted on March 24, 2008 the following labels and insert labeling for the Medication Error and Prevention Division review (see Appendix G, H for images):

- \_\_\_\_\_
- Carton Labeling: 12 mg
  - Insert Labeling (no image)

### 3 RESULTS

#### 3.1 PROPRIETARY NAME RISK ASSESSMENT

##### 3.1.1 Database and information sources

In total, twenty three names were identified as having some similarity to the name Entereg: Interex, Emprin, Integrilin, Ertaczo, Estring, Eulexin, Entelev, Dendrid, \_\_\_\_\_ Enterex, Enteric, Enduron, Enteral, Entocort, Enterin, Entex, Anturane, Inderal, Endrate, \_\_\_\_\_ Entero-H, Coreg, and Engerix-B

Twenty three names were previously evaluated in OSE reviews. The eleven names not previously reviewed are: Emprin, Ertaczo, Eulexin, Entelev, Dendrid, \_\_\_\_\_ Enteric, Enduron, Enteral, Entocort, and Enterin. Four of the eleven names were thought to look like Entereg (Emprin, Ertaczo, Entocort and Eulexin). Two of the eleven were thought to sound like Entereg (Entelev and Dendrid). The remaining five names \_\_\_\_\_ Enteric, Enduron, Enteral and Enterin) were thought to look and sound similar to Entereg.

On March 26, 2008, the name Entereg was searched against the United States Adopted Names (USAN) stem list and the proposed name was found to contain no USAN stems.

##### 3.1.2 Expert panel discussion

The Expert Panel reviewed the pool of names identified by the staff (see section 3.1.1. above). The Expert Panel indicated that the proposed name Entereg has been previously reviewed several times and found acceptable. The Expert Panel expressed concern of the Risk Evaluation Mitigation Strategy (REMS) associated with the product and noted the possibility of restricted distribution for this product.

DDMAC had no concerns regarding the proposed name from a promotional perspective, and did not offer any additional comments relating to the proposed name.

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<sup>7</sup> Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

### **3.1.3 Safety evaluator risk assessment**

The primary Safety Evaluator, affording careful evaluation to drug names beginning with the letters 'E' and 'I', conducted independent searches which identified an additional four names with similarity to Entereg. Three names were identified to have both sound and look-alike similarities: Inderide, Emetrol, and Entrobar. One name was identified to have sound-alike similarity: Entecavir. As such, a total of fifteen names were analyzed to determine if the drug names could be confused with Entereg and if the drug name confusion would likely result in a medication error.

All of the identified names were determined to have some orthographic and/or phonetic similarity to Entereg, and thus determined to present some risk of confusion. However, subsequent failure modes and effects analysis determined that the name similarity between Entereg and the identified names was unlikely to result in medication errors for the fifteen products.

Enteric and Enteral were noted to be medical terms and not associated with the potential of confusion for a medication. Both are known as relating to or affecting the intestines, in which enteric can be expanded further as a coating designed to pass through the intestines unaltered. If either Enteric or Enteral were written as a drug name on a prescription order, further clarification would be needed prior to dispensing.

Enduron (Methyclothiazide), Entelev (Inositol, Nitric Acid, Sodium Sulfite, Potassium Hydroxide, Sulfuric Acid, Catechol) and Eulexin (Flutamide) are discontinued products according to the Orange Book and Clinical Pharmacology Online, respectively. There are no generic equivalents for Entelev (See Appendix B). Although generic equivalents are marketed for Enduron the product characteristics, including dose and strength, do not overlap (See Appendix E).

No information could be found on  which was determined to be a misspelling of the proposed name (See Appendix C).

Enterin (Mesalamine) is a foreign product marketed in Greece. No other information is available on this product in commonly used drug references such as Clinical Pharmacology and Facts and Comparisons (See Appendix D).

For six of the names (Emetrol, Entrobar, Entecavir, Ertaczo, Emprin and Dendrid) FMEA determined that medication errors were unlikely because they do not overlap in strength, dosage, indication of use, or storage requirements with Entereg and have minimal orthographic and/or phonetic similarity to Entereg (See Appendix E).

Of the remaining three names, two names, Entocort and Eulexin, had some numerical overlap with Entereg in achievable dose and the other had increased phonetic similarity (Inderide). However, analysis of the failure modes did not determine the effects of these similarities to result in medication errors in the usual practice setting (See Appendix F and G respectively).

### **3.2 LABEL AND LABELING RISK ASSESSMENT**

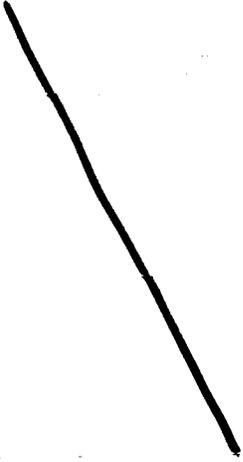
Review of the container labels and carton labeling identified several areas of vulnerability that could lead to medication error, specifically with respect to the proper use of the product, clear communication of the established name, product strength, and definition of clinical parameters.



#### **4 DISCUSSION**

The results of the Proprietary Name Risk Assessment found that the proposed name, Entereg, has some similarity to other proprietary and established drug names, but the findings of the FMEA process indicate that the proposed name does not appear to be vulnerable to name confusion that could lead to medication errors.

The results of the Label and Labeling Risk Assessment found that the presentation of information and design of the proposed container labels and carton labeling appears to be vulnerable to confusion that could lead to medication errors. Specifically, we note problems with the prominence, presentation, and clarity of information that is vital for the safe use of the drug product.



The Risk Evaluation and Mitigation Strategy (REMS) for Entereg is being reviewed under separate cover (RCM 2007-2232).

## 5 CONCLUSIONS

The Proprietary Name Risk Assessment findings indicate that the proposed name, Entereg, does not appear to be vulnerable to name confusion that could lead to medication errors. As such, we do not object to the use of the proprietary name, Entereg, for this product.

The Label and Labeling Risk Assessment findings indicate that the presentation of information and design of the proposed container labels and carton labeling introduces vulnerability to confusion that could lead to medication errors. We believe the risks identified can be addressed and mitigated prior to drug approval, and provide recommendations in Section 6 that aim at reducing the risk of medication errors.

## 6 RECOMMENDATIONS

### 6.1 COMMENTS TO THE DIVISION

#### 6.1 Proprietary name:

The Division of Medication Error Prevention has no objections to the use of the proprietary name Entereg for this product.

If any of the proposed product characteristics as stated in this review are altered prior to approval of the product, we rescind this Risk Assessment finding, and recommend that the name be resubmitted for review.

If the product approval is delayed beyond 90 days from the date of this review, the proposed name must be resubmitted for evaluation.

We would appreciate feedback on the final outcome of this review. We would be willing to meet with the Division for further discussion, if needed. Please copy us on any communication to the sponsor with regard to this review. If you have further questions or need clarifications, please contact Cheryle Milburn, project manager, at 301-796-2084.

### 6.2 COMMENTS TO THE APPLICANT

A. The Division of Medication Error Prevention has no objections to the use of the proprietary name Entereg for this product. If any of the proposed product characteristics as stated in this review are altered prior to approval of the product, we rescind this Risk Assessment finding, and recommend that the name be resubmitted for review.

B. Labels and Labeling

## 7 REFERENCES

### 1. *Adverse Events Reporting System (AERS)*

AERS is a database application in CDER FDA that contains adverse event reports for approved drugs and therapeutic biologics. These reports are submitted to the FDA mostly from the manufactures that have approved products in the U.S. The main utility of a spontaneous reporting system that captures reports from health care professionals and consumers, such as AERS, is to identify potential postmarketing safety issues. There are inherent limitations to the voluntary or spontaneous reporting system, such as underreporting and duplicate reporting; for any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s); and raw counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing risk between products.

### 2. *Micromedex Integrated Index (<http://weblern/>)*

Contains a variety of databases covering pharmacology, therapeutics, toxicology and diagnostics.

### 3. *Phonetic and Orthographic Computer Analysis (POCA)*

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. Likewise, an orthographic algorithm exists which operates in a similar fashion. This is a database which was created for The Division of Medication Error Prevention, FDA.

### 4. *Drug Facts and Comparisons, online version, St. Louis, MO (<http://weblern/>)*

Drug Facts and Comparisons is a compendium organized by therapeutic Course; contains monographs on prescription and OTC drugs, with charts comparing similar products.

### 5. *AMF Decision Support System [DSS]*

DSS is a government database used to track individual submissions and assignments in review divisions.

### 6. *Division of Medication Errors and Prevention proprietary name consultation requests*

This is a list of proposed and pending names that is generated by the Division from the Access database/tracking system.

7. **Drugs@FDA** (<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>)

Drugs@FDA contains most of the drug products approved since 1939. The majority of labels, approval letters, reviews, and other information are available for drug products approved from 1998 to the present. Drugs@FDA contains official information about FDA approved brand name and generic drugs and therapeutic biological products; prescription and over-the-counter human drugs and therapeutic biologicals, discontinued drugs and “Chemical Type 6” approvals.

8. **Electronic online version of the FDA Orange Book**  
(<http://www.fda.gov/cder/ob/default.htm>)

Provides a compilation of approved drug products with therapeutic equivalence evaluations.

9. **United States Patent and Trademark Office** <http://www.uspto.gov>.

Provides information regarding patent and trademarks.

10. **Clinical Pharmacology Online** (<http://weblern/>)

Contains full monographs for the most common drugs in clinical use, plus mini monographs covering investigational, less common, combination, nutraceutical and nutritional products. Provides a keyword search engine.

11. **Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at [www.thomson-thomson.com](http://www.thomson-thomson.com)**

The Pharma In-Use Search database contains over 400,000 unique pharmaceutical trademarks and tradenames that are used in about 50 countries worldwide. The data is provided under license by IMS HEALTH.

12. **Natural Medicines Comprehensive Databases** (<http://weblern/>)

Contains up-to-date clinical data on the natural medicines, herbal medicines, and dietary supplements used in the western world.

13. **Stat!Ref** (<http://weblern/>)

Contains full-text information from approximately 30 texts. Includes tables and references. Among the database titles are: Handbook of Adverse Drug Interactions, Rudolphs Pediatrics, Basic Clinical Pharmacology and Dictionary of Medical Acronyms Abbreviations.

14. **USAN Stems** (<http://www.ama-assn.org/ama/pub/category/4782.html>)

List contains all the recognized USAN stems.

15. **Red Book Pharmacy's Fundamental Reference**

Contains prices and product information for prescription, over-the-counter drugs, medical devices, and accessories.

16. **Lexi-Comp** ([www.pharmacist.com](http://www.pharmacist.com))

A web-based searchable version of the Drug Information Handbook.

**17. Medical Abbreviations Book**

Contains commonly used medical abbreviations and their definitions.

**APPENDICES**

**Appendix A:**

The Medication Error Staff consider the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted. We also compare the spelling of the proposed proprietary name with the proprietary and established name of existing and proposed drug products because similarly spelled names may have greater likelihood to sound similar to one another when spoken or look similar to one another when scripted. The Medication Error Staff also examine the orthographic appearance of the proposed name using a number of different handwriting samples. Handwritten communication of drug names has a long-standing association with drug name confusion. Handwriting can cause similarly *and* dissimilarly spelled drug name pairs to appear very similar to one another and the similar appearance of drug names when scripted has lead to medication errors. The Medication Error Staff apply their expertise gained from root-cause analysis of such medication errors to identify sources of ambiguity within the name that could be introduced when scripting (e.g., “T” may look like “F,” lower case ‘a’ looks like a lower case ‘u,’ etc), along with other orthographic attributes that determine the overall appearance of the drug name when scripted (see detail in Table 1 below). Additionally, since verbal communication of medication names is common in clinical settings, the Medication Error Staff compare the pronunciation of the proposed proprietary name with the pronunciation of other drug names. If provided, we will consider the Sponsor’s intended pronunciation of the proprietary name. However, because the Sponsor has little control over how the name will be spoken in practice, we also consider a variety of pronunciations that could occur in the English language.

**Table 1.** Criteria used to identify drug names that look- or sound-similar to a proposed proprietary name

Type of similarity	Considerations when searching the databases		
	Potential causes of drug name similarity	Attributes examined to identify similar drug names	Potential Effects
Look-alike	Similar spelling	Identical prefix Identical infix Identical suffix Length of the name Overlapping product characteristics	<ul style="list-style-type: none"> <li>Names may appear similar in print or electronic media and lead to drug name confusion in printed or electronic communication</li> <li>Names may look similar when scripted and lead to drug name confusion in written communication</li> </ul>
	Orthographic	Similar spelling	<ul style="list-style-type: none"> <li>Names may look similar</li> </ul>

	similarity	Length of the name Upstrokes Downstrokes Cross-strokes Dotted letters Ambiguity introduced by scripting letters Overlapping product characteristics	when scripted, and lead to drug name confusion in written communication
Sound-alike	Phonetic similarity	Identical prefix Identical infix Identical suffix Number of syllables Stresses Placement of vowel sounds Placement of consonant sounds Overlapping product characteristics	<ul style="list-style-type: none"> <li>Names may sound similar when pronounced and lead to drug name confusion in verbal communication</li> </ul>

**Appendix B:** Products withdrawn and/or discontinued from the market with no generic equivalent available

Proprietary Name	Similarity to Entereg	Year product withdrawn	Availability of generic equivalent
Entelev	Look	Unknown	No generic available

**Appendix C:** Proposed proprietary names that was likely a misspelling of the proposed name

Proprietary Name	Similarity to Entereg
██████	Look and Sound

\*\*\*These names are proprietary and confidential information that should not be released to the public.

**Appendix D:** Identified foreign product name(s) with little or no product information.

Proprietary Name	Similarity to Entereg
Enterin (mesalamine) (Greece)	Look and Sound

**Appendix E:** Products with no numerical overlap in strength and dose.

Product name with potential for confusion	Similarity to Proposed Proprietary Name	Strength	Usual Dose (if applicable)
<b>Entereg (Alvimopan)</b>		<b>12 mg</b>	<b>12 mg administered 30 minutes to 5 hours prior to surgery followed by 12 mg twice daily for up to 7 days for a maximum of 15 doses</b>
Emetrol	Look and Sound	Oral solution: Dextrose, 1.87 g/5ml; Fructose, 1.87 g/5ml; Phosphoric Acid, 21.5 g/5ml	<i>Adults, the elderly, and adolescents:</i> 15 to 30 ml by mouth as a single dose  <i>Children 2-12 years:</i> 5 to 10 ml by mouth as a single dose. May be repeated every 15 minutes as needed until nausea/vomiting subsides, up to 5 doses in 1 hour
Entrobar	Look and Sound	Suspension: 50%	Dose is patient based
Entecavir	Sound	Oral tablets: 0.5 mg and 1 mg Oral solution: 0.05 mg/ml	0.5 to 1 mg daily on an empty stomach
Ertaczo	Look	2 % topical cream	Apply thin layer twice daily for 4 weeks
Dendrid	Sound	0.1 % ophthalmic solution	One drop in affected eye(s) every hour
Enduron	Look and Sound	Oral tablets: 5 mg	2.5 mg to 5 mg by mouth daily
Emprin	Look	Oral tablets: 352 mg	325 mg to 650 mg by mouth every 4 hours, as needed.

**Appendix F:** Potential confusing name with numerical overlap in strength or dose

Failure Mode: (Name confusion)	Causes (could be multiple)	Effects
Entereg (Alvimopan)	12 mg	12 mg administered 30 minutes to 5 hours prior to surgery followed by 12 mg twice daily for up to 7 days for a maximum of 15 doses
Entocort (Budesonide)  3 mg oral capsules	Overlap in achievable dose  Four 3 mg tablets=12 mg	Orthographic differences in the names minimize the likelihood of medication errors in the usual practice settings.  <i>Rationale:</i>  The risk of medication error is reduced by the orthographic differences in the names. The names share the initial "Ent" prefix, but the end portions of the names differ orthographically (down stroke of the letter 'g' in Entereg vs. upstroke and cross stroke of the second letter 't' in Entocort). Additionally, the name Entocort appears longer when scripted.
Eulexin (Flutamide)  125 mg tablets	Numerical overlap in strength  12 mg vs. 125 mg	Orthographic differences in the names minimize the likelihood of medication errors in the usual practice settings.  <i>Rationale:</i>  The risk of medication error is reduced by the orthographic differences in the names. The names share the initial letter 'E' and an upstroke followed by the letter 'e' presented at the third and fourth letter of each name ('te' vs. 'le') but the end portions of the names differ orthographically (down stroke of the letter 'g' in Entereg vs. cross stroke of the second letter 'x' in Eulexin). Additionally, the name Entocort appears longer when scripted.

**Appendix G:** Potential confusing name with no numerical overlap in strength or dose, but increased phonetic similarity

Failure Mode: (Name confusion)	Causes (could be multiple)	Effects
Entereg (Alvimopan)	12 mg	12 mg administered 30 minutes to 5 hours prior to surgery followed by 12 mg twice daily for up to 7 days for a maximum of 15 doses
Inderide Hydrochlorothiazide /propranolol hydrochloride tablets  25 mg/ 40 mg 25 mg/ 80 mg	Overlapping frequency of administration (twice daily)  Similar sound “Enter” vs. “Inder”	Phonetic differences in the names minimize the likelihood of medication errors in the usual practice settings.  <i>Rationale:</i>  The risk of medication errors is reduced by the phonetic differences in the names as well as no overlap in dose/strength. The names share the initial “Inder” vs. “Enter”, sound, however the end portion of each name differs ( “ide” vs. “eg”).  Since Inderide is supplied in two different strengths, a desired strength is necessary when prescribing. The inclusion of product strength should help to minimize the potential for medication error. Additionally, product strengths for Inderide do not sound similar to the product strength for Entereg when spoken.

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Denise Toyer  
4/22/2008 12:50:26 PM  
DRUG SAFETY OFFICE REVIEWER

Carol Holquist  
4/23/2008 10:48:40 AM  
DRUG SAFETY OFFICE REVIEWER

# Memo

**To:** Brian Harvey, MD, PhD  
Division of Gastroenterology Products, HFD-180

**Through:** Nora Roselle, PharmD, Team Leader  
Denise Toyer, PharmD, Deputy Director  
Carol Holquist, RPh, Director  
Division of Medication Errors and Technical Support, HFD-420

**From:** Richard Abate, RPh, MS, Safety Evaluator  
Division of Medication Errors and Technical Support, HFD-420

**Date:** August 15, 2006

**Re:** OSE Consult 03-0034-2; Entereg (Alvimopam) Capsules 12 mg; NDA 21-775

---

This memorandum is in response to a July 27, 2006 request from your Division for a re-review of the proposed proprietary name, Entereg. The proposed name, Entereg, was previously found acceptable by DMETS in reviews dated December 9, 2003 (OSE Consult # 03-0034) and July 19, 2005 (OSE Consult # 03-0034-1). Revised container labels, carton, and insert labeling were also provided for review and comment.

Entereg is indicated to accelerate recovery time of gastrointestinal function following partial large or small bowel resection with primary anastomosis. Entereg is for inpatient use only. Patients will not be discharged on this medication. The recommended dosage 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 the patient is discharged from the hospital.

Since the DMETS review dated July 19, 2005, the sponsor revised the capsule strength  to 12 mg. Because of this revision in strength, DMETS re-reviewed the names from our previous consult, Enterex and Estring, to determine if the new strength poses any safety concerns that were not considered at the time of initial review. The revised strength does not pose any additional look-alike and/or sound-alike concerns with these names.

However, DMETS has identified one additional proprietary name, Interex, as having potential look-alike and sound-alike characteristics with Entereg. Interex is listed as an herbal supplement for male sexual health. Interex contains multiple herbal products in a capsule. The Interex recommended dosage is 2-3 capsules by mouth daily.

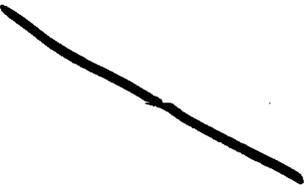
Entereg and Interex may look-alike as a scripted "i" may be misinterpreted as a scripted "e". The middle letters "ntere" appear in the same location in both names adding to the orthographic similarity. The names are phonetically similar because they both have three syllables. The beginning syllable of "EN" is phonetically similar to "IN". The middle syllable of "ter" is the same in both names. However, the ending letter of "g" in Entereg provides orthographic and phonetic differentiation. Benson Pendant distributes Interex through direct to consumer marketing. The telephone number obtained from the Las Vegas better business bureau for Benson Pendant is no longer in service. An internet search using [www.google.com](http://www.google.com) for information regarding Interex produces hits on the Natural Medicines Comprehensive Database and [www.HealthBoards.com](http://www.HealthBoards.com) websites only. While both Entereg and Interex are oral capsules, the dosing regimens are completely different. In addition, Entereg is only indicated for inpatient use. Although orthographic and phonetic similarities exist between Entereg and Interex, the distribution of the products, dosing regimens, and limited information sources for Interex minimize the potential for confusion between the two products.

*entereg*  
*interex*

In review of the container labels, carton and insert labeling for Entereg, DMETS has the following recommendations for revisions to minimize medication errors.

A. 





5. The "Rx only" statement is distracting and separates the established name and the strength. Relocate the "Rx only" statement to the lower third of the main display panel.

In summary, DMETS has no objections to the use of the proprietary name, Entereg. DMETS also recommends implementation of the label and labeling recommendations outlined above that may lead to safer use of the product. Additionally, DDMAC finds the proprietary name acceptable from a promotional perspective.

We consider this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary/established names from this date forward. If you have any questions or need clarification, please contact Diane Smith, Project Manager, at 301-796-0538.

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Nora L. Roselle  
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DRUG SAFETY OFFICE REVIEWER

Denise Toyer  
10/12/2006 08:25:04 AM  
DRUG SAFETY OFFICE REVIEWER  
Also signing for Carol Holquist, Director, DMETS in her  
absence

# Memo

**To:** Robert Justice, MD  
Director, Division of Gastrointestinal and Coagulation Drug Products; HFD-180

**From:** Felicia Duffy, RN, BSN  
Safety Evaluator, Division of Medication Errors and Technical Support  
Office of Drug Safety; HFD-420

**Through:** Alina Mahmud, RPh, MS, Team Leader  
Denise Toyer, PharmD, Deputy Director  
Carol Holquist, RPh, Director  
Division of Medication Errors and Technical Support  
Office of Drug Safety; HFD-420

**Date:** July 12, 2005

**Re:** ODS Consult 03-0034-1; Entereg (Alvimopam Capsules) NDA 21-775

---

This memorandum is in response to a July 5, 2005 request from your Division for a re-review of the proprietary name, Entereg. The proposed proprietary name, Entereg, was found acceptable by DMETS in a review dated October 16, 2003 (ODS consult #03-0034). Container labels and package insert labeling were also provided for review and comment.

Entereg is indicated to accelerate recovery time of gastrointestinal function following post abdominal or pelvic surgery. Entereg is for inpatient use only. Patients will not be discharged on this medication. The recommended dosage is 12 mg twice daily beginning the day after surgery for a maximum of 7 days while the patient is hospitalized or until the patient is discharged from the hospital.

Since the October 16, 2003 review, DMETS identified the proprietary names Enterex and Estring as having potential look-alike and/or sound-alike similarities to Entereg.

1. Enterex may look and sound similar to Entereg. Enterex is a product line for over-the-counter dietary nutritional products. Enterex is available in liquid form as Enterex (plain) and Enterex Diabetic (a meal substitute or snack for diabetics). It is available in powder form as Enterex Glutapak-10 (L-glutamine). Enterex and Entereg look similar because the names are spelled the same except for the last letter ("x" vs. "g"). The names are phonetically similar because they both contain three syllables and begin with "Enter". However, the last letter of each name may also provide some orthographic and phonetic differentiation ("x" vs. "g"). Enterex and Entereg are both consumed orally; however, they are available in different dosage forms (liquid/powder vs. capsules). Both products differ in indication for use (nutritional supplement vs. accelerate recovery time of gastrointestinal function after abdominal surgery). Additionally, Enterex may be used as a snack or as a meal replacement for an unlimited

amount of time, whereas Entereg is dosed twice daily for a maximum of 7 days while in the hospital. Entereg will only be used in the inpatient setting, thus orders for Entereg will always contain the directions for use (e.g., Entereg 12 mg po BID x 5 days). Although Enterex is an over-the-counter product, it can still be ordered in an inpatient setting. Orders for Enterex will likely appear with diet orders in the nutritional area of an inpatient setting, and will be specified with meals or as a snack (e.g., Enterex 1 can prn as a snack or Enterex 1 can for lunch and dinner QD). Furthermore, since Entereg is used only in the inpatient setting, outpatient prescriptions will not be written or called in for this drug product. Although orthographic and phonetic similarities exist between Enterex and Entereg, the specificity of the Entereg order and other differentiating product characteristics will minimize the potential for confusion between the two products.

Entereg / Enterex

Entereg  
Enterex

2. Estring may look similar to Entereg when scripted. Estring is indicated for post menopausal vaginal atrophy. Estring and Entereg both begin with the letter "E" and contain seven letters. They also share the letters "t" and "g" in the same position. The second letter of each name can look similar if they are not prominently scripted ("s" vs. "n"). The fourth through sixth letters may also appear similar if they are not prominently scripted ("rin" vs. "ere"). Estring and Entereg differ in indication for use (vaginal atrophy vs. accelerate recovery time of gastrointestinal function after abdominal surgery), usual dosage (1 ring vs. 2 caps), frequency of administration (every 3 months vs. twice daily), route of administration (vaginal vs. oral), and dosage form (ring vs. capsule). Estring is available in a single strength, and can be written with "take as directed" instructions. Although Entereg is also available in a single strength, the directions for use must be specified since it used only in the hospital setting. Order for Entereg must specify the dose, route of administration and frequency of administration (e.g., Entereg 12 mg po BID x 5 days). Additionally, Estring is written primarily in the outpatient setting. However, if Estring is prescribed in the inpatient setting, it will be ordered as a one time (x1) order (e.g., Estring x 1 for placement prior to discharge). Despite orthographic similarities, the differentiating product characteristics will minimize the potential for confusion and error between Estring and Entereg.

Entereg / Estring

Entereg  
Estring

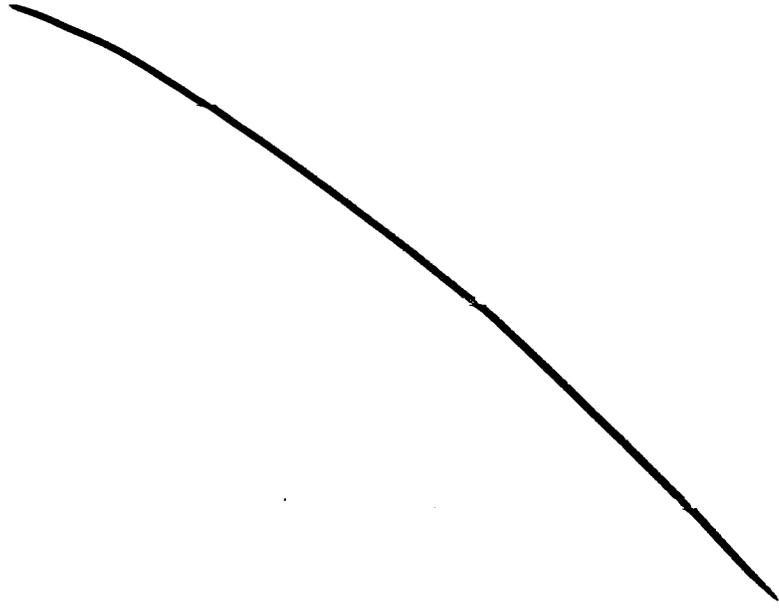
In review of the insert labeling for Entereg, DMETS has attempted to focus on safety issues relating to possible medication errors.

A. GENERAL COMMENTS

1. The curved line that accentuates the proprietary name is distracting and interferes with the readability of the proprietary name. Delete this graphic to avoid misinterpretations or confusion.
2. The dosage form (capsules) should appear juxtapose to the established name. Additionally, the established name and dosage form should be the same typeset. For example:

Entereg  
(Alvimopan Capsules)

B.



In summary, we have no objections to the use of the proprietary name, Entereg. DMETS also recommends implementation of the labeling recommendations outlined in this memo that may lead to safer use of the product. Additionally, DDMAC finds the proprietary name acceptable from a promotional perspective. We consider this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary/established names from this date forward. If you have any questions or need clarification, please contact the medication errors Project Manager, Diane Smith at 301-827-1998.

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Alina Mahmud  
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DRUG SAFETY OFFICE REVIEWER

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7/19/05 09:03:24 AM  
DRUG SAFETY OFFICE REVIEWER

Carol Holquist  
7/19/05 09:06:16 AM  
DRUG SAFETY OFFICE REVIEWER

**Division of Medication Errors and Technical Support (DMETS)  
Office of Drug Safety  
HFD-420; PKLN Rm. 6-34  
Center for Drug Evaluation and Research**

**PROPRIETARY NAME REVIEW**

**DATE OF REVIEW:** October 16, 2003  
**IND #** 56,553  
**NAME OF DRUG:** Entereg (Alvimopam Capsules) [REDACTED] 12 mg  
**IND HOLDER:** Adolor Corporation

**\*\*\*NOTE:** This review contains proprietary and confidential information that should not be released to the public.\*\*\*

**I. INTRODUCTION:**

This consult was written in response to a request from the Division of Gastrointestinal and Coagulation Drug Products, to review the proprietary name Entereg, regarding potential name confusion with other proprietary and established drug names. The container labels, carton labeling and package insert labeling for Entereg were submitted and reviewed for possible interventions in minimizing medication errors. Additionally, an independent analysis of the name was conducted by [REDACTED] and was submitted for review and comment as well.

**PRODUCT INFORMATION**

Entereg Capsules (Alvimopam) is a potent and selective, peripherally restricted antagonist of the human, cloned mu opioid receptor. Entereg is indicated for the management of postoperative ileus to shorten the duration of GI dysfunction in patients undergoing surgery. The recommended dosage and administration of Entereg is [REDACTED] 12 mg by mouth twice daily. Entereg is supplied in film coated [REDACTED]

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**II. RISK ASSESSMENT:**

The medication error staff of DMETS conducted a search of several standard published drug product reference texts<sup>1,2,3</sup> for existing drug names which sound-alike or look-alike to Entereg to a degree here potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted<sup>4</sup>. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name Entereg. Potential concerns regarding drug marketing and promotion related to the proposed names were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. The Expert Panel identified the proprietary names Entex, Anturane, Inderal, Endrate, and  that were thought to have the potential for confusion with Entereg. These products are listed in table 1 (see page 4), along with the dosage forms available and usual dosage.
2. DDMAC did not have concerns about the name Entereg regarding promotional claims.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

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<sup>1</sup> MICROMEDEX Integrated Index, 2003, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

<sup>2</sup> Facts and Comparisons, 2003, Facts and Comparisons, St. Louis, MO.

<sup>3</sup> The Drug Product Reference File [DPR], the DMETS database of proprietary name consultation requests, New Drug Approvals 98-03, and the electronic online version of the FDA Orange Book.

<sup>4</sup> WWW location <http://www.uspto.gov/main/trademarks:htm>

Product Name	Dosage form(s), Established name	Usual adult dose*	Other**
Entereg	Alvimopam Capsules 12 mg	12 mg by mouth twice daily	N/A
Entex	Phenylephrine HCl and Guaifenesin Liquid 7.5 mg/100 mg per 5 mL	5 mL to 10 mL by mouth every 4 to 6 hours, up to 40 mL per day	SA
Entex ER	Phenylephrine HCl and Guaifenesin Capsules 10 mg/300 mg	1 or 2 capsules by mouth every 12 hours	SA
Entex HC	Hydrocodone Bitartrate, Guaifenesin, and Phenylephrine Liquid 5 mg/100 mg/7.5 mg per 5 mL	5 mL to 10 mL by mouth every 4 to 6 hours, up to 40 mL per day	SA
Entex LA	Phenylephrine HCl and Guaifenesin Tablets 30 mg/600 mg	1 tablet by mouth every 12 hours	SA
Entex PSE	Pseudoephedrine and Guaifenesin Tablets 120 mg/600 mg	1 tablet by mouth every 12 hours	SA
Anturane	Sulfipyrazone Tablets, 100 mg Capsules, 200 mg	200 mg to 400 mg daily in two divided doses	SA
Inderal	Propranolol HCl Tablets 10 mg., 20 mg., 40 mg, 60 mg, 80 mg, 90 mg	120 mg -240 mg/day (given bid-tid)	SA
Inderal LA	Propranolol HCl Capsules, sustained release 60 mg, 80 mg, 120 mg, 160 mg	120 mg -160 mg/day	SA
Endrate	Edetate Disodium Concentrate for Injection 20 mL Ampules 150 mg/mL	50 mg/kg/day intravenously	SA
<p>*Frequently used, not all-inclusive.  **L/A (look-alike), S/A (sound-alike)  ***NOTE: This review contains proprietary and confidential information that should not be released to the public.***</p>			

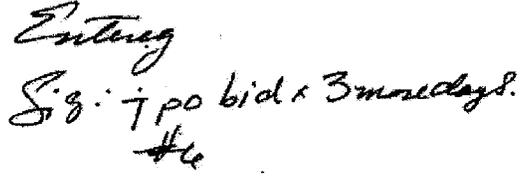
**B. PHONETIC ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)**

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic database that is in the final stages of development for DMETS. The entered search term is converted into its phonemic representation before it runs through the phonetic algorithm. Likewise, an orthographic algorithm exists which operates in a similar fashion. The results from the Entereg queries indicated strong phonetic and orthographic similarities for some of the product names identified in the EPD discussion (see Table 1 in the previous section).

**C. PRESCRIPTION ANALYSIS STUDIES**

1. Methodology:

Three separate studies were conducted within FDA for the proposed proprietary name to determine the degree of confusion of Entereg with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 105 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Entereg (see below). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

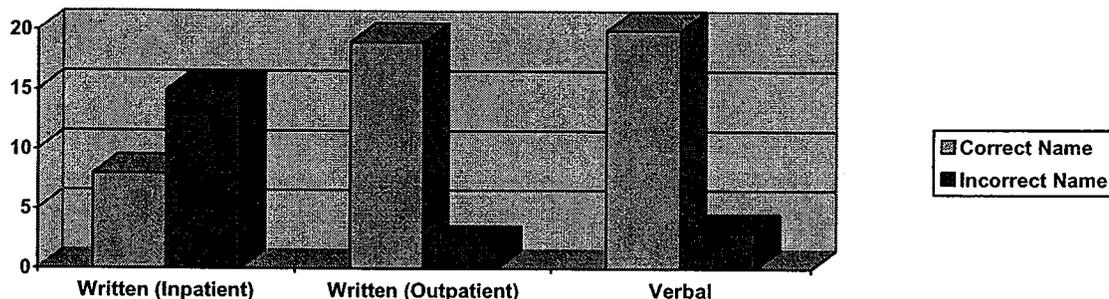
HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
<p>Outpatient RX:</p> 	<p>“The next prescription is for Entereg. Sig 1 po bid for 3 more days. Number 6.”</p>
<p>Inpatient RX:</p> 	

2. Results:

The results are summarized in Table I.

Table I

Study	# of Participants	# of Responses (%)	Correctly Interpreted (%)	Incorrectly Interpreted (%)
Written Inpatient	35	23 (66%)	8 (35%)	15 (65%)
Written Outpatient	31	21 (68%)	19 (90%)	2 (10%)
Verbal	39	23 (59%)	20 (87%)	3 (13%)
Total	105	67 (64%)	47 (71%)	20 (29%)



In the written inpatient study 8 of the 23 respondents (35%) interpreted Entereg correctly. Entereg was misinterpreted by 15 of the 23 respondents (65%). The misinterpretations included Enterez (7), Enterej (3), Entereg (1), Enteres (1), Entenej (1), Enterey (1), and Enteneg (1). None of the misinterpretations represent currently marketed products.

In the written outpatient study 19 of the 21 respondents (90%) interpreted Entereg correctly. The misinterpretations included Enterez (1) and Entneg (1). Neither of the misinterpretations represent currently marketed products.

In the verbal study 20 of the 23 respondents (87%) interpreted Entereg correctly. Two of the misinterpretations were phonetic variations of Entereg. The misinterpretations included Enterig, Intereg, and Etereg. None of the misinterpretations represent currently marketed products. However, Enterig is phonetically similar to enteric which is a term often used in conjunction with medications, such as enteric coated aspirin.

#### D. SAFETY EVALUATOR RISK ASSESSMENT

##### 1. DMETS Analysis

**\*\*\*NOTE: This review contains proprietary and confidential information that should not be released to the public.\*\*\***

In reviewing the proprietary name Entereg, the primary concerns were related to potential confusion with currently marketed products Entex, Anturane, Inderal, Endrate, in addition to ~~\_\_\_\_\_~~ which is an NDA currently under review.

DMETS conducted prescription studies to simulate the prescription ordering process. There was no confirmation that Entereg could be confused with currently marketed products. However, negative findings are not predicative as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to small sample size. The majority of interpretations from the verbal and written prescription studies were phonetic or spelling misinterpretations of the drug name Entereg.

- a. Entereg and Entex may sound similar when they are pronounced. Entex is also available as Entex ER, Entex HC, Entex LA, and Entex PSE. The potential for medication errors between Entereg and any Entex product with a modifier is minimal. Therefore, the potential for confusion between Entereg and Entex products that contain modifiers will not be discussed in this review. Entex is indicated for the relief of nasal congestion, cough and cold symptoms. Entereg and Entex both share the first four letters 'Ente'. However, the last syllable of each name is phonetically different ('reg' vs. 'ex').

Furthermore, Entereg has three syllables while Entex only has two. There are other distinguishing factors between Entereg and Entex that may decrease the potential risk of medication errors. Entereg and Entex have different dosing schedules (twice daily vs. every 4 to 6 hours), dosage forms (capsules vs. liquid), and different usual doses ( 12 mg vs. 5 mL to 10 mL). Entereg has

Overall, the product differences between Entereg and Entex decrease the potential risk of medication errors.

- b. Entereg and Anturane may sound similar when they are pronounced. Anturane is indicated for gouty arthritis. Both Entereg and Anturane have three syllables which contributes to the rhyming qualities of the two names. Entereg and Anturane both begin with a vowel which is followed by the letter 'n' which can increase the sound-alike similarities of the names. The second syllable of each name can also sound similar when pronounced ('ter' vs. 'tur'). However, the last syllable of each name is phonetically different ('reg' vs. 'rane'). Entereg and Anturane also share other similarities. Both Entereg and Anturane are available in solid oral dosage forms (capsules vs. tablets and capsules) and both are dosed twice daily. However, there are distinguishable factors between Entereg and Anturane that may decrease the potential risk of medication errors. Entereg and Anturane have different usual doses ( 12 mg vs. 100 mg to 200 mg), they are packaged differently ( card vs. bulk bottle), and they are available in different package sizes ( vs. bottles of 100, 500, or 1000 capsules or tablets).

The different characteristics will help decrease the potential risk for medication errors between Entereg and Anturane.

- c. Entereg and Inderal may sound similar when they are pronounced. Inderal is also available as Inderal LA. The potential for medication errors between Entereg and any Inderal LA product is minimal since the product contains the modifier LA. Therefore, the potential for confusion between Entereg and Inderal LA will not be discussed in this review. Inderal is indicated for cardiac arrhythmias, myocardial infarctions, hypertrophic subaortic stenosis, pheochromocytoma, hypertension, migraine prophylaxis, angina pectoris, and essential tremor. Both Entereg and Inderal have three syllables which contributes to the possibility of the names sounding similar. Both Entereg and Inderal begin with a vowel which is followed by the letter 'n' which contributes to the sound-alike similarities of the first syllable of the names. The second syllable of each name ('ter' vs. 'der') can also sound similar when pronounced. However, the last syllables ('reg' vs. 'ral') are phonetically different which helps to differentiate them when spoken. Both Entereg and Inderal come in solid oral dosage forms (capsules vs. tablets) and can have similar dosing frequencies (two times daily vs. two to three times daily). Entereg and Inderal also share overlapping numbers in their prescribing strengths ( 12 mg vs. 60 mg or 120 mg). Despite these similarities there are distinguishable factors that may decrease the risk of medication errors between Entereg and Inderal. Inderal is most often used on a chronic basis while Entereg is only used in post-op inpatients for a

period of 7 days. In addition, Entereg and Inderal would be prescribed by different types of physicians (surgeon or gastroenterologist vs. internist or cardiologist). Furthermore, Entereg and Inderal have different conditions of use. Entereg would only be included in post-op orders, which many times may be pre-printed standing orders. While, Inderal, if used on a post-op patient, would generally have also been used on that patient pre-operatively as well.

Overall, there are many similarities between Entereg and Inderal; however, the endings of each name and the conditions of use are distinguishable enough that they decrease the potential risk for medication errors.

- d. Entereg and Endrate can sound similar when pronounced. Endrate is indicated for the treatment of hypercalcemia and digitalis-induced cardiac arrhythmias. Endrate is supplied as a concentrate for injection in 20 mL ampules with a concentration of 150 mg/mL. Entereg and Endrate both begin with 'En' causing the first syllable of both names to be the same. However, the endings of each name 'tereg' vs. 'drate' are phonetically very different. Entereg and Endrate also differ in their route of administration (oral vs. intravenous), usual dose ( 12 mg vs. 50 mg/kg/day), and dosing frequency (twice daily vs. once daily). The differences in the endings of both names, route of administration, usual dose, frequency of administration, dosing, and the strengths help to decrease the potential risk for medication errors.

2.

) Analysis

potential trademark name Entereg. The conducted an independent evaluation of the evaluation identified the following

\*\*\* NOTE: This review contains proprietary and confidential information that should not be released to the public.\*\*\*

names which were not discussed by the Expert Panel: Estring, Integrilin, Entero-H, Coreg, and Engerix-B as names with potential look and/or sound alike confusion with Entereg.

Product Name	Dosage form(s), Established name	Usual adult dose*	Other**
Entereg	Alvimopan Capsules 2 mg	12 mg by mouth twice daily	N/A
Estring	Estradiol Vaginal Ring 2 mg	1 ring inserted into vagina for 3 months	LA
Integrilin	Eptifibatide Injection for solution 0.75 mg/mL and 2 mg/mL	180 mcg/kg bolus, 1-2 mcg/kg infusion	SA
Entero-H***	Barium Sulfate Concentrate for solution 1900 mL, 80% w/v	5-500 mL orally pre-examination 350 mL – 2.5 L rectally pre-examination	SA/LA
Coreg	Carvedilol Tablets 3.125 mg, 6.25 mg, 12.5 mg, 25 mg	3.125 mg – 25 mg twice daily	SA
Engerix-B	Hepatitis B surface antigen Injection 10 mcg/mL and 20 mcg/mL	20 mcg injection at 0, 1, and 6 months	SA
<p>*Frequently used, not all-inclusive.  **L/A (look-alike), S/A (sound-alike)  submitted the name Entero-C listed as the barium sulfate suspension. DMETS' research identified Entero-C as a homeopathic preparation.</p>			

concluded that Entereg had a moderate vulnerability for confusion with the above listed names. After reviewing the product profiles of each of the names identified by , DMETS has determined that the potential for name confusion between Entereg and Integrilin, Entero-H, Coreg, or Engerix-B is decreased due to differentiating product characteristics.

### III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In review of the container labels, carton and insert labeling of Entereg, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement, which might minimize potential user error.

#### A. General Comments

1. Increase the prominence of the proprietary name, established name, and strength.
2. The word "capsule(s)" should appear in conjunction with the established name (e.g., alvimopan capsule).

#### B.

See General Comments A-1 and A-2.

**IV. RECOMMENDATIONS:**

1. DMETS has no objections to the use of the proprietary name Entereg. This is considered a tentative decision and the firm should be notified that this name with its associated labels and labeling must be re-evaluated upon submission of the NDA and approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary and established names from the signature date of this document.
2. DMETS recommends the label and labeling revisions outlined in section III of this review document that might lead to safer use of the product. We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer.
3. DDMAC did not have concerns about the name Entereg regarding promotional claims.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-827-3242.

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**This is a representation of an electronic record that was signed electronically and  
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/s/  
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