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Approval Package for:

APPLICATION NUMBER:

21-590

Trade Name: Fazaclo Orally Disintegrating Tablets,
25 mg and 100 mg.

Generic Name: Clozapine

Sponsor: Alamo Phamaceuticals, LLC

Approval Date: February 10, 2004

Indications: For the management of severely ill schizophrenic patients who fail to respond adequately to standard drug treatment for schizophrenia.

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APPLICATION NUMBER:

21-590

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	X
Approvable Letter	X
Final Printed Labeling	X
Medical Review(s)	X
Chemistry Review(s)	X
EA/FONSI	
Pharmacology Review(s)	
Statistical Review(s)	
Microbiology Review(s)	
Clinical Pharmacology/ Biopharmaceutics Review(s)	X
Administrative/Correspondence Document(s)	X

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APPLICATION NUMBER:

21-590

APPROVAL LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

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 new drug application (NDA) dated January 30, 2003, received January 31, 2003, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Fazaclo (clozapine) Orally Disintegrating Tablets, 25 mg and 100 mg.

We acknowledge receipt of your submission dated December 10, 2003, which constituted a complete response to our action letter of November 29, 2003.

This new drug application provides for the use of Fazaclo for the management of severely ill schizophrenic patients who fail to respond adequately to standard drug treatment for schizophrenia.

We completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved NDA 21-590.**" Approval of this submission by FDA is not required before the labeling is used.

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

We grant a shelf life of 24 months based on the available stability data.

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

We note your acceptance of the following dissolution method and specification as follows:

USP Apparatus	
Rotation speed:	rpm
Volume:	900 mL
Medium:	pH acetate buffer
Tolerance:	Q= % in 15 minutes

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

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

Enclosure

**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
2/10/04 07:00:54 AM

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21-590

APPROVABLE LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

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Attention: Neal R. Cutler, M.D.
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Dear Dr. Cutler:

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We acknowledge receipt of your submissions dated:

March 28, 2003	June 2, 2003	June 11, 2003	July 23, 2003
August 1, 2003	August 13, 2003	October 17, 2003	October 21, 2003
October 30, 2003			

We have completed our review of this application, as submitted, with draft labeling, and it is approvable. Before the application may be approved, however, it will be necessary for you to address the following issues:

Clinical

Prior to implementation of the Fazaclo (Clozapine, USP) Orally Disintegrating Tablet patient registry, we request that you address the following issues (with reference to appropriate page number in volume 1.29):

1. Page 12: Since physicians who register to prescribe Fazaclo must agree to use this product in accordance with labeling, the inclusion/exclusion criteria in the registry protocol should be consistent with labeled indications/contraindications. Under Inclusion Criteria, it is stated that patients with a _____ may receive Fazaclo. However, the labeling of clozapine products does not specify the exact diagnostic criteria to be used in assessing patients for clozapine therapy but, in terms of diagnosis, simply indicates "schizophrenia." We recommend that you delete the qualifier _____.
2. Page 13: For a similar reason, under Exclusion Criteria, the contraindicated use with agents with a well-known potential for agranulocytosis or bone marrow suppression should be added in accordance with current labeling for clozapine products.

3.

4. Page 13: The first paragraph in section 7.3.1 indicates that Fazaclo will be available only to registered physicians who are licensed in the states where they prescribe. The protocol should specify exactly how this will be verified. Additionally, this requirement may exclude many military physicians, who are permitted to possess a license in any state regardless of where they practice in the military healthcare system. Although it is not likely that clozapine is extensively utilized by military physicians, it is possible since the treatment of some psychiatrically disabled military retirees takes place in a military setting. You should consider an accommodation for military physicians.
5. Page 16: For a patient who is newly registered, the registry will notify the pharmacist of the non-rechallenge and registration status and provide a Patient Registration Number (PRN). However, it is not clear how the prescribing physician will be notified of the patient's registration status. This should be specified in the protocol.
6. Page 20: The process for transferring patients who have received another clozapine formulation to Fazaclo is not entirely clear. Section 7.9 indicates that such patients may be switched to Fazaclo by an Alamo registered pharmacist only if the pharmacist receives a current prescription from a physician registered with some clozapine patient registry and an acceptable WBC count within the last 7 days (or last 14 days if being monitored biweekly). The pharmacist must contact the Coordinating Center to facilitate patient registration and identify the affiliated treatment pair (physician/pharmacist) for the switched patient. The WBC count and dispensation information must be submitted to the registry upon patient transfer and the patient must be fully registered in the Alamo registry prior to the next dispensation.
7. The following points require clarification in the protocol:
 - a. It is presumed, but should be explicitly stated, that this process involves a physician/pharmacist pair who have already been utilizing another clozapine formulation to treat the patient being switched. Otherwise, it is not clear how the pharmacist could easily verify that the physician was currently registered under another clozapine patient registry.
 - b. It is also presumed that, for full registration of the patient in the Alamo registry, the physician must register with Alamo if not already registered and must complete the appropriate section of the Patient Registration Form, which requires the physician's signature, prior to the second dispensation of Fazaclo. This should be explained in the protocol.
 - c. According to the Physician Enrollment Form and the Pharmacy/Pharmacist Enrollment Form, the physician agrees not to prescribe Fazaclo and the pharmacist agrees not to dispense Fazaclo prior to receiving a Patient Registration Number (PRN) from the Alamo registry. Additionally, the bottom of the Patient Registration Form contains an order to not dispense treatment until the PRN is received. Since a PRN is not issued to a treatment pair prior to full registration (see Appendix C on page 25), it appears that a patient being switched may be prescribed and dispensed initial treatment with Fazaclo prior to issuing of a PRN. It is suggested that this exception, which may occur frequently, be described in the protocol and on the above forms.

8. Page 21: Section 7.12 states that procedures will be established and maintained for regular auditing of healthcare professionals to insure compliance with product labeling and the registry protocol. The audit procedure should be described in greater detail, to include the proportion of professionals to be audited, what specific information will be examined, and the frequency of auditing. Additionally, if wholesale distributors will be utilized to deliver drug supplies to pharmacies, these distributors should be audited to insure that supplies of Fazaclo are not delivered to non-registered pharmacies.
9. Page 33: The bottom of the WBC Monitoring Form provides the instruction to mail or FAX the completed form to the Alamo registry. However, the top of the form instructs the physician to complete the form and forward it to the pharmacist, who then forwards the form to the registry. The instructions at the bottom should be clarified to insure that the physician forwards the form to the pharmacist and not directly to the registry.

Chemistry, Manufacturing, and Controls

1. A deficiency letter has been sent to _____ the DMF holder for clozapine.
2. We have the following requests:
 - a. Reduce the Individual Unspecified Impurity limit to NMT _____ (Drug Substance Specification) as recommended in ICH Q3A(R): "Impurities in New Drug Substances."
 - b. Reduce the Drug Substance Specifications for Impurities (_____ from NMT _____ to NMT _____ as recommended in ICH Q3A(R) or provide data demonstrating that these impurities have been qualified to _____
 - c. Provide the following information for drug substance method _____ (in Clozapine Bulk Drug Substance): _____

 - d. Provide updated drug substance acceptance specifications.
 - e. Provide details about the maximum time allowed for completion of tablet manufacture and packaging, and allowable hold times between process steps _____
 - f. Provide a commitment that if _____ is needed in the future, prior approval would be obtained from FDA before implementation.
 - g. Provide a sampling plan for the production batch analyses (e.g. beginning, middle, end) of samples to be tested from each batch (release and in-process).
 - h. Change the Related Substances Specifications for Fazaclo (clozapine) 25 mg and 100 mg Tablets to Individual specified, Individual unspecified, and Total impurities according to ICH Q3B(R), Impurities in New Drug Products guideline. Reduce the specifications for Individual unspecified to not more than _____ as recommended in ICH Q3B(R).

- i. Provide specificity of known clozapine related substance, _____ in HPLC Drug Product method. _____ (Identification, Assay, and Uniformity of Dosage Units).
- j. Provide individual chromatograms of known clozapine related substances (Γ _____

- k. Provide individual chromatograms of known _____

- l. _____
- m. In the original submission, you provided data from stability studies on one commercial batch of each strength, 25 mg and 100 mg tablet. Please provide a commitment to continue the long-term studies through the proposed shelf life and the accelerated studies for _____ and to place additional commercial batches, to a total of at least three, on long-term stability studies through the proposed shelf life and on accelerated studies for _____ according to "Guidance for Industry Q1A Stability Testing of New Drug Substances and Products."
- n. Provide updated stability data of the registration stability batches.
- o. Provide updated drug product specifications (release and stability).
- p. Provide NDC Numbers for each proposed tablet strength in the HOW SUPPLIED section of the proposed package insert.

Clinical Pharmacology and Biopharmaceutics

The proposed dissolution specification, Q value of _____ in _____ minutes, is not acceptable. Based on the data, we recommend the following dissolution method and specification:

USP Apparatus: _____
Rotation speed: _____
Volume: 900 mL
Medium: _____
Tolerance: Q= _____ in 15 minutes

In addition, you must submit final printed labeling (FPL) for the drug. Please submit the final printed labeling (FPL) electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format - NDA (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Please submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call Steven D. Hardeman, 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

Enclosure (labeling)