

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-590

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY for NDA # 21-590 SUPPL #

Trade Name Fazaclo Generic Name clozapine

Applicant Name Alamo Pharmaceuticals, LLC HFD- 120

Approval Date 2/10/04

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain 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 an original NDA? YES/ Yes / NO / ___ /

b) Is it an effectiveness supplement? YES / ___ / NO / No /

If yes, what type (SE1, SE2, etc.)?

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 / 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.

The sponsor submitted the results of a single BE study (CS-001-2002) in support of their orally disintegrating tablet formulation for clozapine. They did not claim exclusivity.

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 /No/

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

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

YES /___/ NO /No/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /___/ NO /No/

If yes, NDA # _____ Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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

YES /___/ NO /No/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (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 / yes / NO / ___ /

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

NDA # 19-758 Clozaril (clozapine) tablets

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 9. IF "YES," GO TO PART III.

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S 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 /No_/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

- (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 9:**

- (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 /___/

- (c) 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:

Investigation #1, Study #

Investigation #2, Study #

Investigation #3, Study #

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 /___/

Investigation #3 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:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

- (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 /___/

Investigation #3 YES /___/ NO /___/

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

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

- (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"):

Investigation #__, Study #

Investigation #__, Study #

Investigation #__, Study #

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 /___/ Explain _____	!	NO /___/ Explain _____
_____	!	_____
_____	!	_____
	!	
Investigation #2	!	
YES /___/ Explain _____	!	NO /___/ 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: _____

Signature of Preparer
Title:

Date

Signature of Office or Division Director

Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-610/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OSD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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/s/

Steve Hardeman
3/1/04 10:13:25 AM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

JA/BLA #: 21-590 Supplement Type (e.g. SE5): Supplement Number:

Stamp Date: 1/30/03 Action Date: 2/11/04

HFD 120 Trade and generic names/dosage form: Fazaclo (clozapine) orally disintegrating tablet

Applicant: Alamo Pharmaceuticals, LLC Therapeutic Class: Schizophrenia

Indication(s) previously approved: for the management of severely ill schizophrenic patients who fail to respond adequately to standard drug treatment for schizophrenia.

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: for the management of severely ill schizophrenic patients who fail to respond adequately to standard drug treatment for schizophrenia.

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

Yes: Please proceed to Section A.

Section A: Fully Waived Studies

Reason(s) for full waiver:

There are safety concerns

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:

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

plete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

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:

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

cc: NDA
HFD-960/ Grace Carmouze
(revised 12-22-03)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

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/s/

Steve Hardeman
3/1/04 10:44:12 AM

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

DATE: February 4, 2004

FROM: Thomas P. Laughren, M.D.
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Approval action for NDA 21-590 for an orally disintegrating tablet (ODT)
formulation for clozapine

TO: File, NDA 21-590
[Note: This memo should be filed with the 12-10-03 response to our 11-19-03
approvable letter.]

The sponsor has adequately responded to all pending issues identified in our 11-19-03 letter.

CMC:

-To my understanding, all remaining CMC issues have been resolved, and this application can be approved from this standpoint.

OCPB:

-The only biopharmaceutical issues were dissolution specifications and minor labeling issues. Both issues have been resolved, and this application can be approved from the OCPB standpoint.

Clinical:

-We had asked for certain changes in the proposed patient registry, and also a number of labeling changes. The sponsor has adequately addressed both issues, and we have reached agreement on final labeling.

Conclusions and Recommendations:

-All remaining issues have been resolved, and we have reached agreement on final labeling. Thus, I recommend that we issue an approval letter with the mutually agreed upon final labeling.

cc:

Orig NDA 21-590

HFD-120 DivFile

HFD-120 TLaughren/RKatz/GDubitsky/SHardeman

DOC: NDA21590.02

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/s/

Thomas Laughren :
2/4/04 01:43:24 PM
MEDICAL OFFICER

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

DATE: November 17, 2003

FROM: Thomas P. Laughren, M.D.
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: NDA 21-590 for an orally disintegrating tablet (ODT) formulation for clozapine

TO: File, NDA 21-590

[Note: This memo should be filed with the 1-30-03 original submission.]

This application is intended to support an ODT formulation for clozapine (25 and 100 mg strengths), a drug that is currently available in a standard, immediate release tablet formulation for use in managing treatment resistant schizophrenia (NDA 19-758). This product was developed under IND 61,484, and is intended to improve compliance, i.e., it wouldn't need to be taken with water. We met with the sponsor on 8-31-01 to discuss their plans for this program, and reached agreement that they could submit this as a 505(b)(2) application. It was agreed that they would need a bioequivalence study to show equivalence between this ODT product and Clozaril. We also made clear to the sponsor that they would need to establish a registry system for controlling the distribution of this product with similar features to the systems in place for other clozapine products. The 1-30-03 submission included results of the BE study for the 100 mg strength, dissolution data along with a request for a waiver for a BE study for the 25 mg strength, CMC information, proposed labeling, and plans for a patient registry.

Biopharmaceutics Review

The biopharmaceutics data were reviewed by Carol Noory, Ph.D, from OCPB. The BE study (CS-001-2002) was a 2-way crossover comparing Clozaril 100 mg bid with clozapine ODT 100 mg bid, each for roughly 7 days. The subjects (n=36) were patients with schizophrenia who were in a residual phase of their illness. OCPB has concluded that this study adequately demonstrates the bioequivalence of Clozaril 100 mg and clozapine ODT 100 mg. Dr. Noory also evaluated the dissolution data provided in support of a waiver for the 25 mg strength, and concluded that adequate data had been provided to support this waiver, and also the breaking of the scored ODT tablets for use in initial titration of patients. However, OCPB does not agree with the sponsor's proposed dissolution specifications, and has proposed alternative specifications.

One other issue that needs discussion is Dr. Noory's statement that this program does not support labeling language suggesting that this new ODT formulation can be taken without water. Her

review suggests that the BE study was conducted in such manner that ODT was given with water. However, I have checked on this important detail with the clinical reviewer, Dr. Dubitsky, and he is able to cite references from within the application verifying that, in fact, the ODT was given without water in this key BE study. Dr. Noory's supervisor, Dr. Ramana Uppoor, has acknowledged that she is in agreement with Dr. Dubitsky's resolution of this matter.

DSI Inspections

The site for the BE study was inspected by DSI and found to be acceptable.

CMC Review

-The review of CMC data was done by Chhagan Tele, Ph.D., from the chemistry group. The CMC group has concluded that the application is approvable, and several deficiencies will be conveyed in the approvable letter.

Clinical Review

-Dr. Greg Dubitsky, from the clinical group, reviewed the limited safety data from the BE study, and also any safety data in literature submitted by the sponsor. There were no new findings that would impact on the approvability or labeling of this product. Of note, there was no indication of local irritation from this ODT product.

-Dr. Dubitsky also reviewed the sponsor's proposed registry and WBC monitoring system for this new product, and he concluded that, overall, the planned registry is acceptable. However, he has a number of comments, questions, and suggestions for the sponsor in the finalization of this program. These will be conveyed in the approvable letter.

Labeling

-The sponsor proposed a number of additions to labeling based on literature references they were able to obtain. However, it is our view that these data are generally too incomplete to fairly evaluate these added statements. Thus, we have rejected most of the new language based on this literature review. The labeling changes that are acceptable relate mostly to changes directly relevant to the description and use of this new formulation.

Conclusions and Recommendations

-I recommend that we issue an approvable letter for this NDA, along with our proposed labeling, in anticipation of final approval of this application.

cc:

Orig NDA 21-590

HFD-120/DivFile

HFD-120/TLaughren/RKatz/GDubitsky/SHardeman

DOC: NDA21590.01

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/s/

Thomas Laughren
11/17/03 01:41:08 PM
MEDICAL OFFICER

8 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

Withheld Track Number: Administrative- 1

CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

DATE RECEIVED: MAR-3-2003

DUE DATE: MAY-3-2003
PDUFA DATE: NOV-30-2003

ODS CONSULT #:
 03-0092

TO: Russell Katz, MD
 Director, Division of Neuropharmacological Drug Products
 HFD-120

CC: Steven D. Hardeman, RPh
 Project Manager
 HFD-120

PRODUCT NAME:
 Fazaclo
 (Clozapine Orally Disintegrating Tablets)
 25 mg and 100 mg

NDA SPONSOR:
 Alamo Pharmaceuticals, LLC

NDA #: 21-590

SAFETY EVALUATOR: Marci Lee, PharmD

SUMMARY: In response to a request from the Division of Neuropharmacological Drug Products, HFD-120, the Division of Medication Errors and Technical Support (DMETS) has reviewed the proposed proprietary name, Fazaclo.

DMETS RECOMMENDATION:

1. DMETS has no objection to the use of the proprietary name, Fazaclo. DMETS considers this a final decision. However, if the approval of the NDA is delayed beyond 90 days the firm should be notified that this name with its associated labels and labeling must be re-evaluated. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary and established names from this date forward.
2. DMETS recommends implementation of the labeling revisions as outlined in Section III.
3. DDMAC finds the name, Fazaclo, acceptable from a promotional perspective.

Carol Holquist, RPh
 Deputy Director
 Division of Medication Errors and Technical Support
 Office of Drug Safety
 Phone: (301) 827-3242

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

PROPRIETARY NAME REVIEW

DATE OF REVIEW: October 16, 2003
NDA: 21-590
NAME OF DRUG: Fazaclo (Clozapine Orally Disintegrating Tablets)
25 mg and 100 mg
NDA SPONSOR: Alamo Pharmaceuticals, LLC

I. INTRODUCTION

This consult is written in response to a request from the Division of Neuropharmacological Drug Products (DNDP), HFD-580, for evaluation of the proposed proprietary name, Fazaclo. The proposed blister container label, carton labeling, and professional package insert labeling were reviewed for possible interventions in minimizing medication errors. We note that the labels and labeling submitted contained the proposed proprietary name ' ' instead of Fazaclo. ' was Alamo Pharmaceuticals' first choice for a proprietary name. However, DNDP determined that the proposed name ' was unacceptable because it implied efficacy (i.e., ' \. The sponsor was informed of DNDP's decision but did not submit revised labels and labeling.

PRODUCT INFORMATION

Fzaclo is indicated for the management of severely ill schizophrenic patients who fail to respond adequately to standard drug treatment for schizophrenia.

Fzaclo is associated with a significant risk of agranulocytosis, which is potentially life-threatening. Therefore, a physician and pharmacist registry is required for the distribution of Fzaclo. Participation in a postmarketing surveillance patient registry is required to evaluate patients for clozapine-induced leukopenia.

The recommended starting dose of Fzaclo is 12.5 mg once or twice daily with increases in increments of 25 mg to 50 mg daily. The target dose of 300 mg to 450 mg per day may be achieved by the end of two weeks if the medication is well-tolerated. While many patients respond to doses of 300 mg – 600 mg daily, it may be necessary to raise the dose to the 600 mg – 900 mg range to obtain an acceptable response. Dosing should not exceed 900 mg/day.

Fzaclo will be available as a scored orally disintegrating tablet in dosage strengths of 25 mg and 100 mg. Both tablets will be round and yellow. Fzaclo will be packaged in blister cards containing 6 tablets each.

II. RISK ASSESSMENT

The medication error staff of DMETS conducted a search of several standard published drug product reference texts^{1,2} as well as several FDA databases³ for existing drug names which sound-alike or look-alike to "Fazaclo" to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's trademark electronic search system (TESS) was conducted⁴. The Saegis⁵ Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted prescription analysis studies, involving health care practitioners within FDA. These exercises were conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the names.

A. EXPERT PANEL DISCUSSION

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

1. DDMAC did not have concerns about the name with regard to promotional claims.
2. The Expert Panel identified potential for confusion with Vascor. The product information is listed in Table 1 (See below), including the dosage forms available and usual dosage.

Table 1. Potential Sound-Alike and/or Look-Alike Names Identified by DMETS Expert Panel

Product Name	Established name, Dosage form(s)	Usual adult dose*	Look-alike or Sound-alike
Fazaclo	Clozapine Tablets 25 mg and 100 mg	Initially 12.5 mg daily or BID. Usual range is 300 mg to 600 mg/day. Up to 900 mg/day max.	
Vascor	Bepridil Hydrochloride 200 mg, 300 mg	200 mg - 400 mg by mouth once daily	Sound-alike

*Frequently used, not all-inclusive.

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

² Facts and Comparisons, 2003, Facts and Comparisons, St. Louis, MO.

³ The DMETS database of proprietary name consultation requests, New Drug Approvals 98-03, and the electronic online version of the FDA Orange Book.

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

⁵ Data provided by Thomson & Thomson's SAEGIS(tm) Online Service, available at www.thomson-thomson.com.

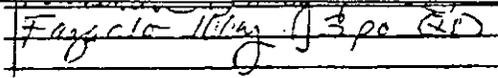
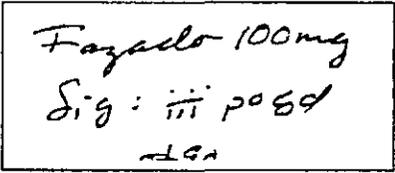
B. PHONETIC ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

DMETS' Phonetic Orthographic Computer Analysis (POCA) database was not available to search at the time of this review.

C. PRESCRIPTION ANALYSIS STUDIES

1. Methodology

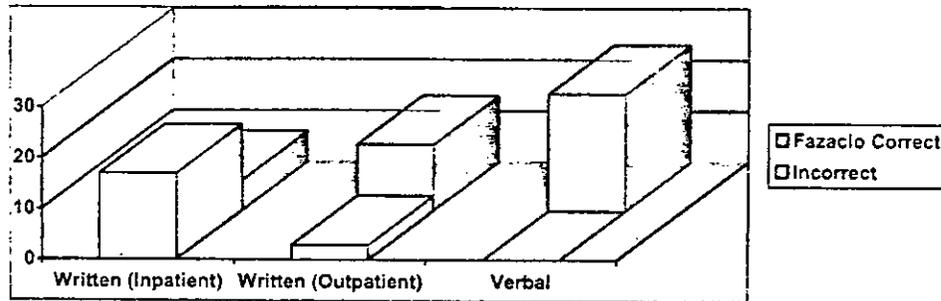
Three separate studies were conducted within FDA for the proposed proprietary name to determine the degree of confusion of Fazaclo with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total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

HANDWRITTEN PRESCRIPTIONS	VERBAL PRESCRIPTION
Fazaclo	
<p><i>Inpatient:</i></p> 	
<p><i>Outpatient:</i></p> 	<p><i>Verbal:</i> "...the last prescription is Fazaclo, a hundred milligrams, he is to take three of those everyday, dispense number ninety, no refills."</p>

2. Results

Table 2. Results of the Prescription Analysis Studies

Study	# of Participants	# of Responses	"Fazaclo" Response	Other Response
Written: Inpatient	35	23 (66%)	17 (74%)	6 (26%)
Written Outpatient	31	16 (52%)	3 (19%)	13 (81%)
Verbal:	39	23 (59%)	0 (0%)	23 (100%)
Total:	105	62 (59%)	20 (32%)	42 (68%)



Among participants in the written prescription studies, 19 of 39 respondents (49%) interpreted the name incorrectly. The majority of the incorrect responses were *Fazado*, where participants interpreted the "-clo" as "-do".

Other misinterpretations of the written prescription studies included: *Fazada*, *Fazaclo*, *Fazacio*, *Fazclo* and *Fozaclo*. None of the interpretations are similar to a currently marketed drug product.

Among participants in the verbal prescription studies, all of the participants interpreted the name incorrectly. However, two of the responses are phonetically equivalent to *Fazaclo*. These responses included *Fasiclo* and *Fazoclo*. Other misinterpretations of the verbal prescription studies included *Farsocort*, *Fasacio*, *Fasacior*, *Fasacol*, *Fasacor*, *Fasecol*, *Fasocoll*, *Faviclo*, *Phasachol*, *Phasacol*, *Vasacor*, *Fazachloe*, *Fazacol*, *Fazichlo*, *Fazidlo*, and *Fazochol*.

The responses "*Fasacol*" and "*Fazacol*" are similar to *Asacol*, which is a product that is currently available in the US marketplace.

D. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name, *Fazaclo*, the primary concern raised was related to *Vasacor*, which already exists in the U.S. marketplace.

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

1. The Expert Panel thought *Fazaclo* and *Vasacor* sound-alike when pronounced. *Vasacor* is indicated for the treatment of chronic stable angina. The beginning letters of each name (Faz vs. Vas) may be phonetically similar when pronounced. However, the endings (ah-cloe vs. kor) of each name are phonetically different. Additionally, *Fazaclo* has three syllables whereas *Vasacor* only has two syllables. The additional syllable and the distinctive endings help to differentiate the two names. The products have overlapping dosing intervals (daily), routes of administration (oral), and

dosage forms (tablet). The 100 mg marketing strength could overlap and the prescribing strength could also potentially overlap (300 mg to 400 mg vs. 200 mg to 600 mg). However, patients receiving Fazaclo will have to be pre-registered in the Fazaclo Orally Disintegrating Tablets Patient Registry and undergo weekly/biweekly white blood cell counts prior to receiving Fazaclo. The different endings and conditions of use will help to minimize the potential for name confusion between Fazaclo and Vascor.

2. Two respondents in the verbal prescription studies misinterpreted Fazaclo as Fazacol and Fasacol, which are phonetically similar to the currently marketed product Asacol. Asacol is indicated for the treatment of mild to moderately active ulcerative colitis and for the maintenance of remission of ulcerative colitis. Although the beginnings (asa vs. faza) of Asacol and Fazaclo may sound phonetically similar the endings are distinctly different. Additionally, the products have different dosing intervals (three times a day vs. daily), strength (400 mg vs. 25 mg and 100 mg), and indication of use. Although, Asacol and Fazaclo have beginning letters that may sound similar, the endings of each name and the different dosing intervals and strength decrease the potential for name confusion between the two products.

III. LABELING, PACKAGING and SAFETY RELATED ISSUES

In the review of the container labels, carton and insert labeling of Fazaclo, DMETS focused on safety issues relating to possible medication errors. We have identified the following areas of possible improvement, which might minimize potential user error.

A. GENERAL COMMENTS

1. Both the Fazaclo 25 mg and 100 mg strengths are presented in red-color font. Increase the differentiation of the dosage strengths by use of font style, highlighting or bolding to make this information more prominent and minimize the likelihood of confusion among the various dosage strengths of Fazaclo.
2. DMETS is unsure why the quantity being marketed is '48 tablets.' Since patients will receive multiples of seven days, we are unsure of the rationale for this quantity size. Please comment.

B. BLISTER LABEL

See General Comment A-1.

C. CARTON LABELING

1. See General Comments A-1 and A-2.
2. Relocate the net quantity so that it does not appear in close proximity to the strength.

D. PACKAGE INSERT LABELING

1. PRECAUTIONS, INFORMATION FOR PATIENTS SUBSECTION

- a. This section should be reprinted at the end of the package insert labeling in accordance with CFR 201.57(f)(2).
- b. The following statements are important to the proper use of the blister packaging configuration. These statements are currently found in the 'DOSAGE AND ADMINISTRATION' section but should also be included in this section.
 - i. The Fazaclo orally disintegrating tablet should be left in the unopened blister until time of use.
 - ii. The orally disintegrating tablet should not be pushed through the foil. Just prior to use, peel the foil from the blister and gently remove the orally disintegrating tablet.

IV. RECOMMENDATIONS

- A. DMETS has no objection to the use of the proprietary name, Fazaclo. This is considered a tentative decision and the firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary and established names from the signature date of this document.
- B. DMETS recommends implementation of the labeling revisions as outlined in Section III.
- C. DDMAC did not have concerns about the name, Fazaclo, with regard to promotional claims.

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

• Marci Lee, PharmD
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur: _____
Denise Toyer, PharmD
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

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

/s/

Denise Toyer
11/12/03 01:45:53 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
11/12/03 02:24:08 PM
DRUG SAFETY OFFICE REVIEWER

Jerry Phillips
11/12/03 02:45:49 PM
DRUG SAFETY OFFICE REVIEWER



February 6, 2003

Russell G. Katz, M.D., Director,
Division of Neuropharmacological Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
12229 Wilkins Avenue
Rockville, Maryland 20852-1833

Re: NDA No. 21-590

_____ (clozapine) Orally Disintegrating Tablets, 25 and 100 mg

General Correspondence: Submission of New Proposed Trade Name, Fazaclo™
Amendment No. 001

Dear Dr. Katz:

Reference is made to our 505(b)(2) Application, NDA No. 21-590, for _____ (clozapine) Orally Disintegrating Tablets, 25 and 100 mg, an atypical antipsychotic indicated for the management of severely ill schizophrenic patients who fail to respond adequately to standard antipsychotic drug treatment, which was submitted to the Agency on January 30, 2003.

This amendment is submitted in response to a January 31, 2003, e-mail correspondence from Mr. Steve Hardeman, Division of Neuropharmacological Drug Products, to Ms. Jeanine Kuczik, Regulatory Advisor, Alamo Pharmaceuticals, LLC (Alamo). In that e-mail, Mr. Hardeman provided the Agency's opinion that the proposed trade name for clozapine orally disintegrating tablets, _____ is not in compliance with 21 CFR 201.10(c)(3), which prohibits the employment of a fanciful proprietary name for a drug or ingredient in such a manner as to imply that the drug or ingredient has some unique effectiveness, and that the proposed trade name, _____ may imply efficacy claims of superiority.

In response to the Agency's concerns, Alamo is submitting the following new proposed trade name, Fazaclo™ (clozapine) Orally Disintegrating Tablets, 25 and 100 mg. We expect that this proposed trade name will be acceptable to the Agency for full review.

If, upon review, our primary proposed trade name, Fazaclo, is considered unacceptable, we are submitting two additional proposed trade names for further review as follows: first back-up proposed trade name, _____ second back-up proposed trade name, _____

Russell G. Katz, M.D.
February 6, 2003
Re: NDA No. 21-590
Page 2

This amendment is submitted by facsimile to Mr. Steve Hardeman, an original amendment is submitted in triplicate to NDA No. 21-590, and a desk copy is provided directly to Mr. Hardeman. All future correspondence to this Application will be submitted as Fazaclo™ (clozapine) Orally Disintegrating Tablets.

If you have any questions or comments regarding this submission, please contact Jeanine Kuczik, Regulatory Advisor, at (908) 542-9388.

Sincerely,



Neal Cutler, M.D.
President and Chief Executive Officer

cc: Mr. S. Hardeman, Food and Drug Administration
Dr. A. DiSanto
Ms. J. Kuczik
Dr. N. Cutler (2 copies)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338
Expiration Date: August 31, 2005
See OMB Statement on page 2.

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE
(Title 21, Code of Federal Regulations, Parts 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT Alamo Pharmaceuticals, LLC	DATE OF SUBMISSION February 6, 2003
TELEPHONE NO. (Include Area Code) 310-358-1600	FACSIMILE (FAX) Number (Include Area Code) 310-854-3965
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): 8501 Wilshire Boulevard Suite 318 Beverly Hills, California 90211	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE NA

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 21-590		
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) Clozapine	PROPRIETARY NAME (trade name) IF ANY <u> </u> (clozapine) Orally Disintegrating Tablets	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any) 8-chloro-11-(4-methylpiperazin-1-yl)-5H-dibenzo[b,e][1,4]diazepine	CODE NAME (If any) NA	
DOSAGE FORM: Orally Disintegrating Tablet	STRENGTHS: 25 and 100 mg	ROUTE OF ADMINISTRATION: Oral

(PROPOSED) INDICATION(S) FOR USE:
For the management of severely ill schizophrenic patients who fail to respond adequately to standard antipsychotic drug treatment

APPLICATION INFORMATION

APPLICATION TYPE (check one) NEW DRUG APPLICATION (21 CFR 314.50) ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
 BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE 505 (b)(1) 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug Clozaril Holder of Approved Application Sandoz Pharmaceutical Corporation/
Novartis AG

TYPE OF SUBMISSION (check one) ORIGINAL APPLICATION AMENDMENT TO PENDING APPLICATION RESUBMISSION
 PRESUBMISSION ANNUAL REPORT ESTABLISHMENT DESCRIPTION SUPPLEMENT EFFICACY SUPPLEMENT
 LABELING SUPPLEMENT CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: NA

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY CBE CBE-30 Prior Approval (PA)

REASON FOR SUBMISSION
General Correspondence: Submission of New Proposed Trade Name, Fazaclo™

PROPOSED MARKETING STATUS (check one) PRESCRIPTION PRODUCT (Rx) OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS PAPER PAPER AND ELECTRONIC ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

See attached sheets.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

 No. 61,484
 JA No. 19-758
DMF Nos.

This application contains the following items: (Check all that apply)	
<input type="checkbox"/>	1. Index
<input checked="" type="checkbox"/>	2. Labeling (check one) <input type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling
<input type="checkbox"/>	3. Summary (21 CFR 314.50 (c))
<input type="checkbox"/>	4. Chemistry section
<input type="checkbox"/>	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
<input type="checkbox"/>	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
<input type="checkbox"/>	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
<input type="checkbox"/>	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
<input type="checkbox"/>	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
<input type="checkbox"/>	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
<input type="checkbox"/>	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
<input type="checkbox"/>	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
<input type="checkbox"/>	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
<input type="checkbox"/>	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
<input type="checkbox"/>	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
<input type="checkbox"/>	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
<input type="checkbox"/>	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
<input type="checkbox"/>	15. Establishment description (21 CFR Part 600, if applicable)
<input type="checkbox"/>	16. Debarment certification (FD&C Act 306 (k)(1))
<input type="checkbox"/>	17. Field copy certification (21 CFR 314.50 (l)(3))
<input type="checkbox"/>	18. User Fee Cover Sheet (Form FDA 3397)
<input type="checkbox"/>	19. Financial Information (21 CFR Part 54)
<input checked="" type="checkbox"/>	20. OTHER (Specify) Proposed Patient Monitoring Registry Protocol

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE Neal R. Cutler, M.D. President and Chief Executive Officer	DATE: February 6, 2003
ADDRESS (Street, City, State, and ZIP Code) 8501 Wilshire Boulevard, Suite 318; Beverly Hills, California 90211		Telephone Number (310) 358-1600
<p>Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:</p> <p>Department of Health and Human Services Food and Drug Administration FR, HFD-99 Rockville Pike Rockville, MD 20852-1448</p> <p>Food and Drug Administration CDER (HFD-94) 12229 Wilkins Avenue Rockville, MD 20852</p> <p>An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.</p>		

MINUTES OF MEETING
PIND #61,484

Drug: Clozapine ODT (orally disintegrating tablets)
Sponsor: Alamo Pharmaceuticals, LLC
Date: August 31, 2001
Where: Conference Room, 4th floor, WOCII, 9:00-9:45am
Purpose: Pre-IND Meeting

FDA Attendees

Thomas Laughren, M.D., Team Leader, Psychopharm
Barry Rosloff, Ph.D., Supervisor, Pharmacology/Toxicology
Greg Dubitsky, M.D., Medical Reviewer
Robert Seevers, Ph.D., Chemistry Team Leader
Lois Freed, Ph.D., Pharmacology/Toxicology Reviewer
Raman Baweja, Ph.D., Team Leader, OCPB
Hong Zhao, Ph.D., OCPB Reviewer
Steve Hardeman, R.Ph. - Regulatory Project Manager

Alamo Attendees

Neal R. Cutler, M.D., President and CEO, Alamo

Anthony R. DiSanto, Ph.D., Vice President of Development, Alamo

Background

Alamo Pharmaceuticals is proposing submission of an NDA for Clozapine ODT (orally disintegrating tablets) under the provisions of 505(b)(2) utilizing the currently approved Novartis NDA for Clozaril® Tablets as the reference listed drug. Clozapine ODT is intended for the management of severely ill schizophrenic patients who fail to respond adequately to standard antipsychotic treatment. This indication is identical to the previously approved indication for Clozaril Tablets that are standard-release tablets. Clozapine ODT is a conventional, immediate-disintegrating, oral tablet designed to be taken with or without water and to disintegrate rapidly in the oral cavity. The rapid disintegration feature is intended to assist in patient compliance and is also expected to provide relief for patients who have difficulty taking solid oral medications.

Alamo asked the following questions (*italics*) in a briefing document dated August 2, 2001.

505(b)(2) Submission

- Does the Agency agree with the proposal to submit Clozapine ODT as a 505(b)(2) application?

The Division confirmed that it is acceptable to file Clozapine ODT as a 505(b)(2) application.

CMC Program

Alamo confirmed that _____ has a separate patent for the _____ dosage forms, _____ not lyophilized formulations.

The manufacturing and stability program presented at this meeting was slightly different from that submitted in the pre-IND briefing document. Alamo explained that the proposed formulation has been changed (_____) and stated that the changes are subtle, primarily with the addition of effervescent excipients (attachment 1). The proposed packaging system has also been changed, from _____ foil/foil blister packaging.

- Does the Agency agree that the manufacturing and stability program presented in Section D is adequate to support the 505(b)(2) application?

Agency response: The Division concluded that the proposed stability and manufacturing programs (as presented in the briefing document and at the meeting [attachment 2]) would present no problem for review. If something unusual arises (e.g., new impurities) from the drug substance source during drug development, further discussions may be required. Other agreements were reached and are outlined below.

CMC discussion

Alamo must provide documentation that each excipient is either USP or NF, or must provide and justify specifications if they are not. For the _____ flavoring, Alamo must provide either a DMF reference or a list of ingredients.

The proposal to submit three pilot batches in the NDA submission is acceptable.

The proposal to submit _____ months of accelerated and 25°C stability data at 505(b)(2) filing is acceptable. The Division would not recommend a refusal to file on the basis of a submission with only _____ months accelerated stability data. If additional stability data are submitted during the early stages of review, the Division will do its best to review it. If the additional stability data are filed during the last _____ months of the review process, the submission could be considered a major amendment and could extend the NDA review clock. The Division confirmed that _____ months accelerated data will support the assignment of a _____ month expiry-dating period.

The Division will require documentation that the submitted analytical methods are suitable to detect any reaction or possible degradation of aspartame, or products due to

possible reactions of aspartame and any excipients/drug substance in the ODT formulation. Product labeling will need to comply with standard aspartame labeling requirements as per 21 CFR 201.21.

The Division requires that Alamo set a disintegration specification for Clozapine ODT, in addition to a dissolution specification. The disintegration test must be conducted at the pH of saliva in the mouth. The disintegration test is necessary to demonstrate that Clozapine ODT disintegration does not change over time; therefore it must be part of the initial stability program. If, after approval, there is no change over time, Alamo may request to withdraw the disintegration test based on submitting data in a pre-approval supplement.

Nonclinical Program

- *We believe that the safety of Clozaril and clozapine has been previously demonstrated in earlier, separate submissions to the FDA. Our plan is to include in our IND and subsequent 505(b)(2) application a detailed summary of preclinical studies supporting Clozaril (clozapine) (NDA # 19-748), as well as references to the literature on preclinical and animal toxicity data on clozapine. We do not plan to conduct any additional nonclinical studies on clozapine. Does the Agency concur with this plan?*

Agency response: The Division stated that the nonclinical program as presented in the briefing document is acceptable.

Nonclinical discussion

The Division noted that, as there is already a large clozapine database within the division, Alamo should resubmit the nonclinical section from the pre-IND briefing document to the IND and include a literature search summarizing any recent data.

Clinical Program

Bioequivalence Waiver

- *Will the Agency agree to a request to waive the bioequivalence requirement for the 25-mg strength of Clozapine ODT if satisfactory results are achieved in the proposed bioequivalence study performed with Clozapine ODT, 100 mg?*

Agency response: The Alamo request for a waiver of the bioequivalence requirement for the 25-mg strength of Clozapine ODT is acceptable as long as additional information, outlined below, is provided.

Clinical discussion:

Alamo must demonstrate that Clozapine ODT follows linear kinetics at steady state and this must be documented fully in the IND. This can be demonstrated by obtaining the data, not generating it, from either the Clozaril package insert, through FOI, or through a literature search.

Alamo should develop dissolution methods to test Clozapine ODT in various pH ranging media (including _____). The data generated from this profile must support the submission of one medium as the regulatory method in the Clozapine ODT proposed specifications.

The Division agreed that the dissolution profile could be conducted on one batch, the biobatch, and data should be generated on both the 25mg and 100mg tablets. The dissolution profile must be comparable for both strengths and the 25mg and 100mg strengths must both meet the same specifications.

Proposed Clinical Trial

- *Alamo welcomes Agency input and advice on the design and conduct of the proposed clinical trial. Does the Agency have any comments on this proposed protocol?*

Agency response: The proposed BE study protocol did not specify which moiety would be measured in the plasma samples. Plasma concentrations of clozapine and the major active metabolite, desmethyl clozapine, should be determined to compare the PK parameters at steady state with both formulations. The following pharmacokinetic data should be reported for the evaluation of bioequivalence of the multiple dose study: individual and mean blood drug concentration levels, C_{max}^{SS} , C_{min}^{SS} , AUC_{0-12h} , T_{max} , $t_{1/2}$ and percent fluctuation $[=100 * (\text{average } C_{max}^{SS} - C_{min}^{SS}) / C_{average}^{SS}]$. The log transformed AUC, C_{max}^{SS} and C_{min}^{SS} data should be analyzed statistically using analysis of variance and 90% confidence interval.

Clinical discussion:

The 90% confidence interval requirement will be applied to the parent compound. Alamo must also measure the active metabolite and report data on the requested parameters; however, this is for information only and will not determine the approvability of the product. If the metabolite does not meet the 90% confidence interval, this would not mean that the protocol technically failed.

Program Agreement

- *As described in Section G, the proposed clinical protocol will be adequate and well controlled, of significant size and duration, and is expected to demonstrate the safety of Clozapine ODT as well as its bioequivalence to the reference-listed drug. Does the Agency agree that this study is sufficient to support the 505(b)(2) application?*

Agency response: The Division agreed that the one clinical protocol proposed in the pre-IND briefing document Alamo is acceptable for 505(b)(2) filing. The final protocol, with the incorporation of the changes requested at this meeting, will be filed to the IND.

Pediatric Waiver Request

- *As the reference-listed drug does not include pediatric labeling, Alamo intends to file for a waiver to the pediatric rule as per 21 CFR 314.55. Is this acceptable to the Agency?*

Agency response: The Division stated that the Alamo request for a waiver of the pediatric rule requirements will not be granted, however, FDA will grant a deferral of the requirements until after NDA approval. Alamo must submit a proposal for the pediatric trial in the 505(b)(2) submission and the study can be conducted as a Phase IV commitment.

Clinical discussion:

The Division stated that clozapine is being used in adolescent schizophrenics, although the extent of the usage is unknown. Therefore, the Agency will require a clinical trial, not a bioequivalence study, in adolescents. The Division is currently working out the details of the protocol design and welcomes any input that Alamo may have into the design of the study. The requirement for a double-blind study is under discussion.

Clozapine ODT Registry

- *Alamo welcomes Agency input and advice on the design and conduct of the proposed Clozapine ODT monitoring registry. Does the Agency have any comments on this proposal?*

Agency response: The Division does not provide details on how sponsors are to design and conduct the clozapine monitoring registry. Alamo must meet the requirements set forth in the approved Clozaril package insert and this must be in place at time of product marketing.

Registry discussion:

Alamo may submit a basic format for its proposed registry in the IND, and the Division is willing to provide comment on the program as details are formalized. The final proposal must be submitted in the 505(b)(2) application; however, it is possible that Clozapine ODT could be approved based on the submitted proposal and some details of the registry could be agreed after approval.

Clozapine ODT IND

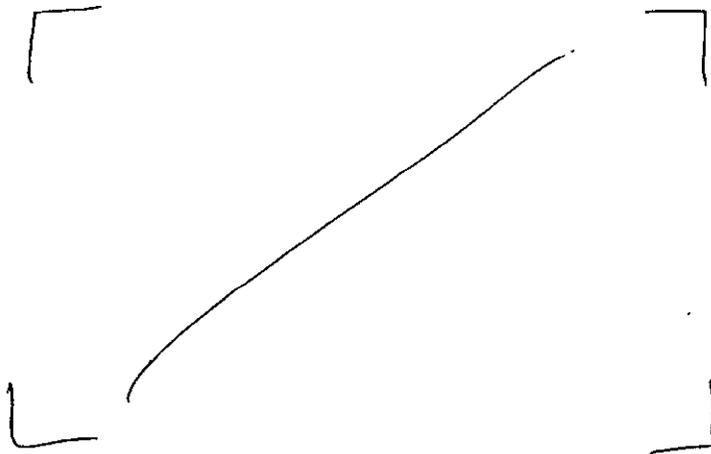
Alamo plans to submit the Clozapine ODT IND in November/December 2001 and plans to initiate the proposed clinical trial in January 2002.

Since the Clozapine ODT program is a somewhat abbreviated program, there is likely no need or time for formal meetings. The Clozapine ODT clinical section will be comprised of the one clinical study report, therefore, there may be no need for a standard pre-NDA meeting. The Division stated that it would be willing to work with Alamo on questions during the review of the IND, specifically with regard to the CMC section, as there may be questions on data presentation or technical issues that may require discussion. Alamo

was advised to submit any questions in writing to Mr. Hardeman, Regulatory Project Manager, via email, and then file the amendment officially to the IND; the team agreed that they would respond to the questions as soon as possible after submission.

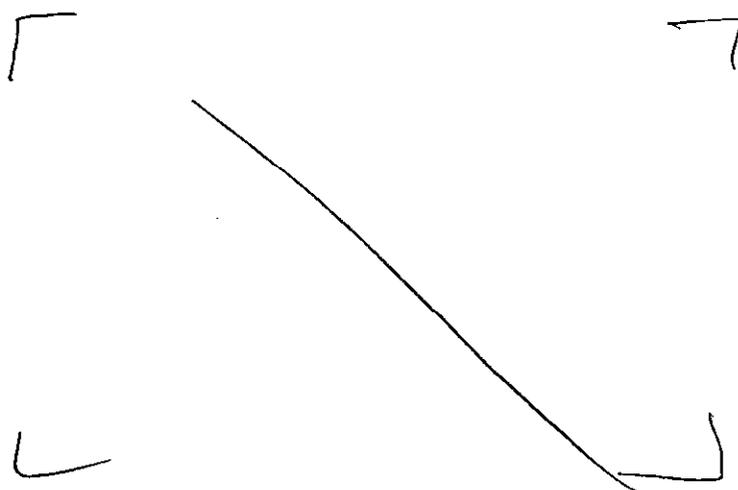
**Clozapine ODT (orally disintegrating tablets) Pre-IND Meeting
August 31, 2001
Attachment 1**

**Representative Formula for
Clozapine ODT (25 mg and 100 mg)**



Clozapine ODT (orally disintegrating tablets) Pre-IND Meeting
August 31, 2001
Attachment 2

**•ICH Stability Plan for Clozapine
ODT (25 mg and 100 mg)**



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

/s/

Russell Katz
9/12/01 10:41:24 AM

Hardeman, Steven D

From: Hare, Donald B
Sent: Wednesday, October 01, 2003 9:48 AM
To: Hardeman, Steven D
Cc: Laughren, Thomas P
Subject: RE: b2 labeling question

Steve:

In my opinion the labeling of a (b)(2) application does not have to be the same as its listed drug. The (b)(2) application is submitted under 505(b)(1) and therefore has to meet today's standards. I can see nothing wrong with approving the (b)(2) with the new warning so long as that is your position.

I equate this situation with another full NDA under review for Clozapine, would you approve without the warnings?

Call if you want to discuss further.

Don

-----Original Message-----

From: Hardeman, Steven D
Sent: Wednesday, October 01, 2003 9:25 AM
To: Hare, Donald B
Cc: Laughren, Thomas P
Subject: b2 labeling question

Don,

We recently sent a supplement request letter to all the atypical antipsychotic NDAs. In that letter we requested that they add a warning about the development of diabetes mellitus and hyperglycemia. We also provided them with the text of the warning.

Here's the problem. We have a 505(b)2 application for clozapine orally disintegrating tablets due this month and the sponsor has accepted our proposed warning labeling verbatim. The reference listed drug (Novartis - Clozapine) has not accepted our labeling and will probably want to argue the point in a meeting later this year.

Is there any reason that we can't go ahead and approve the (b)2 with the new warning?

Thanks,
Steve

CAPT Steven D. Hardeman, R.Ph.
Senior Regulatory Project Manager
Division of Neuropharmacological Drug Products / HFD-120
Food and Drug Administration
Rockville, Maryland 20857

Phone: 301-594-5525
Fax: 301-594-2859
Email: hardemans@cdcr.fda.gov

Hardeman, Steven D

From: Colangelo, Kim M
Sent: Thursday, November 13, 2003 12:58 PM
To: Hardeman, Steven D
Subject: RE: NDA 21-590

Steve,

Thanks! No news is good news - so proceed with your action as planned unless you hear otherwise!
Kim

Kim Colangelo
Associate Director for Regulatory Affairs
Office of New Drugs
CDER/FDA
301-443-5374 - new number as of 10/27/03
301-480-6329 (f)

-----Original Message-----

From: Hardeman, Steven D
Sent: Thursday, November 13, 2003 10:54 AM
To: Colangelo, Kim M
Subject: NDA 21-590

m,

It is quite possible that we will go straight to approval for the 505(b)2 application for Fazaclo (clozapine) orally disintegrating tablets. Although the due date isn't until 11/30/03, due to the holiday and vacation schedules, we plan on taking an action by 11-21-03.

Steve

CAPT Steven D. Hardeman, R.Ph.
Senior Regulatory Project Manager
Division of Neuropharmacological Drug Products / HFD-120
Food and Drug Administration
Rockville, Maryland 20857

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NDA 21-590

DISCIPLINE REVIEW LETTER

Alamo Pharmaceuticals, LLC
Attention: Jeanine Kuczik, R.Ph.
Regulatory Affairs Advisor
8501 Wilshire Boulevard
Suite 318
Beverly Hills, CA 90211

Dear Ms. Kuczik:

Please refer to your pending new drug application (NDA) submitted January 30, 2003, under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for clozapine orally disintegrating tablets.

After reviewing the available data pertaining to the use of atypical antipsychotic medications and diabetes mellitus adverse events, we have concluded that the product labeling for all atypical antipsychotics should be updated to include information about these events.

While we acknowledge that the relationship between atypical antipsychotic use and diabetes mellitus adverse events has not been completely described, we believe the safe use of clozapine can be enhanced by informing prescribers and patients about these events. Increased attention to the signs and symptoms of diabetes mellitus may lead to earlier detection and appropriate treatment, and thus reduce the risk for the most serious outcomes.

We request that you amend the labeling of your pending NDA with the following changes so as to furnish adequate information for the safe and effective use of the drug:

WARNINGS**Hyperglycemia and Diabetes Mellitus**

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including clozapine. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics studied. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at baseline and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

Although we believe that the labeling changes accurately reflect the currently available information about antipsychotic use and diabetes mellitus, we acknowledge that additional labeling changes may be required as new information becomes available. Areas that require additional research include, but are not limited to, identification of subpopulations at greatest risk for diabetes mellitus adverse events, exploration of the relative risk for diabetes mellitus adverse events among the different antipsychotics, and evaluation of potential mechanisms of action.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of this issue. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application.

If you have any questions, call Steven D. Hardeman, R.Ph., Senior Regulatory Project Manager, at (301) 594-5525.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Russell Katz
9/30/03 04:19:07 PM



NO FILING REVIEW ISSUES IDENTIFIED

NDA 21-590

Alamo Pharmaceuticals, LLC
Attention: Neal R. Cutler, M.D.
8501 Wilshire Boulevard, Suite 318
Beverly Hills, CA 90211

Dear Dr. Cutler:

Please refer to your January 30, 2003 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for clozapine orally disintegrating tablets.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application will be filed under section 505(b) of the Act on April 1, 2003 in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing 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.

If you have any questions, call Steven D. Hardeman, R.Ph., Senior Regulatory Project Manager, at (301) 594-5525

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Russell Katz
3/13/03 10:51:20 AM