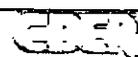


**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-590**

**CHEMISTRY REVIEW(S)**



**NDA 21-590**

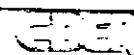
**Fazaclo™ (Clozapine)  
Orally Disintegrating Tablets**

**Alamo Pharmaceuticals, LLC**

**Chhagan G. Tele, Ph.D.**

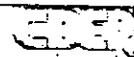
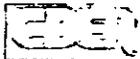
***DIVISION OF NEUROPHARMACOLOGICAL DRUG  
PRODUCTS***

**Review of Chemistry, Manufacturing, and Controls**



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# Chemistry Review Data Sheet

1. NDA 21-590
2. REVIEW #: 2
3. REVIEW DATE: December 15, 2003
4. REVIEWER: Chhagan G. Tele, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original	31-JAN-2003
Amendment (BB)	31-MAR-2003
Amendment (SU)	03-JUN-2003
Amendment (BZ)	12-JUN-2003
Amendment (BB)	24-JUL-2003
Amendment (BC)	04-AUG-2003
Amendment (BC)	14-AUG-2003
Amendment (BC)	20-OCT-2003
Amendment (BL)	22-OCT-2003
CMC Review #1	24-OCT-2003

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment (BL)	31-OCT-2003
Response to Approvable Letter, (BZ)	11-DEC-2003

7. NAME & ADDRESS OF APPLICANT:

Name: Alamo Pharmaceuticals, LLC  
Address: 8501 Wilshire Boulevard, Suite 318, Beverly Hills, CA 90211-3119  
Representative: Jeanine E. Kuczik, Regulatory Advisor  
Telephone: (908) 542-9388

## Chemistry Review Data Sheet

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

- a) Proprietary Name: Fazaclo™  
 b) Non-Proprietary Name (USAN): Clozapine  
 c) Code Name/# (ONDC only): N/A  
 d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 3
  - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b) (2); The RLD is Clozaril® (clozapine) Tablets, 25 mg and 100 mg, Novartis NDA 19-758.

10. PHARMACOL. CATEGORY: For the management of severely ill schizophrenic patients who fail to respond adequately to standard anti-psychotic drug treatment.

11. DOSAGE FORM: Orally Disintegrating Tablet

12. STRENGTH/POTENCY: 25 and 100 mg

13. ROUTE OF ADMINISTRATION: Oral

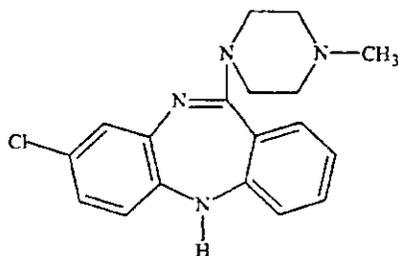
14. Rx/OTC DISPENSED:  Rx  OTC

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:

USAN Name: 8-Chloro-11-(4-methyl-1-piperazinyl)-5H-dibenzo[*b,e*][1,4]diazepine  
 Non-Proprietary Name: Clozapine  
 Chemical Formula: C<sub>18</sub>H<sub>19</sub>ClN<sub>4</sub>  
 Molecular Weight: 326.82  
 CAS registry #: 5786-21-0  
 Structure:



Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF =	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
	II			1	Adequate	30-JAN-2004 Dr. Chhagan Tele	
	II			3	Adequate	11-FEB-2002 Dr. D. Klein	
	III			3	Adequate	24-AUG-2000 Dr. Alan Frankewich	
	II			1	Adequate	18-SEP-2003 Dr. Chhagan Tele	IR Letter sent
	III			3	Adequate	26-FEB-2002 Dr. Arthur Shaw	

<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
NDA	19-758	Clorazil® Tablets
IND	61,484	Commercial IND (schizophrenia)

# CHEMISTRY REVIEW

## Chemistry Review Data Sheet

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Pending		
EES	Acceptable	25-AUG-2003	
Pharm Tox	Pending		
Biopharm	Pending	12-NOV-2003	Carol Noory, Ph.D.
LNC	USAN available Evaluation of proposed trade name FAZACLO -Acceptable	12-NOV-2003	Marcy Lee, PharmD
Methods Validation	Pending		
DMETS	Acceptable	12-NOV-2003	Dennise Toyler, Ph.D.
EA	Acceptable, categorical exclusion granted as per information from Alamo in this NDA	As per this review	Chhagan Tele, Ph.D.
Microbiology	N/A		

# The Chemistry Review for NDA 21-590

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

At this time NDA 21-590 for Fazaclo™ (clozapine, USP) is recommended **APPROVAL** from the CMC standpoint. The approval is based on the acceptable responses to the CMC deficiencies and acceptable recommendation from FDA Office of Compliance for all the drug substance and drug product manufacturing, packaging, labeling, and stability testing facilities.

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

None as per this review.

### II. Summary of Chemistry Assessments

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

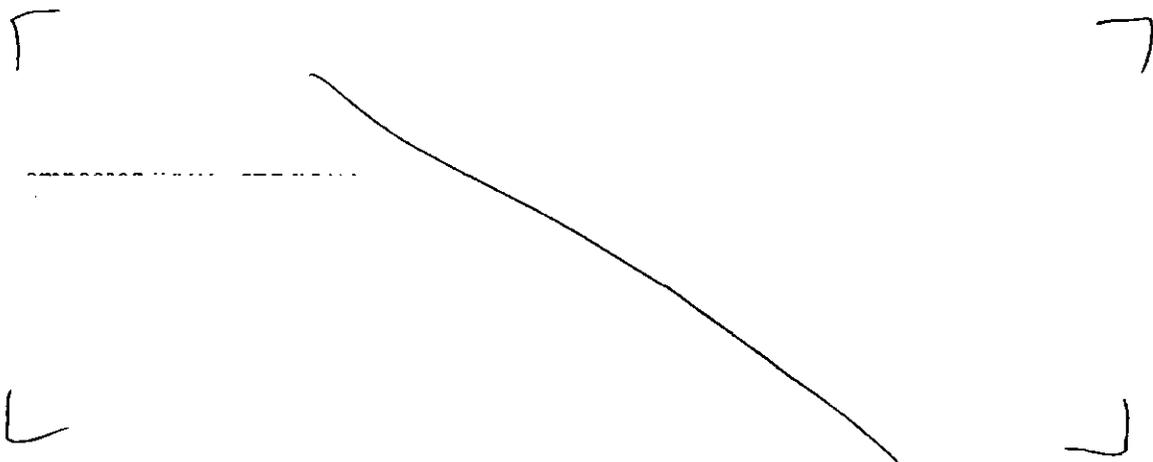
Fazaclo™ (clozapine) Orally Disintegrating Tablets are indicated for the management of severely ill schizophrenic patients who fail to respond adequately to standard anti-psychotic drug treatment for schizophrenia. Clozapine is classified as an 'atypical' antipsychotic drug because its profile of binding to dopamine receptors and its effects on various dopamine mediated behaviors differ from those exhibited by more typical antipsychotic drug products.

Fazaclo™ is to be marketed as an oral dosage form in strengths of 25 and 100 mg. Each tablet contains 25 mg and 100 mg of clozapine. The tablets also contain mannitol, microcrystalline cellulose, crospovidone, sodium bicarbonate, citric acid, mint flavor, ferric oxide (yellow), and magnesium stearate. This product contains aspartame, and is not intended for use by infants. Phenylalanine is a component of aspartame. Each 25 mg orally disintegrating tablet contains 3.1 mg aspartame, thus, 1.74 mg phenylalanine. Each 100 mg orally disintegrating tablet contains 12.4 mg aspartame, thus, 6.96 mg phenylalanine. Alamo provided a validated HPLC method to degradants in Fazaclo tablets. The acceptable compatibility studies of Clozapine, Iron Oxide Yellow, Mannitol (USP), Microcrystalline Cellulose, Sodium Bicarbonate (USP), Citric Acid, Magnesium Stearate ( ) and Mint with aspartame were provided by the sponsor. No significant interactions

Executive Summary Section

between any of the Fazaclo™ (clozapine) ingredients and aspartame. Based on these results the sponsor indicated that aspartame is compatible with all the components in the Fazaclo™ (clozapine) orally disintegrating tablet.

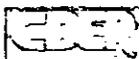
The prototype, clinical, and pilot-scale batches were manufactured at the facility. The commercial scale batches were manufactured at facility. Adequate information was provided for the manufacturing, in-process controls, and sampling plan of the drug product. The commercial-scale manufacturing and packaging process for Fazaclo™ (clozapine) involves



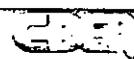
The drug substance, clozapine, is the subject of DMF # held by. The DMF # was reviewed and found adequate by Dr. Chhagan Tele. Clozapine is a yellow, crystalline powder with no chiral centers. All the batches of clozapine drug substance presented in the original NDA were manufactured at the. Batch analysis data of batches was submitted. Validated analytical methods were provided in the DMF. A retest date of has been established for the bulk clozapine drug substance by on the basis of stability data for 2 commercial batches.

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

Fazaclo™ (clozapine) drug product will be marketed in 2 x 3 blister cards for each strength, 25 and 100 mg. The maximum recommended total daily dose is 900 mg/day. Initial treatment with Fazaclo™ (clozapine) begins with one-half of a 25 mg, orally disintegrating tablet (12.5 mg) once or twice daily and then continued with daily dosage increments of 25-50 mg/day, if well-tolerated, to achieve a target dose of 300-450 mg/day by the end of 2 weeks. Subsequent dosage increments should be made no more than once or twice weekly, in increments not to exceed 100 mg. The labeling proposed by the sponsor is very similar to the approved labeling for Clozaril. The labeling was revised for the



## CHEMISTRY REVIEW



### Executive Summary Section

acceptable trade name for clozapine ODT "Fazaclo" and utilized throughout (see DMETS review dated 12-NOV-03 by Marcy Lee, Pharm.D).

Information concerning the remaining half tablet was not provided in the original package insert. In the current package insert section **DOSAGE AND ADMINISTRATION**, subsection **Initial Treatment**, it states that treatment with Fazaclo™ (clozapine, USP) begin with one-half of a 25 mg orally disintegrating tablet (12.5 mg) once or twice daily. The remaining one-half tablet should be destroyed. We recommend that the sponsor change this language to read: the remaining one-half tablet should be disposed of in a way that prevents the accidental ingestion by a child or animal (comment sent to the Medical Officer).

Alamo provided 12 months of stability data at 25° C/60% RH for clinical and registration, batches and 12 months of stability data at 25° C/60% RH storage condition for site-specific commercial batches for both strengths, 25 mg (Batch size 100) and 100 mg (Batch size 100). The applicant has requested a 24 month expiration period (shelf life) for both strengths packaged in blister. We grant a shelf life of 24 months based on the available stability data.

The storage conditions for the drug product were recommended as "Store at 25° C (77° F); excursion permitted to 15-30° C (59-86° F) [see USP Controlled Room Temperature]. Protect from moisture". The package insert instruct the patients not to remove the orally-disintegrating tablet from the blister until the patient is ready to consume the tablet. NDC numbers were not assigned to the Fazaclo™ (clozapine) Orally Disintegrating Tablets of both strengths, 25 mg and 100 mg.

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

NDA 21-590 for Fazaclo™ (clozapine, USP) is recommended to be granted **APPROVAL** from CMC standpoint based on the following:

- All CMC concerns related to the drug substance and drug product sections as outlined in the Chemistry review #1 by Dr. Chhagan G. Tele have been adequately addressed as of this review #2.

### III. Administrative

#### A. Reviewer's Signature

See electronic signatures in DFS.

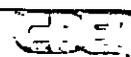
#### B. Endorsement Block

Chemist Name: Chhagan G. Tele, Ph.D.

Chemistry Team Leader Name: Thomas F. Oliver, Ph.D.



## CHEMISTRY REVIEW



### Executive Summary Section

Project Manager Name: Steven Hardeman, Sr. R.Ph.

#### C. CC Block

See DFS.

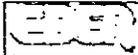
24 Page(s) Withheld

§ 552(b)(4) Trade Secret / Confidential

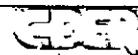
§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

Withheld Track Number: Chemistry- 1



# CHEMISTRY REVIEW



## Chemistry Assessment Section

24-OCT-2003

### FDA CDER EES ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Page 1 of 2

Application : NDA 21590/000  
Org Code : 120  
Priority :

Sponsor: ALAMO PHARMS  
8501 WILSHIRE BLVD STE 318  
BEVERLY HILLS, CA 90211

Stamp Date : 31-JAN-2003  
PDJFA Date : 30-NOV-2003  
Action Goal :  
District Goal: 01-OCT-2003

Brand Name : (CLOZAPINE) ORALLY  
DISINTEGRATI  
Etab. Name:  
Generic Name: CLOZAPINE DISINTEGRATING  
TABLETS 25/100M  
Dosage Form: (TABLET)  
Strength : 25 MG AND 100 MG

FDA Contacts: S. HARDEMAN  
C. TELE  
T. OLIVER

Project Manager (HFD-120) 301-594-5525  
Review Chemist (HFD-120) 301-594-5564  
Team Leader (HFD-810) 301-594-5551

Overall Recommendation: ACCEPTABLE on 25-AUG-2003 by J. D AMBROGIO (HFD-322) 301-827-9049

Establishment :

DMF No:

AADA:

Responsibilities:

Profile : TCM  
Last Milestone: INSPECTION PERFORMED  
Milestone Date: 01-OCT-03

OAI Status: NONE

Establishment :

DMF No:

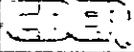
AADA:

Responsibilities:

Profile : TCM  
Last Milestone: INSPECTION PERFORMED  
Milestone Date: 01-OCT-03

OAI Status: NONE

Establishment :



# CHEMISTRY REVIEW



## Chemistry Assessment Section

24-OCT-2003

### FDA CDER EES ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Page 2 of 2

DMF No:

AADA:

Responsibilities:

\_\_\_\_\_

Profile :	CSN	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	19-FEB-03		
Decision :	ACCEPTABLE		
Reason :	BASED ON PROFILE		

Establishment :

\_\_\_\_\_  
\_\_\_\_\_

DMF No:

AADA:

Responsibilities:

\_\_\_\_\_

Profile :	CTL	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	19-FEB-03		
Decision :	ACCEPTABLE		
Reason :	BASED ON PROFILE		

Establishment :

\_\_\_\_\_  
\_\_\_\_\_

DMF No:

AADA:

Responsibilities:

\_\_\_\_\_

Profile :	CTL	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	19-FEB-03		
Decision :	ACCEPTABLE		
Reason :	BASED ON PROFILE		

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this page is the manifestation of the electronic signature.  
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/s/

-----  
Chhagan Tele  
1/30/04 01:15:23 PM  
CHEMIST

Thomas Oliver  
1/30/04 01:19:09 PM  
CHEMIST

**NDA 21-590**

**\_\_\_\_\_ (Clozapine)  
Orally Disintegrating Tablets**

**Alamo Pharmaceuticals, LLC**

**Chhagan G. Tele, Ph.D.**

***DIVISION OF NEUROPHARMACOLOGICAL DRUG  
PRODUCTS***

**Review of Chemistry, Manufacturing, and Controls**

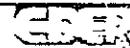
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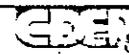
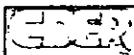
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# Chemistry Review Data Sheet

1. NDA 21-590
2. REVIEW #: 1
3. REVIEW DATE: October 23, 2003
4. REVIEWER: Chhagan G. Tele, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

Original	31-JAN-2003
Amendment (BB)	31-MAR-2003
Amendment (SU)	03-JUN-2003
Amendment (BZ)	12-JUN-2003
Amendment (BB)	24-JUL-2003
Amendment (BC)	04-AUG-2003
Amendment (BC)	14-AUG-2003

7. NAME & ADDRESS OF APPLICANT:

Name: Alamo Pharmaceuticals, LLC  
 Address: 8501 Wilshire Boulevard, Suite 318, Beverly Hills, CA 90211-3119  
 Representative: Jeanine E. Kuczik, Regulatory Advisor  
 Telephone: (908) 542-9388

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name:
- b) Non-Proprietary Name (USAN): Clozapine
- c) Code Name/# (ONDC only): N/A

Chemistry Review Data Sheet

d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b) (2); The RLD is Clozaril<sup>®</sup> (clozapine) Tablets, 25 mg and 100 mg, Novartis NDA 19-758.

10. PHARMACOL. CATEGORY: For the management of severely ill schizophrenic patients who fail to respond adequately to standard anti-psychotic drug treatment.

11. DOSAGE FORM: Orally Disintegrating Tablet

12. STRENGTH/POTENCY: 25 and 100 mg

13. ROUTE OF ADMINISTRATION: Oral

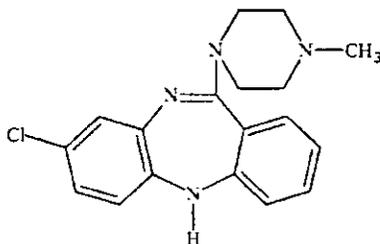
14. Rx/OTC DISPENSED:   X   Rx        OTC

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:

USAN Name:	8-Chloro-11-(4-methyl-1-piperazinyl)-5H dibenzo[ <i>b,e</i> ][1,4]diazepine
Non-Proprietary Name:	Clozapine
Chemical Formula:	C <sub>18</sub> H <sub>19</sub> ClN <sub>4</sub>
Molecular Weight:	326.82
CAS registry #:	5786-21-0
Structure:	



## Chemistry Review Data Sheet

## 17. RELATED/SUPPORTING DOCUMENTS:

## A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
1	II	7	7	1	Inadequate	18-SEP-2003 Dr. Chhagan Tele	Deficient letter sent
2	II	L	L	3	Adequate	11-FEB-2002 Dr. D. Klein	
3	III			3	Adequate	24-AUG-2000 Dr. Alan Frankewich	
4	II			1	Adequate	18-SEP-2003 Dr. Chhagan Tele	IR Letter sent
5	III			3	Adequate	26-FEB-2002 Dr. Arthur Shaw	
6	III			L	L		

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

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

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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")

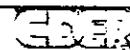
<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

## B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	19-758	Clorazil® Tablets
IND	61,484	Commercial IND (schizophrenia)



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

### 18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Pending		
EES	Acceptable	25-AUG-2003	
Pharm/Tox	Pending		
Biopharm	Pending		
LNC	USAN available Evaluation of proposed trade name-Pending		
Methods Validation	Pending		
OPDRA	Pending		
EA	Acceptable, categorical exclusion granted as per information from Alamo in this NDA	As per this review	Chhagan Tele, Ph.D.
Microbiology	N/A		

## Executive Summary Section

# The Chemistry Review for NDA 21-590

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

At this time NDA 21-590 for \_\_\_\_\_ (clozapine) is recommended APPROVABLE from the CMC standpoint. CMC approval is contingent on adequate responses to the CMC deficiencies related to drug substance and drug product as noted in this review.

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

None as per this review.

### II. Summary of Chemistry Assessments

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

\_\_\_\_\_ (clozapine) Orally Disintegrating Tablets are indicated for the management of severely ill schizophrenic patients who fail to respond adequately to standard anti-psychotic drug treatment for schizophrenia. Clozapine is classified as an 'atypical' antipsychotic drug because its profile of binding to dopamine receptors and its effects on various dopamine mediated behaviors differ from those exhibited by more typical antipsychotic drug products.

\_\_\_\_\_ is to be marketed as an oral dosage form in strengths of 25 and 100 mg. Each tablet contains 25 mg and 100 mg of clozapine \_\_\_\_\_

\_\_\_\_\_ The tablets also contain mannitol, microcrystalline cellulose, crospovidone, sodium bicarbonate, citric acid, mint flavor, ferric oxide (yellow), and magnesium stearate \_\_\_\_\_. This product contains aspartame, and is not intended for use by infants. Phenylalanine is a component of aspartame. Each 25 mg orally disintegrating tablet contains 3.1 mg aspartame, thus, 1.74 mg phenylalanine. Each 100 mg orally disintegrating tablet contains 12.4 mg aspartame, thus, 6.96 mg phenylalanine. Alamo provided validated HPLC method, \_\_\_\_\_ to \_\_\_\_\_ degradants in \_\_\_\_\_ tablets. The acceptable compatibility studies of Clozapine, Iron Oxide Yellow, Mannitol (USP), Microcrystalline Cellulose, Sodium Bicarbonate (USP), Citric Acid, Magnesium Stearate ( \_\_\_\_\_ ) and Mint with aspartame were provided by the sponsor. No significant interactions between any of the \_\_\_\_\_ (clozapine) ingredients and aspartame, \_\_\_\_\_

\_\_\_\_\_ Based on these results the sponsor indicated that aspartame is

## Executive Summary Section

compatible with all the components in the \_\_\_\_\_ (clozapine) orally disintegrating tablet.

The prototype, clinical, and pilot-scale batches were manufactured at the \_\_\_\_\_ facility. The commercial scale batches were manufactured at \_\_\_\_\_ facility. Adequate information was provided for the manufacturing, in-process controls, and sampling plan of the drug product. However, no information was provided for re-processing of the drug product. The commercial-scale manufacturing and packaging process for \_\_\_\_\_ (clozapine) involves \_\_\_\_\_

The drug substance, clozapine, is the subject of DMF # \_\_\_\_\_ held by \_\_\_\_\_ The DMF # \_\_\_\_\_ was reviewed and found deficient by Dr. Chhagan Tele. A Deficiency letter was sent to the DMF holder and the NDA sponsor was notified about the deficiency letter. Clozapine is a yellow, crystalline powder with no chiral centers. All the batches of clozapine drug substance presented in the original NDA were manufactured at the \_\_\_\_\_. Batch analysis data of \_\_\_\_\_ batches was submitted. Validated analytical methods were provided in the DMF. A retest date of \_\_\_\_\_ years has been established for the bulk clozapine drug substance by \_\_\_\_\_ on the basis of \_\_\_\_\_ year stability data for 2 commercial batches.

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

\_\_\_\_\_ (clozapine) drug product will be marketed in 2 x 3 blister cards for each strength, 25 and 100 mg. The maximum recommended total daily dose is 900 mg/day. Initial treatment with \_\_\_\_\_ (clozapine) begins with one-half of a 25 mg, orally disintegrating tablet (12.5 mg) once or twice daily and then continued with daily dosage increments of 25-50 mg/day, if well-tolerated, to achieve a target dose of 300-450 mg/day by the end of 2 weeks. Subsequent dosage increments should be made no more than once or twice weekly, in increments not to exceed 100 mg. Information concerning the remaining half tablet was not provided in the original package insert. The medical officer, Dr. Gregor Dubitsky was informed about this matter. Please refer to the medical

## Executive Summary Section

review for any proposed changes in dosage and administration of \_\_\_\_\_ (clozapine). Alamo provided \_\_\_\_\_ months of stability data at 25° C/60% RH and \_\_\_\_\_ months of stability data at 40° C/75% RH for clinical, registration, and prototype batches and \_\_\_\_\_ months of stability data at both storage conditions for site-specific commercial batches for both strengths, 25 mg (Batch size \_\_\_\_\_) and 100 mg (Batch size \_\_\_\_\_). The applicant has requested a 24 month expiration period (shelf life) for both strengths packaged in blister. We recommended shelf life of \_\_\_\_\_ months on the basis of available stability data.

The storage conditions for the drug product were recommended as "Store at 25° C (77° F); excursion permitted to 15-30° C (59-86° F) [see USP Controlled Room Temperature]. Protect from moisture". The package insert instruct the patients not to remove the orally-disintegrating tablet from the blister until the patient is ready to consume the tablet. NDC numbers were not assigned to the \_\_\_\_\_ (clozapine) Orally Disintegrating Tablets of both strengths, 25 mg and 100 mg.

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

NDA 21-590 for \_\_\_\_\_ (clozapine) is recommended to be granted **Approvable** status from CMC standpoint based on the following:

- CMC concerns related to the drug substance and drug product sections as outlined in the review.
- The deficiencies are detailed at the end of this review to be forwarded to Alamo.

**III. Administrative****A. Reviewer's Signature**

See electronic signatures in DFS.

**B. Endorsement Block**

Chemist Name: Chhagan G. Tele, Ph.D.  
Chemistry Team Leader Name: Thomas F. Oliver, Ph.D.  
Project Manager Name: Steven Hardeman, R.Ph.

**C. CC Block**

See DFS.

71 Page(s) Withheld

§ 552(b)(4) Trade Secret / Confidential

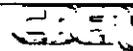
§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

Withheld Track Number: Chemistry-\_\_\_\_\_



# CHEMISTRY REVIEW



## Chemistry Assessment Section

24-OCT-2003

FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
SUMMARY REPORT

Page 1 of 2

Application : NDA 21590/000  
Org Code : 120  
Priority :

Sponsor: ALAMO PHARMS  
8501 WILSHIRE BLVD STE 318  
BEVERLY HILLS, CA 90211

Stamp Date : 31-JAN-2003  
PDUFA Date : 30-NOV-2003  
Action Goal :  
District Goal: 01-OCT-2003

Brand Name : (CLOZAPINE) ORALLY  
DISINTEGRATI  
Estab. Name :  
Generic Name: CLOZAPINE DISINTEGRATING  
TABLETS 25/100M  
Dosage Form: (TABLET)  
Strength : 25 MG AND 100 MG

FDA Contacts: S. HARDEMAN  
C. TELE  
T. OLIVER

Project Manager (HFD-120) 301-594-5525  
Review Chemist (HFD-120) 301-594-5564  
Team Leader (HFD-810) 301-594-5551

Overall Recommendation: ACCEPTABLE on 25-AUG-2003 by J. D AMBROGIO (HFD-322) 301-827-9049

Establishment :

DMF No:

Responsibilities:

Profile : TCM OAI Status: NONE  
Last Milestone: INSPECTION PERFORMED  
Milestone Date: 01-OCT-03

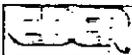
Establishment :

DMF No:

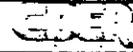
Responsibilities:

Profile : TCM OAI Status: NONE  
Last Milestone: INSPECTION PERFORMED  
Milestone Date: 01-OCT-03

Establishment :



# CHEMISTRY REVIEW



## Chemistry Assessment Section

24-OCT-2003

FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
SUMMARY REPORT

Page 2 of 2

DMF No:

AADA:

Responsibilities:

\_\_\_\_\_  
\_\_\_\_\_

3

Profile : CSN OAI Status: NONE  
Last Milestone: OC RECOMMENDATION  
Milestone Date: 19-FEB-03  
Decision : ACCEPTABLE  
Reason : BASED ON PROFILE

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Establishment :

\_\_\_\_\_  
\_\_\_\_\_

DMF No:

AADA:

Responsibilities:

\_\_\_\_\_

Profile : CTL OAI Status: NONE  
Last Milestone: OC RECOMMENDATION  
Milestone Date: 19-FEB-03  
Decision : ACCEPTABLE  
Reason : BASED ON PROFILE

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Establishment :

\_\_\_\_\_  
\_\_\_\_\_

DMF No:

AADA:

Responsibilities:

\_\_\_\_\_

Profile : CTL OAI Status: NONE  
Last Milestone: OC RECOMMENDATION  
Milestone Date: 19-FEB-03  
Decision : ACCEPTABLE  
Reason : BASED ON PROFILE

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

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Chhagan Tele  
10/24/03 09:57:21 AM  
CHEMIST

Thomas Oliver  
10/24/03 10:08:09 AM  
CHEMIST