CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-775

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 21-775 SUPPL # HFD # 180

Trade Name Entereg

Generic Name alvimopan

Applicant Name Adolor Corporation

Approval Date, If Known expected May 16, 2008

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES ☐ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # YES ☐ ! NO ☐
! Explain:

Investigation #2

IND # YES ☐ ! NO ☐
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

Name of person completing form: Matthew Scherer
Title: Regulatory Project Manager
Date: 5-6-08

Name of Office/Division Director signing form: Joyce Korvick
Title: Deputy Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

Joyce Korvick
5/15/2008 03:16:12 PM

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 21775 Supplement Number: _____NDA Supplement Type (e.g. SE5): _____

Division Name:Division of Gastroenterology Products_____ Stamp Date: August 10, 2007
PDUFA Goal Date: May 10, 2008

Proprietary Name: Entereg

Established/Generic Name: alvimopan

Dosage Form: Capsules

Applicant/Sponsor: Adolor Corp.

Indication(s) *previously approved* (please complete this question for supplements and Type 6 NDAs only):
(1) NA
(2) _____
(3) _____
(4) _____

Q1: Is this application in response to a PREA PMC? Yes ☐ Continue
No ☒ Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #:_____ PMC #:_____

Does the division agree that this is a complete response to the PMC?

☐ Yes. **Skip to signature block.**

☐ No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW ☒ active ingredient(s); ☒ indication(s); ☐ dosage form; ☐ dosing regimen; or ☐ route of administration?*

(b) ☐ No. PREA does not apply. **Skip to signature block.**

**** Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.***

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s):1
(Attach a completed Pediatric Page for each indication in current application.)

Indication: accleration of GI recovery following partial bowel resection surgery with primary anastomosis

Q3: Does this indication have orphan designation?

☐ Yes. PREA does not apply. **Skip to signature block.**

☒ No. Please proceed to the next question.

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL OR AT 301-796-0700.

4: Is there a full waiver for all pediatric age groups for this indication (check one)?

- ☐ Yes: (Complete Section A.)
- ☒ No: Please check all that apply:
  - ☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)
  - ☒ Deferred for the remaining pediatric subpopulations (Complete Sections C)
  - ☐ Completed for some or all pediatric subpopulations (Complete Sections D)
  - ☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
  - ☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification**)

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____
- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- ☐ Evidence strongly suggests that product would be ineffective or unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Justification attached.

studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible#	Not meaningful therapeutic benefit*	Ineffective or unsafe†	Formulation failedΔ
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

\# Not feasible:

- ☐ Necessary studies would be impossible or highly impracticable because:
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease/condition to study
- ☐ Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- ☐ Evidence strongly suggests that product would be ineffective or unsafe in this/these pediatric population(s) (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

- ☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and F and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Sections D and F and complete the PeRC Pediatric Assessment form); and/or (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Sections E and F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for remaining pediatric subpopulations). Complete Section F on Extrapolation.

Check pediatric subpopulation for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification †**	
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Yes	No
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐	☐
☒	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☒	☒	☐	☒	☐
	Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through the partial waivers and deferrals, proceed to Section F. For those pediatric subpopulations for which studies have been completed, proceed to Sections D and F and complete the PeRC Pediatric Assessment form. For those pediatric subpopulations for which additional studies are not needed because the drug is appropriately labeled in one or more pediatric subpopulations, proceed to Sections E and F.

Section D: Completed Studies (for some or all pediatric subpopulations). Complete Section F on Extrapolation.

Pediatric subpopulation(s) in which studies have been completed (check below):

Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: For those pediatric subpopulations for which additional studies are not needed because the drug is appropriately labeled in one or more pediatric subpopulations, proceed to Sections E and F. If there are no further pediatric subpopulations to cover based on the partial waivers, deferrals and completed studies, go to Section F.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations): (Complete section F)

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If studies are not needed because efficacy is being extrapolated from other adult and/or pediatric studies, proceed to Section F. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the target pediatric subpopulation needing studies. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 4/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

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

/s/

Matthew Scherer
4/30/2008 12:57:54 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 21-775 **Supplement Type (e.g. SE5):** _____ **Supplement Number:** _____

Stamp Date: May 9, 2006 **PDUFA Goal Date:** November 9, 2006

HFD 180 **Trade and generic names/dosage form:** Entereg (Alvimopan) Capsules, 6 mg

Applicant: Adolor Corporation **Therapeutic Class:** Type 1

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? *

- ☒ **Yes. Please proceed to the next question.**
- ☐ **No. PREA does not apply. Skip to signature block.**

** SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.*

Indication(s) ***previously approved*** **(please complete this section for supplements only):** N/A

Each indication covered by current application under review must have pediatric studies: ***Completed, Deferred, and/or Waived.***

Number of indications for this application(s): 1

Indication #1: acceleration of time recovery of gastrointestinal function following bowel resection surgery.

Is this an orphan indication?

- ☐ **Yes. PREA does not apply. Skip to signature block.**
- ☒ **No. Please proceed to the next question.**

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**
- ☒ **No: Please check all that apply: ____Partial ____Waiver __X__Deferred ____Completed**

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:** _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below):

Min_____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____
Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☒ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Is this an orphan indication?

- ☐ **Yes. PREA does not apply. Skip to signature block.**
- ☐ **No. Please proceed to the next question.**

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**
- ☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below)::

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is

complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below)::

Min_____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:_____**

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min_____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

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

/s/

Tanya Clayton
11/6/2006 02:22:17 PM

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

BLA # NDA # 21-775	BLA STN# NDA Supplement #	If NDA, Efficacy Supplement Type NA
Proprietary Name: Entereg Established Name: alvimopan Dosage Form: Capsules		Applicant: Adolor Corporation
RPM: Matthew Scherer	Division: HFD 180	Phone # 301-796-2307

NDAs:
NDA Application Type: X 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)

505(b)(2) Original NDAs and 505(b)(2) NDA supplements:
Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):

NA

Provide a brief explanation of how this product is different from the listed drug.
NA

☐ If no listed drug, check here and explain:

Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.

☐ No changes ☐ Updated
Date of check:

If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.

❖ User Fee Goal Date ❖ Action Goal Date (if different)	5-10-08 5-9-08
❖ Actions	
• Proposed action	X AP ☐ TA ☐ AE ☐ NA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☐ None AE 11-3-06, AE 7-21-05
❖ Advertising *(approvals only)* Note: If accelerated approval (21 CFR 314.510/601.41), advertising must have been submitted and reviewed *(indicate dates of reviews)*	X Requested in AP letter ☐ Received and reviewed

[1] The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be filed in the Action Package.

❖ Application Characteristics

Review priority: X Standard ☐ Priority
Chemical classification (new NDAs only): S1

NDAs, BLAs and Supplements:
☐ Fast Track
☐ Rolling Review

☐ Orphan drug designation

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

NDAs and NDA Supplements:
☐ OTC drug

Other:

Other comments:

❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	☐ Yes X No
• This application is on the AIP	☐ Yes X No
• If yes, exception for review granted *(file Center Director's memo in* Administrative Documents *section)*	☐ Yes
• If yes, OC clearance for approval *(file communication in* Administrative Documents *section)*	☐ Yes ☐ Not an AP action
❖ Date reviewed by PeRC (required for approvals only) If PeRC review not necessary, explain: ☐	4-30-08
❖ BLAs only: RMS-BLA Product Information Sheet for TBP has been completed and forwarded to OBPS/DRM (approvals only)	☐ Yes, date
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	X Yes ☐ No
• Press Office notified of action	X Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☐ None X HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

❖ Exclusivity	
• NDAs only: Exclusivity Summary (approvals only) *(file Summary in* Administrative Documents *section)*	5-15-08
• Is approval of this application blocked by any type of exclusivity?	X No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	X No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	X No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	X No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	X No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	X No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs and NDA supplements only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	**X** Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☐ Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

  Answer the following questions for **each** paragraph IV certification:

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

  (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

  *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

  *If "**No**," continue with question (3).*

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

  (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

  *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

  *If "**No**," continue with question (5).*

  (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist	Included 5-20-08
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list.	Included 5-12-08
❖ Documentation of consent/non-consent by officers/employees	Included 5-12-08
Decisional Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	Included 5-16-08
❖ Division Director Summary Review *(indicate date for each review)*	Included 5-16-08
❖ Cross-Discipline Team Leader Review *(indicate date for each review)*	NA
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	AP 5-20-08, AE 11-3-06, AE 7-21-05
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	Included 5-12-08
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	NA
• Original applicant-proposed labeling	Included 8-9-07
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	NA
❖ Patient Package Insert *(write submission/communication date at upper right of first page of PPI)*	
• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	NA
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	NA
• Original applicant-proposed labeling	NA

• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	NA
Medication Guide *(write submission/communication date at upper right of first page of MedGuide)*	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	NA
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	NA
• Original applicant-proposed labeling	NA
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	NA
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date at upper right of first page of each submission)*	
• Most-recent division proposal for (only if generated after latest applicant submission)	NA
• Most recent applicant-proposed labeling	Included 5-2-08
❖ Labeling reviews and any minutes of internal labeling meetings *(indicate dates of reviews and meetings)*	X RPM 4-4-08 X DMEDP 4-23-08, 10-12-06, 7-19-05, 12-9-03 ☐ DRISK X DDMAC 3-4-05 X SEALD 4-15-08 ☐ Other reviews ☐ Memos of Mtgs
Administrative Documents	
❖ Administrative Reviews (RPM Filing Review/Memo of Filing Meeting; ADRA) *(indicate date of each review)*	Included 10-30-06, 4-19-05
NDA and NDA supplement approvals only: Exclusivity Summary *(signed by Division Director)*	Included 5-15-08
• AIP-related documents • Center Director's Exception for Review memo • If approval action, OC clearance for approval	
❖ Pediatric Page *(a new Pediatric Page for each review cycle)*	X Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent. *(Include certification.)*	X Verified, statement is acceptable
❖ Postmarketing Commitment (PMC) Studies	X None
• Outgoing Agency request for postmarketing commitments *(if located elsewhere in package, state where located)*	
• Incoming submission documenting commitment	
❖ Postmarketing Requirement (PMR) Studies	☐ None
• Outgoing communications *(if located elsewhere in package, state where located)*	
• Incoming submissions/communications	Included 4-22-08, 4-15-08
❖ Outgoing communications (letters (except previous action letters), emails, faxes, telecons)	Included
❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings	
• Pre-Approval Safety Conference *(indicate date; approvals only)*	Included 3-20-08
• Regulatory Briefing	X No mtg
• Pre-NDA/BLA meeting *(indicate date)*	Included 2-25-04, 2-23-04

• EOP2 meeting *(indicate date)*	Included 3-12-01
• Other (e.g., EOP2a, CMC pilot programs)	Included 12-7-06, 9-18-06, 3-16-05, 11-23-04
Advisory Committee Meetings	☐ No AC meeting
• Date(s) of Meetings	1-23-08
• 48-hour alert or minutes, if available	Included
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	NA
CMC/Quality Information	
❖ ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	5-12-08, 11-1-06, 7-19-05
❖ PAL/BUD Review(s) *(indicate date for each review)*	None
❖ CMC/product quality review(s) *(indicate date for each review)*	5-6-08, 5-5-08, 10-23-06, 4-26-05, 11-16-04
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date for each review)*	None
❖ BLAs: Product subject to lot release (APs only)	NA
❖ Environmental Assessment (check one) (original and supplemental applications)	
• X Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	See 11-16-04 CMC review p 90
• ☐ Review & FONSI *(indicate date of review)*	
• ☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ NDAs: Microbiology reviews (sterility & apyrogenicity) *(indicate date of each review)*	X Not a parenteral product
❖ Facilities Review/Inspection	
❖ NDAs: Facilities inspections (include EER printout)	Date completed: 7-6-06, 4-25-05 X Acceptable ☐ Withhold recommendation
❖ BLAs: Facility-Related Documents • Facility review *(indicate date(s))* • Compliance Status Check (approvals only, both original and all supplemental applications (except CBEs)) *(indicate date completed, must be within 60 days prior to AP)*	NA ☐ Requested ☐ Accepted ☐ Hold
❖ NDAs: Methods Validation	☐ Completed ☐ Requested ☐ Not yet requested X Not needed
Nonclinical Information	
❖ ADP/T Review(s) *(indicate date for each review)*	5-6-08
❖ Supervisory Review(s) *(indicate date for each review)*	None
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	2-11-08, 1-18-08, 11-26-07, 6-19-07, 11-4-04
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	4-16-08, 1-8-08
❖ ECAC/CAC report/memo of meeting	2-12-08, 12-5-07
Nonclinical inspection review summary (DSI)	None requested

Clinical Information	
Clinical Team Leader Review(s) *(indicate date for each review)*	5-1-08, 10-31-06, 7-14-05
Clinical review(s) *(indicate date for each review)*	2-27-08, 10-31-06, 7-28-06, 7-12-05, 8-10-04
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR ❖ If no financial disclosure information was required, review/memo explaining why not	See 7-12-05 Clinical review p29
❖ Clinical reviews from other review disciplines/divisions/Centers *(indicate date of each review)*	5-5-08, 10-12-06, 9-22-06, 9-15-069-1-06
❖ Clinical microbiology reviews(s) *(indicate date of each review)*	Not needed
❖ Safety update review(s) *(indicate location/date if incorporated into another review)*	See 7-12-05 Clinical review p117
❖ REMS review(s) (including those by OSE) *(indicate location/date if incorporated into another review)*	5-7-08, 12-18-07
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date of each review)*	Not needed
❖ DSI Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☐ None requested
• Clinical Studies	Summary 5-23-05 Letters 6-10-05, 5-23-05, 4-29-05
• Bioequivalence Studies	5-5-08
• Clinical Pharmacology Studies	NA
Biostatistics	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	None
Statistical Team Leader Review(s) *(indicate date for each review)*	None
❖ Statistical Review(s) *(indicate date for each review)*	4-16-08, 11-1-06, 12-19-05, 7-7-05, 7-1-05
Clinical Pharmacology	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	None
❖ Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	None
❖ Clinical Pharmacology review(s) *(indicate date for each review)*	5-8-08, 11-2-06, 7-11-05

Appendix A to Action Package Checklist

IDA or NDA supplemental application is likely to be a 505(b)(2) application if:

(1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
(2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
(3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
(2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
(3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
(2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
(3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA or the OND ADRA.

MEMORANDUM OF MEETING MINUTES

MEETING DATE:	March 20, 2008
TIME:	9:00 AM
LOCATION:	White Oak, Room 5270
APPLICATION:	21-775
DRUG NAME:	Entereg (alvimopan) Capsules
TYPE OF MEETING:	Pre-Approval Safety Conference
MEETING CHAIR:	Ruyi He, Medical Team Leader
MEETING RECORDER:	Matthew Scherer, Regulatory Project Manager

FDA ATTENDEES

Donna Griebel, MD, Director, Division of Gastroenterology Products
Joyce Korvick, MD, MPH, Deputy Director, Division of Gastroenterology Products
Ruyi He, MD, Medical Team Leader, Division of Gastroenterology Products
Marjorie Dannis, MD, Medical Reviewer, Division of Gastroenterology Products
Sushanta Chakder, PhD, Supervisory Pharmacologist, Division of Gastroenterology Products
Tamal Chakraborti, PhD, Pharmacologist, Division of Gastroenterology Products
Sonia Castillo, PhD, Statistical Reviewer, Division of Biometrics
Claudia Karwoski, PharmD, Acting Director, Division of Risk Management, Office of Surveillance and Epidemiology
Joyce Weaver, PharmD, Senior Drug Risk Management Analyst, Division of Risk Management, Office of Surveillance and Epidemiology
Allen Brinker, MD, Medical Officer, Division of Epidemiology, Office of Surveillance and Epidemiology
Ann Corken Mackey, RPh, MPH, Safety Evaluator, Division of Adverse Event Analysis 1, Office of Surveillance and Epidemiology
Matthew Scherer, Regulatory Project Manager, Division of Gastroenterology Products
Cherye Milburn, Regulatory Project Manager, Office of Surveillance and Epidemiology

BACKGROUND:

A New Drug Application (NDA 21-775) was originally submitted on June 25, 2004 for alvimopan capsules to accelerate time to recovery of gastrointestinal function following major abdominal or complex pelvic surgery. The FDA took an approvable action on July 21, 2005 because of insufficient proof of efficacy of alvimopan for the treatment of POI.

The sponsor submitted a Complete Response to the Approvable Letter on May 9, 2006. During review of the second-cycle submission, the sponsor informed the FDA of a numerically higher incidence of serious cardiovascular (CV) events (e.g., acute myocardial infarction) in the alvimopan treatment group, compared to the placebo group, in one of their ongoing opioid induced bowel dysfunction (OBD) trials (Study 14). This study was a one-year long, placebo-controlled, safety study of alvimopan 0.5 mg BID for the treatment of OBD in opioid-experienced patients with chronic non-cancer pain. A second Approvable Action was taken by the FDA on November 3, 2006. The second Approvable Letter requested the final 12-month safety findings including analyses of serious CV events from Study 14; a risk management plan

to minimize the possible CV risk of longer-term alvimopan exposure and off-label use; and a safety update.

The sponsor submitted the second Complete Response (the third cycle submission) to the second Approvable Letter on August 9, 2007. The PDUFA goal date is May 10, 2008. The expected action date is May 9, 2008.

The GI advisory committee meeting took place on January 23, 2008 to discuss efficacy and safety for the POI indication, specific safety issues which were identified in the long term OBD study (serious cardiovascular events, neoplasms and fractures), pre-clinical findings and risk management strategies.

The AC members unanimously agreed that the efficacy results of hospital discharge occurring approximately 1 day earlier were clinically meaningful. The majority of AC members (9 to 6) agreed that the benefits outweighed the risks for short term in- hospital use in patients following partial large or small bowel resection surgery with primary anastomosis.

Alvimopan is a new molecular entity (NME). As such, a pre-approval safety conference with the appropriate representatives of the Office of Surveillance and Epidemiology (OSE) is required.

MEETING OBJECTIVES:

- To satisfy the pre-approval safety conference requirement
- To determine what means are necessary to minimize the risk associated with the use of Entereg, should it be approved

DISCUSSION POINTS:

- The review team agreed that a long-term placebo-controlled study of alvimopan in the OBD population would not be required as a post-marketing commitment.
- The sponsor's proposed study (alvimopan to treat POI in patients undergoing radical cystectomy) will be a post-marketing requirement. The team is generally in agreement with the submitted protocol synopsis, but would like a more detailed protocol prior to the action date.
- The Division requests that the following uses of Entereg be monitored: use related to surgeries other than bowel resection, outpatient use, use for greater than 7 days or 15 doses, use in children, any other off-label use.
- Cardiovascular events, occurrence of neoplasms and bone fractures in patient taking Entereg will also be monitored.
- The Agency will continue to work with the sponsor to finalize the in-progress RiskMAP as well as develop a Risk Evaluation and Mitigation Strategy (REMS). The RiskMAP will serve as the REMS supporting document.

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

/s/

Matthew Scherer
5/5/2008 11:50:24 AM

Scherer, Matthew

From: Scherer, Matthew
Sent: Tuesday, April 29, 2008 10:40 AM
To: 'Linda Young'
Subject: NDA 21-775 (Entereg) additional comments for RiskMAP

Dear Ms. Young,

We have reviewed the revised RiskMAP you submitted on April 17, 2008. We have the following comments:

[redacted]

Regards,

Matthew C. Scherer
Regulatory Project Manager
Division of Gastroenterology Products
CDER/OND/ODEIII
Ph: 301-796-2307
Fax: 301-796-9905

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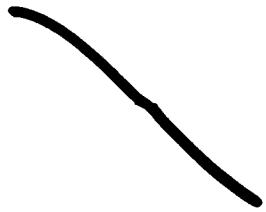
/s/

Matthew Scherer
4/29/2008 10:44:48 AM
CSO

From: Scherer, Matthew
Sent: Friday, April 25, 2008 1:14 PM
To: 'Linda Young'
Subject: NDA 21-775 (Entereg) labeling comments

Ms. Young,

We have reviewed the labeling submitted as part of this NDA. We request the following revisions:



Regards,

Matthew C. Scherer
Regulatory Project Manager
Division of Gastroenterology Products
CDER/OND/ODEIII
Ph: 301-796-2307
Fax: 301-796-9905

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/s/

Matthew Scherer
4/25/2008 01:16:42 PM
CSO

adolor
CORPORATION

700 Pennsylvania Drive
Exton, PA 19341
Tel: 484.595.1500; Fax: 484.595.1520

April 22, 2008

Donna J. Griebel, MD
Division Director
Division of Gastroenterology
Office of Drug Evaluation III
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705

Re: NDA #21-775, Entereg® (alvimopan) Capsules
Response to Information Request 11 April 2008 – Cystectomy Protocol

Dear Dr. Griebel:

Pursuant to an email from Matt Scherer received on 11 April 2008, enclosed is our draft protocol to study alvimopan in radical cystectomy patients, Study 14CL403: A Phase 4, Multicenter, Double-Blind, Placebo-Controlled, Parallel Study of Alvimopan for the Management of Postoperative Ileus in Subjects Undergoing Radical Cystectomy." We have previously submitted an outline of this study as a Phase 4 commitment to the subject NDA. The requested timeline for the study is also attached.

The protocol is marked as draft, and we welcome any comments that the Division may have as we begin to finalize the protocol. We anticipate filing the finalized protocol to Adolor's IND 56,553 in 4-8 weeks after we have the final Duke CV Clinical Events Committee charter incorporated. As you will note on the timeline, the projected date for the final clinical study report is 2012, as we expect recruitment to be rate limiting to a more timely conclusion of the study. The population of radical cystectomy patients and number of centers are limited, thus slower recruitment.

Adolor also seeks the Division's opinion as to the feasibility of

We understand that this NDA and all information contained therein, unless otherwise made public by Adolor Corporation, are CONFIDENTIAL. If you have any questions or need additional information, please contact me at 484-595-1011 by phone or 484-595-1528 by facsimile.

Sincerely,

ADOLOR CORPORATION

Linda G. Young

Linda G. Young, R.Ph., J.D.
Vice President, Regulatory Affairs

8 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Administrative- 16

adolor
CORPORATION

700 Pennsylvania Drive
Exton, PA 19341
Tel: 484.595.1500; Fax: 484.595.1520

April 15, 2008

Donna Griebel, MD
Division Director
Division of Gastroenterology
Office of Drug Evaluation III
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705

Re: NDA 21-775, Entereg® (alvimopan Capsules), Response to Request for Information, Pediatric Plan

Dear Dr. Griebel:

Enclosed is a pediatric plan on the form requested by the Division. We have also enclosed a deferral formatted in accordance with the guidance "How to Comply with the Pediatric Research Act." Adolor is requesting that the initiation of pediatric studies be deferred 18 months post approval of the NDA to allow time to conduct the juvenile animal toxicology studies and discuss any additional adult human safety data required prior to initiating pediatric studies.

The pediatric plan in bowel resection was recently developed with the expertise of pediatric anesthesiologists and a pediatric clinical pharmacologist at the [redacted] in addition to considering the input from a multispecialty Pediatric Advisory Board conducted in 2005. The number of children undergoing bowel resections is quite small, research indicates fewer than 20,000 per year in the United States. The population tends to be grouped in less than one year old for congenital anomalies and in older children and adolescents for Inflammatory Bowel Disease (Crohn's Disease and Ulcerative Colitis). We therefore anticipate a slow enrollment, and it may not be possible to stratify by age group. As you will note in the attached plan, we have estimated it will take approximately 3 years from the time the first clinical site is initiated to submit a report for Study 1, and approximately 2 years for Study 2.

April 15, 2008
Re: NDA 21-775, Entereg® (alvimopan Capsules), Response to Request for Information, Pediatric Plan

This submission consists of one CD, original cover letter and one copy. We understand that this NDA and all information contained therein, unless otherwise made public by Adolor Corporation, are CONFIDENTIAL. If you have any questions or need additional information, please contact me at 484-595-1011 by phone or 484-595-15283 by facsimile.

Sincerely,

ADOLOR CORPORATION

Linda G. Young, R.Ph., J.D.
Vice President, Regulatory Affairs

From: Scherer, Matthew
Sent: Friday, April 11, 2008 11:47 AM
To: 'Linda Young'
Subject: FDA comments on Revised Risk Management Program for Entereg (NDA 21-775)

Attachments: 4-11-08 Comments on March 24 submission.doc

Linda,

Please see the attached file containing the Agency's comments on your Revised Risk Management Program for Entereg dated March 24, 2008.

Regards,

Matthew C. Scherer
Regulatory Project Manager
Division of Gastroenterology Products
CDER/OND/ODEIII
Ph: 301-796-2307
Fax: 301-796-9905

4-11-08 Comments on March 24 s...

2 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Administrative- 17

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/s/

Matthew Scherer
4/11/2008 12:40:26 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-775

ADVICE LETTER

Adolor Corporation
Attention: Linda G. Young, R.Ph., J.D.
Vice President, Regulatory Affairs
700 Pennsylvania Drive
Exton, PA 19341-1127

Dear Ms. Young:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Entereg (alvimopan) Capsules.

We also refer to your submission dated August 9, 2007 which includes a package insert in SPL format.

The following issues/deficiencies have been identified in your proposed labeling. Please address these issues as soon as possible.

Highlights Section:

[redacted]

Full Prescribing Information:

[redacted]

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

Sincerely,

{See appended electronic signature page}

Julieann DuBeau, M.S.N., R.N.
Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Julieann DuBeau
4/4/2008 11:31:17 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-775

Adolor Corporation
Attention: Linda G. Young, R.Ph., J.D.
Vice President, Regulatory Affairs
700 Pennsylvania Drive
Exton, PA 19341-1127

Dear Ms. Young:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Entereg (alvimopan) Capsules.

We also refer to your January 11, 2008 and January 25, 2008 submissions providing clarification of interpretation of mouse carcinogenicity data and for findings the rat carcinogenicity study as requested by the Executive Carcinogenicity Advisory Committee (Exec CAC).

We have reviewed the referenced material and have the following comments:

1. We do not concur with your interpretation and conclusion of the mouse carcinogenicity study results.

2. We stand by our conclusion that alvimopan caused statistically significant increase in the incidences of fibroma, fibrosarcoma and sarcoma in the skin/subcutis and osteoma/osteosarcoma in bones of female mice.

3. Your clarification for the rat carcinogenicity study as requested by the Exec CAC is adequate and acceptable. Based on your clarification and following the reanalysis of the rat tumor data, we conclude that the rat study is negative.

If you have any questions, call me at 301-796-2307.

Sincerely,

{See appended electronic signature page}

Matthew Scherer
Regulatory Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Matthew Scherer
2/28/2008 05:37:48 PM

Executive CAC (Addendum to the meeting minutes dated December 4, 2007)

Date of Meeting: January 15, 2008

Committee: Abby Jacobs, Ph.D., OND IO, Exec CAC Member
Tim McGovern, Ph.D., DPAP, Exec CAC Member
Joyce Korvick, M.D., DGP, Deputy Director
Ling Chen, Ph.D., Statistician
Karl Lin, Ph.D., Statistician
Tamal Chakraborti, Ph.D., DGP, Pharm Tox Reviewer
Sushanta Chakder, Ph.D., DGP, Pharm Tox Supervisor

Author of Draft: Tamal Chakraborti, Ph.D.

The following information reflects a brief summary of the Committee discussion and its recommendations.

NDA #: 21-775
Drug Name: Entereg® (Alvimopan, ADL8-2698)
Sponsor: Adolor Corporation, Exton, PA

Alvimopan is a relatively selective, competitive, preferably peripherally acting, μ-opioid receptor antagonist that is being developed for the treatment of postoperative ileus (POI under the IND 56,553, Adolor Corporation) and for the treatment of chronic opioid-induced bowel dysfunction [redacted]

Rat Carcinogenicity Study

The sponsor responded to the Division facsimile dated December 17, 2007, in which clarification was requested by the Executive CAC for findings in the rat study. The Exec CAC requested the following clarification for the rat carcinogenicity study (from the Exec CAC meeting minutes dated December 4, 2007):

"The Committee tentatively concluded that there were no drug-related tumor findings in either sex. However, the Committee asked for a clarification of the discrepancy between the incidence of thymoma (epithelial) in the thymus of male rats in the tumor data set submitted for statistical review (Male: 3 of 57, 0 of 60, 0 of 60, 2 of 58 and 3 of 58 for Group 1, 2, 3, 4 and 5, respectively) and that presented in the study report for the pharmacology/toxicology review (Male: 0 of 57, 0 of 60, 0 of 60, 0 of 58, and 1 of 58 for Group 1, 2 4, 5 and 6, respectively, from Table 7, page 161 of the study report)."

The sponsor clarified that the thymus was missing from 3 rats from Group 1, 2 rats from Group 5 and 2 rats from Group 6, and that was why the total number of tissues examined was less than 60 for these dose groups. As per the CDER Guidance for Industry (IT3: Providing Regulatory Submissions in Electronic Format; 1999), the missing tissues were

included in the tumor dataset submitted for statistical review. In the Complete Response dated August 9, 2007, the numeric code '3' in the ORGANEXM column was used to identify when tissues were missing. The sponsor stated that it would appear that the group incidence for thymoma (epithelial) referred to in the Exec CAC's recommendation and conclusion may assume their occurrence in the missing tissues, resulting in a noted incidence of 3 of 57, 0 of 60, 0 of 60, 2 of 58 and 3 of 58 for Groups 1, 2, 4, 5 and 6, respectively. The sponsor examined their "Excel" spreadsheet derived from the SAS (statistical analysis system) file that had failed to find an explanation why the missing tissues appeared to have been associated with thymoma (epithelial) leading to the discrepancy noted by the Agency. The sponsor confirmed that the incidence of diagnosed thymoma (epithelial) tumors is as stated in the final report.

Based on the sponsor's clarification, the statistical reviewer corrected the original tumor data in the rat database and reran the Peto trend test on the corrected data. The result from Peto's trend test showed that the dose response for the incidence of thymoma (epithelial) was not statistically significant ($p > 0.025$). The statistical reviewer concluded that there was no significant tumor finding in the rat carcinogenicity study (Statistical Review of NDA 21-775, Addendum dated February 8, 2008).

Executive CAC Recommendations and Conclusions:

Rat Study:

1. The Committee concurred that the study was adequate.
2. The Committee concurred that the rat study was negative based on sponsor's clarification of the reported data, as requested by the Exec CAC.

David Jacobson-Kram, Ph.D.
Chair, Executive CAC

cc:\
/Division File, DGP
/SChakder, DGP
/TChakraborti, DGP
/CSO/PM/MScherer/DGP
/ASeifried, OND IO

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/s/

Abby Jacobs
2/12/2008 01:39:51 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-775

Adolor Corporation
Attention: Linda G. Young, R.Ph., J.D.
Vice President, Regulatory Affairs
700 Pennsylvania Drive
Exton, PA 19341-1127

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. We also refer you to your August 9, 2007 Complete Response.

On December 31, 2007, we received an amendment, dated December 28, 2007, to this application. This submission provided additional datasets and statistical analyses. Furthermore, on February 7, 2008, we received your proposed Risk Minimization Action Plan (RiskMAP), dated February 7, 2008. Each of these submissions is considered a major amendment and was received within 3 months of the user fee goal date. Therefore, as provided for in 21 CFR 314.60, we are extending the goal date by three months to provide time for a full review of these submissions. The extended user fee goal date is May 10, 2008.

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

Sincerely,

{See appended electronic signature page}

Julieann DuBeau, M.S.N., R.N.
Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Julieann DuBeau
2/8/2008 10:10:45 AM

Summary Minutes of the Gastrointestinal Drugs Advisory Committee
January 23, 2008
Location: Hilton Washington DC Silver Spring, the Maryland Ballroom
8727 Colesville Road, Silver Spring, MD

All external requests for the meeting transcripts should be submitted to the CDER, Freedom of Information Office.

These summary minutes for the January 23, 208 of the Gastrointestinal Drugs Advisory Committee of the Food and Drug Administration were approved on 1/28/08

I certify that I attended the January 23, 2008, meeting of the Gastrointestinal Drugs Advisory Committee of the Food and Drug Administration meeting and that these minutes are accurately reflects what transpired.

Mimi T. Phan, Pharm.D., R.Ph.
Designated Federal Official

Alan L. Buchman, M.D., M.S.P.H
Acting-Chair

4 Page(s) Removed.

See the Advisory Committee Meeting Information located on the FDA Website Below.

http://www.fda.gov/ohrms/dockets/ac/
[transcripts]

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-775

Adolor Corporation
Attention: Linda G. Young, R.Ph., J.D.
Vice President, Regulatory Affairs
700 Pennsylvania Drive
Exton, PA 19341-1127

Dear Ms. Young:

Please refer to your New Drug Application for Entereg (alvimopan) Capsules. We also refer to your 104-week mouse and rat carcinogenicity study reports submitted August 9, 2007.

Our Executive Carcinogenicity Assessment Committee (Executive CAC) reviewed your study reports on December 4, 2007. A copy of the final report of the Executive CAC regarding Entereg (alvimopan) Capsules is enclosed. Please provide the clarification requested under the rat study in the attached meeting minutes dated December 4, 2007.

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

Sincerely,

{See appended electronic signature page}

Julieann DuBeau, M.S.N., R.N.
Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

Executive CAC
Date of Meeting: December 4, 2007

Committee: David Jacobson-Kram, Ph.D., OND IO, Chair
Abby Jacobs, Ph.D., OND IO, Member
Tim McGovern, Ph.D., DPAP, Alternate Member
Sushanta K. Chakder, Ph.D., DGP, Acting Team Leader
Tamal Chakraborti, Ph.D., DGP, Presenting Reviewer

Author of Draft: Tamal Chakraborti, Ph.D.

The following information reflects a brief summary of the Committee discussion and its recommendations.

NDA #: 21-775
Drug Name: Entereg® (Alvimopan, ADL8-2698)
Sponsor: Adolor Corporation, Exton, PA

Alvimopan is a relatively selective, competitive, preferably peripherally acting, μ-opioid receptor antagonist that is being developed for the treatment of postoperative ileus (POI under the IND 56,553, Adolor Corporation) and for the treatment of chronic opioid-induced bowel dysfunction [redacted] Results from the Study SB-767905/014, a long-term safety study of alvimopan for the treatment of OBD in chronic non-cancer patients, demonstrated an imbalance in reports of serious cardiovascular events (myocardial infarction/MI), an apparent increase in the incidence of benign and malignant neoplasms in the alvimopan group relative to the placebo group and an increase in the incidence of bone fractures when compared to the placebo. The Division asked the sponsor to submit the full reports of the carcinogenicity studies in rats and mice. In this submission, the sponsor submitted reports of carcinogenicity studies with alvimopan in mice and rats.

Mouse Carcinogenicity Study

Carcinogenicity summary: In a 104-week oral (gavage) study in CD-1 mice, animals (60/sex/group) were administered 0 (purified water), 0 (vehicle), 100, 1000 or 4000 mg/kg/day SB-767905-KW in 10% (w/v) aqueous acacia (10 mL/kg). The dose selection was per the ExecCAC recommendations. Survival in the female group at 100 mg/kg/day fell below 15 animals in Week 101, and all surviving females in this group were sacrificed in Week 101. Survival in the vehicle control female group fell below 15 in Week 102, and all remaining females from all groups were killed in Weeks 102/103. For male mice, survival at 1000 mg/kg/day and 4000 mg/kg/day was higher than the vehicle control group. In males, the water control demonstrated significantly lower mortality than the vehicle control. For females, there was no significant difference in mortality between the two control groups. There were no significant treatment-related effects on clinical signs, food consumption, body weight, hematology, and gross pathology.

Alvimopan caused significant increase in the incidences of fibroma, fibrosarcoma and sarcoma in the skin/subcutis, and osteoma/osteosarcomas in bones of female mice.

Rat Carcinogenicity Study

In a 104-week oral (gavage) study in SD rats, animals (60/sex/group) were administered 0 (water), 0 (vehicle), 100, 200 or 500 mg/kg/day SB-767905-KW in 10% (w/v) aqueous acacia (5 mL/kg). The dose selection was per the ExeCAC recommendations. Treatment with SB-767905-KW had no effect on survival in either sex. There were no significant in-life findings associated with treatment with SB-767905-KW. Macroscopic observations included statistically significant increased incidence of enlargement of the deep cervical lymph nodes in male decedent rats at 500 mg/kg/day. In males, a statistically significant increased incidence of enlargement of lumbar lymph nodes was observed at high dose. There is an apparent discrepancy between the data presented for the incidence of thymoma (epithelial) in the thymus of male rats in the tumor data set submitted for statistical review and that presented in the study report for the pharmacology/toxicology review. Overall, there appear to be no significant tumor findings in either sex.

Executive CAC Recommendations and Conclusions:

Mice Study:

1. The Committee concurred that the study was adequate.
2. The Committee concurred that alvimopan caused significant increases in the incidences of fibroma, fibrosarcoma and sarcoma in the skin/subcutis, and osteoma/osteosarcoma in bones of female mice.

Rat Study:

1. The Committee concurred that the study was adequate.
2. The Committee tentatively concluded that there were no drug-related tumor findings in either sex. However, the Committee asked for a clarification of the discrepancy between the incidence of thymoma (epithelial) in the thymus of male rats in the tumor data set submitted for statistical review (Male: 3 of 57, 0 of 60, 0 of 60, 2 of 58 and 3 of 58 for Group 1, 2, 3, 4 and 5, respectively) and that presented in the study report for the pharmacology/toxicology review (Male: 0 of 57, 0 of 60, 0 of 60, 0 of 58, and 1 of 58 for Group 1, 2, 3, 4, 5 and 6, respectively, from Table 7, page 161 of the study report).

David Jacobson-Kram, Ph.D.
Chair, Executive CAC

cc:\
/Division File, DGP
/SChakder, DGP
/TChakraborti, DGP
/CSO/PM/MScherer/DGP
/ASeifried, OND IO

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/s/

David Jacobson-Kram
12/5/2007 11:41:02 AM

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/s/

Matthew Scherer
1/17/2008 12:33:34 PM
Signing for Julieann DuBeau, M.S.N., R.N.
Chief, Project Management
Staff

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

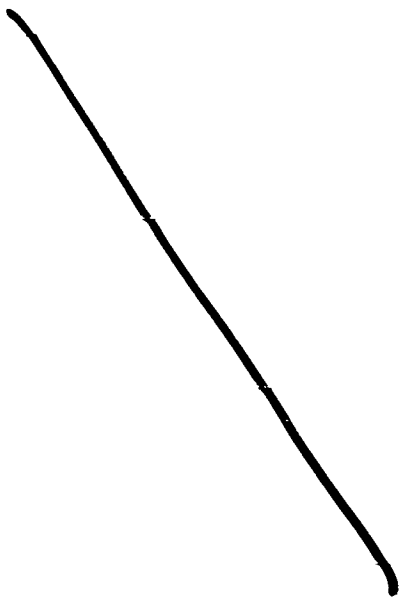
NDA 21-775

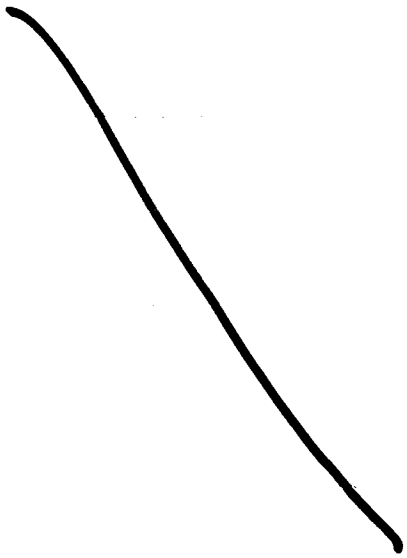
Adolor Corporation
Attention: Linda G. Young, R.Ph., J.D.
Vice President, Regulatory Affairs
700 Pennsylvania Drive
Exton, PA 19341-1127

Dear Ms. Young:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Entereg (alvimopan) Capsules.

We expect to receive advice from the Gastrointestinal Drugs Advisory Committee regarding the measures that may be needed to minimize the risks of long-term use of Entereg. We expect the discussion at the Advisory Committee meeting to be useful in designing the final Risk Minimization Action Plan (RiskMAP), should Entereg be approved for marketing. Nevertheless, we have reviewed the RiskMAP, and have the following preliminary comments:





4. In addition to the routine pharmacovigilance described in your submission, we ask that you submit your pharmacovigilance plan for this product. This plan should include a commitment to submit any adverse event related to ischemic cardiovascular events, tumors, or bone fractures as a 15-day Safety Reports, per reporting regulations 21 CFR 314.80.

If you have any questions, call me at 301-796-2307.

Sincerely,

{See appended electronic signature page}

Matthew Scherer
Regulatory Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Matthew Scherer
1/17/2008 10:29:39 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-775

INFORMATION REQUEST LETTER

Adolor Corporation
Attention: Linda G. Young, R.Ph., J.D.
Vice President, Regulatory Affairs
700 Pennsylvania Drive
Exton, PA 19341-1127

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. We also refer to your submission dated August 9, 2007, and the December 17, 2007, teleconference between the FDA, Adolor and GlaxoSmithKline to discuss the time to event calculations.

As discussed at the recent teleconference, we are reviewing your submission and have the following information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Please provide the following:

1. The code used to produce the time to event plots (figures 2 and 4) for the post operative ileus (POI) indication
2. A time to event plot for study SB-767905/014 for the opioid induced bowel dysfunction (OBD) indication
3. A time to event plot for the non-cancer, non-014 studies
4. The hazard ratios for the plots listed in items 1, 2 and 3 above
5. The datasets for GSK007
6. In addition, for each of the following studies:

   POI – 13C206, 13C213, 13C214, 14CL302, 14CL306, 14CL308, 14CL313, 14CL314, and SB-767905/001
   OBD – SB-767905/007, SB-767905/008, SB-767905/011, SB-767905/012, SB-767905/013, SB-767905/014, 13C217, 13C304, and ABD101684

   Please include the following information:
   - Study ID
   - Investigator ID
   - Unique Subject ID
   - Treatment Dose/Regimen

- Last Date of Follow-up (whether it be hospital discharge, phone follow-up, discontinuation, death, last GI assessment, etc.)
- Flag for the type of last follow-up (that is, hospital discharge, phone follow-up, discontinuation, death, last GI assessment, etc.)
- Day of last follow-up calculated as = "Last Date of Follow-up" - "First Dose Date" + 1

For each subject, please provide the information, as one line of data per subject, as a SAS dataset in version 5 SAS transport format.

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

Sincerely,

{See appended electronic signature page}

Brian Strongin, R.Ph., M.B.A.
Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Brian Strongin
12/20/2007 10:42:14 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-775

INFORMATION REQUEST LETTER

Adolor Corporation
Attention: Linda G. Young, R.Ph., J.D.
Vice President, Regulatory Affairs
700 Pennsylvania Drive
Exton, PA 19341-1127

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. We also refer to your complete responses dated May 9, 2006 and August 9, 2007.

We are reviewing the Clinical section of your submission and have the following information request. We request a prompt written response in order to continue our evaluation of your NDA.

> Please provide the number of patients that did not complete studies 13C206, 13C213, 13C214, 14CL302, 14CL306, 14CL308, 14CL313, 14CL314, and SB-767905/001. Include all patients that did not have a final study visit, follow-up phone call or did not complete the study for any other reason. For each patient, provide the patient ID number, treatment group, adverse events, an explanation for the lack of follow-up, and all other relevant information. Please organize this information by study. In addition, present this information for all of the above-listed studies combined.

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

Sincerely,

{See appended electronic signature page}

Julieann DuBeau, M.S.N., R.N.
Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Julieann DuBeau
10/9/2007 04:28:20 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-775

Adolor Corporation
Attn: Linda G. Young
Vice President, Regulatory Affairs
700 Pennsylvania Drive
Exton, PA 19341

Dear Ms Young:

We acknowledge receipt on August 10, 2007 of your August 9, 2007 resubmission to your new drug application for Entereg (Alvimopan) Capsules, 12 mg.

We consider this a complete, class 2 response to our November 3, 2006 action letter. Therefore, the user fee goal date is February 10, 2008.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We reference the deferral granted on March 12, 2001 for the pediatric study requirement for this application.

If you have any question, call me at (301) 796-2307.

Sincerely,

{See appended electronic signature page}

Matthew C Scherer
Regulatory Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Matthew Scherer
8/27/2007 02:59:09 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-775

Adolor Corporation
Attention: Linda G. Young, R.Ph., J.D.
Vice President, Regulatory Affairs
700 Pennsylvania Drive
Exton, PA 19341-1127

Dear Ms. Young:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Entereg (alvimopan) Capsules. We also refer to your June 15, 2007, submission of Proposed Content of Complete Response to the FDA's Approvable Letter dated November 6, 2006 as well as a follow-up teleconference on May 29, 2007.

We have reviewed the referenced material and have the following comments and recommendations.

1. You should conduct a bone marrow micronucleus test with ADL 08-0011 to further explore the genotoxic potential of the metabolite.

2. From a pharmacology/toxicology standpoint, your proposal to include final reports of the 2-year carcinogenicity studies in mice and rats in the Complete Response to the Agency letter appears to be acceptable.

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

Sincerely,

{See appended electronic signature page}

Joyce Korvick, M.D., M.P.H.
Deputy Director
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Joyce Korvick
8/10/2007 03:25:04 PM

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODEIII

FACSIMILE TRANSMITTAL SHEET

DATE: March 9, 2007

To: Linda Y. Harver	**From:** Brian Strongin, R.Ph., M.B.A.
Company: Adolor Corporation	Division of Gastroenterology Products
Fax number: 484-595-1528	**Fax number:** (301) 796-9905
Phone number: 484-595-1011	**Phone number:** (301) 796-2120

Subject: Preliminary Responses to Clinical and Biopharm Questions From December 7, 2006 Meeting for NDA 21-775

Total no. of pages including cover: 8

Comments:

Our responses to the clinical and biopharm questions from the December 7, 2006 meeting are attached.

Document to be mailed: ☐ YES ☑ NO

NDA 21-775 Entereg (alvimopan) Capsules
December 7, 2006 – Responses to Clinical and Biopharm Questions

As discussed in our December 7, 2006 meeting, we provide the following responses to the questions below regarding the proposed definition of cardiovascular events, content of the safety update, and the PK question for the planned response to the November 3, 2006 approvable letter for NDA 21-775.

1. Definition of CV events

Based on our discussion with the Division at the December 7th meeting, CV events will be defined by those conditions specified by FDA in their table contained in the Information Request dated October 3rd 2006 (attached): Summary CV events in POI Population. This same table will be prepared for the OBD population based on the pooled OBD studies in the non-cancer subjects and for GSK Study SB-767905/014 alone. The format and the contents of this CV event table are illustrated below in Tables 1-3:

Table 1
Summary of CV Events in POI Population
Studies: 13C206, 13C213, 13C214, 14CL302, 14CL306, 14CL308, 14CL313, 14CL314, and SB-767905/001

	Alvimopan Group[1] (N=2610)		Placebo Group (N=1365)		Relative Risk (Alvimopan vs Placebo)
CV Event Category	n (%)	Subject ID	n (%)	Subject ID	(95% CI)
All Cause Death	x (x.xx)		x (x.xx)		x.xx (x.xx, x.xx)
Death from CV events	x (x.xx)		x (x.xx)		x.xx (x.xx, x.xx)
MI: Overall	x (x.xx)		x (x.xx)		x.xx (x.xx, x.xx)
Fatal	x (x.xx)		x (x.xx)		
Non-Fatal	x (x.xx)		x (x.xx)		
Unstable Angina	x (x.xx)		x (x.xx)		x.xx (x.xx, x.xx)
Non-fatal CVA	x (x.xx)		x (x.xx)		x.xx (x.xx, x.xx)
CHF: Overall	x (x.xx)		x (x.xx)		x.xx (x.xx, x.xx)
Fatal	x (x.xx)		x (x.xx)		
Non-Fatal	x (x.xx)		x (x.xx)		
Serious Arrhythmia	x (x.xx)		x (x.xx)		x.xx (x.xx, x.xx)
Fatal	x (x.xx)		x (x.xx)		
Non-Fatal	x (x.xx)		x (x.xx)		

[1] Alvimopan group included the following alvimopan doses: 1mg (N=27), 3mg (N=35), 6mg (N=898) and 12mg (N=1650). All doses were administered as BID regimen for up to 7 postoperative days plus a pre-op dose on the day of surgery.

Table 2
Summary of CV Events in OBD Population
Studies: SB-767905/011, SB-767905/012, SB-767905/013, SB-767905/014, 13C217, and 13C304

	Alvimopan Group[1] (N=1728)		Placebo Group (N=790)		Relative Risk (Alvimopan vs Placebo)
CV Event Category	n (%)	Subject ID	n (%)	Subject ID	(95% CI)
All Cause Death	x (x.xx)		x (x.xx)		x.xx (x.xx, x.xx)
Death from CV events	x (x.xx)		x (x.xx)		x.xx (x.xx, x.xx)
MI: Overall	x (x.xx)		x (x.xx)		x.xx (x.xx, x.xx)
Fatal	x (x.xx)		x (x.xx)		
Non-Fatal	x (x.xx)		x (x.xx)		
Unstable Angina	x (x.xx)		x (x.xx)		x.xx (x.xx, x.xx)
Non-fatal CVA	x (x.xx)		x (x.xx)		x.xx (x.xx, x.xx)
CHF: Overall	x (x.xx)		x (x.xx)		x.xx (x.xx, x.xx)
Fatal	x (x.xx)		x (x.xx)		
Non-Fatal	x (x.xx)		x (x.xx)		
Serious Arrhythmia	x (x.xx)		x (x.xx)		x.xx (x.xx, x.xx)
Fatal	x (x.xx)		x (x.xx)		
Non-Fatal	x (x.xx)		x (x.xx)		

[1]Alvimopan group included the following alvimopan dose and regimen: 0.5mg QD (N=401), 1mg QD (N=197), 0.5mgBID (N=1000), and 1mg BID (N=130).

Table 3
Summary of CV Events in Study SB-767905/014

CV Event Category	Alvimopan 0.5mg BID (N=538) n (%)	Subject ID	Placebo Group (N=267) n (%)	Subject ID	Relative Risk (Alvimopan vs Placebo) (95% CI)
All Cause Death	x (x.xx)		x (x.xx)		x.xx (x.xx, x.xx)
Death from CV events	x (x.xx)		x (x.xx)		x.xx (x.xx, x.xx)
MI: Overall	x (x.xx)		x (x.xx)		x.xx (x.xx, x.xx)
Fatal	x (x.xx)		x (x.xx)		
Non-Fatal	x (x.xx)		x (x.xx)		
Unstable Angina	x (x.xx)		x (x.xx)		x.xx (x.xx, x.xx)
Non-fatal CVA	x (x.xx)		x (x.xx)		x.xx (x.xx, x.xx)
CHF: Overall	x (x.xx)		x (x.xx)		x.xx (x.xx, x.xx)
Fatal	x (x.xx)		x (x.xx)		
Non-Fatal	x (x.xx)		x (x.xx)		
Serious Arrhythmia	x (x.xx)		x (x.xx)		x.xx (x.xx, x.xx)
Fatal	x (x.xx)		x (x.xx)		
Non-Fatal	x (x.xx)		x (x.xx)		

2. Content of Safety Update

Safety Update Requirement in the Letter	Adolor's Proposal	Rationale
1. Describe in detail any significant changes or findings in the safety profile	None	No new data have been generated for the proposed indication of POI since May 9, 2006.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows		
▪ Present new safety data from the studies for the proposed indication using the same format as the original NDA submission ▪ Present tabulation of the new safety data combined with the original NDA data ▪ Include tables that compare frequencies of adverse events in the original NDA with the re-tabulated frequencies described in the bullets above.	1. The CV table presented to FDA on October 4, 2006 will be re-submitted without any new data, since no new studies have been conducted since May 9, 2006 for this indication. See Table 1 for mock. 2. The pooled AE dataset from all POI studies and the SAS program used to generate the CV table for the POI population will be submitted.	The potential for CV risk is the primary concern at this time for the POI indication, therefore the safety update will present CV AEs only.

Safety Update Requirement in the Letter	Adolor's Proposal	Rationale
▪ For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials	1. The CV table will reflect pooled data from all OBD studies and for study 014 in non-cancer patients in the same format as the October 4, 2006 submission. See Tables 2 and 3 for mock format and contents. 2. Fatal SAEs and non-fatal SAEs will be tabulated from the recently completed 7 studies in other indication as follows: ▪ 3 OBD studies in non-cancer population. ▪ 1 OBD study in cancer patients ▪ 2 studies in healthy volunteers ▪ 1 study from acute combo program in healthy volunteers. 3. The AE dataset pooled AEs in the original NDA and the new AEs from the recently completed OBD studies will be provided as well as the SAS program used to generate the CV table for the OBD population. 4. A blinded SAE table will be generated for the ongoing shoulder study (alvimopan 0.5mg or 3mg co-administered with hydrocodone/APAP).	The safety update will focus on CV events. The same CV table prepared for POI will also be generated for OBD based on all available OBD data and 12-month data from study 014. Only minimum OBD data (188 subjects from studies 13C207 and 13C304) were included in the original NDA; No new AE tables will be generated for the pooled OBD, however, AE dataset containing all OBD studies will be submitted to the Division. SAE tabulations will focus on the newly completed 7 clinical studies.
3. Present a re-tabulation of the reason for premature study discontinuation by incorporating the drop-outs from newly completed studies. Describe any new trends of patterns identified.	None	No new data have been generated for the proposed indication of POI since May 9, 2006.
4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.	CRFs and narratives will be provided for all deaths and discontinuations due to AEs and SAEs from the 7 newly completed studies.	

Safety Update Requirement in the Letter	Adolor's Proposal	Rationale
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new and the original NDA data.	None	No new data have been generated for the proposed indication of POI since May 9, 2006.
6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.	None	Alvimopan is not marketed elsewhere.
7. Provide English translations of current approved foreign labeling not previously submitted.	None	Alvimopan is not marketed elsewhere.

Response:

The proposed definition of cardiovascular events and content of the safety update are acceptable.

3. Question on PK data.

The Division requested "The individual PK parameters for the BE study should be submitted as an electronic file in a readily analyzable format".

Please let us know if the Division prefers to receive the individual plasma concentration data used to estimate the PK parameters for each subject as a workbook of WinNonlin.

Response:

The individual pharmacokinetic parameters for the bioequivalence study should be submitted as an electronic file in a readily analyzable format.

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/s/

Brian Strongin
3/9/2007 12:40:57 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-775

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

Dear Ms. Harver:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Entereg (alvimopan) Capsules.

We also refer to the meeting between representatives of your firm and the FDA on December 7, 2006. The purpose of the meeting was to discuss your proposed response to the November 3, 2006 approvable letter for NDA 21-775.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-1008.

Sincerely,

{See appended electronic signature page}

Brian Strongin, R.Ph.,M.B.A.
Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

MEETING DATE: December 7, 2006
TIME: 11:00AM
LOCATION: White Oak Building #22, Conference Room 1309
APPLICATION: NDA 21-775
DRUG NAME: Entereg (alvimopan) Capsules
TYPE OF MEETING: Type C: Post-Action Meeting

MEETING CHAIR: Ruyi He, M.D.

MEETING RECORDER: Brian Strongin, R.Ph., M.B.A.

FDA ATTENDEES: (Title and Office/Division)

Attendee	Title	Office/Division
Julie Beitz, M.D.	Director	Office of Drug Evaluation III
Brian E. Harvey, M.D., Ph.D.	Director	Division of Gastroenterology Products
Joyce Korvick, M.D., M.S.	Deputy Director	Division of Gastroenterology Products
Ruyi He, M.D.	Medical Team Leader	Division of Gastroenterology Products
Marjorie Dannis, M.D.	Medical Officer	Division of Gastroenterology Products
Sonia Castillo, Ph.D.	Biometrics Reviewer	Division of Gastroenterology Products
Marie Kowblansky, Ph.D.	Chemistry Team Leader	Office of New Drug Quality Assurance
Zhengfang Ge, Ph.D.	Review Chemist	Office of New Drug Quality Assurance
Jasti Choudary, Ph.D., B.V.Sc.	Supervisory Pharmacologist	Division of Gastroenterology Products
Brian Strongin, R.Ph., M.B.A.	Chief, Project Management Staff	Division of Gastroenterology Products

EXTERNAL CONSTITUENT ATTENDEES:

Adolor Corporation

Attendee	Title
James E. Barrett, Ph.D.	Sr. Vice President, R & D, Chief Scientific Officer and President, Research
Wei Du, Ph.D.	Vice President, Biometrics
Linda Y. Harver, R.Ph., J.D.	Vice President, Regulatory Affairs
David Jackson, M.D.	Chief Medical Officer
Randall Mack	Vice President, Project Management
Lee Techner, DPM	Sr. Director, Clinical Research and Development

Adolor Consultants

Attendee	Title
[redacted]	

GlaxoSmithKline

Attendee	Title
Eric Carter, Ph.D., M.D.	Vice President, Clinical Development and Medical Affairs, GI Therapeutic Area Head
Eric Mortenson, Ph.D., M.D.	Group Director, Musculoskeletal, Inflammation, Gastrointestinal and Urology
Elizabeth (Betty) Nies, M.S.	Sr. Director, Regulatory Affairs

BACKGROUND:

NDA 21-775 for Entereg (alvimopan) Capsules was submitted June 25, 2004 for the proposed indication to accelerate time to recovery of gastrointestinal function following abdominal or pelvic surgery. An approvable action was taken July 21, 2005. The letter requested an additional efficacy study and a safety update. Adolor submitted a complete response to the approvable letter on May 9, 2006. A second approvable action was taken November 3, 2006. The approvable letter requested 12-month safety findings from Study SB767905/014, a risk management plan, and a safety update.

MEETING OBJECTIVES:

The desired outcome of this meeting is that agreement be reached between Adolor and the Division on the content, format, and timing of review for the proposed complete response to the action letter.

DISCUSSION POINTS:

Question 1:
In our teleconference on November 3, the Division indicated that it would provide more detailed information regarding the Agency's review of the current cardiovascular safety data from clinical trials of alvimopan at this post-action meeting. Can the Division provide that detail on the discussion and outcome of both the internal regulatory briefing and the consult

review performed by the Division of Cardiovascular and Renal Drug Products that led to the action outlined in the November 3, 2006 Approvable Letter? This information will help guide us if revisions are necessary in the draft product labeling and/or a risk management plan is required.

Response:
The long-term opoid-induced bowel dysfunction data indicate a numerical increase for alvimopan treated patients compared to placebo in cardiovascular (CV) serious adverse events. With respect to the myocardial infarction (MI) reports, when Study SB-767905/014 interim data are taken into consideration, there is a numerical increase for alvimopan treated patients compared to placebo in the MI incidence rates expressed per 100 patient years. The apparent imbalance in reported MIs is driven by reports from Study SB-767905/014 which is currently ongoing.

Summary of Discussion – Question #1

See the Summary of Discussion – Question #2

Question 2:
a) Can the Division share its current perspective regarding the potential impact of the discussion and outcome above on proposed short-term use of alvimopan in postoperative ileus (POI) and [redacted]

Response:
The potential impact on proposed short-term use of alvimopan in postoperative ileus (POI) and [redacted] depend on the final results of Study SB-767905/014 which is currently ongoing. At the time of your complete response, your submission should include the finalized, quality assessed/quality controlled databases which provide the basis for your report.

b) At this time, does the Division agree with the Sponsor's assessment that there are no safety concerns regarding alvimopan use in the bowel resection population? If not, please provide specific safety concerns the Division has at this time.

Response:
The long-term data indicates a numerical increase for alvimopan treated patients compared to placebo in CV serious adverse events that may be potential safety concerns regarding alvimopan use in the short-term bowel resection population. Our final determination of safety and efficacy will be based upon the entirety of the data generated by the use of your drug as submitted in your NDA and supplements.

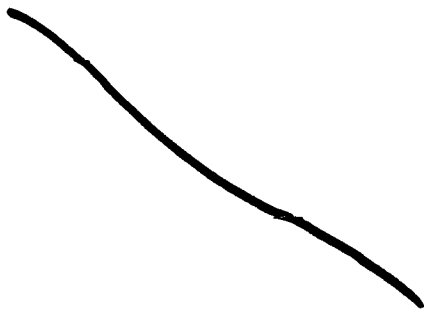
Summary of Discussion - Questions #1 and #2

The FDA stated that they were concerned with all severe CV events and that EKG, troponin, and CV symptoms should be assessed. More complete data are better.

In response to the sponsor's question, the FDA replied that the next steps after receiving Study SB-767905/014 final data are dependent on the nature of the data.

In response to the FDA's question, the sponsor stated that the final report for Study SB-767905/014 will probably be completed by June or July 2007. If the complete response to the approvable letter is submitted before the study report has been completed, the FDA advised the sponsor to verify that there will be no changes in the CV data when the report is submitted.

Question 3:
If the 12-month safety data from study SB-767905/014 does not change the current safety profile, i.e., there are no new cardiovascular serious adverse events reported in either the alvimopan or placebo treatment arms of that study, the following approach to a risk management plan is proposed for POI:



Under the circumstances described above, would these measures be sufficient to address the Division's concerns? If not, what additional measures would the Division recommend?

Response:

Summary of Discussion – Question #3

The FDA advised that Contraindications must be based on data and that Warnings may be more appropriate in some situations.

Question 4:
If the 12-month safety data from study SB-767905/014 does not change the current safety profile, i.e., there are no new cardiovascular serious adverse events reported in either the alvimopan or placebo treatment arms of that study, would revisions to the currently proposed POI label need to include information communicating this information (i.e. cardiovascular events in Study SB-767905/014)? If so, can the Division provide guidance on the nature and extent of such changes in the label that would be satisfactory?

Response:
All pertinent data regarding the use of your drug may need to be included in your label to help fully inform prescribers of the potential risks and benefits. However, we need to discuss your proposed POI label in more detail after reviewing Study SB-767905/014 (12 months data).

Summary of Discussion – Question #4

No discussion for this question

Question 5:
If the 12-month safety data from study SB-767905/014 does not change the current safety profile, i.e., there are no new cardiovascular serious adverse events reported in either the alvimopan or placebo treatment arms of that study, and the responses to questions 3 and 4 above are adequately addressed, does the Division foresee any remaining issues that would preclude the approval of alvimopan for POI?

Response:
We do not foresee any remaining issues at this time other than those outlined in our approvable letter dated November 3, 2006. It is premature to discuss the approval of alvimopan before reviewing your Study SB-767905/014 (12 months data). However, please see the Additional Clinical Pharmacology Comments below, since your inability to address these issues adequately could preclude the approval of the 12mg capsule.

Summary of Discussion – Question #5

No discussion for this question

Question 6:
From the cut-off date of December 23, 2005 for the alvimopan NDA Complete Response to February 28, 2007 (the proposed cut-off date for this NDA amendment), there will be no studies under the POI indication that have initiated nor will there be any POI studies that have completed. Tables 1 and 2 identify 8 studies under other indications (non-cancer OBD population: 3 studies; cancer OBD population: 1 study; healthy volunteers: 3 studies; surgical population [co-administration of alvimopan

and hydrocodone/APAP]: 1 study) that either have completed or will be ongoing during this period. With respect to the Safety Update as requested in the November 3, 2006 Approvable Letter, Adolor proposes that the safety update at the time of this NDA amendment will include:
1. Updated analyses of cardiovascular events in the OBD population as outlined in the September 6, 2006 Information Request from the Division (see mock tables in Tables 3, 4, and 5).
2. Separate tables with all SAEs from the 7 recently completed studies for each treatment group for each population (non-cancer OBD population, cancer OBD population, and healthy volunteers). The events will be displayed by system organ class and MedDRA preferred terms.
3. Tables with blinded SAEs for the ongoing study 28CL228. The events will be displayed by system organ class and MedDRA preferred terms.
4. Integrated AE dataset (ie, SAS dataset) for the completed OBD studies.
Does the Division agree with this proposal? If not, please provide details as to what data would be required to adequately address the Division's request for a safety update.

Response:
You should include analyses of cardiovascular events in both the POI and the OBD population, and short-term (<14 days) and long-term (>14 days) population. Also, you should provide analyses of cardiovascular events for Study SB-767905/014. In addition to the SAS datasets, please provide SAS programs used to populate the safety data tables.

Summary of Discussion – Question #6

The sponsor asked if their proposal for the content and format for the safety update (Attachment #1) is acceptable. The FDA stated that the proposal is acceptable.

Question 7:
We realize that discussion of labeling is generally a review issue and will be driven by the data. However, excluding the safety-related sections of the product labeling, could the Division provide some perspective/direction at this time regarding their current thoughts on other areas of the draft labeling for which the data are already available, such as Clinical Studies, Indications & Usage, and Dosage & Administration, so that we may begin the process of making appropriate revisions to those sections?

Response:
You should change your proposed label to the new physician's labeling rule format. Please see the "New Requirements for Prescribing Information" section of the CDER website at www.fda.gov/cder. We need to discuss your labeling in more detail after reviewing your Study SB-767905/014 (12 months data).

Summary of Discussion – Question #7

No discussion for this question

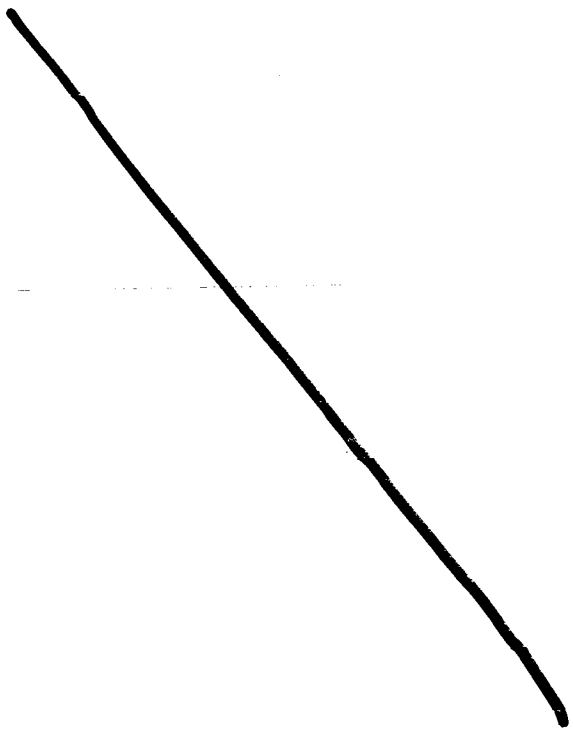
Question 8:
The proposed response to the November 3, 2006 Action Letter will include, as requested, a safety update including the datasets and narratives from the completed safety study, SB-767906/014, a risk management plan, and draft labeling. Therefore, we believe this information could be considered a Class 1 resubmission. Can the Division provide its current perspective on how the resubmission will be classified and a potential timeline for review/action?

Response:
The resubmission will include new clinical data which will likely be classified as Class 2 resubmission and will have a 6 month review period.

Summary of Discussion for Question #8

The FDA added that a complete response to the approvable letter would include more clinical data than is usually found in a Class 1 resubmission. They added that the assessment of risk and the development of a risk management plan is driving the need for more data.

Question 9:



Summary of Discussion – Question #9

No discussion for this question

Question 10:
Adolor proposes to amend the stability protocol for the NDA registration batches of Entereg 12 mg Capsules [redacted] between the 24-and [redacted] time points. Does the Agency agree that the expiration date may be extended to [redacted] as soon as satisfactory stability data are obtained on the commercial scale registration batches? And, could the proposed stability protocol amendment be submitted in the amendment noted in the paragraph above within the same review cycle as Complete Responses to the Action Letter?

Response:
It will be acceptable to submit a revised stability protocol with your resubmission. Also, the expiration date may be extended to [redacted] as soon as acceptable stability data are obtained, but you will need to submit documentation supporting this extension in expiration period in the next annual report .

Summary of Discussion – Question #10

No discussion for this question

Additional Clinical Pharmacology Comments:

The 12-mg capsule formulation was not [redacted] submission and the BE study to establish the bioequivalence of one 12-mg capsule to two 6-mg capsules was not submitted to the NDA until late in this review cycle (9/15/06). A full evaluation of this BE study could not be conducted in this review cycle because of time constraint. A cursory review of the BE study revealed that the report lacks the following information:

A. Subjects were required to take 240 mL of water 30 minutes before dosing and another 240 mL of water at the time of dosing. This is a deviation from the conventional design for BE studies, in which 240 mL of water was required only at the time of dosing. You should explain the purpose and impact of this additional 240 mL water intake 30 minutes before dosing.

B. The individual PK parameters for the BE study should be submitted as an electronic file in a readily analyzable format.

You may pursue the approval of the 12-mg strength [redacted]

Summary of Discussion – Clinical Pharmacology Comments

The sponsor asked if the Division prefers to receive the individual plasma concentration data used to estimate the PK parameters for each subject as a workbook of WinNonlin. The FDA responded that the sponsor's proposal is acceptable and that PK parameters for each subject should be properly organized (e.g., sequence, period, treatment, etc.) in WinNonlin and/or SAS transport format.

The sponsor stated that they planned to submit the PK data before the complete response is ready.

DECISIONS (AGREEMENTS) REACHED:

None

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

None

ACTION ITEMS:

None

ATTACHMENTS/HANDOUTS:

Attachment #1: Content and Format of Safety Update

Attachment #1
Proposed Format and Content for Safety Update

1. Definition of CV events

Based on our discussion with the Division at the December 7th meeting, CV events will be defined by those conditions specified by FDA in their table contained in the Information Request dated October 3rd 2006 (attached): Summary CV events in POI Population. This same table will be prepared for the OBD population based on the pooled OBD studies in the non-cancer subjects and for GSK Study SB-767905/014 alone. The format and the contents of this CV event table are illustrated below in Tables 1-3:

Table 1
Summary of CV Events in POI Population
Studies: 13C206, 13C213, 13C214, 14CL302, 14CL306, 14CL308, 14CL313, 14CL314, and SB-767905/001

	Alvimopan Group[1] (N=2610)		Placebo Group (N=1365)		Relative Risk (Alvimopan vs Placebo)
CV Event Category	n (%)	Subject ID	n (%)	Subject ID	(95% CI)
All Cause Death	x (x.xx)		x (x.xx)		x.xx (x.xx, x.xx)
Death from CV events	x (x.xx)		x (x.xx)		x.xx (x.xx, x.xx)
MI: Overall	x (x.xx)		x (x.xx)		x.xx (x.xx, x.xx)
Fatal	x (x.xx)		x (x.xx)		
Non-Fatal	x (x.xx)		x (x.xx)		
Unstable Angina	x (x.xx)		x (x.xx)		x.xx (x.xx, x.xx)
Non-fatal CVA	x (x.xx)		x (x.xx)		x.xx (x.xx, x.xx)
CHF: Overall	x (x.xx)		x (x.xx)		x.xx (x.xx, x.xx)
Fatal	x (x.xx)		x (x.xx)		
Non-Fatal	x (x.xx)		x (x.xx)		
Serious Arrhythmia	x (x.xx)		x (x.xx)		x.xx (x.xx, x.xx)
Fatal	x (x.xx)		x (x.xx)		
Non-Fatal	x (x.xx)		x (x.xx)		

[1] Alvimopan group included the following alvimopan doses: 1mg (N=27), 3mg (N=35), 6mg (N=898) and 12mg (N=1650). All doses were administered as BID regimen for up to 7 postoperative days plus a pre-op dose on the day of surgery.

Table 2
Summary of CV Events in OBD Population
Studies: SB-767905/011, SB-767905/012, SB-767905/013, SB-767905/014, 13C217, and 13C304

	Alvimopan Group[1] (N=1728)		Placebo Group (N=790)		Relative Risk (Alvimopan vs Placebo)
CV Event Category	n (%)	Subject ID	n (%)	Subject ID	(95% CI)
All Cause Death	x (x.xx)		x (x.xx)		x.xx (x.xx, x.xx)
Death from CV events	x (x.xx)		x (x.xx)		x.xx (x.xx, x.xx)
MI: Overall	x (x.xx)		x (x.xx)		x.xx (x.xx, x.xx)
Fatal	x (x.xx)		x (x.xx)		
Non-Fatal	x (x.xx)		x (x.xx)		
Unstable Angina	x (x.xx)		x (x.xx)		x.xx (x.xx, x.xx)
Non-fatal CVA	x (x.xx)		x (x.xx)		x.xx (x.xx, x.xx)
CHF: Overall	x (x.xx)		x (x.xx)		x.xx (x.xx, x.xx)
Fatal	x (x.xx)		x (x.xx)		
Non-Fatal	x (x.xx)		x (x.xx)		
Serious Arrhythmia	x (x.xx)		x (x.xx)		x.xx (x.xx, x.xx)
Fatal	x (x.xx)		x (x.xx)		
Non-Fatal	x (x.xx)		x (x.xx)		

[1]Alvimopan group included the following alvimopan dose and regimen: 0.5mg QD (N=401), 1mg QD (N=197), 0.5mgBID (N=1000), and 1mg BID (N=130).

Table 3
Summary of CV Events in Study SB-767905/014

CV Event Category	Alvimopan 0.5mg BID (N=538) n (%)	Subject ID	Placebo Group (N=267) n (%)	Subject ID	Relative Risk (Alvimopan vs Placebo) (95% CI)
All Cause Death	x (x.xx)		x (x.xx)		x.xx (x.xx, x.xx)
Death from CV events	x (x.xx)		x (x.xx)		x.xx (x.xx, x.xx)
MI: Overall	x (x.xx)		x (x.xx)		x.xx (x.xx, x.xx)
Fatal	x (x.xx)		x (x.xx)		
Non-Fatal	x (x.xx)		x (x.xx)		
Unstable Angina	x (x.xx)		x (x.xx)		x.xx (x.xx, x.xx)
Non-fatal CVA	x (x.xx)		x (x.xx)		x.xx (x.xx, x.xx)
CHF: Overall	x (x.xx)		x (x.xx)		x.xx (x.xx, x.xx)
Fatal	x (x.xx)		x (x.xx)		
Non-Fatal	x (x.xx)		x (x.xx)		
Serious Arrhythmia	x (x.xx)		x (x.xx)		x.xx (x.xx, x.xx)
Fatal	x (x.xx)		x (x.xx)		
Non-Fatal	x (x.xx)		x (x.xx)		

2. Content of Safety Update

Safety Update Requirement in the Letter	Adolor's Proposal	Rationale
1. Describe in detail any significant changes or findings in the safety profile	None	No new data have been generated for the proposed indication of POI since May 9, 2006.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows		
▪ Present new safety data from the studies for the proposed indication using the same format as the original NDA submission ▪ Present tabulation of the new safety data combined with the original NDA data ▪ Include tables that compare frequencies of adverse events in the original NDA with the re-tabulated frequencies described in the bullets above.	1. The CV table presented to FDA on October 4, 2006 will be re-submitted without any new data, since no new studies have been conducted since May 9, 2006 for this indication. See Table 1 for mock. 2. The pooled AE dataset from all POI studies and the SAS program used to generate the CV table for the POI population will be submitted.	The potential for CV risk is the primary concern at this time for the POI indication, therefore the safety update will present CV AEs only.

Safety Update Requirement in the Letter	Adolor's Proposal	Rationale
▪ For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials	1. The CV table will reflect pooled data from all OBD studies and for study 014 in non-cancer patients in the same format as the October 4, 2006 submission. See Tables 2 and 3 for mock format and contents. 2. Fatal SAEs and non-fatal SAEs will be tabulated from the recently completed 7 studies in other indication as follows: ▪ 3 OBD studies in non-cancer population. ▪ 1 OBD study in cancer patients ▪ 2 studies in healthy volunteers ▪ 1 study from acute combo program in healthy volunteers. 3. The AE dataset pooled AEs in the original NDA and the new AEs from the recently completed OBD studies will be provided as well as the SAS program used to generate the CV table for the OBD population. 4. A blinded SAE table will be generated for ongoing Study 17CL228 (alvimopan 0.5mg or 3mg co-administered with hydrocodone/APAP).	The safety update will focus on CV events. The same CV table prepared for POI will also be generated for OBD based on all available OBD data and 12-month data from study 014. Only minimum OBD data (188 subjects from studies 13C207 and 13C304) were included in the original NDA; No new AE tables will be generated for the pooled OBD, however, AE dataset containing all OBD studies will be submitted to the Division. SAE tabulations will focus on the newly completed 7 clinical studies.
3. Present a re-tabulation of the reason for premature study discontinuation by incorporating the drop-outs from newly completed studies. Describe any new trends of patterns identified.	None	No new data have been generated for the proposed indication of POI since May 9, 2006.
4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.	CRFs and narratives will be provided for all deaths and discontinuations due to AEs and SAEs from the 7 newly completed studies.	
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new and the original NDA data.	None	No new data have been generated for the proposed indication of POI since May 9, 2006.

Safety Update Requirement in the Letter	Adolor's Proposal	Rationale
6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.	None	Alvimopan is not marketed elsewhere.
7. Provide English translations of current approved foreign labeling not previously submitted.	None	Alvimopan is not marketed elsewhere.

Please confirm that the Division agrees with the above definition of CV events and the proposal for the content of the safety update. If not, please advise as to what revisions should be made.

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

/s/

Brian Strongin
12/21/2006 02:35:35 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-775

Adolor Corporation
Attention: Linda Y. Harver, R.Ph., J.D.
Vice-President Regulatory Affairs
700 Pennsylvania Drive
Exton, PA 19341

Dear Ms. Harver:

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

We also refer to your November 9, 2006, correspondence, received November 13, 2006, requesting a meeting to discuss the November 3, 2006 action letter.

Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type-C meeting as described in our guidance for industry titled *Formal Meetings with Sponsors and Applicants for PDUFA Products* (February 2000). The meeting is scheduled for:

Date: December 7, 2006
Time: 11:00-12:00 PM
Location: White Oak CDER Building #22
Conference Room 1309
10903 New Hampshire Avenue
Silver Spring, MD 20993

Tentative CDER participants:

Julie Beitz, M.D., Office Director
Brian E. Harvey, M.D., Ph.D., Director
Joyce Korvick, M.D., M.P.H., Deputy Director
Ruyi He, M.D., Team Leader
Marjorie Dannis, M.D., Medical Officer
Stella Grosser, Ph.D., Biometrics Team Leader
Sonia Castillo, Ph.D., Biometrics reviewer
Suliman Al-Fayoumi, Ph.D., Biopharmaceuticals Review
Marie Kowblansky, Ph.D., Chemistry Team Leader
Zhengfang Ge, Ph.D., Chemistry Reviewer
Jasti Choudary, Ph.D. B.V.Sc., Supervisory Pharmacologist

Tamal Chakraborti, Ph.D., Pharmacology Reviewer
Brian Strongin, R.Ph., M.B.A., Chief, Project Management Staff

Please have all attendees bring photo identification and allow 15-30 minutes to complete security clearance. If there are additional attendees, email that information to me at susan.daugherty@fda.hhs.gov so that I can give the security staff time to prepare temporary badges in advance.

Provide the background information for this meeting (three copies to the IND and 15 desk copies to me) at least one month prior to the meeting.

If you have any questions, call me at (301) 796-0878.

Sincerely,

{See appended electronic signature page}

Susan Daugherty
Regulatory Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation IIII
Center for Drug Evaluation and Research

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

/s/

Susan B. Daugherty
11/17/2006 03:47:28 PM

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-775 Supplement # N/A Efficacy Supplement Type SE- N/A

Trade Name: Entereg
Established Name: Alvimopan Capsules
Strengths:

Applicant: Adolor Corporation
Agent for Applicant: N/A

Date of Application: May 9, 2006
Date of Receipt: May 9, 2006
Date clock started after UN:
Date of Filing Meeting: June 19, 2006
Filing Date: July 9, 2006
Action Goal Date (optional): November 3, 2006 User Fee Goal Date: November 9, 2006

Indication(s) requested: Entereg is indicated to accelerate time recovery of gastrointestinal function following abdominal pelvic surgery.

Type of Original NDA: (b)(1) ☒ (b)(2) ☐
OR
Type of Supplement: (b)(1) ☐ (b)(2) ☐

NOTE:

(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2), complete Appendix B.

(2) If the application is a supplement to an NDA, please indicate whether the NDA is a (b)(1) or a (b)(2) application:

☒ NDA is a (b)(1) application OR ☐ NDA is a (b)(2) application

Therapeutic Classification: S ☒ P ☐
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐
Chemical Classification: (1,2,3 etc.) 1
Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES ☒ NO ☐

User Fee Status: Paid ☐ Exempt (orphan, government) ☐
Waived (e.g., small business, public health) ☒

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the*

product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the user fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application? YES ☐ NO ☒
  If yes, explain:

- Does another drug have orphan drug exclusivity for the same indication? YES ☐ NO ☒

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES ☐ NO ☐

  If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES ☐ NO ☒
  If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES ☐ NO ☐

- Does the submission contain an accurate comprehensive index? YES ☒ NO ☐

- Was form 356h included with an authorized signature? YES ☒ NO ☐
  If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES ☒ NO ☐
  If no, explain:

- If an electronic NDA, does it follow the Guidance? N/A ☐ YES ☒ NO ☐
  If an electronic NDA, all forms and certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format? All sections of the NDA were submitted electronically. The administrative volume including forms and certifications was also submitted in paper

  Additional comments: This is a 2nd cycle submission.

- If an electronic NDA in Common Technical Document format, does it follow the CTD guidance? N/A ☒ YES ☐ NO ☐

- Is it an electronic CTD (eCTD)? N/A ☐ YES ☐ NO ☒
  If an electronic CTD, all forms and certifications must either be in paper and signed or be electronically signed.

  Additional comments:

- Patent information submitted on form FDA 3542a? YES ☐ NO ☒

- Exclusivity requested? YES, _____ Years NO ☒
  ***NOTE:** An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*

- Correctly worded Debarment Certification included with authorized signature? YES ☐ NO ☒
  If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

  NOTE: *Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."*

- Financial Disclosure forms included with authorized signature? YES ☒ NO ☐
  (Forms 3454 and 3455 must be included and must be signed by the APPLICANT, not an agent.)
  NOTE: *Financial disclosure is required for bioequivalence studies that are the basis for approval.*

- Field Copy Certification (that it is a true copy of the CMC technical section)? Y ☐ NO ☐

- PDUFA and Action Goal dates correct in COMIS? YES ☒ NO ☐
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

- List referenced IND numbers: [redacted] 56,553

- End-of-Phase 2 Meeting(s)? Date(s) March 12 and 13, 2001 NO ☐
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) March 24 and 25, 2004 NO ☐
  If yes, distribute minutes before filing meeting.

Project Management

- Was electronic "Content of Labeling" submitted? YES ☒ NO ☐
  If no, request in 74-day letter.

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?
  YES ☒ NO ☐

- Risk Management Plan consulted to ODS/IO? N/A ☒ YES ☐ NO ☐

- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? Y ☒ NO ☐

- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A ☒ YES ☐ NO ☐

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?
  N/A ☒ YES ☐ NO ☐

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A ☒ YES ☐ NO ☐

- Has DOTCDP been notified of the OTC switch application? YES ☐ NO ☐

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? YES ☐ NO ☐

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES ☒ NO ☐
  If no, did applicant submit a complete environmental assessment? YES ☐ NO ☐
  If EA submitted, consulted to Florian Zielinski (HFD-357)? YES ☐ NO ☐
- Establishment Evaluation Request (EER) submitted to DMPQ? YES ☒ NO ☐
- If a parenteral product, consulted to Microbiology Team (HFD-805)? YES ☐ NO ☐

ATTACHMENT

MEMO OF FILING MEETING

DATE: June 19, 2006

BACKGROUND: Entereg is indicated for the management of Post Operative Ileus (POI). This is 2nd cycle for this application. The sponsor received an Approvable Action on July 21, 2005 for first cycle. This application was accepted under the "Continuous Marketing Applications: Pilot I-Reviewable Units for Fast Track Products under PDUFA." This NDA was submitted electronically. The administrative volume is also submitted by paper. This NDA qualifies for a standard review.
(Provide a brief background of the drug, e.g., it is already approved and this NDA is for an extended-release formulation; whether another Division is involved; foreign marketing history; etc.)

ATTENDEES:
Brian E. Harvey, M.D., Ph.D.
Ruyi He, M.D.
Eric Brodsky, M.D.
Sonia Castillo, Ph.D.
Stella Grosser, Ph.D.
Zhengfang Ge, Ph.D.
Marie Kowblansky, Ph.D.
Tamal Chakraborti, Ph.D.
Melissa Furness, BS

ASSIGNED REVIEWERS (including those not present at filing meeting) :

Discipline	**Reviewer**
Medical:	Eric Brodsky, M.D.
Secondary Medical:	N/A
Statistical:	Stella Grosser, Ph.D.
Pharmacology:	Tamal Chakraborti, Ph.D.
Statistical Pharmacology:	N/A
Chemistry:	Zhengfang Ge, Ph.D.
Environmental Assessment (if needed):	N/A
Biopharmaceutical:	Sue Chih Lee, Ph.D.
Microbiology, sterility:	N/A
Microbiology, clinical (for antimicrobial products only):	
DSI:	
Regulatory Project Management:	Tanya Clayton
Other Consults:	Cardio-Renal, Karen Hicks; OSE, Richard Abate; DMETS; DDMAC

Per reviewers, are all parts in English or English translation? YES ☒ NO ☐
If no, explain:

CLINICAL FILE ☒ REFUSE TO FILE ☐

- Clinical site inspection needed? YES ☐ NO ☒

- Advisory Committee Meeting needed? YES, date if known _____ NO ☒

- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?
  N/A ☐ YES ☐ NO ☐

CLINICAL MICROBIOLOGY	N/A ☒	FILE ☐	REFUSE TO FILE ☐
STATISTICS	N/A ☐	FILE ☒	REFUSE TO FILE ☐
BIOPHARMACEUTICS		FILE ☒	REFUSE TO FILE ☐
• Biopharm. inspection needed?			YES ☐ NO ☒
PHARMACOLOGY	N/A ☐	FILE ☒	REFUSE TO FILE ☐
• GLP inspection needed?			YES ☐ NO ☒
CHEMISTRY		FILE ☒	REFUSE TO FILE ☐
• Establishment(s) ready for inspection?			YES ☒ NO ☐
• Microbiology			YES ☐ NO ☒

ELECTRONIC SUBMISSION:
Any comments: This is 2nd cycle submission. All of the inspections were completed during the 1st cycle.

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

☐ The application is unsuitable for filing. Explain why:

☒ The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.

- ☐ No filing issues have been identified.
- ☐ Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1.☐ If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.

2.☐ If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

3.☒ Convey document filing issues/no filing issues to applicant by Day 74.

Regulatory Project Manager, HFD-180

Appendix A to NDA Regulatory Filing Review

An application is likely to be a 505(b)(2) application if:

(1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
(2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
(4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications

1. Does the application reference a listed drug (approved drug)? YES ☐ NO ☐

   If "No," skip to question 3.

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):

3. The purpose of this and the questions below (questions 3 to 5) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval and that should be referenced as a listed drug in the pending application.

   (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved? YES ☐ NO ☐

   (***Pharmaceutical equivalents*** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

   If "No," skip to question 4. Otherwise, answer part (b).

   (b) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES ☐ NO ☐
   (The approved pharmaceutical equivalent(s) should be cited as the listed drug(s).)

   *If "**Yes**," skip to question 6. Otherwise, answer part (c).*

   (c) Have you conferred with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007)? YES ☐ NO ☐

   *If "**No**," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.*

4. (a) Is there a pharmaceutical alternative(s) already approved? YES ☐ NO ☐

   (***Pharmaceutical alternatives*** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

   If "No," skip to question 5. Otherwise, answer part (b).

   (b) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES ☐ NO ☐
   (The approved pharmaceutical alternative(s) should be cited as the listed drug(s).)

   NOTE: *If there is more than one pharmaceutical alternative approved, consult the Director, Division of*

Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007) to determine if the appropriate pharmaceutical alternatives are referenced.

*If "**Yes**," skip to question 6. Otherwise, answer part (c).*

(c) Have you conferred with the Director, Division of Regulatory Policy II, ORP? YES ☐ NO ☐

If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.

5. (a) Is there an approved drug product that does not meet the definition of "pharmaceutical equivalent" or "pharmaceutical alternative," as provided in questions 3(a) and 4(a), above, but that is otherwise very similar to the proposed product?

YES ☐ NO ☐

If "No," skip to question 6.

*If "**Yes**," please describe how the approved drug product is similar to the proposed one and answer part (b) of this question. Please also contact the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007), to further discuss.*

(b) Is the approved drug product cited as the listed drug? YES ☐ NO ☐

6. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

7. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). YES ☐ NO ☐

8. Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 21 CFR 314.101(d)(9)). YES ☐ NO ☐

9. Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). YES ☐ NO ☐

10. Are there certifications for each of the patents listed for the listed drug(s)? YES ☐ NO ☐

11. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):

NOTE: *IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must* ***subsequently*** *submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)].*

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):

☐ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):

12. Did the applicant:

- Identify which parts of the application rely on information (e.g. literature, prior approval of another sponsor's application) that the applicant does not own or to which the applicant does not have a right of reference?

  YES ☐ NO ☐

- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

  YES ☐ NO ☐

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

  N/A ☐ YES ☐ NO ☐

- Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?

  N/A ☐ YES ☐ NO ☐

13. If the (b)(2) applicant is requesting 3-year exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

    - Certification that at least one of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

      YES ☐ NO ☐

    - A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

      YES ☐ NO ☐

    - EITHER

      The number of the applicant's IND under which the studies essential to approval were conducted.

      IND# _____ NO ☐

      OR

      A certification that the NDA sponsor provided substantial support for the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

      YES ☐ NO ☐

14. Has the Associate Director for Regulatory Affairs, OND, been notified of the existence of the (b)(2) application?

    YES ☐ NO ☐

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/s/

Tanya Clayton
10/30/2006 06:19:33 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-775

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

Dear Ms. Harver:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Entereg™ (alvimopan) Capsules.

We also refer to the meeting between representatives of your firm and the FDA on September 18, 2006. The purpose of the 90 day meeting was to discuss the review status of your complete response submitted May 9, 2006, regarding your July 22, 2005 Approvable letter.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-0871.

Sincerely,

{See appended electronic signature page}

Tanya Clayton, B.S.
Regulatory Health Project Manager
Division of Gastroenterology Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

Meeting Date: September 18, 2006

Time: 11:00-12:00 PM

Location: White Oak Building #22, Conference Room 1421

Application: NDA 21-775; Entereg

Type of Meeting: Type C

Meeting Chair: Ruyi He, M.D.

Meeting Recorder: Tanya Clayton, B.S.

FDA Attendees, Titles, and Office/Division:

Division of Gastroenterology Drug Products

Brian E. Harvey, M.D., Ph.D.	Division Director
Joyce Korvick, M.D., M.P.H.	Deputy Division Director
Ruyi He, M.D.	Medical Team Leader
Eric Brodsky, M.D.	Medical Reviewer
Dennis Bashaw, Pharm. D.	Clinical Pharmacology Team Leader
Sue Chih Lee, Ph.D.	Clinical Pharmacology Reviewer
Stella Grosser, Ph.D.	Biometrics Team Leader
Sonia Castillo, Ph.D.	Biometrics Reviewer
Marie Kowblansky, Ph.D.	Pharmaceutical Assessment Lead
Jasti Choudary, Ph.D., B.V.Sc.	Supervisory Pharmacologist
Tanya Clayton, B.S.	Regulatory Health Project Manager

Office of Drug Evaluation III

Julie Beitz, M.D.	Acting Director

Office of Surveillance and Epidemiology

Mary Dempsey, B.S.	Risk Management Program Officer

External Constituent Attendees and Titles:

Adolor Corporation:

Linda Y. Harver, R.Ph., JD	Vice President, Regulatory Affairs
James E. Barrett, Ph.D.	Sr. Vice President, Chief Scientific Officer and President, Research
Wei Du, Ph.D.	Vice President, Biometrics
David Jackson, M.D.	Sr. Vice President, Research and Development
Lee Techner, DPM	Senior Director, Clinical Research and Development

GlaxoSmith Kline:

Eric Carter, M.D., Ph.D.	Vice President, Clinical Development and Medical Affairs, GI Therapeutic Area Head
Elizabeth (Betty) Nies, MS	Sr. Director, Regulatory Affairs
Andrew Zalewski, M.D.	Group Director, Cardiovascular Clinical Development
David McSorley, M.P.H.	Senior Director, Statistics and Programming

Background:

On July 12, 2006 the firm requested a 90 day meeting for the purpose of discussing the review status of their complete response submitted May 9, 2006, regarding your July 22, 2005 Approvable letter.

A subsequent August 17, 2006 background package was submitted, which contained 8 questions for discussion.

Following introductions, the sponsor agreed to proceed directly to the questions for discussion.

Discussion Points: (bullet format):

Question 1: Adolor recognizes and appreciates that the NDA review is ongoing. However, would the Division be willing to share any issues that have been identified at this stage of the review and work with Adolor to determine a process and timelines to address these issues as soon as possible?

Response

We are concerned about the higher incidence of serious cardiovascular (CV) events [e.g., myocardial infarctions (MIs)] in the alvimopan treatment group, compared to the placebo treatment group, in the opioid-induced constipation (OIC) studies. Currently, we are evaluating if this is a CV signal associated with longer-term alvimopan use.

We need to address the following issues as part of our review of this application:

1) **If this is a CV signal associated with longer-term alvimopan use, does this CV risk extend to the short-term use of alvimopan [i.e., in bowel resection (BR) surgery patients]?**
2) **If there is a CV signal with alvimopan use, what is the benefit/risk of alvimopan use in BR surgery patients?**
3) **If the CV signal is only associated with long-term alvimopan use — not short-term use in BR surgery patients — will a RiskMAP (e.g., restriction to hospital use, restriction to general surgeons, restriction to 15 alvimopan capsules per BR surgery patient) improve the benefit/risk profile of alvimopan use in the BR surgery population (i.e., reducing the risk of off-label long-term use)?**
4) **If the CV signal is only associated with long-term alvimopan use — not short-term use in BR surgery patients — will a boxed warning AND/or WARNINGS regarding CV risk in long-term use improve the benefit/risk profile of alvimopan use in the BR surgery population?**

We await your proposed late September 2006 submission of updated responses to our August 1, 2006 information request [which will include the unblinded 6-month data from your one-year OIC safety study (Study 14)] and your responses to our September 13, 2006 (including the unblinded 6–month data from Study 14) and September 8, 2006 information requests.

Question 2: If no significant issues have been identified at this stage of the review, what is the Division's current perspective regarding feasibility of, or potential for, approval on or before the November 9th action date?

Response

See our answer to question 1.

Question 3: What is the status of the review of the CMC NDA Amendment #004, submitted January 31, 2006 to support improved methodology and the marketing of a 12 mg capsule. My we assume that if the NDA is approved, the 12 mg capsule [redacted]

Response

The 12mg capsule is under CMC review and will be part of the action for this review cycle.

Question 4: Is the Division able to identify and provide to us dates for teleconferences or meetings regarding the labeling to permit approval by the November 9th PDUFA date?

Response

We will schedule a teleconference with you to discuss any remaining issues (e.g., labeling, risk management plan, CV safety).

Question 5: Will the Division request conversion of the final labeling to SPL format?

Response

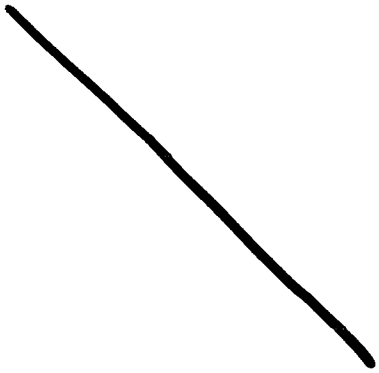
Yes.

Question 6: The Division has previously granted Adolor a deferral for the pediatric studies required under PREA until after Entereg is approved for use in POI in adults. Because bowel resection surgery and POI are not common in a pediatric population, Adolor proposes a full or partial waiver for this indication. Please refer to the attached document for background and rationale of the proposal. What is the Division's preferred approach and potential timeline to discuss PREA commitments for alvimopan?

Response

Until we fully assess the CV risk of alvimopan in adult patients, we are likely to grant a deferral of submission of all assessments of alvimopan in bowel resection (BR) surgery patients in all pediatric age groups (i.e., neonates, infants, children, and adolescents).

As you know, currently there are no products approved for the treatment of postoperative ileus (POI) in pediatric BR surgery patients. An intravenous alvimopan formulation would be an age "appropriate formulation" in the pediatric BR surgery population.

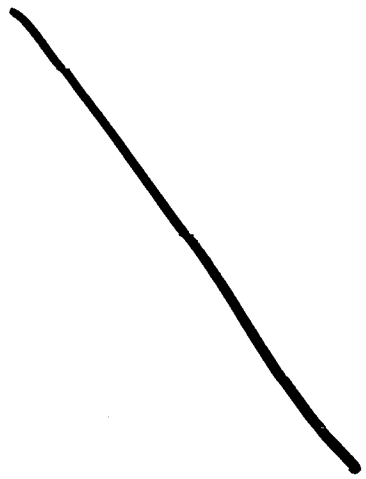


Question 8: Does the Division have any comments at this time that may not be specifically related to or solicited by the proposed questions or suggestions that need to be addressed for Entereg to be approved on or before the PDUFA date of November 9, 2006?

Response

Yes, we have the following questions:

1. **For each treatment group, what proportion of the BR surgery patients in the pooled eight U.S. POI studies (i.e., Studies 13C206, 13C213, 13C214, 14CL302, 14CL306, 14CL308, 14CL313, and 14CL314) had the following outcomes: discharged to home, discharged to a skilled nursing facility, remained in the hospital on POD 7, and remained in the hospital on POD 10?**
2. **What is your estimated timeframe for submitting responses to our September 13, 2006 and September 6, 2006 (with the 6-month safety data from Study 14) information requests?**
3. **Will you propose a RiskMAP for the BR surgery patients?**
4. **Provide the narratives on the following patients (study treatment received) in the POI studies: GSK001-34-00520 (alvimopan 6 mg), 14CL313-24-24002 (alvimopan 12 mg), 14CL302-53-01306 (alvimopan 6 mg), 14CL302-57-01233 (alvimopan 6 mg), 14CL313-04-04013 (placebo), 14CL313-04-04031 (alvimopan 6 mg), 14CL313-16-16008 (alvimopan 6 mg), and 14CL313-33-33015 (placebo).**



Additional Clinical Pharmacology Comments

Provide solubility data for Alvimopan in PEG [redacted] at 37° C.

Provide information to support the bioequivalence of one 12mg capsule to two 6mg capsules.

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/s/

Tanya Clayton
10/16/2006 12:54:37 PM

Ruyi He
10/16/2006 02:05:53 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-775

INFORMATION REQUEST LETTER

Adolor Corporation
Attention: Linda Y. Harver, R.Ph., J.D.
Vice President, Regulatory Affairs & Quality Assurance
700 Pennsylvania Drive
Exton, PA 19341-1127

Dear Ms. Harver:

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).

We also refer to your submission dated May 9, 2006.

We are reviewing the Clinical section of your submission and have the following information requests. .

1. What proportion of patients in the nine pooled post-operative ileus (POI) studies (i.e., Studies 206, 214, 213, 302, 306, 308, 313, GSK001, and 314) had a follow telephone call within 5 days, 7 days, 14 days, and 30 days of their last study dose?

2. What proportion of patients in the nine pooled POI studies had a follow-up safety visit within 5 days, 7 days, 14 days, and 30 days of their last study dose?

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

Sincerely,

{See appended electronic signature page}

Brian S. Strongin, R.Ph., M.B.A.
Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Susan B. Daugherty
9/13/2006 04:38:36 PM
Signing for Brian Strongin, CPMS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-775

INFORMATION REQUEST LETTER

Adolor Corporation
Attention: Linda Y. Harver, R.Ph., J.D.
Vice President, Regulatory Affairs & Quality Assurance
700 Pennsylvania Drive
Exton, PA 19341-1127

Dear Ms. Harver:

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).

We also refer to your submission dated May 9, 2006.

We are reviewing the Clinical section of your submission and have the following information requests for the postoperative ileus (POI) population (Studies 13C206, 13C213, 13C214, 13CL302, 13CL308, 13CL313, 13CL314, SB-767905/001, and 13CL306); the noncancer opioid-induced constipation (OIC) population* (Studies SB-767905/011, SB-767905/012, SB-767905/013, SB-767905/014, 13CL217, and 13C304); and the Study SB-767905/014 population:

1. Provide the percentage of patients in each treatment group in each population that had the following baseline cardiovascular risk factors (prior to study entry): diabetes, hypertension, current or recent smoking history, and obesity (BMI $\geq$ 30). Provide the mean age in each treatment group in each population.

2. Provide the change in mean systolic and diastolic blood pressure and change in mean heart rate (baseline to last reading during the treatment period) for each treatment group in each population.

3. Provide the incidences of each of the following events in each treatment group in each population: all cause death, cardiovascular death, nonfatal myocardial infarction (MI), congestive heart failure, stroke, unstable angina, and serious arrhythmia. Provide the relative risks (RRs) with 95% confidence intervals of these seven events in each population.

4. Provide the incidences in each treatment group in each population of the Antiplatelet Trialist Collaboration composite endpoint (non-fatal MI, nonfatal stroke, vascular death, and death from an unknown cause). Vascular death is defined as a cardiac, cerebrovascular, venous thromboembolic, hemorrhagic, or other vascular death. Provide the RRs with 95% confidence intervals for this composite endpoint in each population.

* We did not include the two single dose OIC studies (Studies 13C208 and 13C209) in the OIC population.

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

Sincerely,

{See appended electronic signature page}

Brian S. Strongin, R.Ph., M.B.A.
Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Susan B. Daugherty
9/6/2006 04:55:09 PM
Signing for Brian Strongin, CPMS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-775

INFORMATION REQUEST LETTER

Adolor Corporation
Attention: Linda Y. Harver, R.Ph., J.D.
Vice President, Regulatory Affairs & Quality Assurance
700 Pennsylvania Drive
Exton, PA 19341-1127

Dear Ms. Harver:

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).

We also refer to your submission dated May 9, 2006.

We are reviewing the Clinical section of your submission and have the following information requests.

1. Given the increased incidence of serious cardiovascular events associated with the alvimopan groups in the opioid-induced constipation trials, compared to the placebo groups, please propose new labeling for Entereg (alvimopan) for the post-operative ileus indication.

2. Please refer to our August 1, 2006 information request to GlaxoSmithKline. In this request, for all questions relating to serious cardiovascular events please include serious arrhythmias and serious cerebral vascular events (i.e., strokes).

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

Sincerely,

{See appended electronic signature page}

Brian S. Strongin, R.Ph., M.B.A.
Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Cristi Stark
8/23/2006 04:39:56 PM
signing for Brian Strongin, R.Ph., M.B.A.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-775

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

Dear Ms. Harver:

We acknowledge receipt on May 9, 2006 of your May 9, 2006 resubmission to your new drug application for Entereg® (Alvimopan) Capsules.

We consider this a complete, class 2 response to our June 21, 2005 action letter. Therefore, the user fee goal date is November 9, 2006.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We reference the deferral granted in the March 23, 2004 meeting minutes for the pediatric study requirement for this application.

If you have any question, call me at (301) 796-0871.

Sincerely,

{See appended electronic signature page}

Tanya Clayton, B.S.
Regulatory Health Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Tanya Clayton
5/23/2006 05:16:25 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-775

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

Dear Ms. Harver:

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

We have reviewed the referenced material and have the following requests for information:

1. The potential of alvimopan and ADL 08-0011 as CYP inducers should be evaluated with hepatocytes from at least 3 donors. (The studies conducted for alvimopan were inadequate and no studies were conducted for ADL 08-0011.)"

2. The following comments pertain to the population PK analysis:

   - Vss/F was estimated to be 1949 L from the population PK analysis, which is much higher than expected from a Vss estimate of 30 L following IV administration and a F of <10%. The model does not seem to describe well the alvimopan pharmacokinetics.
   - Some covariates were found to impact on the fraction of drug absorbed (F). It is unclear whether the covariates were tested for their impact on CL (or CL/F).
   - Analysis on creatinine clearance may be inaccurate. It is noted that, in the population PK dataset, creatinine clearance (CLcr) ranged up to >300 mL/min. In the calculation of CLcr, adjustment may be made for subjects with high BMI. Alternatively, a maximum limit in CLcr may be imposed in the population PK analysis. This, however, does not seem to have been done based on the control codes provided.
   - For analysis pertaining to drug-drug interactions, separate analysis should be performed for each drug. In addition, a table should be provided listing the number of patients on each dose.
   -

These are not approvability issues, but we look forward to working with you in the future to incorporate important findings in product labeling.

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

Sincerely,

{See appended electronic signature page}

Brian E. Harvey, M.D., Ph. D.
Director
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Joyce Korvick
7/21/05 03:16:42 PM
for Dr. Brian E Harvey

ADMINISTRATIVE REVIEW OF NDA ACTION PACKAGE
OFFICE OF DRUG EVALUATION III

NDA: 21-775
Drug: Entereg (alvimopan) Capsules
Classification: 1 S
Sponsor: Adolor
Project Manager/CSO: Melissa Furness

Reviewer: Bronwyn Collier, ADRA ODE III
Review Date: July 19, 2005

Review Cycle 1
Date Submitted: June 25, 2004
Date Received: June 25, 2004
Goal Date: (extended) July 25, 2004
Proposed Action: approvable

	STATUS	COMMENTS
ACTION LETTER	draft	
EXCLUSIVITY CHECKLIST	N/A	
DEBARMENT STATEMENT	confirmed	
PEDIATRIC PAGE	N/A	
TRADE NAME REVIEW	completed	Trade name acceptable. Comments on labeling will be conveyed in the next review cycle.
DSI AUDITS	acceptable	
FACILITY INSPECTIONS	acceptable	

REVIEWS	STATUS	COMMENTS
DIV. SUMMARY REVIEW	completed	
CLINICAL	completed	
SAFETY UPDATE	included in clinical review	
FINANCIAL DISCLOSURE REVIEW	completed - included in clinical review	

STATISTICAL	completed	
BIOPHARM	completed	
CMC	completed	
EA	included in CMC review	categorical exclusion accepted
MICRO (validation of sterilization)	N/A	
STABILITY (stats)	included in CMC review	
PHARM/TOX	completed	
CAC (stats)	N/A	
CAC/ECAC REPORT	N/A	

Labeling: Response to clinical deficiencies will impact significantly on labeling. Comments on labeling will be deferred to next review cycle.
Postmarketing Commitments: none
Advisory Committee Meeting: N/A

Comments: Regulatory and policy requirements met.

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/s/

Bronwyn Collier
7/19/05 03:45:28 PM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: May 19, 2005

Mary Lewis (MML) for

To: Linda Harver, R.Ph., J.D.	**From:** Melissa Hancock Furness
Company: Adolor Corporation	Division of Gastrointestinal & Coagulation Drug Products
Fax number: 484-595-1528	**Fax number:** 301-443-9285
Phone number: 484-595-1011	**Phone number:** 301-827-7450

Subject: Pharmacology and biopharmaceutics Information Request, NDA 21-775

Total no. of pages including cover: 3

Comments: See attached page.

Document to be mailed: ☑ YES ☐ NO

NDA 21-775

1. Renal impairment study (Study 14CL116):
   Subject #16022 had a creatinine clearance of 95mL/min (as listed in the population PK dataset) but was designated as a moderate impairment patient. Please clarify and correct the analysis accordingly.

2. Population PK analysis (PLT04-02):

   a. The datasets for ADL 08-0011 appear to be in error and include only concentration data for Alvimopan, but not ADL 08-0011. Please submit the correct datasets.

   b. Provide the control codes and output for base model (before adding any covariate) and final model for Alvimopan and ADL 08-0011.

   c. Provide a scatter plot (ADL 08-0011 CL/F vs. Alvimopan CL/F) similar to the one on page 78 of PPK report, but include only studies in healthy subjects. (This is because data in renal or hepatic impairment or Crohn's disease may confound the results.) Provide separate plots based on age and single dose/steady state. This means two plots for single dose (i.e., age <65 years and age ≥65 years) and two plots for steady state.

   d. Provide an analysis for study 308 to check on the correlation between Alvimopan exposure (AUC) and obs./pred. ratio for ADL 08-011 (page 75 of the PPK report), including a scatter plot of Alvimopan AUC vs. ratio for ADL 08-011.

3. In vitro metabolism study (Study 13/14PH01/Report #PD-FR-028-0102):
   Was freshly isolated human hepatocytes (in addition to cryopreserved human hepatocytes) used in the study to determine the metabolism of Alvimopan? If so, provide the results for our review.

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/s/

Mary Lewis
5/19/05 04:07:30 PM
CSO
signing for Melissa Hancock Furness

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: May 5, 2005

TO: Melissa Furness, Regulatory Health Project Manager
Eric Brodsky, M.D., Medical Officer
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

THROUGH: Ni A. Khin, M.D., Branch Chief
Good Clinical Practice Branch 1
Division of Scientific Investigations

FROM: Khairy W. Malek, M.D., Ph.D.

SUBJECT: Evaluation of Clinical Inspections

NDA: 21-775

APPLICANT: Adolor Corporation

DRUG: Entereg (alvimopan) Capsules

CHEMICAL CLASSIFICATION: 3

THERAPEUTIC CLASSIFICATION: Type S; Standard Review

INDICATION: To Accelerate Time to Recovery of Gastrointestinal Function following Abdominal or Pelvic Surgery

CONSULTATION REQUEST DATE: August 9, 2004

ACTION GOAL DATE: July 25, 2005

I. BACKGROUND:

Entereg is an opioid antagonist which selectively reverses inhibition of GI motility. In this NDA application, the sponsor included the results of protocols # 14CL308 and #14CL313 entitled: "A Multicenter Phase III, Double-Blind, Placebo-Controlled, Parallel Study of ADL8-2698 in

Opioid-Induced Postoperative Bowel Dysfunction/Postoperative Ileus." The objective of the study was to demonstrate that Entereg (alvimopan) speeds recovery of GI function in subjects undergoing partial small/large bowel resection with primary anastomosis or total abdominal hysterectomy.

I. RESULTS (by protocol/site):

NAME	CITY	STATE	ASSIGNED DATE	RECEIVED DATE	CLASSIFICATION
Alex Pue, M.D.	San Diego	CA	11/24/04	3/25/05	VAI
Martin McCarter M.D.	Denver	CO	11/24/04	3/22/05	VAI
Sander Binderow,M.D.	Atlanta	GA	11/24/04	3/30/05	VAI
Donald Kim, M.D.	Grand Rapids	MI	11/24/04	3/10/05	VAI

Protocol # 14CL308

1. Alex Pue, M.D. San Diego, CA: Acceptable

a. What was inspected: The field investigator reviewed the records of 20 subjects out of 70 enrolled.

b. Limitations of inspection: There was no limitation of the inspection.

c. General Observations: Protocol required tests were not performed for 3 subjects. Hematology analysis was not performed at the hospital discharge for subjects # 2067 and 2069; Urine analysis was not performed at screening for subject 2068 and at discharge for subject 2069; Blood test for LDH was not performed at the hospital discharge of subject 2068.

d. The data from this site can be used in support of the NDA.

2. Martin McCarter, M.D., Denver, CO: Acceptable

a. What was inspected: The field investigator reviewed the records of 23 out of 59 subjects randomized.

b. Limitation of inspection: there was no limitation of inspection.

c. General Observations: There were protocol violations observed: subject #1167 was given ketorolac on POD 2 and 3; the blood sample of subject #2139 for PK analysis was taken more than 4 hours after drug administration instead of the protocol specified 2 hours;

urine analysis was not done at screening and discharge for subject # 1167; and at hospital discharge for subject # 1085; subjects #2136 and 2141 missed one dose of the drug instead of the 2 doses.

d. The data from this site can be used in support of the NDA.

Protocol # 14 CL313

3. Sander Binderow, M.D., Atlanta, GA: Acceptable

a What was inspected: The field investigator reviewed the records of 19 out of 38 subjects.

b. There was no limitation of the inspection.

c. There was a few protocol violation found. Although the protocol allows the use of antiemetics intraoperatively, thirteen subjects (5 in the placebo group and 8 in the Entereg group) were given various anti-emetics (promethazine, droperidol or dolasetron), which are prohibited concomitant drugs, post-operatively. Subject #4032 was enrolled despite meeting the exclusion criterion as the subject was on methadone. These protocol deviations were reported in data listing provided in the NDA.

d. The data from this study can be used in support of the NDA.

4. Donald Kim, M.D., Grand Rapids, MI.: Acceptable

a. What was inspected: The field investigator reviewed the records of 11 subjects out of 35 enrolled.

b. Limitations of inspection: There was no limitation of the inspection.

c. General observations/commentary: Some violations were observed, mainly protocol violations and inaccurate records. The protocol violations were: LDH, direct bilirubin, and microscopic urine analysis were not done for all subjects at this site; 12 subjects (9001, 9002, 9005, 9012, 9017, 9018, 9019, 9021, 9022, 9025, 9030, and 9032) received prohibited concomitant medications such as ketorolac, anti-emetics, laxatives and opioids; certain protocol required tests and assessments were done for several subjects. The time for "First toleration of liquids" and "Able to tolerate solids" was not recorded correctly for subjects #9004 and 9027; the surgery start time was not documented for subject #9020.

d. Overall, the data can be used in support of the NDA.

III. OVERALL ASSESSMENT OF FINDINGS:

As stated above, there are multiple instances of protocol deviations. These violations reported at the 4 sites do not seem to affect the overall validity and reliability of the data. The data from all 4 sites can be used in support of the NDA. No follow-up is required.

Khairy W. Malek
Medical Officer

CONCURRENCE:

Supervisory comments

Ni A. Khin, M.D.
Branch Chief
Good Clinical Practice Branch 1
Division of Scientific Investigations

DISTRIBUTION:
NDA 21-775
HFD-45/Division File/Reading File
HFD-45/Program Management Staff (electronic copy)
HFD-46/Khin/Malek
HFD-46/GCPB1 File

O:Entereg summary.rev_050505.doc

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/s/

Ni Aye Khin
5/5/05 05:24:22 PM
MEDICAL OFFICER

MEMORANDUM OF TELECON

DATE: April 19, 2005

APPLICATION NUMBER: NDA 21-775, Entereg, Alvimopan Capsules

BETWEEN:

Name: Linda Harver, VP, Regulatory
Dr. Wei Du,, VP, Biometrics
Dr. Bruce Wallin, VP, Clinical
David Jackson, Sr. VP, R&D
Andy Gustafson, VP, Regulatory, GSK
Phone: 484-595-1011
Representing: Adolor Corporation

AND

Name: Tanya Clayton, B.S., Regulatory Health Project Manager
Sonia Castillo, Ph.D., Statistics Reviewer
Stella Grosser, Ph.D., Statistics Team Leader
Eric Brodsky, M.D., Medical Reviewer

Representing: Division of Gastrointestinal & Coagulation Drug Products, HFD-180

SUBJECT: To discuss the agency's expectations for the background information in reference to the upcoming data meeting scheduled for May 24, 2005.

This teleconference was initiated by the sponsor. The purpose of this teleconference was to speak with the biometrics team to ensure they provide all pertinent background information for the upcoming May 24, 2005 data meeting. Dr. Castillo requested that the firm provide the statistical methodology and justification for using the mean time to event in the presence of censoring. She also informed the sponsor that the justification should not be in the form of tables, for it should be written. The sponsor agreed to provide the information as requested.

Tanya Clayton, B.S.
Regulatory Health Project Manager

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/s/

Tanya Clayton
4/20/05 05:55:09 PM
CSO

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-775 Supplement # N/A Efficacy Supplement Type SE- N/A

Trade Name: Entereg
Established Name: Alvimopan Capsules
Strengths:

Applicant: Adolor Corporation
Agent for Applicant: N/A

Date of Application: June 25, 2004
Date of Receipt: June 25, 2004
Date clock started after UN:
Date of Filing Meeting:
Filing Date: August 24, 2004
Action Goal Date (optional): User Fee Goal Date: July 25, 2005

Indication(s) requested: Entereg is indicated to accelerate time recovery of gastrointestinal function following abdominal pelvic surgery.

Type of Original NDA: (b)(1) ☒ (b)(2) ☐
OR
Type of Supplement: (b)(1) ☐ (b)(2) ☐

NOTE:

(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2), complete Appendix B.

(2) If the application is a supplement to an NDA, please indicate whether the NDA is a (b)(1) or a (b)(2) application:

☒ NDA is a (b)(1) application OR ☐ NDA is a (b)(2) application

Therapeutic Classification: S ☒ P ☐
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐
Chemical Classification: (1,2,3 etc.) 1
Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES ☒ NO ☐

User Fee Status: Paid ☐ Exempt (orphan, government) ☐
Waived (e.g., small business, public health) ☒

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the*

product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the user fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application? YES ☐ NO ☒
  If yes, explain:

- Does another drug have orphan drug exclusivity for the same indication? YES ☐ NO ☒

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES ☐ NO ☐

  If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES ☐ NO ☐
  If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES ☐ NO ☐

- Does the submission contain an accurate comprehensive index? YES ☒ NO ☐

- Was form 356h included with an authorized signature? YES ☒ NO ☐
  If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES ☒ NO ☐
  If no, explain:

- If an electronic NDA, does it follow the Guidance? N/A ☐ YES ☒ NO ☐
  If an electronic NDA, all forms and certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format? All sections of the NDA were submitted electronically. The administrative volume including forms and certifications was also submitted in paper

  Additional comments:

- If an electronic NDA in Common Technical Document format, does it follow the CTD guidance? N/A ☒ YES ☐ NO ☐

- Is it an electronic CTD (eCTD)? N/A ☐ YES ☐ NO ☒
  If an electronic CTD, all forms and certifications must either be in paper and signed or be electronically signed.

  Additional comments:

- Patent information submitted on form FDA 3542a? YES ☒ NO ☐

- Exclusivity requested? YES, _____ Years NO ☒
  ***NOTE:** An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*

- Correctly worded Debarment Certification included with authorized signature? YES ☒ NO ☐
  If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

  NOTE: *Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."*

- Financial Disclosure forms included with authorized signature? YES ☒ NO ☐
  (Forms 3454 and 3455 must be included and must be signed by the APPLICANT, not an agent.)
  NOTE: *Financial disclosure is required for bioequivalence studies that are the basis for approval.*

- Field Copy Certification (that it is a true copy of the CMC technical section)? Y ☐ NO ☐

- PDUFA and Action Goal dates correct in COMIS? YES ☒ NO ☐
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

- List referenced IND numbers: 56,553

- End-of-Phase 2 Meeting(s)? Date(s) March 12 and 13, 2001 NO ☐
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) March 24 and 25, 2004 NO ☐
  If yes, distribute minutes before filing meeting.

Project Management

- Was electronic "Content of Labeling" submitted? YES ☒ NO ☐
  If no, request in 74-day letter.

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?
  YES ☒ NO ☐

- Risk Management Plan consulted to ODS/IO? N/A ☒ YES ☐ NO ☐

- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? Y ☒ NO ☐

- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A ☒ YES ☐ NO ☐

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?
  N/A ☒ YES ☐ NO ☐

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A ☒ YES ☐ NO ☐

- Has DOTCDP been notified of the OTC switch application? YES ☐ NO ☐

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? YES ☐ NO ☐

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES ☒ NO ☐
  If no, did applicant submit a complete environmental assessment? YES ☐ NO ☐
  If EA submitted, consulted to Florian Zielinski (HFD-357)? YES ☐ NO ☐
- Establishment Evaluation Request (EER) submitted to DMPQ? YES ☐ NO ☐
- If a parenteral product, consulted to Microbiology Team (HFD-805)? YES ☐ NO ☐

ATTACHMENT

MEMO OF FILING MEETING

DATE: August 6, 2004

BACKGROUND: Entereg is indicated for the management of Post Operative Ileus (POI). This application was accepted under the "Continuous Marketing Applications: Pilot I-Reviewable Units for Fast Track Products under PDUFA." This NDA was submitted electronically. The administrative volume is also submitted by paper. This NDA qualifies for a standard review.
(Provide a brief background of the drug, e.g., it is already approved and this NDA is for an extended-release formulation; whether another Division is involved; foreign marketing history; etc.)

ATTENDEES:
Joyce Korvick, M.D., M.P.H.
Ruyi He, M.D.
Eric Brodsky, M.D.
Wen Jen Chen, Ph.D.
Ramesh Raghavachari, Ph.D.
Zhengfang Ge, Ph.D.
Suresh Doddapaneni, Ph.D.
Sue Chih Lee, Ph.D.
Jasti Choudary, Ph.D.
Tamal Chakraborti, Ph.D.
Melissa Furness, BS
Tanya Clayton, BS

ASSIGNED REVIEWERS (including those not present at filing meeting) :

Discipline	**Reviewer**
Medical:	Eric Brodsky, M.D.
Secondary Medical:	N/A
Statistical:	Wen Jen Chen, Ph.D.
Pharmacology:	Tamal Chakraborti, Ph.D.
Statistical Pharmacology:	N/A
Chemistry:	Ramesh Raghavarchi, Ph.D. and Zhengfang Ge, Ph.D.
Environmental Assessment (if needed):	N/A
Biopharmaceutical:	Sue Chih Lee, Ph.D.
Microbiology, sterility:	N/A
Microbiology, clinical (for antimicrobial products only):	
DSI:	Kharey Malik, M.D.
Regulatory Project Management:	Tanya Clayton, Melissa Furness
Other Consults:	Kristina Arnwine, PharmD (DMETS), Shannon Benedetto (DDMAC)

Per reviewers, are all parts in English or English translation? YES ☒ NO ☐
If no, explain:

CLINICAL FILE ☒ REFUSE TO FILE ☐

- Clinical site inspection needed? YES ☒ NO ☐
- Advisory Committee Meeting needed? YES, date if known _____ NO ☒
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? N/A ☐ YES ☐ NO ☐

CLINICAL MICROBIOLOGY	N/A ☒	FILE ☐	REFUSE TO FILE ☐
STATISTICS	N/A ☐	FILE ☒	REFUSE TO FILE ☐
BIOPHARMACEUTICS		FILE ☒	REFUSE TO FILE ☐

- Biopharm. inspection needed? YES ☐ NO ☒

PHARMACOLOGY	N/A ☐	FILE ☒	REFUSE TO FILE ☐

- GLP inspection needed? YES ☐ NO ☒

CHEMISTRY		FILE ☒	REFUSE TO FILE ☐

- Establishment(s) ready for inspection? YES ☒ NO ☐
- Microbiology YES ☐ NO ☒

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

☐ The application is unsuitable for filing. Explain why:

☒ The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.

- ☐ No filing issues have been identified.
- ☒ Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. ☐ If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
2. ☐ If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
3. ☒ Convey document filing issues/no filing issues to applicant by Day 74.

Regulatory Project Manager, HFD-180

Appendix A to NDA Regulatory Filing Review

An application is likely to be a 505(b)(2) application if:

(1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
(2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
(4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications

1. Does the application reference a listed drug (approved drug)? YES ☐ NO ☐

   *If "**No**," skip to question 3.*

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):

3. The purpose of this and the questions below (questions 3 to 5) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval and that should be referenced as a listed drug in the pending application.

   (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

   YES ☐ NO ☐

   (***Pharmaceutical equivalents*** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

   *If "**No**," skip to question 4. Otherwise, answer part (b).*

   (b) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES ☐ NO ☐
   (The approved pharmaceutical equivalent(s) should be cited as the listed drug(s).)

   *If "**Yes**," skip to question 6. Otherwise, answer part (c).*

   (c) Have you conferred with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007)? YES ☐ NO ☐

   *If "**No**," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.*

4. (a) Is there a pharmaceutical alternative(s) already approved? YES ☐ NO ☐

   (***Pharmaceutical alternatives*** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

   *If "**No**," skip to question 5. Otherwise, answer part (b).*

   (b) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES ☐ NO ☐
   (The approved pharmaceutical alternative(s) should be cited as the listed drug(s).)

   ***NOTE:** If there is more than one pharmaceutical alternative approved, consult the Director, Division of*

Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007) to determine if the appropriate pharmaceutical alternatives are referenced.

*If "**Yes**," skip to question 6. Otherwise, answer part (c).*

(c) Have you conferred with the Director, Division of Regulatory Policy II, ORP? YES ☐ NO ☐

*If "**No**," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.*

5. (a) Is there an approved drug product that does not meet the definition of "pharmaceutical equivalent" or "pharmaceutical alternative," as provided in questions 3(a) and 4(a), above, but that is otherwise very similar to the proposed product?

YES ☐ NO ☐

*If "**No**," skip to question 6.*

*If "**Yes**," please describe how the approved drug product is similar to the proposed one and answer part (b) of this question. Please also contact the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007), to further discuss.*

(b) Is the approved drug product cited as the listed drug? YES ☐ NO ☐

6. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

7. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). YES ☐ NO ☐

8. Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 21 CFR 314.101(d)(9)). YES ☐ NO ☐

9. Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). YES ☐ NO ☐

10. Are there certifications for each of the patents listed for the listed drug(s)? YES ☐ NO ☐

11. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):

NOTE: *IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must* ***subsequently*** *submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)].*

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):

☐ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):

12. Did the applicant:

- Identify which parts of the application rely on information (e.g. literature, prior approval of another sponsor's application) that the applicant does not own or to which the applicant does not have a right of reference?

  YES ☐ NO ☐

- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

  YES ☐ NO ☐

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

  N/A ☐ YES ☐ NO ☐

- Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?

  N/A ☐ YES ☐ NO ☐

13. If the (b)(2) applicant is requesting 3-year exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

    - Certification that at least one of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

      YES ☐ NO ☐

    - A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

      YES ☐ NO ☐

    - EITHER

      The number of the applicant's IND under which the studies essential to approval were conducted.

      IND# _____ NO ☐

      OR

      A certification that the NDA sponsor provided substantial support for the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

      YES ☐ NO ☐

14. Has the Associate Director for Regulatory Affairs, OND, been notified of the existence of the (b)(2) application?

    YES ☐ NO ☐

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/s/

Tanya Clayton
4/19/05 04:30:10 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-775

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

Dear Ms. Harver:

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

On April 11, 2005, we received your April 8, 2005 major amendment to this application. The receipt date is within 3 months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is July 25, 2005.

If you have any questions, call me at (301) 827-7450.

Sincerely,

{See appended electronic signature page}

Melissa Hancock Furness
Regulatory Health Project Manager
Division of Gastrointestinal & Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

Melissa Furness
4/19/05 02:53:53 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-775

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

Dear Ms. Harver:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Entereg™ (alvimopan) Capsules.

We also refer to the meeting between representatives of your firm and the FDA on March 16, 2005. The purpose of the meeting was to discuss your proposed amended indication statement and address Agency questions in reference to GSK European Study 001.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 827-4005.

Sincerely,

{See appended electronic signature page}

Tanya Clayton, B.S.
Regulatory Health Project Manager
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

Meeting Date: March 16, 2005

Time: 2:30-4:00 PM

Location: Parklawn Building, Conference Room C

Application: NDA 21-775; Entereg

Type of Meeting: Type C

Meeting Chair: Ruyi, He M.D.

Meeting Recorder: Tanya Clayton, B.S.

FDA Attendees, Titles, and Office/Division:

Office of Drug Evaluation III

Julie Beitz, M.D.	Deputy Director

Division of Gastrointestinal and Coagulation Drug Products

Joyce Korvick, M.D., M.P.H.	Acting Division Director
Ruyi He, M.D.	Medical Team Leader
Eric Brodsky, M.D.	Medical Reviewer
Fathia Gibril, M.D.	Medical Reviewer
Sue Chih Lee, Ph.D.	Biopharm Reviewer
Tamal Chakroborti, Ph.D.	Pharmacology Reviewer
Sonia Castillo, Ph.D.	Statistical Reviewer
Tanya Clayton, B.S.	Regulatory Health Project Manager

External Constituent Attendees and Titles:

Adolor Corporation:

Linda Y. Harver, R.Ph., JD	Vice President, Regulatory Affairs
Bruce A. Wallin, M.D.	Vice President, Clinical Research & Development
James E. Barrett, Ph.D.	Sr. Vice President, Chief Scientific Officer and President, Research
Wei Du, Ph.D.	Vice President, Biometrics
Joseph F. Foss, M.D.	Senior Medical Director, Clinical Research and Development
David Jackson, M.D.	Sr. Vice President, Research and Development
Lee Techner, DPM	Senior Medical Director, Clinical Research and Development
Bruce A. Wallin, M.D.	Vice President, Clinical Research and Development

GlaxoSmith Kline:

Eric Carter, M.D., Ph.D.	Vice President, Clinical Development and Medical Affairs, GI Therapeutic Area Head
Elizabeth Nies, MS	Sr. Director, Regulatory Affairs

Background:

On January 21, 2005 the firm requested a Type C meeting for the purpose of discussing their proposed amended indication statement as well as address Agency questions in reference to GSK European Study 001.

A subsequent February 14, 2005 background package was submitted, which contained 8 questions.

Following introductions, the attendees proceeded directly to the questions for response.

Discussion Points: (bullet format):

QUESTIONS:

Question 1:

Adolor has submitted three efficacy studies with two of these studies significant at the 6 mg dose and one of these studies significant at the 12 mg dose. Adolor has proposed the 12 mg dose based on the totality of the data. Does the fact that only one study demonstrated significance for the primary endpoint at the 12 mg dose preclude approval of the 12 mg dose in the labeling?

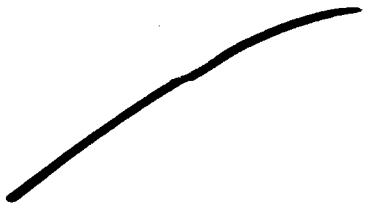
Agency Response

We concur with you that only one phase 3 efficacy study (out of four studies, 3 US, 1 foreign) demonstrated statistical significance of the 12 mg treatment group over the placebo group. However, in addition to statistical significance, we will also weigh heavily the clinical meaningfulness of the results (i.e., the difference in time to recovery between groups). In our review, we will look at the totality of the results, including the studies that have positive and negative results for their primary and secondary endpoints, and results with the 6 mg dose.

If the efficacy benefit of alvimopan can not be demonstrated at the 12 mg dose, it may be difficult to accept the efficacy benefit at the 6 mg dose.

This issue about the clinical meaningfulness is one that we plan to discuss before an advisory committee in the future.

Question 2:



Agency Response

We concur that the phase III data did not support a clinically meaningful benefit for alvimopan in the hysterectomy subpopulation.

The concept of a complex hysterectomy patient was not pre-specified. The post-hoc analysis results in the small number of complex hysterectomy patients should be validated in larger pre-specified clinical trials.

You should provide sufficient evidence to demonstrate that differences in regional practices explain the dissimilar results in the trials.

Question 7:

We appreciate that the Agency has not received the clinical study report for GSK study 001 and may still be reviewing the data submitted by Adolor on January 31. However, does the Agency have any initial thoughts and/or questions regarding study 001 that it can share with us at this time?

Agency Response

We are in the process of reviewing Study 001 and have no specific comments at this time.

Question 8:

Does the Agency have any comments at this time that may not be specifically related to or solicited by the proposed questions?

Agency Response

We are aware that a large US phase III trial (Study 14CL314) in BR patients evaluating the 12 mg dose is currently ongoing. Given that results from this study will likely address concerns we have about the efficacy of alvimopan in the BR population, we will need to review these data in order to reach a decision regarding the approvability of your application.

Meeting Update

We are going to schedule a meeting to discuss the data early May 2005. Following discussion, both parties agree there will be no advisory committee during this review cycle.

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/s/

Tanya Clayton
4/12/05 06:24:39 PM

Ruyi He
4/12/05 06:33:14 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-775

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

Dear Ms. Harver:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Entereg (Alvimopan) Capsules

Review Priority Classification: Standard (S)

Date of Application: June 25, 2004

Date of Receipt: June 25, 2004

Our Reference Number: NDA 21-775

The application was filed on August 24, 2004 in accordance with 21 CFR 314.101(a). The user fee goal date is April 25, 2005.

The acknowledgement for Reviewable Unit 003 (RU-003) was inadvertently sent on July 17, 2004. However, the submission was acknowledged as Reviewable Unit 003 and should have been acknowledged as the complete NDA. As a result, RU-003 does not exist. This correspondence serves as your NDA acknowledgement.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Send all electronic or mixed electronic and paper submissions to the Central Document Room at the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room (CDR)
5901-B Ammendale Road
Beltsville, MD 20705-1266

If your submission only contains paper, send it to the following address:

Courier/Overnight Mail/U.S. Postal Service:
Center for Drug Evaluation and Research
Division of Gastrointestinal and Coagulation Drug Products
Attention: Division Document 8B-45
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call me at (301) 827-4005.

Sincerely,

{See appended electronic signature page}

Tanya Clayton, B.S.
Regulatory Health Project Manager
Division of Gastrointestinal and Coagulation
Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Tanya Clayton
3/9/05 04:24:04 PM

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: 01/24/05

To: Linda Harver	**From:** Melissa Furness
Company: Adolor Corporation	Division of Gastrointestinal and Coagulation Drug Products
Fax number: 484-595-1528	**Fax number:** 301-443-9285
Phone number: 484-595-1011	**Phone number:** 301-827-7450

Subject: Information Request for NDA 21-775 (Entereg)

Total no. of pages including cover: 3

Comments:

Please find attached a Clinical Pharmacology Information Request.

Document to be mailed: YES √ NO

Clinical Pharmacology Information Reuqest:

1. The proposed label states that the active metabolite is not important for the efficacy. Provide the supporting evidence, including a summary of antibiotic use in patients who participated in clinical trials. This should include statistics on type of antibiotics, route of administration, dosing regimen and efficacy results. Any evidence that use of antibiotics reduced or eliminated the production of the amide hydrolysis metabolite should also be provided.

2. Does the plasma drug concentrations reflect the efficacy? Or is the efficacy derived from local action? Clarify and provide the supporting evidence.

3. Please provide an update regarding the current status of study 14CL314. In addition, please provide a timeline for the submission of the final reports related to study 14CL314.

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/s/

Melissa Furness
1/24/05 10:33:15 AM
CSO

Melissa Furness
1/24/05 10:37:27 AM
CSO

MEMORANDUM OF MEETING MINUTES

Meeting Date: November 23, 2004

Time: 1:30 – 3:00 PM

Application: NDA 21-775
Entereg (alvimopan)

Sponsor: Adolor Corporation

Type of Meeting: Type C Meeting

Meeting Chair: Ruyi He, M.D.

Meeting Recorder: Melissa Furness, B.S.

FDA Attendees:

Division of Gastro-Intestinal and Coagulation Drug Products (HFD-180)

Kathy Robie-Suh, M.D., Ph.D., Acting Deputy Director
Ruyi He, M.D., Medical Team Leader, GI Drugs
Eric Brodsky, M.D., Medical Officer
Ramesh Raghavachari, Ph.D., Chemistry Reviewer
Zhefang Ge, Ph.D., Chemistry Reviewer
Tamal Chakraborti, Ph.D., Pharmacology Reviewer
Sonia Castillo, Ph.D., Biometrics Reviewer
Stella Grosser, Ph.D., Biometrics Team Leader
Melissa Furness, B.S., Regulatory Health Project Manager

Office if Drug Evaluation III

Julie Beitz, M.D., Deputy Director, Office of Drug Evaluation III

Sponsor Attendees:

Adolor Corporation

James E. Barrett, PhD, Chief Scientific Officer and President, Research
Wei Du, PhD, Vice President, Biometrics
Joseph F. Foss, MD, Director, Clinical Research and Development
Linda Y. Harver, RPh, JD, Vice President, Regulatory Affairs
David Jackson, MD, Sr. Vice President, Research and Development
Lee Techner, DPM, Director, Clinical Research and Development
Bruce A. Wallin, MD, Vice President, Clinical Research and Development

GlaxoSmithKline

Eric Carter, PhD, MD, Vice President, Clinical Development and Medical Affairs, GI Therapeutic Area Head
Eric Mortensen, PhD, MD, Group Director, Musculoskeletal, Inflammation, Gastrointestinal and Urology
ElizabethA. Nies, MS, Sr. Director, Regulatory Affairs

Meeting Objectives:

For the sponsor to receive feedback regarding their pending NDA's status and possible deficiencies.

Discussion:

QUESTIONS:

1. What are the review or approval issues identified to date in the CMC section of the NDA? What are the Division's expectations of the firm in clarifying or resolving any perceived deficiencies in the application for CMC prior to the NDA PDUFA date?

   Please refer to our DR letter for the minor CMC deficiencies. You should be able to address the deficiencies. You may request a teleconference if further clarification is needed.

2. What are the review or approval issues identified to date in Item 5 of the NDA? What are the Division's expectations of the firm in clarifying or resolving any perceived deficiencies in the application for pharmacology/toxicology prior to the NDA PDUFA date?

   None.

3. Does the Agency concur that acceleration of GI recovery represents the management of POI? If not, what does the agency perceive are the differences between these concepts?

   Yes. The acceleration of GI recovery is important in the treatment of POI.

4. Does the section on the "Categorization of Phase 3 Trials," Section 4.2.2 of this document, together with information submitted in the NDA, provide adequate clarification that study 14CL306 was not designed nor was it submitted as an efficacy trial? If not, can the agency please provide its rationale and explain the level of importance it will attribute to the efficacy data from this trial (14CL306) relative to the three prospectively designed Phase 3 primary efficacy trials (14CL302, 14CL308 and 14CL313)?

The efficacy outcomes in the 3 pre-specified efficacy phase 3 trials (14CL302, 14CL308 and 14CL313) may be more important than the efficacy outcome in the 1 pre-specified safety trial (14CL306).

However, efficacy will be evaluated in all 4 Alvimopan phase 3 trials in the treatment of POI.

5. Can the FDA provide perspective regarding why the secondary endpoint "time to discharge order written" was mentioned and not others?

   All 7 pre-specified secondary endpoints will be reviewed.

6. Will the agency consider the supportive efficacy data derived from the secondary endpoints for both the 6 mg and 12 mg dosage groups across all three Phase 3 efficacy trials when evaluating the efficacy of alvimopan for the proposed indication?

   Yes.

7. Does the agency agree that the placebo responses observed across the three efficacy studies are reflective of surgical subtype(s) included in each study and that the demonstration of a positive primary efficacy endpoint in study 14CL313 was not due to a "poor" placebo response but to the fact that this study focused primarily on bowel resection patients?

   The Clinical portion of your NDA is still under review; consequently, we can not address this question at this time.

8. Does the Agency agree that the placebo response in the bowel resection subpopulation is consistent across the three efficacy studies?

   The Clinical portion of your NDA is still under review; consequently, we can not address this question at this time.

9. Has the agency identified any additional questions or issues regarding the sponsor's medical rationale for recommending the 12 mg dose [redacted]

   The Clinical portion of your NDA is still under review; consequently, we can not address this question at this time.

10. Regulatory: Does the FDA have any initial thoughts it can share with us at this time regarding a potential Advisory Committee (AC) review/discussion of this NDA? When do you anticipate a decision regarding an AC meeting and when/how is this decision communicated to the Sponsor? When do you anticipate an AC meeting for a standard NDA will be scheduled?

    The Entereg AC Meeting will take place on March 10, 2005.

11. Regulatory: What interactions, meetings and/or teleconferences, do you anticipate with the Sponsor and when would these interactions occur prior to a planned AC meeting? Would the Division consider/agree to schedule such interactions now, in advance of a final decision regarding an AC, to ensure these dates are on the calendar?

Two (FDA/Adolor Corporation) meetings have been arranged:

Thursday February 3, 2005 (a teleconference)
Friday, February 25 (face-face meeting)

Additional Discussion:

Adolor: ***Ms. Harver asked if Adolor would receive the Medical and Statistical review at one of the two scheduled AC meetings in February.***
FDA: ***Dr. He stated that their review would not be available in February because it is unlikely to be finished and approved until closer to the action date. The FDA will have identified the issues for discussion at the AC by Feb. 3rd for review with Adolor.***
FDA: ***Dr. Beitz said the Feb. 3rd meeting is 2-3 weeks before they have to have their background package finalized for the AC. Adolor may receive the BD by the Feb. 25th meeting; it should be available about 14 days before the meeting. Adolor will see the draft questions by the Feb. 25th meeting; the final questions will not be available until 2 days before the meeting.***
Adolor: ***Ms. Harver asked if the Division would have a surgeon at the AC meeting.***
FDA: ***Dr. Robie-Suh said they would have a surgeon as well as an OB/Gyn, and they invited Adolor to do the same.***

12. Does the FDA have any preliminary comments on the language we propose to express use of alvimopan in the "management of POI", i.e., "acceleration of time to recovery of GI function after abdominal or pelvic surgery"?

The Clinical portion of your NDA is still under review; consequently, we can not address this question at this time.

13. Regulatory: What is the Division's process and preferred format for labeling discussions? Is it possible for the Division to estimate the timing for these discussions and permit a calendar entry at this time to ensure dates are available?

The following 3 labeling teleconferences have been arranged:

1) Thursday, March 31, 2005
2) Thursday, April 7, 2005
3) Thursday, April 14, 2005

Please note that these dates are tentative and could be subject to change.

14. Have any other potential issues been identified at this stage of the review beyond those communicated in the filing letter that the FDA can share with us?

Our answers represent our initial thoughts about your NDA. Our opinions may change as we continue to review your NDA.

Additional Discussion:

Adolor: Ms. Harver asked the Division if they could help Adolor understand the process in the assessment of alvimopan in the determination of priority or standard review and the determination and the designation of alvimopan as a fast-track drug.
FDA: Dr. He said fast track was granted because of the unmet medical need for the serious condition of POI, but, for priority review, the NDA clinical data should indicate a significant clinical benefit for the potential population. The agency found that the 3 studies were "controversial" in the outcomes, and from their early review at the time of the letter, the response did not appear to be robust for a proven significant clinical benefit to the proposed population compared to placebo. The analysis of the data is not just one of safety or efficacy – although Dr. He commented that he is not saying at this time that alvimopan isn't safe and effective, but at that time alvimopan did not appear to offer a significant clinical benefit because of so many "controversial" studies. He pointed out the differences in the hours shown and the placebo response, stating that perhaps the results will appear different in the subgroups.
Adolor: Adolor pointed out that as the review continues, they hoped the reviewers would see the safety and efficacy of alvimopan in these studies.

FDA: Dr. Brodsky then said he had a few questions to pose in an Information Request letter or offer Adolor the opportunity to address at the meeting.
Adolor: The company chose to address any issues at the meeting.
FDA: Regarding GI[3] and also the secondary solid food - When it is stated that a solid meal has to be eaten, how much must be eaten to be satisfactory, 50%, 75%, what amount?
Adolor: Dr. Wallin defined "solid food" as any food that requires chewing. The food had to be tolerated for 4 hours after that meal, with toleration meaning no significant nausea and no vomiting. It was explained as "almost all", "most of the solid meal" and no significant nausea and no vomiting to qualify for toleration.
FDA: Dr. Brodsky: Is "most" 51%?
Adolor: Dr. Wallin explained that from the instructions to the coordinators, it was 95% of the meal.
FDA: Dr. Brodsky accepted - "Ok, most likely 95%."
FDA: Dr. Brodsky: What is meant by significant nausea, was this measured on a VAS scale?"
FDA: Dr. Techner said that significant nausea was defined as that which required intervention, as determined by the clinician. If the subject did not tolerate solid food, he reverted back to an earlier stage diet, for example liquids. In addition, Dr. Techner added some clarification to Dr. Brodsky's question regarding amount of solid food required for "toleration". Dr. Techner said that toleration of solid food was a driver for both recovery of GI function and discharge. Therefore, the PIs would require more than just a few bites

of solid food for this endpoint. Dr. Techner also confirmed that the 4 hours was measured from the end of the meal, not the beginning. The time recorded as toleration of solid food was the point of toleration, 4 hrs post the meal.

FDA: Dr. Brodsky: Patients got clear liquids on POD1 and food on POD2 - was this automatic, even if the patient was nauseous?

Adolor: Adolor responded that it was not automatic. The sites were encouraged to offer liquids and solids, and Adolor tried to follow the more aggressive pathway that surgeons are now following.

FDA: Dr. Brodsky asked about the progression of diet – liquids then to solids?

Adolor: Adolor confirmed it was liquids to solids, but it could vary according to the hospital.

FDA: Dr. Brodsky: What did the chest x-rays imply?

Adolor: Dr. Wallin responded that at the EOP2 meeting, FDA was looking for minimizing the GI dysfunction – the bloating and post-op morbidities that the drug might be influencing. If a patient has these GI events, they might not be breathing as deeply. Chest x-rays were collected as an objective measure of pulmonary morbidities.

FDA: Dr. Brodsky confirmed that these were not on every patient – just those with potential problems.

Adolor: Dr. Eric Carter added that if the PI thought on exam that there may be pneumonia or atelectasis, then the patient would get an x-ray.

Adolor: Dr. Wallin said that with POI, there is the potential that if the patient vomits, the patient is at risk for aspiration, which could lead to pneumonia or other worse outcomes.

FDA: Dr. Brodsky: The patient could get 8 days of drug/placebo, POD 0 and POD 7, what if the patient goes home early? What if the patient doesn't get GI[3]? If at POD 10, the patient hasn't reached the endpoint - at Day 11, what time is given, what number is given?

Adolor: Dr. Wallin explained that subjects were censored at 264 hours (10 days plus the day of surgery = 264 hours), and they were observed for SAEs. Everyone got a maximum of 7 days dosing. The study meds were stopped at Day 7. In Phase 2, assessments stopped at that time. In Phase 3, the patients were assessed after Day 7, up to Day 10, as long as they were in the hospital. The coordinators and surgeons would still see the patients b.i.d. to try to understand when the events did occur.

Adolor: Dr. Du explained the censoring rule that not all subjects who did not have an event would be censored at Day 10. Subjects could be censored at time of the last observation, if it occurred in the 10-day period. If the patient had an observation on Day 11, the subject was censored at Day 10. It would depend on how many days of observations were available. In total, about 5% were treatment failures – they finished the study but never achieved an endpoint. A Responder was defined as the dichotomization of the primary endpoint based on the median time to achieve GI[3] recovery in the Phase 2 POI trials, and was 108 hours for the BR/rTAH subpopulation and was 60 hours for the sTAH subpopulation.

FDA: Dr. Brodsky: In terms of the MITT and ITT, I understand the patient needed the predesignated surgery and one evaluation of efficacy; when did evaluations start? Evaluations were b.i.d. starting post op at the beginning of POD1.

Adolor: Adolor confirmed that if the patient had surgery and no evaluations, they were in the ITT, but not the MITT. It was confirmed for Dr. Brodsky that the patient needed to have the protocol specified surgery in order to get POI, i.e. that this specific surgery was

needed in order to have the illness to treat. If the patient got a diverting colostomy, there would be no endpoint. The intent of the trial and the informed consent form, which was signed before the pre-op dose, was for all subjects to have the protocol specified surgery, but not all patients stayed in that regimen. Some with signed informed consent received the pre-op dose, after which the surgery was cancelled. There is a category of subjects in the ISE that for a variety of reasons the subjects did not have a post-op assessment, i.e. patients received a epidural instead of general anesthesia, these patients were discontinued at the end of surgery. Some surgeons kept the NG tubes in, and those subjects had to be discontinued. 93% of patients were in the MITT.
FDA: Dr. Brodsky asked about the percentage of the last group.
Adolor: Dr. Du reported that about 51 of 2174 subjects were discontinued without any efficacy observations.
FDA: Dr. Brodsky said it would be helpful to know which dataset has this information.
Adolor: Dr. Du responded with the location of the information (dataset EVAL).

FDA: Dr. Beitz asked Adolor to take some time at the Feb. 25th meeting to offer some of the presentation planned for the AC.
Adolor: Dr. Wallin said he would do.
FDA: Dr. He said the Feb. 3rd teleconference is only for FDA to relay to us the issues for the AC, "it is not for argument." Adolor will be informed of the potential problems.
Adolor: Adolor acknowledged the purpose of that first meeting.

Adolor: Dr. Du asked if the datasets she had sent in response to a question by Dr. Chen were satisfactory.
FDA: Dr. Castillo responded that she is still going through the NDA's datasets and is getting familiar with them.
Adolor: Dr. Du said she had sent Dr. Chen the datasets and SAS programs with macros in them, but that he made a second request for programs without the SAS macros.
FDA: Dr. Grosser said that Dr. Chen was on another project but was still available for consult.
Adolor: Dr. Du offered to send to Dr. Castillo the same SAS program for Study 306 that was provided for the other 3 efficacy studies.

FDA: Dr. Brodsky then asked if Adolor excluded Crohn's patients from the protocols. It was confirmed that these patients were included in the program and they primarily had small bowel resections. Dr. Brodsky asked about the number of Crohn's patients in the database and the distribution between small bowel and large bowel resection in these patients.
Adolor: Dr. Du pointed out the table in the BD reflecting this information and confirmed that it was less than 100 patients. (Post meeting note: There is a total of 101 small bowel resection subjects in the POI program, and 47 of the 101 subjects had Crohn's disease).
Adolor: Dr. Techner said that these patients could get either, but he believed most of these patients received small bowel resections.
Adolor: Dr. Wallin pointed out that at the EOP2 meeting, the medical reviewer asked for a special PK study in active Crohns and quiescent Crohns because it was suspected that these patients might have higher blood levels. Adolor conducted the study and saw no

significant difference in blood levels. Some quiescent patients had slightly higher plasma levels than normal human volunteers.

<u>FDA:</u> The meeting was adjourned and Dr. He said Melissa Furness would forward questions to Adolor as the review progresses and that Adolor may receive an IR letter requesting more information in December.

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/s/

Ruyi He
12/20/04 03:54:45 PM

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: November 22, 2004

To: Linda Harver, R.Ph., J.D. Vice President, Regulatory Affairs	**From:** Melissa Hancock Furness Regulatory Health Project Manager
Company: Adolor Corporation	Division of Gastrointestinal and Coagulation Drug Products
Fax number: 484-595-1528	**Fax number:** 301-443-9285
Phone number: 484-595-1011	**Phone number:** 301-827-7450

Subject: NDA 21-775 – 09/15/04 Meeting Request- Responses to the questions submitted in your October 25, 2004 Meeting Background Package

Total no. of pages including cover: 3

Comments:

Attached are the FDA answers to your questions (in **bold**). You have the option of canceling our meeting of November 23, 2004 if these answers are clear to you. If you choose to have the meeting, we will be prepared to clarify any questions you have regarding our responses. However, please note that if there are any major changes to your development plan (based upon our responses herein), we will not be prepared to discuss, nor reach agreement on, such changes at the meeting. Any modifications to the development plan or additional questions, for which you would like FDA feedback, should be submitted as a new meeting request. Please let me know as soon as possible whether you are canceling the meeting.

Document to be mailed: √ YES NO

QUESTIONS:

1. What are the review or approval issues identified to date in the CMC section of the NDA? What are the Division's expectations of the firm in clarifying or resolving any perceived deficiencies in the application for CMC prior to the NDA PDUFA date?

   Please refer to our DR letter for the minor CMC deficiencies. You should be able to address the deficiencies. You may request a teleconference if further clarification is needed.

2. What are the review or approval issues identified to date in Item 5 of the NDA? What are the Division's expectations of the firm in clarifying or resolving any perceived deficiencies in the application for pharmacology/toxicology prior to the NDA PDUFA date?

   None.

3. Does the Agency concur that acceleration of GI recovery represents the management of POI? If not, what does the agency perceive are the differences between these concepts?

   Yes. The acceleration of GI recovery is important in the treatment of POI.

4. Does the section on the "Categorization of Phase 3 Trials," Section 4.2.2 of this document, together with information submitted in the NDA, provide adequate clarification that study 14CL306 was not designed nor was it submitted as an efficacy trial? If not, can the agency please provide its rationale and explain the level of importance it will attribute to the efficacy data from this trial (14CL306) relative to the three prospectively designed Phase 3 primary efficacy trials (14CL302, 14CL308 and 14CL313)?

   The efficacy outcomes in the 3 pre-specified efficacy phase 3 trials (14CL302, 14CL308 and 14CL313) may be more important than the efficacy outcome in the 1 pre-specified safety trial (14CL306).

   However, efficacy will be evaluated in all 4 Alvimopan phase 3 trials in the treatment of POI.

5. Can the FDA provide perspective regarding why the secondary endpoint "time to discharge order written" was mentioned and not others?

   All 7 pre-specified secondary endpoints will be reviewed.

6. Will the agency consider the supportive efficacy data derived from the secondary endpoints for both the 6 mg and 12 mg dosage groups across all three Phase 3 efficacy trials when evaluating the efficacy of alvimopan for the proposed indication?

   Yes.

7. Does the agency agree that the placebo responses observed across the three efficacy studies are reflective of surgical subtype(s) included in each study and that the demonstration of a positive primary efficacy endpoint in study 14CL313 was not due to a "poor" placebo response but to the fact that this study focused primarily on bowel resection patients?

   The Clinical portion of your NDA is still under review; consequently, we can not address this question at this time.

8. Does the Agency agree that the placebo response in the bowel resection subpopulation is consistent across the three efficacy studies?

   The Clinical portion of your NDA is still under review; consequently, we can not address this question at this time.

9. Has the agency identified any additional questions or issues regarding the sponsor's medical rationale for recommending the 12 mg dose

   The Clinical portion of your NDA is still under review; consequently, we can not address this question at this time.

10. Regulatory: Does the FDA have any initial thoughts it can share with us at this time regarding a potential Advisory Committee (AC) review/discussion of this NDA? When do you anticipate a decision regarding an AC meeting and when/how is this decision communicated to the Sponsor? When do you anticipate an AC meeting for a standard NDA will be scheduled?

    The Entereg AC Meeting will take place on March 10, 2005.

11. Regulatory: What interactions, meetings and/or teleconferences, do you anticipate with the Sponsor and when would these interactions occur prior to a planned AC meeting? Would the Division consider/agree to schedule such interactions now, in advance of a final decision regarding an AC, to ensure these dates are on the calendar?

    Two (FDA/Adolor Corporation) meetings have been arranged:

    Thursday February 3, 2005 (a teleconference)
    Friday, February 25 (face-face meeting)

12. Does the FDA have any preliminary comments on the language we propose to express use of alvimopan in the "management of POI", i.e., "acceleration of time to recovery of GI function after abdominal or pelvic surgery"?

    The Clinical portion of your NDA is still under review; consequently, we can not address this question at this time.

13. Regulatory: What is the Division's process and preferred format for labeling discussions? Is it possible for the Division to estimate the timing for these discussions and permit a calendar entry at this time to ensure dates are available?

The following 3 labeling teleconferences have been arranged:

1) Thursday, March 31, 2005
2) Thursday, April 7, 2005
3) Thursday, April 14, 2005

Please not that these date are tentative and could be subject to change.

14. Have any other potential issues been identified at this stage of the review beyond those communicated in the filing letter that the FDA can share with us?

Our answers represent our initial thoughts about your NDA. Our opinions may change as we continue to review your NDA.

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/s/

Melissa Furness
11/22/04 02:24:05 PM
CSO

Melissa Furness
11/22/04 02:27:52 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-775/RUC-002

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

Dear Ms. Harver:

Please refer to your new drug application (NDA) for Entereg (alvimopan) Capsules, submitted under the Continuous Marketing Application (CMA)-Pilot 1 Program.

We also refer to your May 27, 2004 reviewable unit (RU) for the Chemistry, Manufacturing, and Controls portion of your NDA.

We have completed our review of this RU and have identified the following deficiencies:

1. Regarding the Drug Substance:

   a. [redacted]

   b. [redacted]

   c. Provide the actual yield and the theoretical yield for all of the intermediates and the final product (drug substance) based on your batch test data. Provide data in a tabular format.
   d. Either provide regulatory information for the drug substance container closure system, or provide a letter of authorization cross referencing a Drug Master File.

2. Regarding the Drug Product:

   a. Provide dissolution data for all sampling times described in your test method, including the sampling time at 15 minutes.
   b. [redacted]

We are providing these comments to you before we complete our review of the complete application to give you preliminary notice of issues that we have identified. These comments are being provided to you in conformance with the guidance "Continuous Marketing Applications: Pilot 1 – Reviewable Units for Fast Track Products under PDUFA" and do not reflect a final decision on the information reviewed. Issues may be added, deleted, expanded upon, or modified as we review the complete application.

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

Sincerely,

{See appended electronic signature page}

Liang Zhou, Ph.D.
Chemistry Team Leader for the
Division of Gastrointestinal and
Coagulation Drug Products, (HFD-180)
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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/s/

Marie Kowblansky
11/18/04 03:33:17 PM
Marie Kowblansky, Acting Chemistry Team Leader for Liang Zhoul

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

DISCIPLINE REVIEW LETTER

NDA 21-775/RU-001

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

Dear Ms. Harver:

Please refer to your New Drug Application (NDA) for Entereg (Alvimopan) Capsules, submittedunder the Continuous Marketing Application (CMA)-Pilot 1 program.

We also refer to your May 4, 2004 reviewable unit (RU) for the Nonclinical Pharmacology and Toxicology portion of your NDA.

We have completed our review of this RU and have not identified any potential deficiencies at this time.

This letter is being provided to you in conformance with the guidance "Continuous Marketing Applications: Pilot 1 – Reviewable Units for Fast Track Products under PDUFA" and does not reflect a final decision on the information reviewed. Issues may be identified as we review the complete application.

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

Sincerely,

{See appended electronic signature page}

Brian Strongin R.Ph., M.B.A.
Chief, Project Management Staff
Division of Gastrointestinal & Coagulation
Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Melissa Furness
11/4/04 05:22:47 PM
signing for Brian Strongin

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: October 28, 2004

To: Linda Harver, R.Ph., J.D.	**From:** Melissa Hancock Furness Regulatory Health Project Manager
Company: Adolor Corporation	Division of Gastrointestinal and Coagulation Drug Products
Fax number: 484-595-1528	**Fax number:** 301-443-9285
Phone number: 484-595-1011	**Phone number:** 301-827-7450

Subject: NDA 21-775

Total no. of pages including cover: 2

Comments:

This fax is to notify you that we are planning to have a GI advisory committee meeting regarding your product, alvimopan (NDA 21-775), on either 03/09/05 or 03/10/05.

Should you have questions, please contact me at 301-827-7450.

Best regards,

Melissa

Document to be mailed: √ YES NO

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/s/

Melissa Furness
10/28/04 03:38:38 PM
CSO

Melissa Furness
10/28/04 03:42:53 PM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: September 30, 2004

To: Linda Harver, R.Ph., J.D. Vice President, Regulatory Affairs	**From:** Melissa Hancock Furness Regulatory Health Project Manager
Company: Adolor Corporation	Division of Gastrointestinal and Coagulation Drug Products
Fax number: 484-595-1528	**Fax number:** 301-443-9285
Phone number: 484-595-1011	**Phone number:** 301-827-7450

Subject: NDA 21-775 – 09/15/04 Meeting Request

Total no. of pages including cover: 3

Comments:

This will confirm the meeting between Adolor Corporation and the FDA to be held on November 23, 2004 from **1:30 – 3:00 PM**. I am also attaching a tentative list of attendees from the FDA who will be attending this meeting.

Document to be mailed: √ YES NO

The following is a tentative list of FDA participants:

Dr. Florence Houn, Director, ODE III

Dr. Julie Beitz, Deputy Director, ODE III

Dr. Joyce Korvick, Acting Director, DGCDP

Dr. Kathy Robie-Suh, Acting Deputy Director, DGCDP

Dr. Ruyi He, Medical Team Leader

Dr. Eric Brodsky, Medical Reviewer

Dr. Liang Zhou, Chemistry Team Leader

Dr. Ramesh Raghavachari, Chemistry Reviewer

Dr. Suresh Doddapaneni, Biopharmaceutics Team Leader

Dr. Sue Chi Lee, Biopharmaceutics Reviewer

Dr. Jasti Choudary, Supervisory Pharmacologist

Dr. Tamal Chakraborti, Pharmacology Reviewer

Dr. Stella Grosser, Statistics Team Leader

Dr. Wen Jen Chen, Statistical Reviewer

Ms. Melissa Furness, Regulatory Health Project Manager

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/s/

Melissa Furness
9/30/04 01:26:20 PM

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: September 8, 2004

To: Linda Harver, R.Ph., J.D.	**From:** Melissa Hancock Furness Regulatory Health Project Manager
Company: Adolor Corporation	Division of Gastrointestinal and Coagulation Drug Products
Fax number: 484-595-1528	**Fax number:** 301-443-9285
Phone number: 484-595-1011	**Phone number:** 301-827-7450

Subject: NDA 21-775

Total no. of pages including cover:

Comments:

Please note that your Application has been classified as a Standard Review, therefore, your PDUFA goal date will be April 25, 2005. Should you have questions, please contact me at 301-827-7450.

Best regards.

Document to be mailed: √ YES NO

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/s/

Melissa Furness
9/8/04 01:59:01 PM
CSO

Melissa Furness
9/8/04 02:01:58 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-775

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

Dear Ms. Harver:

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

We also refer to your submissions dated May 4, 2004 and May 27, 2004.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on August 24, 2004 in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues from an overview of the submission:

1) It appears that 12 mg of Entereg demonstrated statistical significance over placebo in the primary efficacy endpoint [the time to tolerate the first solid meal and (the time to the first bowel movement or first flatus)] in only one (313) of the four Phase III efficacy trials (302, 308, 313, and 306).

2) It appears that 12 mg of Entereg demonstrated statistical significance over placebo in a secondary endpoint (time to discharge written) in only two (313 and 308) of the four Phase III efficacy trials.

3) In Trial 313, the demonstration of a positive primary efficacy endpoint may have been due to the poor placebo response.

Therefore, we are concerned that the efficacy results for 12 mg of Entereg may not be adequate for the proposed indication.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We do not expect a response to this letter, and we may not review any such response during the current review cycle.

If you have any questions, call Tanya Clayton, B.S., Regulatory Project Manager, at (301) 827-4005.

Sincerely,

{See appended electronic signature page}

Joyce Korvick, M.D., M.P.H.
Acting Director
Division of Gastrointestinal & Coagulation
Drug Products, HFD 180
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Joyce Korvick
9/7/04 03:20:40 PM

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: August 10, 2004

To: Linda Harver, R.Ph., J.D.	**From:** Tanya D. Clayton, BS Regulatory Project Manager
Company: Adolor Corporation	Division of Gastrointestinal and Coagulation Drug Products
Fax number: 484-595-1528	**Fax number:** 301-443-9285
Phone number: 484-595-1011	**Phone number:** 301-827-4005

Subject: Information Request for NDA 21-775 (Entereg)

Total no. of pages including cover: 3

Comments:

Please find attached an Information Request, per our Statistical Reviewer.

Document to be mailed: YES √NO

INFORMATION REQUEST **Date: August 10, 2004**

NDA: 21-775
Sponsor: Adolor Corporation.
Drug: Entereg (Alvimopan) Capsules

Indication: Management of Postoperative Ileus

Dear Ms. Harver:

In order to complete the review for Entereg, please provide the following information for the three Studies 14CL302, 14CL308, and 14CL313.

I. Please provide data for each of the three Studies 14CL302, 14CL308, and 14CL313 electronic format consistent with the guidance, *Regulatory Submissions in Electronic Format; General Considerations.* It is suggested that the following variables be included:

Study number;
Investigator or Center code;
Country;
Patient discounted (yes or no);
Patient number/ID;
Treatment group (Placebo, Alvimopan 6 mg, or Alvimopan 12 mg);
Randomized population (yes or no);
Treated population (yes or no);
Safety population (yes or no);
Modified Intent-to-treat population (yes or no);
Efficacy Evaluable population (yes or no);
Gender;
Age;
Race;
Weight;
GI: Time to recovery of GI Function (GI^3);
BMSOLID: Time to Max (Tolerability of Solids, First BM);
READY: Time to Ready for Hospital Discharge;
FLATUS: Time to First Flatus;
BM: Time to First Bowel Movement;
SOLID: Time to First Solid Food;
DISCHARGE: Time to Hospital Discharge Order Written;
TONES: Time to First Bowel Tones;
LIQUID: Time to First Liquid Food;
BMFLATUS: Time to Min (First Flatus, First BM);
RESPOND: Responder;
VOMITING: Vomiting (Episodes);
NGREINS: Need for Reinsertion of NGT

Protocol-Specified surgery (Small BR, Large BR, Simple TAH, or Radical TAH);
Reason for Surgery (for example: Bleeding, Cancer, etc.);
Time Duration of Surgery;
First dose to start of surgery;
Total opioid consumption (pre- and intra-surgery);
Average of daily postoperative opioid consumption;
Geographic region of the site;

For each item without variable name, please provide interpretation/annotation.

II. For the three Studies 14CL302, 14CL308, and 14CL313, please provide programs (including SAS PHREG and SAS LIFETEST procedures, etc.) used for the statistical efficacy analyses for both Primary and Secondary Efficacy Endpoints stated in the section of Efficacy Analyses (Section 9.7.4.3) from the electronic submission for Clinical STUDY REPORT.

To the data set described in section I above, please add any additional variables needed (but not included in the data set) for the above analyses. Please also modify the programs to be able to read data from the data set described by section I.

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: August 6, 2004

To: Linda Harver, R.Ph., J.D.	**From:** Tanya D. Clayton, BS Regulatory Project Manager
Company: Adolor Corporation	Division of Gastrointestinal and Coagulation Drug Products
Fax number: 484-595-1513	**Fax number:** 301-443-9285
Phone number: 484-595-1011	**Phone number:** 301-827-4005

Subject: Information Request for NDA 21-775 (Entereg)

Total no. of pages including cover: 2

Comments:

Please find attached an Information Request, per our Statistical Reviewer.

Document to be mailed: YES √NO

Please provide hardcopies for the following three studies:

1. 14CL302
2. 14CL308
3. 14CL313

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/s/

Tanya Clayton
8/6/04 02:22:37 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-775/RU-003

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

Dear Ms. Harver:

We have received a reviewable unit (RU) of your new drug application (NDA) submitted under the Continuous Marketing Application (CMA)-Pilot 1 program for the following:

Name of Drug Product:	Entereg (Alvimopan) Capsules
Date of Submission:	June 25, 2004
Date of Receipt:	June 25, 2004
Our Reference Number:	NDA 21-775
Reviewable Unit:	RU-003

Unless we notify you otherwise within 60 days of the above receipt date, we will accept this presubmission as an RU. The user fee goal date for us to complete our review of this RU will be December 25, 2004.

Please cite the NDA number listed above on the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

Courier/Overnight Mail/U.S. Postal Service:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastrointestinal and Coagulation Drug Products, HFD-180
Attention: Division Document Room
5901-B Ammendale Road
Beltsville, Maryland 20705

If you have any questions, call me at (301) 827-4005.

Sincerely,

{See appended electronic signature page}

Tanya Clayton, B.S.
Regulatory Project Manager
Division of Gastrointestinal and Coagulation Drug Products, HFD-180
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Tanya Clayton
7/17/04 02:32:19 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-775/RU-002

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

Dear Ms. Harver:

We have received a reviewable unit (RU) of your new drug application (NDA) submitted under the Continuous Marketing Application (CMA)-Pilot 1 program for the following:

Name of Drug Product:	Entereg (Alvimopan) Capsules
Date of Submission:	May 27, 2004
Date of Receipt:	June 1, 2004
Our Reference Number:	NDA 21-775
Reviewable Unit:	RU-002

Unless we notify you otherwise within 60 days of the above receipt date, we will accept this presubmission as an RU. The user fee goal date for us to complete our review of this RU will be December 1, 2004.

Please cite the NDA number listed above on the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

Courier/Overnight Mail/U.S. Postal Service:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastrointestinal and Coagulation Drug Products, HFD-180
Attention: Division Document Room
5901-B Ammendale Road
Beltsville, Maryland 20705

If you have any questions, call me at (301) 827-4005.

Sincerely,

{See appended electronic signature page}

Tanya Clayton, B.S.
Regulatory Project Manager
Division of Gastrointestinal and Coagulation Drug Products, HFD-180
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Tanya Clayton
6/21/04 10:36:44 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-775

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

Dear Ms. Harver:

We have received the first section of your New Drug Application (NDA) submitted under the program for Continuous Marketing Applications: Pilot 1- Reviewable Units for Fast Track Products under PDUFA pursuant to section 112 of the Food and Drug Administration Modernization Act of 1997 (section 506 of the Federal Food, Drug, and Cosmetic Act) for the following:

Name of Drug Product: Entereg (Alvimopan) Capsules

Date of Submission: May 4, 2004

Date of Receipt: May 5, 2004

Our Reference Number: NDA 21-775

Content: Nonclinical Pharmacology and Toxicology unit

Unless we notify you within 60 days of the receipt date that this reviewable unit is not sufficiently complete to permit a substantive review, we will file this reviewable unit on July 6, 2004 in accordance with 21 CFR 314.101(a). If this reviewable unit is filed, the user fee goal date will be November 5, 2004.

Please cite the NDA number assigned to this application at the top of the first page of every communication concerning this reviewable unit, future reviewable units, and the full application.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We reference the deferral granted on March 12, 2001 for the pediatric study requirement for this application.

Address all additional reviewable units as follows:

Courier/Overnight Mail/U.S. Postal Service:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastrointestinal and Coagulation Drug Products, HFD-180
5901-B Ammendale Road
Beltsville, Maryland 20705

If you have any questions, call Tanya Clayton, B.S., Regulatory Project Manager, at (301) 827-4005.

Sincerely,

{See appended electronic signature page}

Tanya Clayton, B.S.
Regulatory Project Manager
Division of Gastrointestinal and Coagulation
Drug Products, HFD-180
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Tanya Clayton
6/21/04 10:14:20 AM

Pre NDA

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 56,553

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

Dear Dr. Harver:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Alvimopan.

We also refer to the meeting between representatives of your firm and the FDA on February 25, 2004. The purpose of the meeting was to obtain the Agency's guidance on your proposed plans for NDA submission as well as the format and content intended to support your proposed labeling indication.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 827-4005.

Sincerely,

{See appended electronic signature page}

Tanya Clayton, B.S.
Regulatory Project Manager
Division of Gastrointestinal and Coagulation
Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

Meeting Date: February 25, 2004

Time: 1:00-2:30 PM

Location: Parklawn Building, Potomac Conference Room

Application: IND 56,553; Alvimopan

Type of Meeting: Type B, Pre-NDA (CMC)

Meeting Chair: Liang Zhou, Ph.D.

Meeting Recorder: Tanya Clayton, B.S.

FDA Attendees, Titles, and Office/Division:

Division of Gastrointestinal and Coagulation Drug Products

Liang Zhou, Ph.D.	Chemistry Team Leader
Ramesh Raghavachari, Ph.D.	Chemistry Reviewer
Zhengfang Ge, Ph.D.	Chemistry Reviewer
Hugo Gallo Torres, M.D.	Medical Team Leader
Tanya Clayton, B.S.	Regulatory Project Manager

External Constituent Attendees and Titles:

Adolor Corporation:

Carrie Frey, M.S., MBA	Vice President, Project Management
Deanne D. Garver, Ph.D.	Vice President, Preclinical Research & Development
Linda Y. Harver, R.Ph., JD	Vice President, Regulatory Affairs
Bruce A. Wallin, M.D.	Vice President, Clinical Research & Development
Michael Dougherty	Senior Vice President

[redacted]

Virendra Kumar, Ph.D.	Director of Process Chemistry
George Mauren	Senior Director, Commercial Manufacturing

GlaxoSmith Kline:

Mark Owen, Ph.D.	Director, Regulatory Affairs, Manufacturing

Background:

On December 29, 2003, the firm requested an Pre-NDA, CMC meeting for the purpose of obtaining the Agency's guidance on their proposed plans for NDA submission as well as the format and content intended to support their proposed labeling indication.

A subsequent January 26, 2004 background package was submitted, which contained 8 questions.

Following introductions, the attendees proceeded directly to the questions for response.

Discussion Points: (bullet format):

General

1. Have the CMC issues at the End of Phase 2 Meeting been covered to the satisfaction of the Agency and are the data and table of contents presented in the CMC Briefing Document (BD) sufficient to support submission of the NDA for alvimopan in the preoperative and postoperative Setting?

FDA response:

From the CMC point of view, it appears to be acceptable. However, this is a review issue.

Drug Substance:

2. Does the Agency agree to the approach for release and stability testing of the drug substance?

FDA response:

The proposed stability plan for the drug substance appears to be acceptable.

3. Does the Agency agree to the proposed stability protocols supporting the NDA drug substance registration lots? Twenty-four month data are available on one lot of drug substance used to formulate a clinical trial drug product batch. Twelve-month data will be available for the three remaining lots. A re-test date of [redacted] will be proposed in the NDA.

FDA response:

It appears to be acceptable. However, re-testing period for the drug substance will depend upon the stability data provided in the NDA submission.

4. Does the Agency have comment on the format and content of the drug substance section of the NDA?

FDA response:

The format appears to be acceptable. For the specifications please include a listing of test methods by identifying code.

Additional comments regarding the drug substance specifications:

Drug Substance (API):

- **Purity-HPLC: Based on your stability batch test data provided, the impurities acceptance criteria for [redacted] appear to be too high and these specifications should be tightened.**
- [redacted]
- **Assay-HPLC:**
- [redacted]
- **Heavy Metals: Clarify what method will be used for heavy metals testing.**
- **Residual Solvents: Tighten residual solvent acceptance criteria based on batch test data.**

  - **Adolor intends not to include [redacted] in the NDA as a specified impurity in the final API. An in-process control has been implemented prior to the isolation of the API.**
  - **Sponsor will provide the test method code numbers in the NDA and the content as outlined in the Table of Contents appears to be acceptable.**

Drug Product:

5. Does the Agency agree to the approach for release and stability testing of the drug product?

FDA response:

The proposed release tests appear to be sufficient however the acceptance criteria will be a review issue. Please ensure that adequate justification of the acceptance criteria is provided. The proposed stability protocol for the drug product appears to be acceptable.

6. Does the Agency agree to the proposed stability protocol supporting the NDA drug product registration lots at the proposed commercial manufacturing facility? Twenty-four month data are available on three primary NDA batches of drug product at approximately 40% of the commercial scale. Six-month data will be available on one commercial scale batch. [redacted]

FDA response:

Expiry dating will depend upon the stability data provided in the NDA submission.

Statistical analysis of the stability data will be needed for projection of an expiry past available real time data. Potency and impurities should be within 95% confidence interval at the proposed expiry. Additionally accelerated data should show no adverse trends.

7. Does the Agency have comment on the proposed dissolution method and specification?

FDA response:

Proposed USP dissolution method and specification appears to be acceptable.

8. Does the Agency have comment on the format and content of the drug product section of the NDA based upon the annotated table of contents and the sample stability data table in 10-point font?

FDA response:

The proposed content and format appears to be acceptable.

Additional comments regarding Drug Product Specifications:

Drug Product:

- **Degradation Products/impurities: Based on the batch data in this submission provided, these specifications appear to be too broad and should be tightened.**
- **Chiral - HPLC: [redacted] for the drug product than the drug substance. Does the amount of impurity increase during stability studies or is it a process impurity from the drug substance? Please clarify.**
- **Please explain why a [redacted] test is not proposed. For the specifications please include a listing of test methods by identifying code.**

- Please provide analytical data showing the percentage composition of all the impurities in the drug substance for the following lots: OR 12098.N.00.01; OR 12098.N.01.D1.01 and OR 12098.N.00.03.
  (The above lots were used in the pre-clinical and clinical studies.)

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/s/

Tanya Clayton
3/25/04 01:31:11 PM

Liang Zhou
3/25/04 02:18:56 PM

Pre NDA

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 56,553

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

Dear Dr. Harver:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Alvimopan.

We also refer to the meeting between representatives of your firm and the FDA on February 23, 2004. The purpose of the meeting was to obtain the Agency's guidance on your proposed plans for NDA submission as well as the format and content intended to support your proposed labeling indication.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 827-4005.

Sincerely,

{See appended electronic signature page}

Tanya Clayton
Regulatory Project Manager
Division of Gastrointestinal and Coagulation
Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

Meeting Date: February 23, 2004

Time: 11:00-12:30 PM

Location: Parklawn Building, Potomac Conference Room

Application: IND 56,553; Alvimopan

Type of Meeting: Type B, Pre-NDA

Meeting Chair: Joyce Korvick, M.D., M.P.H.

Meeting Recorder: Tanya Clayton, B.S.

FDA Attendees, Titles, and Office/Division:

Division of Gastrointestinal and Coagulation Drug Products

Robert Justice, M.D., M.Sc.	Division Director
Joyce Korvick, M.D., M.P.H.	Deputy Division Director
Robert Prizont, M.D.	Medical Reviewer
Jasti Choudary, Ph.D., B.V.Sc.	Supervisory Pharmacologist
Suliman AL-Fayoumi, Ph.D.	Biopharmaceutical Reviewer
Stella Grosser, Ph.D.	Statistical Team Leader
Milton Fan, Ph.D.	Statistical Reviewer
Zei-Pao Huang	Review Technologist (Office of Information Management)
Tanya Clayton, B.S.	Regulatory Project Manager

External Constituent Attendees and Titles:

Adolor Corporation:

Wei Du, Ph.D.	Vice President, Biometrics
Joseph Foss, M.D.	Clinical Research Director, Clinical Research & Development
Carrie Frey, M.S., MBA	Vice President, Project Management
Deanne D. Garver, Ph.D.	Vice President, Preclinical Research & Development
Linda Y. Harver, R.Ph., JD,	Vice President, Regulatory Affairs
David Jackson, M.D.	Sr. Vice President, Research & Development
Lee M. Techner, D.P.M., Medical Affairs	Director, Clinical Research & Development
Bruce A. Wallin, M.D., Vice President	Clinical Research & Development

GlaxoSmith Kline:

Elizabeth Nies	Senior Director, Regulatory Affairs
Eric Carter, M.D.	Vice President, Clinical Development and Medical Affairs
Craig Metz	Vice President Regulatory Affairs

Background:

On December 29, 2003, the firm requested an Pre-NDA meeting for the purpose of obtaining the Agency's guidance on their proposed plans for NDA submission as well as the format and content intended to support their proposed labeling indication.

A subsequent January 23, 2003 background package was submitted, which contained 22 questions.

Following introductions, the attendees proceeded directly to the questions for response.

Discussion Points: (bullet format):

Clinical

1. Based on our current understanding of the data from our development program and the information summarized in this briefing document we feel that Entereg [redacted] 12 mg provide clinically and statistically significant effect across study endpoints. Does the Agency have any preliminary comments regarding dose selection?

Agency's Response
No, the final dose selection should be based not only on efficacy, but on the proportion of adverse events associated with each dose level.

2. Does the FDA have comments/suggestions at this time on the proposed information or presentation of data in the Clinical Studies or any other section of the DRAFT package insert (provided in Appendix A)?

Agency's Response
No, we have no comments/suggestions at this time.

3. The Phase 3 protocols stipulated administration of the first dose of Entereg 2 hours prior to surgery. Actual administration times varied. Based on the dosing times reflected in the clinical data and supporting rationale provided in the BD, we propose that the Dosage and Administration section of the Prescribing Information state that the pre-operative dose of alvimopan should be administered no less than 30 minutes and up to 5 hours prior to surgery. Would the FDA consider this feasible?

Agency's Response
Yes, we will consider the proposal. You will need to provide an adequate justification in the NDA.

4. Does the FDA have additional comments based on the clinical data provided in the BD?

Agency's Repsonse
No, we have no additional comments.

Clinical Pharmacology/Pharmacokinetics (PK)

5. At the EOP2 meeting, information on the primary metabolite of alvimopan in humans and absorption of alvimopan was discussed. As a result of that discussion, the FDA recommended several additional studies be conducted. These recommended additional nonclinical and clinical studies have been conducted as reflected in the NDA table of contents and described in the BD. Does the FDA agree that these investigations address its request for additional information on the primary metabolite and absorption of alvimopan?

Agency's Response
Yes, you have adequately addressed the request for additional clinical information on the primary metabolite and absorption of Alvimopan. Please explain how you have evaluated absorption of Alvimopan in animal studies as per our request at the March 1, 2002 meeting.

- **The sponsor stated that they are using the same analytical method in both the clinical and non-clinical studies.**

6. At the second EOP2 meeting (March 2002), Adolor agreed to conduct a study in subjects with severe hepatic impairment in addition to the study in subjects with mild and moderate hepatic impairment. The study originally planned to recruit 3 to 6 such subjects. Based on the information presented in the BD, will the Division accept the study with 3 subjects as supportive of the proposed labeling direction for this special population?

Agency's Repsonse
Given the limited and highly variable data on PK in patients with severe hepatic impairment, the label may contraindicate the use of Alvimopan in this group of patients.

- **The sponsor proposes to stop the current study and submit data on 3 subjects only. This is acceptable.**

7. The *in vitro*, *in vivo* and clinical data presented in the BD indicate that neither alvimopan nor its active metabolite (ADL 08-0011) causes QT interval prolongation. Does the Division agree that the NDA submission is acceptable with a QTc study as an ongoing study, results to be submitted in the 120-day safety update?

Agency's Repsonse
Yes, this is acceptable.

8. Does the FDA have any additional comments based on the clinical pharmacology/PK data included in the BD?

Agency's Repsonse
No, we have no additional comments at this time.

Statistics

9. Does the FDA agree with the data pooling methodology and the format of the summary tables specified in the SAPs for the ISS and ISE?.

Agency's Repsonse
No, we do not agree with the proposed data pooling methodology for the ISE. The Cox model for pooling data should include the main effects: treatment, study and surgery type and some interactions between the main effects. The interactions between study and surgery type, between treatment by study and between treatment and surgery type should be tested. The categories used for stratification variable (surgery type) should be used for surgery type. The format for the summary tables specified in the SAPS for the ISS and ISE appear to be acceptable. The methodology for ISS is acceptable.

10. The Joint SAP for the POI Phase 3 efficacy protocols was submitted to the FDA on March 3, 2003, Serial #141. The comments and approval from the FDA were received on April 16, 2003 (re Appendix G). An Addendum to the Joint SAP, in which two additional analyses were added (analysis on time to toleration of solid food and first bowel movement and a summary of means for all time to events using the area under the Kaplan Meier survival curves), was submitted to the IND on August 22, 2003. The same efficacy analyses will be performed for the ISE. Does the FDA have any additional statistical comments based on the review of the information provided in the SAPs and BD?

Agency's Repsonse

Please see the comments based on the information provided in the SAP for ISE:

- **All treated patient analysis should be included.**
- **Proportional hazard (PH) assumption of the Cox model and goodness of fit should be assessed.**
- **Categories used for stratification variable (surgery type) should be used for the categories for factor.**
- **A summary table including coefficients, stand error, p-value, HR, 95% confidence interval, and P(PH) should be included.**
- **Summary of results from evaluation of assumption of PH and goodness of fit should be provided.**
- **For analysis of proportion of responders, the definition of responder used for individual study should be used for ISE analysis.**

General

11. Does the Division concur that the clinical and nonclinical data, as described in the BD, are sufficient to support submission of an initial NDA for oral alvimopan for the proposed indication?

Agency's Repsonse

Yes, the clinical and nonclinical data appear sufficient to support submission of an initial NDA for oral Alvimopan.

12. At the time of NDA submission, Adolor will request priority review. We appreciate that the decision regarding priority review will be made at the FDA's 45-day meeting. However, can the Division comment on the feasibility/potential of the proposed NDA being granted priority review?

Agency's Repsonse

This will be considered at the time of filing.

13. Adolor submitted a request for fast-track designation on December 17, 2003. Will the FDA consider a continuous marketing application or rolling NDA review for the planned Alvimopan application?

Agency's Repsonse
Please clarify your question.

- **The sponsor indicated they would like to request an CMA, Pilot 1. Their intent would be to submit the pharmacology/toxicology May 1, 2004 and the CMC June 1, 2004 prior to the NDA submission.**

14. At this time, does the Division anticipate that this proposed use of Alvimopan will be the subject of an Advisory Committee?

Agency's Repsonse
This will be determined at the time of filing.

15. The FDA's minutes of our March 2001 EOP2 meeting reflect an agreement that pediatric studies would be a Phase 4/post-approval commitment to permit the evaluation of safety and efficacy in adults prior to administration in children. Will the FDA confirm the agreement that pediatric trials will be deferred until this NDA is approved for alvimopan use in adults?

Agency's Repsonse
We confirm that pediatric trials will be deferred until a regulatory decision on this NDA has been made.

16. Will the FDA confirm the agreement that carcinogenicity studies will not be required for the initial NDA filing for the proposed acute hospital indication?

Agency's Repsonse
Yes, carcinogenicity studies are not needed for this indication.

NDA Content and Format

17. Does the Division agree with the proposed NDA table of contents and format reflected in the enclosed CD outlining the eNDA (reference Appendix H)?

Agency's Repsonse
Yes, we agree with the proposed NDA table of contents and format.

- **The sponsor requested further direction regarding formatting of the label in SML.**

18. Does the Division agree with the proposed electronic NDA filing as detailed in the BD? (The cover letter and certifications will be filed in one paper volume. It is the sponsor's intent to have all data and reports reviewed electronically.)

Agency's Repsonse
Yes, we agree with the proposed electronic NDA filing.

19. Are the legacy documents, e.g. prior sponsor's IND data/reports, shown in Item 5 of the e-NDA (found in the e-NDA demo CD in Appendix H) sufficient as .pdf files (scans only)? These are identified in the BD for ease of location in the electronic NDA demo.

Agency's Repsonse
Yes, the legacy documents as proposed are sufficient.

20. Does the Agency agree with the proposed datasets (found in the datasets CD included with the BD) for efficacy, safety and pharmacokinetics?

Agency's Repsonse
Yes, we agree with the proposed datasets.

21. Does the Agency agree with the proposed safety narratives and listings as indicated in the BD?

Agency's Repsonse
Yes, we agree with the proposed safety narratives and listings as indicated.

22. Does the FDA have any additional comments/recommendations regarding format and/or content of the proposed NDA?

Agency's Repsonse
No, we have no additional comments regarding format of the proposed NDA.

Comments from the Office of Drug Safety

- If the sponsor and/or FDA believe that there are product risks that merit more than conventional professional product labeling (i.e. package insert (PI) or patient package insert (PPI)) and postmarketing surveillance to manage risks, then the Sponsor is encouraged to engage in further discussions with FDA about the nature of the risks and the potential need for a risk management program.

- If the NDA/BLA application includes risk management programs or pharmacovigilance plans and will be submitted in the Common Technical Document format, please submit as follows:

  Risk Management Programs

  2.5.5 Overview of Safety with appropriate cross references to section
  2.7.4 Summary of Clinical Safety
  and any other relevant sections of the Common Technical Document for the NDA/BLA application.

  Pharmacovigilance plans

  2.5.5 Overview of Safety, with any protocols for specific studies provided in 5.3.5.4 Other Clinical Study Reports or other sections as appropriate
  (e.g., module 4 if the study is a nonclinical study).

  If the application is not being submitted as a Common Technical Document, include proposed plans for risk management in the
  NDA Clinical Data Section (21 CFR 314.50 (d)(5)) or
  BLA Clinical Data Section (21 CFR 601.25(b)(3))
  and clearly label and index them.

- For the most recent publicly available information on CDER's views on risk management plan activities, please refer to the draft Concept Papers on Risk Management Programs and Risk Assessment of Observational Data: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment which can be located electronically at http://www.fda.gov/cder/meeting/riskManageII.htm and http://www.fda.gov/cder/meeting/riskManageIII.htm .

- If there is any information on product medication errors from the premarketing clinical experience, ODS requests that this information be submitted with the NDA/BLA application.

- The sponsor is encouraged to submit the proprietary name and all associated labels and labeling for review as soon as available.

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/s/

Tanya Clayton
3/23/04 10:02:10 AM

Joyce Korvick
3/23/04 04:59:40 PM
for Dr. Robert Justice

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 56,553

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

Dear Ms. Harver:

Please refer to the meeting between representatives of your firm and FDA on March 12, 2001. The purpose of the meeting was a clinical End of Phase II meeting.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 827-1602 or (301) 827-7310.

Sincerely,

{See appended electronic signature page}

Alice Kacuba, R.N., MSN, RAC
Regulatory Health Project Manager
Division of Gastrointestinal & Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

Meeting Date: March 12, 2001
Time: 12:30 – 2:00 PM
Location: Parklawn Building, Conference Room "Q"

Application: IND 56,553, ADL 8-2698 Capsules

Type of Meeting: Clinical EOP 2 Meeting

Meeting Chair: Lilia Talarico

Meeting Recorder: Alice Kacuba

FDA Attendees, Titles, and Office/Division:

Division of Gastrointestinal and Coagulation Drug Products (HFD-180)

Lilia Talarico, M.D.; Division Director
Hugo Gallo-Torres, M.D., Ph.D.; Medical GI Team Leader
Jasti Choudary, B.V.Sc., Ph.D.; Supervisory Pharmacologist
Alice Kacuba, R.N., MSN, RAC; Regulatory Health Project Manager

Division of Biometrics III (HFD-720)

Tom Permutt, Ph.D.; Statistical Team Leader
Milton Fan, Ph.D.; Statistical Reviewer

Division of Pharmaceutical Evaluation II (HFD-870)

Suliman Al-Fayoumi, Ph.D.; Biopharmaceutics Reviewer

External Constituent Attendees and Titles:

Adolor Corporation

Randall Carpenter, M.D.; Vice President, Clinical Research

[redacted]

Deanne D. Garver, Ph.D.; Vice President, Preclinical Development
Linda Y. Harver, R.Ph., JD; Vice President, Regulatory Affairs
David Jackson, M.D.; Senior Vice President, Research & Development
William Schmidt, Ph.D.; Vice President, Technical Affairs
Mahmoud Seyedsadr, Ph.D.; Director, Biostatistics

Background: IND 56, 553 for ADL 8-2698 Capsules is currently being investigated for post-operative ileus (POI) and management of opioid bowel dysfunction. An initial clinical meeting was held between the Adolor and the Division and the Office on October 16, 2000. Today's clinical EOP2 meeting is a follow-up from that meeting. A separate chemistry, manufacturing and controls meeting is scheduled for March 13, 2001.

Discussion Points (bullet format): The format of these meeting minutes provide for the firm's questions in regular print, followed the Division's responses in bolded printed and subsequent discussion in italics print.

1. Will the Division agree that the scope of the clinical development plan (studies conducted and planned) is adequate to support the indication of management of postoperative ileus, assuming that the risk/benefit assessment at the conclusion of the trials is positive?

- **We agree with the general approach to your drug development plan. However, you will need 2 adequate, well controlled, well designed trials for your indication.**
- **We have some additional questions regarding the proposed Phase III study:**
  -Clarify the 2 studies. Are they POI alone or POI following surgery and receiving opioid therapy related to the surgical procedure?
  -Clarify the types of surgeries. Is it all patients, regardless of the surgical procedure or are the patients being selected by surgical procedure? Are certain surgical procedures not included?
  -How will the standardization of the procedures to assess efficacy, including specific surgical interventions, be done?
  -How will the standardization of the procedures to assess safety be done?
  -Identify primary and secondary endpoints of efficacy.
  -Investigate effects of higher doses such as 12 mg.

After some discussion, it was agreed that the achievement of both time to recovery of upper GI function and time to recovery of lower GI function are necessary to demonstrate efficacy. This reduction in time to return of GI function must be clinically significant. According to the firm, it is expected that a return to GI function will lead to earlier discharge from the hospital. Dr. Talarico stressed that it had to be shown that GI function had to be resolved such that the patient was ready for discharge. It was agreed that the firm will add a question to the case report forms to document when the investigator feels that the patient is ready for discharge from the GI perspective. If the patient remains hospitalized after the return of GI function, the reasons will be documented on the case report forms.

a. Will the Division agree that the subject population included in Trial 14C305, assessing nausea and vomiting as primary endpoints after major surgery in subjects at the same dosing regimen as the POI trials, is a representative subject population to support safety for the POI indication?

- **Yes, for safety. The difference in duration of therapy will have to be addressed.**

According to the firm, the duration of the trials is the same.

b. Will the Division agree that the observed ten-fold safety margin is adequate to support safety in man? Adolor has been unable to identify dose-limiting toxicity in human trials at daily doses (120 mg) ten times higher than the expected single dose for this indication (12 mg).

- **It is premature to respond to this question. The available data are not enough. We do not know if the safety margin is acceptable.**

c. Will the Division agree that the development plan adequately addresses safety in special populations including geriatrics, patients with inflammatory bowel disease, and patients with hepatic or renal impairment?

- **We do not have enough data to respond to this question.**

During discussion it was clarified that a geriatric subpopulation analysis will be made from the currently planned studies. The geriatric population is defined as a population at least 65 years old. Adolor also will analyze those being 75 years and older.

d. Will the Division agree with plans to exclude drug interaction studies?

- **No, we do not have adequate data to support the exclusion of drug interaction studies.**

During discussion, it was agreed that further information was needed. In addition, the issue of whether some drugs may be pushed through the GI track quicker, thus resulting in being less bioavailable and absorbed less, needs to be addressed. According to the firm, in normal volunteers, ADL 8-2698 Capsules did not speed GI transit time. The firm will examine the concomitant medications being utilized in the clinical trials to help address this issue.

e. Will the Division accept an NDA with the deferral of pediatric data to a Phase IV commitment?

- **Yes.**

2. [redacted]

- **We do not have enough data to address this question.**

3. Will the FDA accept our NDA filing with a commitment to file the carcinogenicity data during the review period?

   - **For the indication of POI, when the drug is administered only for 7 days, carcinogenicity studies may not be needed.**

   - **For other indications, submission of carcinogenicity study data during the review cycle is not acceptable.**

4. [redacted]

   - **We can not answer this at the present time.**

[redacted]

Additional comments:

Dr. Talarico advised the firm that if they decided to pursue a fast track designation, to refer to the guidance document for fast track designation, available on the Agency's website, and submit a package for review and determination.

Dr. Talarico also informed the firm that, upon submission of an NDA for the indication of POI, the firm could request priority review along with providing a justification, and the review team would consider the request during the filing period.

[redacted]

Minutes Preparer:

Chair Concurrence:

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/s/

Lilia Talarico
4/24/01 05:02:57 PM

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

/s/

Alice Kacuba
4/25/01 10:38:35 AM