

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-775**

**CHEMISTRY REVIEW(S)**

## MEMORANDUM

Date: May 12, 2008

To: NDA 21-775

From: Elaine Morefield, Ph.D.  
Division Director  
Pre-marketing Assessment Division II  
ONDQA

Subject: Addendum to the Tertiary review of ONDQA recommendation for NDA 21-775 Entereg (alvimopan) 12 mg capsules.

I have assessed the addendum to ONDQA review of NDA 21-775, and all labeling issues appear to be resolved. I concur with the approval recommendation from a CMC perspective.

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/s/

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Elaine Morefield  
5/12/2008 10:59:29 AM  
CHEMIST



Chemistry Assessment Section

**Memorandum**

Date: May 5, 2008  
From: Zhengfang Ge, Ph.D., Reviewer  
Through: Moo-Jhong Rhee, Ph.D., Branch Chief  
To: NDA 21-775 Entereg (alvimopan) 12 mg capsules  
Subject: Addendum to Review #3 regarding Labeling

The labeling has been reviewed for NDA 21-775. The sponsor modified container labels/carton based on the Agency's recommendation. Some minor wording was modified in the labeling. From the CMC prospective, the final labeling is satisfactory and this NDA can be approved.

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/s/

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Zhengfang Ge  
5/6/2008 11:25:21 AM  
CHEMIST

Moo-Jhong Rhee  
5/6/2008 01:13:34 PM  
CHEMIST  
Chief, Branch III

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**INTEROFFICE MEMORANDUM**

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**DATE:** 11/1/2006  
**TO:** NDA 21-775  
**FROM:** ELAINE MOREFIELD, PH.D.  
DIRECTOR, PRE-MARKETING ASSESSMENT DIVISION II  
**SUBJECT:** REVISED TERTIARY REVIEW CONCURRENCE OF NDA 21-775, ENTEREG  
(ALVIMOPAN) CAPSULES

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NDA 21-775, Entereg (Alvimopan) capsules, was submitted by Adolor Corporation. The chemistry and manufacturing controls have been reviewed by Dr. Zhengfang Ge and approved by Dr. Moo-Jhong Rhee. They have made a recommendation that this NDA may be approved from a CMC perspective.

I have completed a tertiary review of this application. I have reviewed the API and finished product specifications and process controls and find them to be acceptable from a scientific and regulatory perspective. As this NDA is approvable, the labeling review has not been fully completed. Labeling revisions were recommended in this review. For future note, there is a mistake in the prescription information line number 15; ~~\_\_\_\_\_~~ All other CMC related issues appear to be resolved in an acceptable manner. Therefore, I concur with the recommendation that NDA 21-775 may be approved from a CMC perspective provided the labeling is revised in an acceptable manner.

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/s/

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Elaine Morefield

11/1/2006 03:52:10 PM

CHEMIST

Division Director, Pre-Marketing Division II, ONDQA

**NDA 21-775**

**Entereg (alvimopan), Capsules 12 mg  
Adolor Corporation**

**Division of Gastrointestinal Drug Products**

**Zhengfang Ge, Ph.D.**

**Branch III, Division of Pre-Marketing Assessment II  
Office of New Drug Quality Assessment**



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# Chemistry Review Data Sheet

1. NDA # 21-775
2. REVIEW # 3
3. REVIEW DATE: Oct 18, 2006
4. REVIEWER: Zhengfang Ge
5. PREVIOUS DOCUMENTS:

Previous Documents

Original submission - RUC  
N 21-775 N-000-BC  
N21-775 N-000-BC

Document Date

May 27, 2004  
September 24, 2004  
December 02, 2004

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

N21-775 N-004-BC  
N21-775 N-BZ

Document Date

Jan 31, 2006  
May 9, 2006

7. NAME & ADDRESS OF APPLICANT:

Name: Adolor Corporation  
Address: 700 Pennsylvania Drive, Exton, PA 19341  
Representative: Linda Harver, V.P. Regulatory Affairs  
Telephone: 484-595-1011

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Entereg Capsules

Chemistry Review Data Sheet

- b) Non-Proprietary Name (USAN): Alvimopan
- c) Code Name/# (ONDC only): ADL 8-2698
- d) Chem. Type/Submission Priority (ONDQA only):
  - Chem. Type: 1
  - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: This application was filed under the provisions of section 505(b)(1) of Federal Food, Drug and Cosmetic act and 21 CFR 314.50.

10. PHARMACOL. CATEGORY:  $\mu$ -Opioid receptor antagonist

11. DOSAGE FORM: Capsules

12. STRENGTH/POTENCY: 12 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED:  Rx  OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

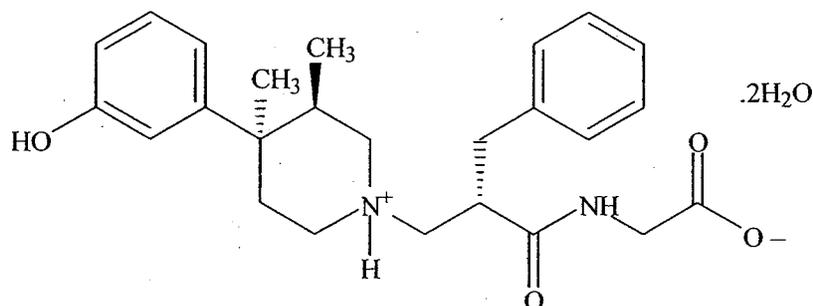
SPOTS product – Form Completed

Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



## Chemistry Review Data Sheet

**Name:**

[[2(S)-[[4(R)-(3-hydroxyphenyl)-3(R),4-dimethyl-1-piperidyl]methyl]-1-oxo-3-phenylpropyl]amino]acetic acid dihydrate

**Molecular Formula:** C<sub>25</sub>H<sub>32</sub>N<sub>2</sub>O<sub>4</sub>·2H<sub>2</sub>O

**Molecular Weight:** 460.6

## 17. RELATED/SUPPORTING DOCUMENTS:

## A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
—	IV	—		4	N/A		

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

### B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Review # 1 and 2	NDA 21, 775	Review of original submission
AE letter	July 21, 2005	

### 18. STATUS:

#### ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not Applicable		
EES	Acceptable	06-Jul-2006	Office of Compliance
Pharm/Tox	Not Applicable		
Biopharm	Not Applicable		
LNC	Not Applicable		
Methods Validation	Submit post market		
DMETS	Pending		
EA	No Change		Same as original review
Microbiology	Not Applicable		Oral dosage form

#### OGD:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology			
EES			
Methods Validation			
Labeling			
Bioequivalence			
EA			
Radiopharmaceutical			

### 19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. \_\_\_ Yes \_\_\_ No If no, explain reason(s) below:

# The Chemistry Review for NDA 21-775

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

From CMC point of view, this NDA can be approved provided that the sponsor agrees to the following labeling changes:

- The applicant should delete the words [REDACTED] and add "inactive ingredient" in front of polyethylene glycol in the labeling description section. The established name (alvimopan) and dosage form should be displayed in the same line instead of displayed in separate lines. The graphics in the carton may need to be removed pending DMETS review.

#### 1. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Not applicable.

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

##### Drug Substance:

The drug substance (alvimopan) is a new molecular entity with three chiral centers. It is a derivative of phenyl piperidine. The drug substance is synthesized in [REDACTED] steps. CMC review of the original NDA submission found the drug substance satisfactory. In this resubmission, the sponsor proposed [REDACTED] alvimopan synthesis. The change of the [REDACTED]

methods and added an additional testing site. The updated analytical methods are reviewed and found adequate. Updated batch results including one batch of the drug substance using improved [REDACTED] are reviewed and found adequate.

##### Drug Product:

[REDACTED]  
[REDACTED] In this amendment, the sponsor added a new dose strength of drug product (12 mg capsules) and stated that only 12 mg will be marketed upon approval of this NDA. The composition difference of 12 mg capsules [REDACTED]

[REDACTED] in the amount of polyethylene glycol (PEG) [REDACTED] The

Executive Summary Section

sponsor also made changes for the capsule shell color and the ink for 12 mg drug product, however, the components of the color and ink are the same as those described in the original NDA [REDACTED]. An alternative testing site is added for release and stability testing of both drug substance and drug product, GMP inspection of this testing site has found adequate by Office of Compliance dated 6-Jul-2006. [REDACTED] improved test methods are provided for the drug product. The updated analytical methods are reviewed and found adequate. The updated stability data [REDACTED] for 12 mg drug products are reviewed and found adequate for granting 24 months of expiring date.

**B. Description of How the Drug Product is Intended to be Used**

ENTEREG (Alvimopan 12 mg, anhydrous) is indicated to accelerate time to recovery of gastrointestinal function following abdominal or pelvic surgery. The following doses were proposed in the labeling:

**Usual dose in adults:** The recommended adult dose of ENTEREG is 12 mg. The initial dose should be administered within no fewer than 30 minutes and no more than 5 hours prior to the scheduled start of surgery. Administer 12 mg twice daily beginning the day after surgery for a maximum of 7 days while the patient is hospitalized or until discharged from the hospital.

**C. Basis for Approvability or Not-Approval Recommendation**

[REDACTED]  
 CMC point of view. The review of this amendment found that the sponsor provided improved manufacturing process for the drug substance with adequate process controls. The amendment review also found that the sponsor provided adequate information for composition of 12 mg dose strength of the drug product and the modified analytical methods. The updated stability data is adequate to support 24 months of expiring date. The GMP inspection of the manufacturing facilities has found that the facilities are adequate. Except for the following minor labeling changes needed, the sponsor in general provided adequate CMC information in the labeling.

- In the labeling description section, delete the words [REDACTED] and add "inactive ingredient" in front of polyethylene glycol.
- The established name (alvimopan) and dosage form should be displayed in the same line instead of displayed in separate lines.
- The graphics in the carton may be promotional and need to be removed pending DMETS review conclusion.

**III. Administrative**

**A. Reviewer's Signature**

IN DFS

Executive Summary Section

**B. Endorsement Block**

ChemistName/Date: Same date as the review  
ChemistryTeamLeaderName/Date  
ProjectManagerName/Date

**C. CC Block**

38 Page(s) Withheld

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Draft Labeling

Deliberative Process

Withheld Track Number: Chemistry- 5

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/s/

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Zhengfang Ge  
10/18/2006 02:38:01 PM  
CHEMIST

Moo-Jhong Rhee  
10/23/2006 12:46:46 PM  
CHEMIST  
Chief, Branch III

NDA 21-775

Entereg (Alvimopan) — Capsules

**CHEMISTRY DIVISION DIRECTOR REVIEW**

Applicant:

Adolor Corporation  
700 Pennsylvania Drive  
Exton, PA 19341

Indication: For the treatment of post-operative ileus

Pharmacological Category:  $\mu$ -Opioid receptor antagonist

Presentation: Capsule, \_\_\_\_\_

EER Status: Acceptable

Consults: None

Post Approval Agreements: None

The NDA was received as RUC dated May 27, 2004, and chemistry review #1 with CMC deficiencies was entered into DFS on November 16, 2004. Amendment, dated December 1, 2004 was submitted in response to the Agency communication dated November 18, 2004. Chemistry review #2 was completed on April 26, 2005, with approval recommendation from CMC.

**Drug Substance:**

The drug substance is a new molecular entity with three chiral centers. It is a derivative of phenyl piperidine. The drug substance was synthesized in three steps. The drug substance was well characterized. The validation of the analytical methods used for determining the specifications and stability conditions appears to be adequate. The applicant has provided data to show that drug substance is quite stable by forced degradation using extreme conditions.

\_\_\_\_\_

\_\_\_\_\_ The stability data on the drug substance provided appears to be adequate.

**Conclusion**

Drug substance is satisfactory.

**Drug Product:**

Adolor took over the ownership of the IND and conducted clinical studies on the 6 mg formulation under IND 56,553, [REDACTED]. After ownership of the IND was transferred to Adolor, two manufacturing facilities, [REDACTED] produced drug product batches of alvimopan 6 mg (anhydrous) capsules for clinical studies. [REDACTED] will also be the manufacturer of the commercial drug product. The original formulation of drug product manufactured by [REDACTED] and the formulation used by [REDACTED] are identical with the exception of the capsule color and markings. Three NDA registration stability batches of drug product (0104.01.001, 0104.01.002, and 0104.01.003) were manufactured by [REDACTED] and packaged in the proposed commercial packaging. The NDA registration batches ranged from [REDACTED]. The proposed commercial batch size is [REDACTED]. One NDA commercial scale stability batch of drug product (0104.004) was manufactured by [REDACTED] and packaged in the proposed commercial packaging. Stability data on the drug product provided appears to be adequate. Based on the stability results, the sponsor proposed an expiration date of 24 months when stored under 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

All associated DMFs are acceptable

The overall Compliance recommendation is 'acceptable'.

**Overall Conclusion**

From a CMC perspective the application is recommended for approval.

Blair A. Fraser, PhD  
Deputy Director, DNDC II/ONDC

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/s/

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Blair Fraser

7/19/05 11:09:51 AM

CHEMIST

Blair A. Fraser, Ph.D., Acting for Eric Duffy, Ph.D.



**NDA 21-775**

**Entereg (alvimopan)**

**Adolor Corporation**

**Ramesh Raghavachari, Ph.D.**

**(Drug Substance)**

**&**

**Zhengfang Ge, Ph.D.**

**(Drug Product)**

**DNDC II, Office of New Drug Chemistry**

**for**

**Division of Gastrointestinal and Coagulation Drug Products**

**HFD-180**



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B. Endorsement Block.....	10
C. CC Block .....	10

11/26/05



# CHEMISTRY REVIEW



Chemistry Review Data Sheet

## Chemistry Review Data Sheet

1. NDA # 21-775
2. REVIEW # 2
3. REVIEW DATE: April 25, 2005
4. REVIEWER: Ramesh Raghavachari (Drug Substance) & Zhengfang Ge (Drug Product)

### 5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
None	

### 6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original submission - RUC	May 27, 2004
N 21-775 N-000-BC	September 24, 2004
N21-775 N-000-BC	December 02, 2004
N21-775 N-000-BZ	January 26, 2005
N21-775 N-000-BZ	January 28, 2005

### 7. NAME & ADDRESS OF APPLICANT:

Name:	Adolor Corporation
Address:	700 Pennsylvania Drive, Exton, PA 19341
Representative:	Linda Harver, V.P. Regulatory Affairs
Telephone:	484-595-1011



## CHEMISTRY REVIEW



### Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Entereg Capsules
- b) Non-Proprietary Name (USAN): Alvimopan
- c) Code Name/# (ONDC only): N/A
- d) Chem. Type/Submission Priority (ONDC only):
  - Chem. Type: 1
  - Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: This application was filed under the provisions of section 505(b)(1) of Federal Food, Drug and Cosmetic act and 21 CFR 314.50.

10. PHARMACOL. CATEGORY:  $\mu$ -Opioid receptor antagonist

11. DOSAGE FORM: Capsules

12. STRENGTH/POTENCY:

13. ROUTE OF ADMINISTRATION: Oral

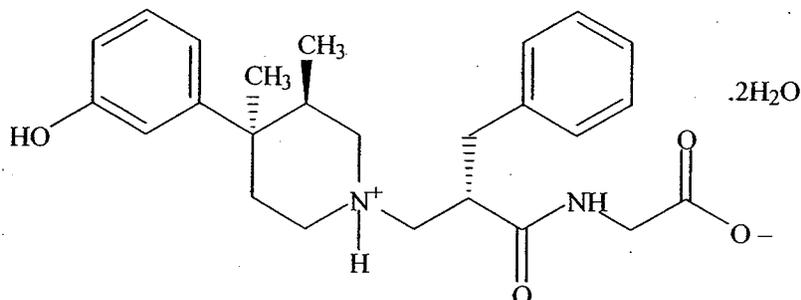
14. Rx/OTC DISPENSED:  Rx  OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

## Chemistry Review Data Sheet

**16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:**

**Name:**

[[[2(S)-[[[4(R)-(3-hydroxyphenyl)-3(R),4-dimethyl-1-piperidyl]methyl]-1-oxo-3-phenylpropyl]amino]acetic acid dihydrate

**Molecular Formula:** C<sub>25</sub>H<sub>32</sub>N<sub>2</sub>O<sub>4</sub>.2H<sub>2</sub>O

**Molecular Weight:** 460.6

**17. RELATED/SUPPORTING DOCUMENTS:**
**A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
█	IV	█	█	7	Adequate		Contacted DMF holder. A new amendment was sent on 23-Sep-2004. It will be reviewed when the amendment is added to the DMF (see review section)
█	IV	█	█	3	Adequate	11-June-2003 and 30-Dec-	



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

						2002	
	III			4	N/A		
	III			4	N/A		

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

### B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Dated 06-08-04 & 07-20-2004	I 56,553	IND amendment

### 18. STATUS:

#### ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not Applicable		
EES	Acceptable	April 25, 2005	Office of Compliance
Pharm/Tox	Approval	Nov. 11, 2004	Tamal Chakraborti, Ph.D.
Biopharm	Pending		
LNC	Not Applicable		
Methods Validation	Not Applicable		
DMETS	Pending		
EA	See review notes		
Microbiology	Not Applicable		Oral dosage form



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

### OGD:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology			
EES			
Methods Validation			
Labeling			
Bioequivalence			
EA			
Radiopharmaceutical			

### 19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. \_\_\_ Yes \_\_\_ No If no, explain reason(s) below:

**Appears This Way  
On Original**

# The Chemistry Review for NDA 21-775

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

Based on the CMC point of view this NDA is recommended for approval. The overall EES recommendation is "acceptable" as of April 25, 2005. The report is appended to this review.

#### 1. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Not applicable.

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

##### Drug Substance:

The drug substance is a new molecular entity with three chiral centers. It is a derivative of phenyl piperidine. The drug substance was synthesized in [redacted] steps. The applicant has been asked to provide data to show that there is [redacted]

[redacted] The reference standard data provided does not meet the purity standards required since the elemental analyses data for the final drug substance and one intermediate [redacted] provided is beyond an acceptable range. The applicant has not provided the yield of the intermediates and the product obtained during production in each step of the development. It is important that is data is consistent with the expected yields or less to discount any undetectable inorganic materials. The above points have been addressed to the applicant as deficiencies. The validation of the analytical methods used for determining the specifications and stability conditions appear to be adequate. The applicant has provided data to show that drug substance is quite stable by forced degradation using extreme conditions. The drug substance is stored [redacted]

[redacted] The stability data on the drug substance provided appears to be adequate.



Chemistry Assessment Section

Drug Product:



Adolor took over the ownership of the IND and conducted clinical studies on the 6 mg formulation under IND 56,553 [redacted]. After ownership of the IND was transferred to Adolor, two manufacturing facilities, [redacted]

[redacted] produced drug product batches of alvimopan 6 mg (anhydrous) capsules for clinical studies. [redacted] will also be the manufacturer of the commercial drug product. The original formulation of drug product manufactured by [redacted] and the formulation used by [redacted] are identical with the exception of the capsule color and markings. Three NDA registration stability batches of drug product (0104.01.001, 0104.01.002, and 0104.01.003) were manufactured by [redacted] and packaged in the proposed commercial packaging. The NDA registration batches ranged from [redacted]. The proposed commercial batch size is [redacted]. One NDA commercial scale stability batch of drug product (0104.004) was manufactured by [redacted] and packaged in the proposed commercial packaging. Stability data on the drug product provided appears to be adequate. Based on the stability results, the sponsor proposed an expiration date of 24 months when stored under 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

**B. Description of How the Drug Product is Intended to be Used**

ENTEREG (Alvimopan [redacted], anhydrous) is indicated to accelerate time to recovery of gastrointestinal function following abdominal or pelvic surgery. The following doses were proposed in the labeling:

**Usual dose in adults:** The recommended adult dose of ENTEREG is 12 mg [redacted] capsules). The initial dose should be administered within no fewer than 30 minutes and no more than 5 hours prior to the scheduled start of surgery. Administer 12 mg twice daily beginning the day after surgery for a maximum of 7 days while the patient is hospitalized or until discharged from the hospital.

**Pediatric Use:** [redacted]

**Geriatric Use:** [redacted]

**Renal Impairment:** [redacted]



Chemistry Assessment Section

**Hepatic Impairment:**



**C. Basis for Approvability or Not-Approval Recommendation**

Not applicable.

**III. Administrative**

**A. Reviewer's Signature**

Signed electronically in DFS by Ramesh Raghavachari, Ph.D. Review Chemist, HFD-180.

Signed electronically in DFS by Zhengfang Ge, Ph.D. Review Chemist, HFD-180.

**B. Endorsement Block**

Signed electronically in DFS by Liang Zhou, Ph.D. Chemistry Team Leader, HFD-180.

Ramesh Raghavachari/Date:

Zhengfang Ge/ Date:

Liang Zhou/Date:

Melissa Furness/Date:

**C. CC Block**

NDA 21-775

HFD-180/Chemistry Reviewer/traghavachari

HFD-180/Chemistry Reviewer/zge

HFD-180/Chemistry Team Leader/lzhou

HFD-180/Project Manager/mfurness

HFD-180/Div File/NDA 21-775

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Deliberative Process

Withheld Track Number: Chemistry- 6

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/s/

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Ramesh Raghavachari

4/26/05 11:54:31 AM

CHEMIST

Review of the response from the sponsor for the  
DR letter and includes the EES overall recommendation.

Zhengfang Ge

4/26/05 04:57:14 PM

CHEMIST

Liang Zhou

4/26/05 05:05:13 PM

CHEMIST

**NDA 21-775**

**Entereg (alvimopan)**

**Adolor Corporation**

**Ramesh Raghavachari, Ph.D.**  
**(Drug Substance)**

**&**

**Zhengfang Ge, Ph.D.**  
**(Drug Product)**

**DNDC II, Office of New Drug Chemistry**  
**for**  
**Division of Gastrointestinal and Coagulation Drug Products**  
**HFD-180**



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# Chemistry Review Data Sheet

1. NDA # 21-775
2. REVIEW # 1
3. REVIEW DATE: September 2004
4. REVIEWER: Ramesh Raghavachari (Drug Substance) & Zhengfang Ge (Drug Product)

5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

None

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

Original submission - RUC  
N 21-775 N-000-BC

May 27, 2004  
September 24, 2004

7. NAME & ADDRESS OF APPLICANT:

Name: Adolor Corporation  
Address: 700 Pennsylvania Drive, Exton, PA 19341  
Representative: Linda Harver, V.P. Regulatory Affairs  
Telephone: 484-595-1011

## 8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Entereg Capsules
- b) Non-Proprietary Name (USAN): Alvimopan
- c) Code Name/# (ONDC only): N/A
- d) Chem. Type/Submission Priority (ONDC only):
  - Chem. Type: 1
  - Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: This application was filed under the provisions of section 505(b)(1) of Federal Food, Drug and Cosmetic act and 21 CFR 314.50.

10. PHARMACOL. CATEGORY:  $\mu$ -Opioid receptor antagonist

11. DOSAGE FORM: Capsules

12. STRENGTH/POTENCY:

13. ROUTE OF ADMINISTRATION: Oral

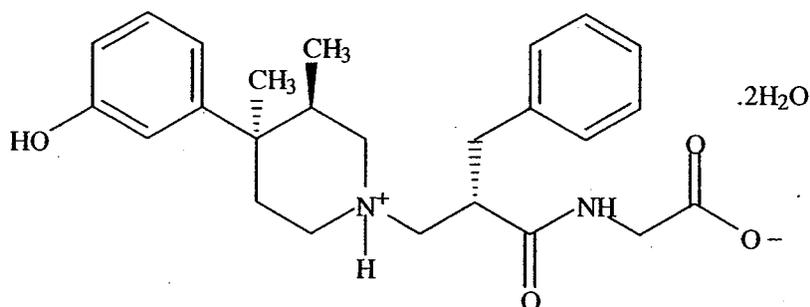
14. Rx/OTC DISPENSED:   X   Rx        OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

       SPOTS product – Form Completed

  X   Not a SPOTS product

**16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:**



**Name:**

[[2(S)-[[4(R)-(3-hydroxyphenyl)-3(R),4-dimethyl-1-piperidyl)methyl]-1-oxo-3phenylpropyl]amino]acetic acid dihydrate

**Molecular Formula:** C<sub>25</sub>H<sub>32</sub>N<sub>2</sub>O<sub>4</sub>.2H<sub>2</sub>O

**Molecular Weight:** 460.6

**17. RELATED/SUPPORTING DOCUMENTS:**

**A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
█	IV		█	7	Adequate		Contacted DMF holder. A new amendment was sent on 23-Sep-2004. It will be reviewed when the amendment is added to the DMF (see review section)
█	IV		█	3	Adequate	11-June-2003 and 30-Dec-	



## Chemistry Review Data Sheet

						2002	
	III			4	N/A		
	III			4	N/A		

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

### B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Dated 06-08-04 & 07-20-2004	I 56,553	IND amendment

### 18. STATUS:

#### ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not Applicable		
EES	Pending		
Pharm/Tox	Not Applicable		
Biopharm	Pending		
LNC	Not Applicable		
Methods Validation	Pending		
DMETS	Pending		
EA	See review notes		
Microbiology	Not Applicable		Oral dosage form

#### OGD:



Chemistry Review Data Sheet

<b>CONSULTS/ CMC RELATED REVIEWS</b>	<b>RECOMMENDATION</b>	<b>DATE</b>	<b>REVIEWER</b>
Microbiology			
EES			
Methods Validation			
Labeling			
Bioequivalence			
EA			
Radiopharmaceutical			

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt.  Yes  No If no, explain reason(s) below:

**Appears This Way  
On Original**

# The Chemistry Review for NDA 21-775

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

Based on the CMC point of view this NDA approvable pending adequate response for the information requested in the list of deficiencies to be communicated to the applicant in section III of this review.

#### 1. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Not applicable.

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

##### Drug Substance:

The drug substance is a new molecular entity with three chiral centers. It is a derivative of phenyl piperidine. The drug substance was synthesized in [REDACTED] steps. The applicant has been asked to provide data to show that there is [REDACTED]

[REDACTED] The reference standard data provided does not meet the purity standards required since the elemental analyses data for the final drug substance and one intermediate [REDACTED] provided is beyond an acceptable range. The applicant has not provided the yield of the intermediates and the product obtained during production in each step of the development. It is important that is data is consistent with the expected yields or less to discount any undetectable inorganic materials. The above points have been addressed to the applicant as deficiencies. The validation of the analytical methods used for determining the specifications and stability conditions appear to be adequate. The applicant has provided data to show that drug substance is quite stable by forced degradation using extreme conditions. The drug substance is stored in [REDACTED]

[REDACTED] The stability data on the drug substance provided appears to be adequate.

Executive Summary Section

**Drug Product:**

Adolor took

over the ownership of the IND and conducted clinical studies on the 6 mg formulation under IND 56,553 [REDACTED]. After ownership of the IND was transferred to Adolor, two manufacturing facilities, [REDACTED] produced drug product batches of alvimopan 6 mg (anhydrous) capsules for clinical studies. [REDACTED] will also be the manufacturer of the commercial drug product. The original formulation of drug product manufactured by [REDACTED] and the formulation used by [REDACTED] are identical with the exception of the capsule color and markings. Three NDA registration stability batches of drug product (0104.01.001, 0104.01.002, and 0104.01.003) were manufactured by [REDACTED] and packaged in the proposed commercial packaging. The NDA registration batches ranged from [REDACTED] capsules. The proposed commercial batch size is [REDACTED]. One NDA commercial scale stability batch of drug product (0104.004) was manufactured by [REDACTED] and packaged in the proposed commercial packaging. Stability data on the drug product provided appears to be adequate. Based on the stability results, the sponsor proposed an expiration date of 24 months when stored under 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

**B. Description of How the Drug Product is Intended to be Used**

ENTEREG (Alvimopan [REDACTED] anhydrous) is indicated to accelerate time to recovery of gastrointestinal function following abdominal or pelvic surgery. The following doses were proposed in the labeling:

**Usual dose in adults:** The recommended adult dose of ENTEREG is 12 mg [REDACTED]. The initial dose should be administered within no fewer than 30 minutes and no more than 5 hours prior to the scheduled start of surgery. Administer 12 mg twice daily beginning the day after surgery for a maximum of 7 days while the patient is hospitalized or until discharged from the hospital.

**Pediatric Use:** [REDACTED]

**Geriatric Use:** [REDACTED]

**Renal Impairment:** [REDACTED]

**Hepatic Impairment:**



**C. Basis for Approvability or Not-Approval Recommendation**

Not applicable.

**III. Administrative**

**A. Reviewer's Signature**

**B. Endorsement Block**

ChemistName/Date: Same date as draft review  
ChemistryTeamLeaderName/Date  
ProjectManagerName/Date

**C. CC Block**

81 Page(s) Withheld

Trade Secret / Confidential

Draft Labeling

Deliberative Process

Withheld Track Number: Chemistry-7

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

/s/

-----  
Ramesh Raghavachari  
11/16/04 10:55:28 AM  
CHEMIST

Zhengfang Ge  
11/16/04 11:02:04 AM  
CHEMIST

Liang Zhou  
11/16/04 11:23:03 AM  
CHEMIST

DR letter needs to be issued before RUC Goal date.

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Application : NDA 21775/000      Sponsor: ADOLOR  
Org Code : 180      700 PENNSYLVANIA DR  
Priority : 1S      EXTON, PA 193411127

Stamp Date : 25-JUN-2004      Brand Name : ENTEREG (ALVIMPOMAN) [REDACTED]

PDUFA Date : 25-JUL-2005      CAPSULE

Action Goal :      Estab. Name:

District Goal: 24-FEB-2005      Generic Name: ALVIMOPAN

Dosage Form: (CAPSULE)

Strength : [REDACTED]

Contacts: T. CLAYTON      Project Manager (HFD-180)      301-827-4005  
R. RAGHAVACHARI      Review Chemist (HFD-180)      301-827-7469  
L. ZHOU      Team Leader (HFD-180)      301-827-1251

---

Overall Recommendation:      ACCEPTABLE on 25-APR-2005 by J. D AMBROGIO (HFD-322) 301-827-  
9049

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Establishment : CFN : [REDACTED]      FEI : [REDACTED]

DMF No:      AADA:

Responsibilities: [REDACTED]

Last Milestone: OC RECOMMENDATION

Milestone Date: 21-JUN-04

Decision : ACCEPTABLE

Reason : BASED ON PROFILE

---

Establishment : CFN : ██████ FEI : ██████

DMF No: ██████ AADA: ██████

Responsibilities: ██████

File : CHG OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 25-APR-05

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

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Establishment : CFN : ██████ FEI : ██████

DMF No: ██████ AADA: ██████

Responsibilities: ██████

ESTABLISHMENT EVALUATION REQUEST

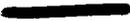
SUMMARY REPORT

File : CHG OAI Status: NONE  
Last Milestone: OC RECOMMENDATION  
Milestone Date: 21-JUN-04  
Decision : ACCEPTABLE  
Reason : BASED ON PROFILE

---

Establishment : CFN : FEI : 

  
DMF No: AADA:

Responsibilities: 

Profile : CHG OAI Status: NONE  
Last Milestone: OC RECOMMENDATION  
Milestone Date: 13-OCT-04  
Decision : ACCEPTABLE  
Reason : BASED ON PROFILE

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Establishment : CFN :  FEI : 

  
No: AADA:

Profile : CSN OAI Status: NONE

Milestone: OC RECOMMENDATION

Milestone Date: 23-FEB-05

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

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**Appears This Way  
On Original**