CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-775

RISK ASSESSMENT and RISK MITIGATION 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:	May 2, 2008
To:	Donna Griebel, MD, Director Division of Gastrointestinal Products
Thru:	Claudia Karwoski, PharmD, Acting Director Division of Risk Management (DRISK) Office of Surveillance and Epidemiology (OSE)
From:	OSE Entereg Risk Management Review Team: Scientific Lead: Joyce Weaver, PharmD, Senior Risk Management Analyst, DRISK Team Members: Richard Abate, RPh, MS, Safety Evaluator, DMEDP Marcia Britt, PhD, Regulatory Health Specialist, DRISK Ann Corken Mackey, RPh, MPH, Safety Evaluator, DAEA Mary Dempsey, Risk Management Program Coordinator, DRISK Jodi Duckhorn, MA, Social Scientist and the Team Leader, Patient Labeling and Education Team, DRISK Cherye Milburn, Regulatory Health Project Manager, DEPI Mary Willy, PhD, Senior Risk Management Analyst, DRISK Kendra Worthy, PharmD, Drug Utilization Data Specialist, DEPI
Subject:	Review of Risk Evaluation and Mitigation Strategy (REMS)
Drug Name(s):	Entereg (alvimopan)
Submission Number:	
Application Type/Number:	21-775
Applicant/Sponsor:	Adolor Corporation
OSE RCM #:	2007-2232

CONTENTS

EXECUTIVE SUMMARY

Entereg is a mu-opioid receptor antagonist that is currently under review for use to accelerate bowel recovery following bowel resection surgery. As part of the complete response to the November 2006 approvable letter, the Sponsor submitted a RiskMAP addressing the risk of ischemic cardiovascular events with long-term use. The approvable letter stated that the RiskMAP could include a restriction to inpatient use. The Sponsor submitted a brief proposal to restrict use as outlined in the approvable letter. After discussion of the RiskMAP by the Gastrointestinal (GI) Drugs Advisory Committee at an January 23, 2008 meeting, and after subsequent discussion of the RiskMAP between the Sponsor and the Agency, agreement was reached on the education plan, the tools to be used within the RiskMAP, the implementation plan, the frequency of reporting to the Agency, and the data points to be included in the reports to the Agency. To meet the requirements of the Food and Drug Administration Amendments Act of 2007 (FDAAA), the RiskMAP will be converted to a Risk Evaluation and Mitigation Strategy (REMS).

1 BACKGROUND

Entereg (alvimopan) is a mu-opioid receptor antagonist being evaluated for the proposed indication of accelerating the time to recovery following partial large or small bowel resection surgery with primary anastomosis. The proposed dosage regimen for Entereg is one 12mg capsule 30 minutes to 5 hours before bowel resection surgery, followed by 12mg twice daily for up to 7 days after surgery for a maximum of 15 doses.

The Agency has taken two previous approvable actions on this application. The first approvable letter, issued July 21, 2005, cited a lack of sufficient proof of efficacy for accelerating recovery of gastrointestinal function following bowel resection surgery. The Sponsor was requested to provide at least one additional adequate and well-controlled study establishing superiority over placebo. Additionally, the Sponsor was requested to justify the conclusion that the median reduction in time to gastrointestinal recovery relative to placebo would be clinically meaningful.

The Sponsor submitted a complete response to the approvable letter on May 9, 2006. However, before the Agency acted on the application, the Sponsor notified the agency of a cardiovascular toxicity signal noted in an interim analysis in an ongoing long-term study. A second approvable letter was issued November 3, 2006. This letter cited the need to submit the 12-month safety findings from this study, including analyses of myocardial infarction, unstable angina, and other serious cardiovascular events in this study. Secondly, the approvable letter stated that the Sponsor should develop a risk management plan that includes elements to a) communicate the possible cardiovascular risk of longer-term alvimopan exposure, and b) minimize off-label use. The letter advised that the plan could include appropriate labeling for prescribers and patients, and restriction of alvimopan use to hospital settings.

A meeting of the GI Drugs Advisory Committee was held January 23, 2008 to consider the application. The OSE background document for the advisory committee meeting is presented in Appendix A. The committee concluded that the post-operative ileus clinical trial results showing faster recovery of gastrointestinal function following bowel resection surgery with the use of alvimopan were clinically meaningful, and that the benefits of alvimopan exceeded its risks (9 of 14 votes). Nevertheless, most of the committee members (8 of 14 votes) had concerns regarding cardiovascular safety for the short-term (i.e., 7 days or 15 doses) use of alvimopan 12mg capsules in patient following partial large or small bowel resection surgery with primary anastomosis. The committee members unanimously voted that a stronger risk management plan was needed to prevent outpatient use and longer-term inpatient use. Finally, there was consensus within the

committee that additional safety data were needed to address the cardiovascular, neoplastic, and bone fracture safety signals.

Following the advisory committee meeting, the Sponsor and the Agency reached agreement on the components of the RiskMAP, including the education plan, the tools to be used, the implementation plan, the frequency of reporting to the Agency, and the data points to be included in the reports to the Agency.

The Sponsor has been notified that it will be necessary to convert the proposed RiskMAP to REMS. Feedback from the Office of Chief Counsel (OCC) on the draft REMS (drafted by OSE) is pending. Guidance will be given to the Sponsor after OCC comments on the pending REMS.

2 METHODS AND MATERIALS

2.1 DATA AND INFORMATION SOURCES

The following Adolor Corporation Risk Management submissions were reviewed:

- Proposed Risk Management Plan for Alvimopan in the Management of POI Following Bowel Resection Surgery, submitted to the NDA August 9, 2007, available in EDR;
- Amendment #5 Risk Management Program for 12mg Capsules, submitted to the NDA February 7, 2008, available in EDR;
- Risk Management Program for Entereg (alvimopan) 12mg Capsules; Revised Submission, submitted to the NDA March 24, 2008, available in EDR; and
- Risk Management Program for Entereg (alvimopan) 12mg Capsules; Revised Submission, submitted to the NDA April 17, 2008, available in EDR.

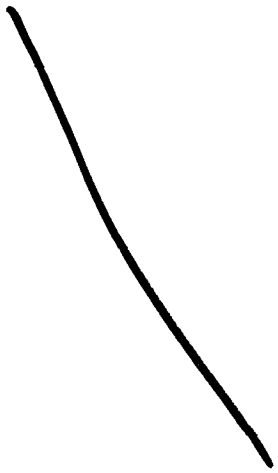
2.2 ANALYSIS TECHNIQUES

[redacted]

3 RESULTS OF REVIEW

3.1 PROPOSED RISKMAP

[redacted]



3.2 CONVERSION OF THE RISKMAP TO REMS

3.2.1 CONSIDERATION OF REMS

The Food and Drugs Amendments Act of 2007 (FDAAA) lays out the following points to be considered when determining that a REMS is needed to ensure that the benefits of a drug outweigh its risks.

A. The estimated size of the population likely to use the drug involved.

*In the United States, about 343,000 patients have bowel resection surgery annually. (*Healthcare Costs and Utilization Project [HCUP]. 2005 National Statistics. Available at: http://www.ahrq.gov/HCUPnet. Accessed April 21, 2008.*)*

B. The seriousness of the disease or condition being treated by the drug.

Postoperative ileus is common following bowel resection surgery (Livingston, EH, Passaro, EP, Jr. Postoperative ileus. Dig Dis Sci 1990;35:121-32.), and can lead to longer hospital stay. Although not examined in the Entereg clinical

3 Page(s) Withheld

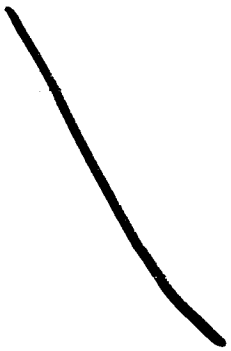
✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

REMS

15



4 DISCUSSION

The Sponsor has proposed a RiskMAP that attempts to limit the use of Entereg to short-term use to minimize the risk of cardiovascular events that have been observed only with longer-term use. The Sponsor proposes the following elements:

The amended RiskMAP now proposed by the Sponsor adequately responds to the questions that OSE posed to the Advisory Committee during its January 2008 meeting. Additional measures that were included in the amended RiskMAP include Sponsor control over who purchases the product (rather than wholesaler control), registration of hospitals after attestation of conditions of safe use, and education of healthcare personnel involved in using the product. Although cardiac safety data will not be collected within the RiskMAP, a post-marketing study will be required of the Sponsor to collect additional safety data.

The proposed RiskMAP can be converted to REMS comprised of a communication plan, elements to assure safe use, an implementation plan, and evaluation of elements to assure safe use. We have drafted a REMS using the components of the RiskMAP proposal dated April 17, 2008.

5 CONCLUSIONS AND RECOMMENDATIONS

The RiskMAP proposal dated April 17, 2008 contains components appropriate to include in a REMS, including a communication plan, elements to assure safe use (restriction to inpatient use, hospital registration, a drop-ship distribution program, and a limitation on dosage), an implementation system, a timetable for submission of assessments, and assessments of the

REMS. We believe that a REMS comprised of these components will appropriately mitigate the risk of myocardial infarction observed with longer term use. We have prepared a draft cover letter and REMS (Appendix B) using the components in the RiskMAP submission. These documents can be sent to the Sponsor to be used as a template.

APPENDICES

Appendix A:

OSE BACKGROUND DOCUMENT FOR THE JANUARY 18, 2008 ADVISORY COMMITTEE MEETING

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:	December 18, 2007
To:	FDA Gastrointestinal Drugs Advisory Committee
Thru:	Gerald Dal Pan, MD, MHS
From:	OSE Entereg Risk Management Review Team: Richard Abate, RPh, MS, Safety Evaluator, DMETS Ann Corken Mackey, RPh, MPH, Safety Evaluator, DDRE Mary Dempsey, Risk Management Program Coordinator Lanh Green, PharmD, MPH, Safety Evaluator Team Leader, DDRE Claudia Karwoski, Pharm.D., Team Leader Risk Management Cherye Milburn, Regulatory Health Project Manager, DSRCS Kellie Taylor, PharmD, MPH, Team Leader, DMETS Joyce Weaver, PharmD, Senior Risk Management Analyst Mary Willy, PhD, Senior Risk Management Analyst Kendra Worthy, PharmD, Drug Utilization Data Specialist, DSRCS
Subject:	Review of RiskMAP Proposal
Drug Name(s):	Entereg (alvimopan)
Application Type/Number:	21-775
Applicant/sponsor:	Adolor Corporation
OSE RCM #:	2007-2232

1 INTRODUCTION

Entereg (alvimopan) is an opioid receptor antagonist being evaluated for the proposed indication of accelerating the time to recovery following partial large or small bowel resection surgery with primary anastomosis. The proposed dosage regimen for Entereg is one 12mg capsule 30 minutes to 5 hours before bowel resection surgery, followed by 12mg twice daily for up to 7 days after surgery for a maximum of 15 doses.

The sponsor submitted a Risk Minimization Action Plan (RiskMAP) addressing the risk of ischemic cardiovascular events observed with long-term use, by restricting its use to short term inpatient use. The primary method proposed to prevent outpatient use is to establish agreements with wholesalers to sell Entereg only to hospitals. While we agree that limiting use of Entereg to short-term use may be an acceptable approach to minimizing cardiovascular events, the Sponsor's proposal raises a number of important issues and challenges. We recommend the Advisory Committee members discuss the proposed RiskMAP and its implementation with regard to these issues. The details of this discussion will be considered in the final design of the RiskMAP program.

2 BACKGROUND

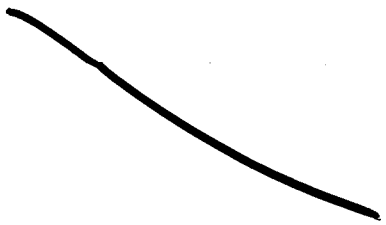
The Agency has taken two previous approvable actions on this application. The first approvable letter, issued July 21, 2005, cited a lack of sufficient proof of efficacy for accelerating recovery of gastrointestinal function following bowel resection surgery. The sponsor was requested to provide at least one additional adequate and well-controlled study establishing superiority over placebo. Additionally, the sponsor was requested to justify the conclusion that the median reduction in time to gastrointestinal recovery relative to placebo would be clinically meaningful.

The sponsor submitted a complete response to the approvable letter on May 9, 2006. The sponsor submitted data that indicates alvimopan achieves a one-day shorter hospital stay in gastrointestinal resection patients compared to placebo. However, before the Agency acted on the application, the sponsor notified the Agency of a cardiovascular toxicity signal [redacted]. A second approvable letter was issued November 3, 2006. This letter cited the need for the sponsor to submit the 12-month safety findings from this study, including analyses of myocardial infarction, unstable angina, and other serious cardiovascular events. Secondly, the approvable letter stated that the sponsor should develop a RiskMAP that includes elements to a) communicate the possible cardiovascular risk of longer-term alvimopan exposure, and b) minimize off-label use. The letter advised that the RiskMAP could include appropriate labeling for prescribers and patients, and restriction of alvimopan use to hospital settings.

Review of the Sponsor's safety data in response to the approvable letter has revealed that long-term use (6-12 months) results in an increased risk of cardiovascular ischemic events compared to placebo. Short-term use (defined as duration "not to exceed 7.5 days") has not been associated with increased cardiovascular ischemic events, although study patients were not followed to ascertain all cardiovascular events, especially events occurring after hospital discharge. The cardiovascular signal was observed in a long-term trial that used much lower doses (the most commonly used dose was 0.5mg BID) than the dose proposed for short-term use (12mg BID).

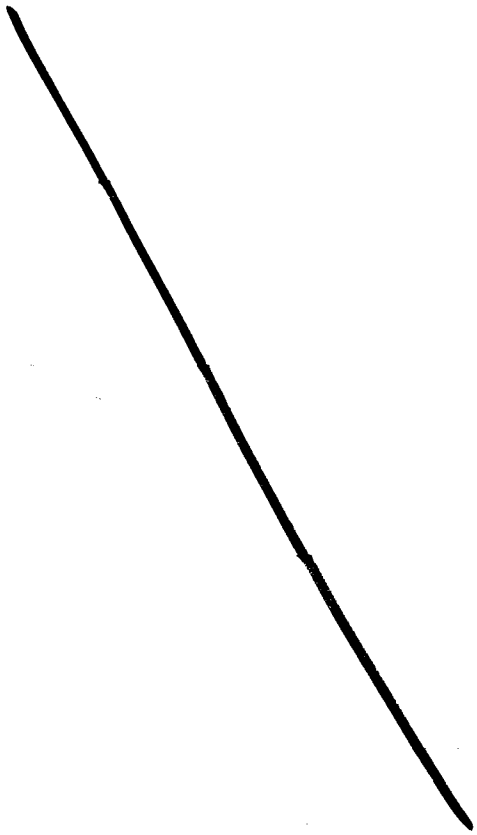
Other safety issues noted in the safety review of alvimopan include an increased incidence of tumors in the treatment group, and increased incidence of bone fractures in the treatment group. The cardiovascular, neoplasia, and fracture safety signals all were observed in long-term study for opioid-induced bowel dysfunction.

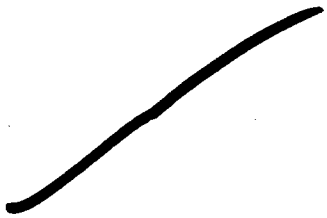
3 SUMMARY OF PROPOSED RISKMAP FOR ENTEREG

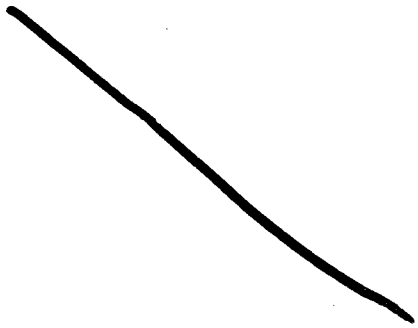


[1] Adolor Corporation Proposed Risk Management Plan for Alvimopan in the Management of POI Following Bowel Resection Surgery, submitted to the NDA August 9, 2007,

Can longer term use and outpatient use with Entereg be prevented by limiting sales by wholesalers to hospitals only?







5 CONCLUSION

The sponsor submitted a RiskMAP addressing the risk of ischemic cardiovascular events with long-term use. The primary method proposed to accomplish this is to establish agreements with wholesalers to sell Entereg only to hospitals. We agree with the Sponsor's overall approach; however, the proposal raises a number of important issues and challenges that we request the Advisory Committee discuss. The details of this discussion will be considered in the final design of the RiskMAP program.

APPENDIX B- Letter to Sponsor about Conversion of RiskMAP to REMS and Proposed REMS Template

NDA 21-775

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

Dear Ms. Young:

Please refer to your June 25, 2004 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Entereg (alvimopan) Capsules, 12 mg.

We also refer to your complete response submission dated August 9, 2007.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the FDCA to authorize FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if the Secretary determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)(1)). This provision took effect on March 25, 2008.

In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for Entereg® (alvimopan) to ensure that the benefits of the drug outweigh the risks of myocardial infarction. Your Entereg Risk Minimization Action Plan should be re-submitted as a Proposed Risk Evaluation and Mitigation Strategy (REMS) with a REMS Supporting Document according to the format and content outlined below.

The *REMS* should include concise information describing the REMS elements proposed to be included in the approved REMS for alvimopan. This document will create enforceable obligations. A template for the REMS is included in Attachment A.

[redacted]

For administrative purposes, all submissions related to this REMS must be clearly designated "**Risk Evaluation and Mitigation Strategy (REMS)**".

We request a prompt written response in order to continue our evaluation of your NDA.

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

Sincerely,

{See appended electronic signature page}

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

4 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

REMS
15A

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Office of Surveillance and Epidemiology
Division of Drug Risk Evaluation

Date:	April 14, 2008
To:	Donna Griebel, MD Director, Division of Gastroenterology Drug Products
Through:	Solomon Iyasu, MD, MPH Director, Division of Epidemiology Office of Surveillance and Epidemiology
From:	Shewit Bezabeh, MD, MPH Epidemiologist, Division of Epidemiology
Subject:	Study protocol review: risk of cardiac events following short-term exposure to alvimopan
Drug Name(s):	alvimopan (Entereg)
Submission Number:	NDA 21-775
Application Type/Number:	post-approval commitment
Applicant/sponsor:	Adolor Corporation
OSE RCM #:	2008- 2007-2232

INTRODUCTION

Alvimopan (Entereg) is a new molecular entity which acts as a peripheral opioid-receptor antagonist. The clinical development program was initiated for two different indications: a short term indication for patients with post operative ileus (POI) and a long-term treatment for individuals with opioid induced bowel dysfunction (OBD). Over the course of the development program an imbalance of cardiovascular events was observed in the long-term (OBD) exposed population. In response, the sponsor has elected to pursue only the POI indication and short-term drug exposure. The sponsor also proposes to implement restricted distribution system for the product through a Risk Management program and is planning to further assess the potential cardiovascular safety signal by conducting additional, placebo–controlled, randomized trial in the POI population.

As of 15 April 2008, the Division of Gastroenterology Drug Products (DGDP) plans to approve alvimopan with a Risk Management program and a post approval commitment for a placebo-controlled randomized trial to assess the risk for cardiovascular events in short–term (POI) exposure in the hospital setting. The drug would not be distributed for ambulatory (retail) use. The sponsor has submitted a protocol synopsis of the proposed study. OSE was asked to evaluate the potential safety concerns and to comment on the adequacy of the protocol to address them. The sponsor's proposed indication for alvimopan is: "Acceleration of time to upper and lower gastrointestinal recovery following partial large and small bowel resection surgery with primary anastmosis." No other product is currently approved for POI.

Regulatory history

The alvimopan IND was initially submitted in 1998 and received fast track designation for POI in 2004. In 2005, the NDA was granted an approvable action due to insufficient evidence for efficacy. During May 2006 review for a Complete Response, serious cardiovascular adverse events were observed in an ongoing OBD study. The NDA received a second approvable action and the sponsor was asked to provide the final 12 month long-term safety findings for all the studies and Risk Management plan. Review of the submitted long-term safety data in April 2007 identified an elevated risk for cardiovascular events, neoplasms, and bone fractures in the long-term OBD studies. At this time DGDP placed the NDA application on full clinical hold. The sponsor submitted a Complete Response to the hold in August 2007. The safety and

efficacy of alvimopan for use in POI was presented to the Gastrointestinal Drugs Advisory committee in January 23, 2008 where the committee was asked to comment / consider if the submitted results for POI studies were clinically meaningful and to consider the robustness of any potential safety concerns (i.e., risk for cardiovascular events, neoplasia, and bone fracture).[1]

In summary, the Committee voted that the studies met the stated endpoints, specifically the "ready to be discharged," endpoint. The committee voted 8 to 6 that there was some concern for the cardiovascular risk and that this risk had not been adequately addressed in the clinical development program. Some of the major concerns raised during the meeting included: lack of adequate patient follow-up, lack of additional data specific to cardiovascular endpoints, and the fact that the risk was observed in single, long-term study. The committee concluded that there may be a weak signal for all three safety concerns.

Prior studies

The POI Clinical development program consisted of six Phase III clinical studies (302, 306, 308, 313, 001 and 314). The studies were all randomized, double-blind, placebo-controlled, multi-centered trials in patients undergoing partial large or small bowel resection (BR) or total abdominal hysterectomy (TAH). All patients on chronic opioids were excluded from the studies. All studies, except Study 001, were conducted in the US and Canada. [Study 001 was conducted in Europe and Australia.] Study 306 consisted of patients enrolled for TAH surgery only. Initial review of study 306 demonstrated no efficacy in the study population of TAH and the sponsor subsequently narrowed the indication to the BR surgery population only. Study 306 was not included in the overall efficacy evaluation.

The efficacy of the drug was based on the observed difference of mean lengths of hospital stay as the time from end of surgery to time of discharge order written in subjects treated with alvimopan when compared to placebo (302, 308, 313, and 314).

Safety Review

For the purpose of this consult memorandum, both clinical programs of POI and OBD are summarized here briefly.

POI clinical Program:

Due to the numerical imbalance of cardiovascular events observed in the alvimopan treatment group (0.5 mg BID) in the long-term OBD study (study 014), the agency requested collection of additional source of documentation (e.g. ECG tracings, cardiac biomarkers) for all POI patients with CV events of interest. As outlined at the Jan 2008 AC meeting, the worldwide POI safety population consisted of 1,365 subjects in placebo arms and a total of 2,610 subjects in treatment arms. Of these subjects in the treatment arms, 62 were exposed to 1-3 mgs, 898 subjects to 6 mg dose and 1,650 subjects to the 12 mg dose of alvimopan. The cardiovascular adverse events of interest were death, death from cardiovascular events, myocardial infraction (MI), unstable angina, cerbrovascular accident (CVA), congestive heart failure (CHF), serious arrhythmia, and cardiac arrest. Review of the submitted data did not show any cardiovascular excess or imbalance in the treatment group when compared to placebo. There were a total 13/2610 (0.5%) deaths in the alvimopan group compared to 9/1365 (0.7%) in the placebo group with calculated relative risk of 0.8. Analysis of deaths from cardiovascular events showed 4/2610 (0.2%) deaths in the treatment arm compared to 2/1365 (0.2%) deaths in placebo arms for a relative risk of 1.0. Cardiovascular events were noted in 51/2,610 (2%) alvimopan-treated subjects compared with 39/1,365 (2.9%) of patients treated with placebo. Further data analysis for other ischemic events and serious cardiovascular events did not reveal any excess or imbalance between the two treated groups.

OBD clinical program:

The OBD safety population consisted of subjects with both cancer and non-cancer pain and, included a total of 1,888 individuals in the drug exposed group (at least one dose of alvimopan) and 860 subjects in the placebo group. Of these, 538 in the treatment arm and 267 in the placebo arm had at least 12 months of exposure were enrolled in study 014. Four deaths (0.2%) were noted in the alvimopan group compared to 2 deaths (0.3%) in the placebo group

for a relative risk of 0.9. This was observed in the non-cancer pain OBD population. Analysis of all cardiovascular events showed 21events (1.2%) observed in the treatment group compared to 4 cardiovascular events (0.5%) events in the placebo group for a relative risk of 2.4. Further analysis noted that the excess cardiovascular events were observed in Study 014 only in the non-cancer pain subjects. In study 014, there were a total of 14 (2.6%) patients with a cardiovascular event compared to zero events on the placebo arm. When time to cardiovascular event was analyzed, all events were observed after greater than 14 days of exposure and the majority (18/26) of patients with a cardiovascular event cases were observed between 31-90 days of drug exposure. The implication of these findings for the short-term exposed POI population was not clear.

MATERIALS REVIEWED

An eight page protocol synopsis titled "A Phase 4, Multicenter, Double Blind, Placebo Controlled, and Parallel Study of Alvimopan for the Management of Postoperative Ileus in Subjects Undergoing Radical Cystectomy," dated March, 2 2008 was reviewed. The primary objective of this study is to demonstrate that alvimopan 12 mg (daily OR 6 mg BID) accelerates recovery of gastrointestinal function in subjects undergoing radical cystectomy.

The secondary objectives are as follows:

- to demonstrate that earlier GI recovery with alvimopan 12 mg reduces length of hospital stay (LOS) in subjects undergoing radical cystectomy
- to evaluate the effect of alvimopan 12 mg on prespecified postoperative ileus (POI) related postoperative morbidities in subjects undergoing radical cystectomy
- to evaluate the overall and cardiovascular safety of alvimopan 12 mg in subjects undergoing radical cystectomy

Methodology

This is a randomized, double-blind, placebo-controlled, parallel study of alvimopan 12 mg or placebo administered by mouth (PO) BID in approximately 280 subjects undergoing radical cystectomy. All procedures must be performed by open laparotomy. Patients will be stratified

based on the presence (or absence) of existing cardiovascular disease (i.e., previous myocardial infarction, coronary revascularization (coronary artery bypass grafting [CABG], percutaneous coronary intervention [PCI]), cerebrovascular accident/transient ischemic attack, peripheral arterial disease). On the day of surgery, subjects will be randomized in a 1:1 ratio to receive either alvimopan 12 mg PO or matching placebo to be administered no sooner than 30 minutes and no later than 5 hours before the scheduled start of surgery, then BID (according to the hospital BID dosing interval) beginning on postoperative day 1 until hospital discharge or for a maximum of 7 days of postoperative treatment. Patients will return for a postoperative visit 30 days following the last dose of study medication.

General safety assessments will include recording of opioid consumption, adverse events occurring during the study, results of routine laboratory tests, and vital signs at screening and at the end of the study. In addition, enhanced monitoring and evaluation of cardiovascular safety will include recording of baseline cardiovascular risk factors and existing cardiovascular disease, baseline and follow-up ECG assessments and adverse event review by an Independent Cardiovascular Clinical Events Committee. All potential cardiovascular AEs of interest will be identified ("triggered") through a rigorous and comprehensive survey of all CRF and AE data and will be reviewed and adjudicated in blinded fashion by the CEC. Adjudication of cardiovascular events of interest will occur in real-time during the conduct of the study.

DISCUSSION

A notable imbalance in cardiovascular events was observed in a single long-term study of alvimopan used chronically to treat OBD. In this study (study 014), all of the cardiovascular events were observed after 14 days of exposure and most occurred between day 31 and 90. No imbalance of cardiovascular risk was seen in single or pooled studies of short term (7-day) alvimopan used for POI. However, the POI study designs had a number of limitations to fully assess potential CV events. Some of the limitations included; poor or no proper follow-up, lack

of collection of important safety endpoints such as standardized collection of 30 or 60 day morbidity and mortality data, and lack of a prospective definition and assessment for cardiovascular events during conduct of the study and after study completion. In summary, the POI studies were not adequately designed to assess any cardiovascular risk.

CONCLUSIONS AND RECOMMENDATIONS

There is a plan to approve alivompan for short term (7 day) indication in POI population. However, due in particular to one study, the cardiovascular safety of alivompan in the POI population should be subjected to further, prospective study. The sponsor has now submitted a protocol synopsis to assess this potential risk and plans to implement a Risk Management plan map to limit distribution (hospital) and duration (7 days) after approval. The submitted protocol synopsis appears to be adequate to evaluate any potential cardiovascular risk in the POI population. In addition, the planned enhanced monitoring, baseline risk factor recording and follow-up assessment will help ascertain any potential cardiovascular risk in the exposed population.

We recommend that the sponsor should submit a more detailed protocol with sample size justification. In addition, the sponsor should submit a time line showing study initiation, patient accrual completion, study completion and final study report due dates. We believe it to be prudent that this protocol be fully vetted by the Agency and a timeline for it's completion to the satisfaction of the Agency agreed to prior to primary approval for the POI indication. Furthermore, it is also prudent that prior to expanding the indication for any long-term use, the potential cardiovascular, fracture and neoplasm risk should be assessed by conducting a placebo-controlled randomized study(ies) in the appropriate population.

Shewit Bezabeh MD, MPH

REFERENCES

1. http://www.fda.gov/ohrms/dockets/ac/cder08.html#gdac

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

/s/

Shewit Bezabeh
5/5/2008 09:48:56 AM
MEDICAL OFFICER

Solomon Iyasu
5/5/2008 04:50:40 PM
MEDICAL OFFICER

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:	December 18, 2007
To:	FDA Gastrointestinal Drugs Advisory Committee
Thru:	Gerald Dal Pan, MD, MHS, Director Office of Surveillance and Epidemiology (OSE)
From:	OSE Entereg Risk Management Review Team: Richard Abate, RPh, MS, Safety Evaluator, DMETS Ann Corken Mackey, RPh, MPH, Safety Evaluator, DDRE Mary Dempsey, Risk Management Program Coordinator Lanh Green, PharmD, MPH, Safety Evaluator Team Leader, DDRE Claudia Karwoski, Pharm.D., Team Leader Risk Management Cherye Milburn, Regulatory Health Project Manager, DSRCS Kellie Taylor, PharmD, MPH, Team Leader, DMETS Joyce Weaver, PharmD, Senior Risk Management Analyst Mary Willy, PhD, Senior Risk Management Analyst Kendra Worthy, PharmD, Drug Utilization Data Specialist, DSRCS
Subject:	Review of RiskMAP Proposal
Drug Name(s):	Entereg (alvimopan)
Application Type/Number:	21-775
Applicant/sponsor:	Adolor Corporation
OSE RCM #:	2007-2232

1 INTRODUCTION

Entereg (alvimopan) is an opioid receptor antagonist being evaluated for the proposed indication of accelerating the time to recovery following partial large or small bowel resection surgery with primary anastomosis. The proposed dosage regimen for Entereg is one 12mg capsule 30 minutes to 5 hours before bowel resection surgery, followed by 12mg twice daily for up to 7 days after surgery for a maximum of 15 doses.

The sponsor submitted a Risk Minimization Action Plan (RiskMAP) addressing the risk of ischemic cardiovascular events observed with long-term use, by restricting its use to short term inpatient use. The primary method proposed to prevent outpatient use is to establish agreements with wholesalers to sell Entereg only to hospitals. While we agree that limiting use of Entereg to short-term use may be an acceptable approach to minimizing cardiovascular events, the Sponsor's proposal raises a number of important issues and challenges. We recommend the Advisory Committee members discuss the proposed RiskMAP and its implementation with regard to these issues. The details of this discussion will be considered in the final design of the RiskMAP program.

2 BACKGROUND

The Agency has taken two previous approvable actions on this application. The first approvable letter, issued July 21, 2005, cited a lack of sufficient proof of efficacy for accelerating recovery of gastrointestinal function following bowel resection surgery. The sponsor was requested to provide at least one additional adequate and well-controlled study establishing superiority over placebo. Additionally, the sponsor was requested to justify the conclusion that the median reduction in time to gastrointestinal recovery relative to placebo would be clinically meaningful.

The sponsor submitted a complete response to the approvable letter on May 9, 2006. The sponsor submitted data that indicates alvimopan achieves a one-day shorter hospital stay in gastrointestinal resection patients compared to placebo. However, before the Agency acted on the application, the sponsor notified the Agency of a cardiovascular toxicity signal noted in an interim analysis in an ongoing long-term study in the Opioid Bowel Dysfunction Clinical Development Program. A second approvable letter was issued November 3, 2006. This letter cited the need for the sponsor to submit the 12-month safety findings from this study, including analyses of myocardial infarction, unstable angina, and other serious cardiovascular events. Secondly, the approvable letter stated that the sponsor should develop a RiskMAP that includes elements to a) communicate the possible cardiovascular risk of longer-term alvimopan exposure, and b) minimize off-label use. The letter advised that the RiskMAP could include appropriate labeling for prescribers and patients, and restriction of alvimopan use to hospital settings.

Review of the Sponsor's safety data in response to the approvable letter has revealed that long-term use (6-12 months) results in an increased risk of cardiovascular ischemic events compared to placebo. Short-term use (defined as duration "not to exceed 7.5 days") has not been associated with increased cardiovascular ischemic events, although study patients were not followed to ascertain all cardiovascular events, especially events occurring after hospital discharge. The cardiovascular signal was observed in a long-term trial that used much lower doses (the most commonly used dose was 0.5mg BID) than the dose proposed for short-term use (12mg BID). Other safety issues noted in the safety review of alvimopan include an increased incidence of tumors in the treatment group, and increased incidence of bone fractures in the treatment group. The cardiovascular, neoplasia, and fracture safety signals all were observed in long-term study for opioid-induced bowel dysfunction.

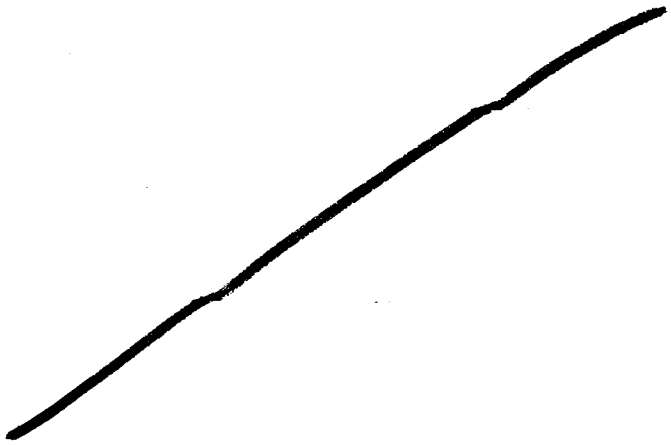
2 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

REMS
15B



5 CONCLUSION

The sponsor submitted a RiskMAP addressing the risk of ischemic cardiovascular events with long-term use. The primary method proposed to accomplish this is to establish agreements with wholesalers to sell Entereg only to hospitals. We agree with the Sponsor's overall approach; however, the proposal raises a number of important issues and challenges that we request the Advisory Committee discuss. The details of this discussion will be considered in the final design of the RiskMAP program.

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

/s/

Mary Dempsey
12/18/2007 10:07:52 AM
DRUG SAFETY OFFICE REVIEWER

Gerald DalPan
12/18/2007 12:09:20 PM
MEDICAL OFFICER

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINSTRATION	**OSE POSTMARKETING SAFETY REVIEW**	
TO: Brian Harvey, M.D., Ph.D., Director, Division of Gastrointestinal Products, Office of New Drug Evaluation III	FROM: Cynthia Kornegay, Ph.D., DDRE, Office of Surveillance and Epidemiology	OSE PID # 060610
DATE REQUESTED: September 11, 2006	REQUESTOR/Phone #: Eric Brodsky, M.D., 6-0855	
DATE RECEIVED: August 7, 2006		
DRUG (Est): Alvimopan	NDA/IND # 021-775	SPONSOR: GlaxoSmithKline
DRUG NAME (Trade): Entereg	THERAPEUTIC CLASSIFICATION: Opioid antagonist	
EVENT: cardiovascular events		

Executive Summary:

A review of the original NDA document for short-term (7-days) treatment of post-operative ileus (the primary indication that the applicant is seeking) did not reveal a potential cardiovascular safety signal based on the review of available documents of the premarketing safety database. The total exposure safety data base was n= 3326 patients. However, as with all drug products, it is still possible that a safety signal will emerge with wider use of the product.

A safety concern has been raised from an on-going trial of the same drug for a different indication. The applicant submitted an interim report of an on-going long-term (one year) trial using low dose of the drug (0.5 mg) for the indication of opioid-induced constipation. In this document, the sponsor describes eight serious cardiovascular adverse events occurring in eight individuals in the active treatment arm versus no serious cardiovascular adverse events in the individuals in the placebo arm. The sponsor has concluded that this is a statistical anomaly, however, their submission provided inadequate information to support that claim. In addition, no baseline demographic or cardiovascular data was submitted, so assessment of baseline demographic and cardiovascular risk factors is not possible.

At this time, there is not enough information to make any definitive conclusions about the safety profile of long-term use of alvimopan. However, given the serious nature of the adverse event in question on the one hand and given the indication that this drug is undergoing study, a careful deliberation is warranted regarding the potential risk/benefit calculus of long-term use dications as well as diligent toxicity monitoring in all on-going trials of this drug.

an aid to the division, DDRE has also provided a table of currently available drug products that, due to serious safety concerns, have restrictions on the environment (e.g., hospital, doctor's office, etc.) and/or the distribution of the drug.

Reason for Request/Review:

Eight serious adverse cardiovascular events occurred in the active treatment arm (537 patients) of a long-term, low-dose study of alvimopan for opioid-induced constipation, while no events occurred in the placebo arm (268 patients). These eight adverse cardiovascular events include myocardial infarction (6), unstable angina (1), and shortness of breath (1) (possible congestive heart failure). The division requested that DDRE provide advice regarding the safety profile of alvimopan for its primary indication of post-operative ileus (POI).

Discussion / Conclusions:

Alvimopan is a novel μ-opioid receptor antagonist. The original indication for use was to accelerate the time to recovery GI function following abdominal or pelvic surgery in patients not taking chronic opioids. The originally proposed dosage regimen was 12 mg BID for a maximum of seven days, with the initial dose occurring just prior to the scheduled start of surgery. The Integrated Review of Safety for this indication described 11 deaths in the alvimopan-treated group, while 7 occurred in the placebo group. Based on a review of each of the individual deaths, the medical officer concluded that it was not likely that any of these incidents were related to alvimopan treatment.

In the U.S.-based POI trials, there were 16 cardiac serious adverse events (0.9%) in the alvimopan group vs. 13 (1.7%) in the placebo group. European trials showed 11 (<2%) events in the active treatment groups vs. 6 (2%) events in the placebo group. In addition, there was a single event of chest pain in a trial of OBD in non-cancer patients. No further information was provided for this case. In the U.S. trials, 2 (0.1%) cardiac events led to study discontinuation in the active treatment group vs. 4 (0.5%) events in the placebo group. The percentage of adverse events for each group was similar and did not show a distinct pattern.

The sponsor's latest submission is an interim analysis of an ongoing 12-month, low-dose (0.5 mg BID) trial of alvimopan for opioid-induced constipation. In this trial, 8 individuals in the active treatment arm have had a serious cardiovascular adverse event, while no individuals in the placebo arm have reported an event. Although the sponsor has concluded that this is a statistical anomaly, their submission provided inadequate information to support that claim. The sponsor did not submit any baseline data for the ongoing study, so assessment of baseline demographic and cardiovascular risk factors is not possible. It is anticipated that the sponsor will submit further information when this study concludes in February 2007.

Based on a review of the medical officer's and sponsor documents, there does not seem to be a cardiovascular safety signal for the short-term indication of POI at this time. The total exposure safety database for this short-term duration treatment is n= 3326. Pending the receipt of data from the current long-term trial, the long-term cardiovascular risk of alvimopan should be re-evaluated. As an aid to the division, DDRE was also asked to provide examples of other drug products that, due to significant safety concerns, have restricted access to the drug by restricting the environments in which they are available and administered (Table 1).

Table 1. Examples of other drug products with restricted environments and/or distribution.

Drug Product	Safety Concern	Action
ofetilide (Tikosyn®)	ventricular arrhythmia	Black box warning that includes a statement that patients "initiated or re-initiated on Tikosyn® should be placed for a minimum of 3 days in a facility that can provide calculations of creatinine clearance, continuous electrocardiographic monitoring, and cardiac resuscitation." Information is repeated in the Warning and Dosage and Administration sections of the label.
Fentanyl iontophoretic transdermal system (Ionsys™)	opioid misuse or abuse, overdose, ingestion, unintended exposure to hydrogel, respiratory depression, death	Black box warning that includes the statement that Ionsys™ "should only be used for the treatment of hospitalized patients. Treatment...should be discontinued before patients are discharged from the hospital." Information is repeated in the Contraindication, Warning, and Overdose sections.
Abarelix (Plenaxis™)	immediate onset anaphylactic reactions including hypotension and syncope	Black box warning that includes the statement that "Following each injection of Plenaxis™, patients should be observed for at least 30 minutes in the office and in the event of an allergic reaction, managed appropriately." Information is repeated in the Dosage and Administration and How Supplied sections. In addition, a risk management program (the Plenaxis™ PLUS Program) was implemented. Key features of this program include registration of physicians prior to dispensing, and pharmacist verification of physician registration and obtaining a confirmation number prior to dispensing for each dose.
Mifepristone (Mifeprex)	fatal infection, sepsis, prolonged heavy bleeding	Black box warning describing adverse events of concern. Medication Guide and Patient Agreement issued to patient at when product given. Patient Agreement must be signed prior to mifeprex administration.
Natalizumab (Tysabri™)	progressive multifocal leukoencephalopathy (PML), resulting in severe disability or death	Black box warning describing the adverse event of concern. A restricted distribution program (TOUCH™) is in place to ensure that "only prescribers, infusion centers, and pharmacies associated with infusion centers registered with the program are able to prescribe, distribute, or infuse the product." Additional information is provided in the Warning section.

Reviewer's Signature / Date:	**Team Leader's Signature / Date:**
sion Director Signature / Date:	**Office Director Signature / Date:**
achments:	
Cc: NDA # **HFD-XXX (Division File)/Requestor/** **HFD-440 DD/TL/SE/Chron/Drug** **Electronic File Name:**	

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

/s/

Cynthia Kornegay
8/31/2006 03:30:46 PM
DRUG SAFETY OFFICE REVIEWER

Rosemary Johann-Liang
9/1/2006 11:01:14 AM
MEDICAL OFFICER