

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-590

MEDICAL REVIEW

Review and Evaluation of Clinical Data
NDA #21-590

Sponsor: Alamo Pharmaceuticals
Drug: Fazaclo (Clozapine) Orally
Disintegrating Tablets
Proposed Indication: Treatment-Resistant Schizophrenia
Material Submitted: Response to 11-19-03 Approvable
Letter
Correspondence Date: December 10, 2003
Date Received: December 11, 2003

I. Background

Alamo Pharmaceuticals submitted this NDA on 1-30-03 to gain marketing approval of their orally disintegrating tablet formulation of clozapine (Fazaclo) for the treatment of refractory schizophrenia. The application was reviewed and an approvable letter was issued on 11-19-03.

This letter delineated a number of clinical issues regarding their proposed patient registry that would need to be addressed. Additionally, the letter conveyed numerous requested revisions to their proposed labeling which had been submitted on 10-30-03.

In addition, the letter communicated a number of requests regarding chemistry, manufacturing, and controls issues as well as a request from the biopharmaceutics reviewers for implementation of a specific dissolution method and specification.

Finally, we had requested that introductory promotional materials be forwarded to the Division of Drug Marketing, Advertising, and Communications (DDMAC).

This submission provides Alamo's response to all of the concerns and requests raised in the approvable letter. The review below will focus on the clinical issues, i.e., the patient registry and product labeling.

II. Response to Approvable Letter

A. Patient Registry

Attachment 2 of this submission provides responses to clinical comments about the patient registry.

Clinical Issues 1, 2, and 3

Issues 1, 2, and 3 in the clinical section of the approvable letter requested changes to the Inclusion/Exclusion criteria contained in the sponsor's protocol for the Fazaclo Patient Registry so that these criteria were consistent with product labeling.

The sponsor indicates that since the Clozaril National Registry does not provide inclusion/exclusion criteria, these criteria will be removed from their registry to avoid confusion and for consistency with the Clozaril National Registry. These criteria are fully described in Fazaclo labeling, which is consistent with Clozaril labeling.

Removal of these criteria from their protocol is acceptable since the actual usage of Fazaclo will be guided by labeling and not the protocol.

Clinical Issue 4

Issue 4 in the clinical section of our letter requests information on how licensure of prescribing clinicians would be verified, as described in the registry protocol, as well as requesting an exemption for an in-state licensure requirement for military physicians.

Alamo states that they will remove references to state licensure requirements and ask only for the prescriber's DEA number or other identification number (e.g., social security number) for identification purposes. This is similar to requirements for physicians enrolled in the Clozaril National Registry.

This is acceptable.

Clinical Issue 5

We had asked that the protocol be amended to describe how the physician would be informed of the eligibility and enrollment status of a patients beginning Fazaclo therapy.

Information will be added to indicate that the patient's physician will be notified of non-rechallenge status and Patient Registration Number by mail, fax, or e-mail.

This is acceptable.

Clinical Issues 6 and 7

We had asked the sponsor to amend the registry protocol to more clearly describe the process of registering physicians when either the patient switched from another formulation of clozapine to Fazaclo or changed healthcare providers (Issues 6, 7a, and 7b). We also requested that they clarify certain forms to indicate that, in the case of a patient being switched to Fazaclo, drug may be dispensed before receipt of a Patient Registration Number (Issue 7c).

In response, Alamo has modified the protocol to clearly state that, for patients switching to the Fazaclo formulation or changing physicians, the Coordinating Center will contact the prescriber to insure registration of the physician. They have also added information to the Patient Registration Form, Physician Enrollment Form, and Pharmacy/Pharmacist Enrollment Form as well as to the description of the patient registration process in their protocol to clearly state that patients being switched to Fazaclo may receive drug before a Patient Registration Number is issued.

These changes adequately address our concerns.

Clinical Issue 8

We had requested that the sponsor specify in further detail their procedure for auditing healthcare professionals to insure compliance with labeling and the registry protocol. We also asked that they audit wholesale distributors who may be involved in delivering supplies of Fazaclo to pharmacies.

Alamo presents further information about how they will deal with information that suggests usage not in compliance with labeling as well as for auditing the timeliness of registry data submissions and the management of patients with low WBC counts. Audits will also be conducted of the accuracy of physician and pharmacy information provided at the time of registration and of wholesalers to insure that only registered pharmacies receive supplies of drug.

Although the frequency of audits and the percentage of records that will be examined is still not described, I consider the sponsor's description to be adequate since the Agency has never set detailed standards for auditing registry data for any clozapine product.

Clinical Issue 9

We asked Alamo to amend the bottom of the WBC Monitoring Form to clearly indicate that the pharmacist, not physician, was to forward the form to the registry.

The following statement has been added to the bottom of the form:

"Pharmacist: Once this form is received from the Affiliated Physician this completed form should be mailed or FAXed to the FAZACLO Patient Registry."

This change sufficiently addresses our concern.

Other Changes to the Patient Registry

In addition to the above changes pursuant to issues listed in our approvable letter, the sponsor has proposed additional modifications to the registry:

- the trade name has been changed to Fazaclo throughout the protocol.
- the registry objectives have been reworded to indicate that Fazaclo would be available through registered (as opposed to registered and qualified) physicians and pharmacists only; the registry objective is to encourage and support (as opposed to require) adherence to the WBC monitoring schedule as outlined in labeling.
- the description of the design of the registry has been reworded to indicate that it is part of an open-label post-marketing surveillance program.
- the WBC Monitoring Form will be modified to include fields for collecting information on daily dosage and the medication dispensation date.
- the Patient Registration Form will be amended to collect information about the patient's race similar to the form used in the Clozaril National Registry.

I have no objection to these changes.

B. Product Labeling

Alamo has accepted all of the revisions requested by the Agency in our approvable letter. However, they have made further revisions, as displayed in Attachment 5 of this submission, to provide consistency with Clozaril labeling or to provide correct information about Fazaclo as presented in original NDA submission:

- the trade name "FAZACLO™ (Clozapine, USP)" has been used consistently throughout labeling.
- under CLINICAL PHARMACOLOGY/Absorption, Distribution, Metabolism, and Excretion, the sponsor has revised the figures for steady state Cmax, Tmax, and Cmin in accordance with data provided in the original submission and repeated in Attachment 5, page 55, of this submission.
- in the third paragraph of this same section, the sponsor has added mention of the inactive metabolites of clozapine for consistency with Clozaril labeling.
- under PRECAUTIONS/Pharmacokinetic-Related Interactions, the sponsor has deleted mention of _____ from the second paragraph and _____ from the third paragraph for consistency with Clozaril labeling.
- the date (DECEMBER 2003), code (T2003-12), and space for a bar-code number have been added to the end of labeling.
- numerous minor editorial changes have been made as shown in Attachment 5, pages 7 and 24.

These changes appear to be acceptable from a clinical perspective.

III. Conclusions and Recommendations

Reviews of this response by the Office of New Drug Chemistry and the Office of Clinical Pharmacology and Biopharmaceutics are pending at this time.

Additionally, launch promotional materials will be evaluated by DDMAC.

From a clinical standpoint, Alamo's response to the concerns raised in our 11-19-03 approvable letter is satisfactory and it is recommended that this application be approved.

Gregory M. Dubitsky, M.D.
December 24, 2003

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cc: NDA #21-590
HFD-120 (Div. File)
HFD-120/GDubitsky
/TLaughren
/PAndreason
/SHardeman

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/s/

Greg Dubitsky
12/24/03 06:46:23 PM
MEDICAL OFFICER

Thomas Laughren
2/4/04 01:40:27 PM
MEDICAL OFFICER

I agree that this NDA can be approved; see
memo to file for more detailed comments.--TPL

REVIEW AND EVALUATION OF CLINICAL DATA

Application Information

NDA#: 21-590
Sponsor: Alamo Pharmaceuticals
Due Date: November 30, 2003

Drug Name:

Generic Name: Clozapine — Disintegrating
Tablets
Trade Name: Fazaclo (proposed)

Drug Categorization:

Pharmacological Class: Atypical Antipsychotic
Proposed Indication: Refractory Schizophrenia
Dosage Forms: 25 and 100mg Tablets
Route: Oral

Review Information

Clinical Reviewers: Gregory M. Dubitsky, M.D.
Completion Date: September 27, 2003

NDA 21-590
Clozapine Fast Disintegrating Tablets
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EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on Approvability

From a clinical perspective as of the date of this review, it is recommended that this application be granted approvable status; final approval should be contingent on resolution of concerns regarding the Alamo patient registry (see section VIII) and product labeling (see section XI).

B. Recommendation for Phase 4 Studies

I have no recommendations for Phase 4 studies.

II. Summary of Clinical Findings

A. Brief Overview of the Clinical Program

This application is intended to support the approval of a fast dissolving tablet formulation of clozapine for the management of patients with treatment-resistant schizophrenia.

This is a 505(b)(2) application in which the data supporting the safety and efficacy of this product are those pertaining to Clozaril, the marketed innovator clozapine product, which was approved under NDA 19-758 and was launched in the U.S. in 1990. Approval of this application depends on a demonstration of bioequivalence between this product and Clozaril. Alamo conducted study CS-001-2002 for this purpose. Also, since clozapine is associated with agranulocytosis and all clozapine products are dispensed under a controlled distribution system that mandates registration and regular white blood cell count (WBC) monitoring, approval is also contingent on Alamo's establishment of an acceptable patient registry and monitoring plan.

B. Efficacy

The sponsor provides no new efficacy data in this application. Efficacy relies on investigations conducted with the innovator product, Clozaril.

C. Safety

The small amount of safety data derived from the bioequivalence study, CS-001-2002, suggests no hazard associated with this product that would preclude its approval or warrant a major change to product labeling vis-à-vis Clozaril labeling. The determination of safety for this product relies almost entirely on investigations conducted with the innovator product, Clozaril.

D. Registry and WBC Monitoring System

The sponsor has proposed a protocol for a patient, physician, and pharmacist registry and procedures for monitoring and tracking WBC counts for patients treated with this clozapine product. This protocol was reviewed and deemed to be generally acceptable by the undersigned. There are, however, a number of minor concerns with this proposal that should be addressed by the Alamo prior to implementation and product launch. These are discussed in section VIII below.

E. Dosing

Dosing will be essentially identical to that for Clozaril. The vulnerability of this product to moisture requires that it be stored in blister packaging until immediately before use and that any product removed from the blister that is not consumed be discarded.

F. Special Populations

The development plan included no studies in special populations.

CLINICAL REVIEW

I. Introduction

A. Background

Clozapine is an atypical antipsychotic marketed by Novartis Pharmaceuticals as Clozaril for the management of treatment resistant schizophrenia and to reduce the risk of recurrent suicidal behavior in schizophrenia and schizoaffective disorders. Additionally, two generic formulations of clozapine are marketed in the U.S. for treatment resistant schizophrenia.

Alamo Pharmaceuticals has developed a  disintegrating tablet formulation of clozapine for use in treatment resistant schizophrenia (referred to as clozapine  fast disintegrating tablets or clozapine  DT in this review). This product has been developed under IND 61,484 and has the currently proposed proprietary name of Fazaclo Orally Disintegrating Tablets. The rapid disintegration characteristic is intended to improve patient compliance and to assist patients who have difficulty taking solid oral medications.

Alamo is seeking approval of clozapine  DT under the provisions of 505(b)(2) of the Federal Food, Drug, and Cosmetic Act using Clozaril Tablets as the reference-listed drug. This application is supported by one study intended to demonstrate the bioequivalence between clozapine  DT and Clozaril administered as 100mg bid at steady state (study CS-001-2002) and information which supports a waiver of in vivo bioequivalence requirements for the 25mg strength (see section III.B).

B. Major Safety Findings with Clozapine

Due to an appreciable risk of agranulocytosis associated with clozapine treatment, all clozapine products are distributed under controlled systems which require frequent monitoring of white blood cell (WBC) counts in order for patients to receive clozapine.

Other significant adverse events associated with clozapine include seizures, myocarditis, and orthostatic hypotension which can be profound and be accompanied by respiratory or

cardiac arrest, particularly during initial titration with rapid dose escalation. In addition, there are several reports of clozapine-emergent hyperglycemia and diabetes and related complications such as ketoacidosis.

C. Administrative History

A pre-IND meeting was held with representatives of Alamo on 8-31-01. During this meeting, the Division confirmed that it was acceptable to file the application for clozapine DT as a 505(b)(2) application. We agreed that the one proposed clinical protocol was acceptable for a 505(b)(2) filing and we provided feedback on the data analysis for this proposed bioequivalence study. The Division also stated that a WBC monitoring plan must be submitted in the 505(b)(2) application but that the product could be approved based on their proposed plan with some details decided after approval. The proposed manufacturing and stability program and nonclinical program were discussed (see the 9-12-01 meeting minutes for details). Alamo planned to market 25 and 100mg tablets and requested a waiver of the bioequivalence requirement for the 25mg strength if bioequivalence was shown for the 100mg strength. We indicated that we would grant a waiver under specific conditions that were discussed with the sponsor.

An IND application, to include the protocol for study CS-001-2002, was submitted to the Agency on 1-16-02. This study was intended to demonstrate the bioequivalence of the 100mg clozapine DT to the Clozaril 100mg tablet at steady state in patients with schizophrenia. It was allowed to proceed following a team meeting on 2-14-02.

The 505(b)(2) application for clozapine DT was submitted on 1-30-03 and received by the Agency on 1-31-03. A Refuse-to-File meeting was held on 3-11-03 and the application was deemed to be fileable. The PDUFA Due Date is 11-30-03.

In a 1-31-03 E-mail, the FDA Project Manager, Steven Hardeman, informed the sponsor that their originally proposed trade name, _____, would likely not be acceptable. He suggested that the sponsor propose a few more trade names for Agency consideration. The sponsor subsequently suggested the trade name "Fazaclo."

A 120-Day Safety Update to the NDA, consisting of an updated literature search, was submitted on 6-2-03.

D. Proposed Instructions for Use

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

E. Foreign Marketing

Clozapine DT has not been marketed in any foreign country nor has any application for clozapine DT been filed with any foreign regulatory agency by Alamo as of 6-2-03.

II. Clinically Relevant Findings from Consultant Reviews

A. Biopharmaceutics

The review of the bioequivalence study CS-001-2002 by the Office of Clinical Pharmacology and Biopharmaceutics is pending completion at this time.

B. Chemistry

The review of chemistry, manufacturing and controls data by the Office of New Drug Chemistry has not yet been completed.

C. DSI Clinical Site Inspection

The Division of Scientific Investigations was consulted to inspect both the clinical site for study CS-001-2002 as well as the analytical site for that study. Inspection reports have not yet been issued.

D. DMETS

The Division of Medication Errors and Technical Support was consulted to evaluate the acceptability of the sponsor's latest trade name proposal, Fazaclo. The report of this assessment has not yet been completed.

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacodynamics

No new pharmacodynamic data are presented in this NDA.

B. Pharmacokinetics¹

1. Study CS-001-2002

Study CS-001-2002 was a randomized, open-label, multiple-dose, two-way crossover study to demonstrate the bioequivalence of the 100mg clozapine \bullet DT and 100mg Clozaril tablet at steady state in patients with schizophrenia (age 18-59). Patients were not in acute exacerbation and were not considered treatment resistant. This trial was conducted by Michelle Middle, MB, ChB, of South Africa Clinical Trials, Western Cape, South Africa.

After admission to an inpatient unit, all patients began treatment with Clozaril and underwent a five day dose titration period during which the daily Clozaril dose was increased from 25mg to 150mg. Subjects were then randomized to a two-way crossover treatment sequence lasting 6.5 days for each treatment (i.e., 6.5 days of Clozaril 100mg bid then 6.5 days of clozapine \bullet DT 100mg bid or vice-versa). Doses were given at 8:00AM and 8:00PM. Each dose of Clozaril was taken with 240 ml of water. Water was not permitted during administration of clozapine \bullet DT. Doses were dispensed to study nurses who ensured that each dose was correctly administered.

On days 12 and 19, blood samples were taken predose and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 9, and 12 hours post-dose and assayed for clozapine and desmethylclozapine to determine bioequivalence.

¹ Pharmacokinetic data will be reviewed in greater detail by staff from the Office of Clinical Pharmacology and Biopharmaceutics (OCPB).

Thirty-six patients were enrolled in this study and 33 completed the trial. Of the 33 completers, 30 subjects were found to be at steady state for the two active species, clozapine and desmethylclozapine, after both 6.5 day treatment periods. Steady state was determined by comparing the trough concentrations on days 12 and 19 with those of the previous days (days 11 and 18, respectively). Changes in plasma concentration greater than — were considered to indicate lack of steady state.

The resulting PK parameters for the two active moieties were similar for the two treatment periods in both the completer group and the steady state group. For the parent drug in the steady state group, the ratios (90% CI) of geometric means for the primary PK parameters were as follows:

Cmax	97.6% (90.9-105%)
Cmin	103% (96.6-110%)
AUC ₀₋₁₂	99.2% (94.4-104%) ²

Thus, the study concludes that the 100mg clozapine FDT was bioequivalent to the 100mg Clozaril tablet after multiple dosing.

2. In Vivo Waiver for the 25mg Strength

The sponsor cites a study of intravenous and oral clozapine in rats as evidence that clozapine demonstrates linear pharmacokinetics at steady state.³ Additionally, although not cited by the sponsor, current Clozaril labeling states that steady state dosing with clozapine 37.5mg, 75mg, and 150mg bid produced linearly dose-proportional changes in clozapine AUC, Cmax, and Cmin.

The sponsor also indicates that all active and inactive ingredients in the 25mg clozapine FDT formulation are present in exactly the same proportion as the active and inactive ingredients in the 100mg formulation. The two tablet strengths are compressed using the same final blend with the 100mg tablet weight being four times that for the 25mg tablet.

² Ratio of clozapine FDT/Clozaril.

³ Sun L and Lau C. Intravenous and oral clozapine pharmacokinetics, pharmacodynamics, and concentration-effect relations: acute tolerance. Eur J Pharmacology 2000;398:225-238.

Alamo further states that the dissolution profile for the 25mg strength is similar to that of the 100mg strength.

Therefore, on the basis of linear pharmacokinetics, proportional tablet composition, and similar dissolution profiles, Alamo requests a waiver for a bioequivalence study of the 25mg tablet strength.

IV. Description of Clinical Data Sources

A. Primary Development Program •

1. Patient Enumeration by Study Type

The sponsor's primary clinical development plan consisted of the bioequivalence study CS-001-2002. This was a inpatient, randomized, open-label, multiple dose, two-way crossover study in 36 patients with schizophrenia.

2. Demographic Characteristics

The two treatment sequences were similar with respect to mean age, age range, gender, and race.⁴ The mean age for all patients was 39.8 years and the age range was 24 to 56 years. Most patients were female (63.9%). Most patients were of mixed racial origin (77.8%); only 13.9% of the patients were white.

3. Extent of Exposure

After an initial 5 day period of dose titration with Clozaril up to 75mg bid, patients were randomized to one of two treatment sequences: Clozaril/ Clozapine DT (N=18) or Clozapine DT/Clozaril (N=18). Each treatment consisted of 100mg bid and was administered for 6.5 days.

A total of 36 patients received study drug and 33 completed all treatment phases. Three patients dropped out due to adverse events:

- Patient 806 completed Clozaril titration and was withdrawn in Period I after receiving Clozaril for 1.5 days.
- Patient 809 completed Clozaril titration and Period I (clozapine DT) but dropped out in period II after receiving Clozaril for 5.5 days.

⁴ Demographic data are presented in Volume 1.14, page 132.

-Patient 811 completed Clozaril titration and was withdrawn in period I after receiving Clozaril for 6.5 days.

B. Published Literature

The sponsor provided a review of selected literature articles relevant to the efficacy and safety of clozapine.⁵ Alamo did acknowledge that this literature review is not exhaustive. The limited nature of the review was discussed at the Refuse-to-File meeting and it was decided that the submitted review was sufficient.

Additionally, the 120-Day Safety Update, submitted 6-2-03, presents the results of a literature search conducted using PubMed for articles relevant to the clinical safety as well as the pharmacodynamics and pharmacokinetics of clozapine that were published between 11-1-02 and 5-22-03.

Literature findings are discussed in section VII.B.5.

V. Clinical Review Methods

A. Items Utilized in the Review

Items used in the clinical review of this NDA are listed in Table V-1 below.

Submission Date	Items Reviewed
January 30, 2003	CS-001-2002 Clinical Study Report Proposed Labeling Financial Disclosure Certification Case Report Tabulations Case Report Forms Patient Registry Protocol
June 2, 2003	120-Day Safety Update

B. Specific Methods Used to Evaluate Data Quality

The consistency of adverse event documentation between Case Report Forms, Narrative Summaries (located in volume 1.14, pages 111 and 112), and the adverse event data listing AE.xpt was audited by the undersigned. This audit was

⁵ See volume 1.14, pages 35-39.

conducted for all three patients who dropped out due to adverse experiences in study CS-001-2002.⁶ Two of the three Narrative Summaries did not contain complete information regarding adverse experiences, lacking chemistry laboratory data (Patient #806) and temperature and WBC data (Patient #811). Thus, evaluation of these cases relied primarily on the Case Report Forms.

Additionally, the coding of investigator adverse event terms (verbatim terms) to MedDRA preferred terms for study CS-001-2002 was audited by the undersigned. This audit was conducted by comparing AEVENT terms to the corresponding PT_NAME terms in the adverse event data listing ADVC.xpt. It was noted that certain preferred terms appeared to be pseudospecific. These included the following groups of preferred terms:

Dyspepsia/Dyspepsia aggravated
Constipation/Constipation aggravated
Fatigue/Malaise

This may result in a deflated reporting rate for these experiences since occurrences would be split into different preferred terms instead of combined under a common preferred term. Since an examination of adverse event reporting rates in this trial was not an objective of the safety review (for reasons discussed in section VII.A), this issue will not impact on the safety conclusions drawn below. No other coding errors or irregularities were noted.

DSI inspections were also performed.

C. Adherence to Accepted Ethical Standards

Study CS-001-2002 was conducted according to procedures designed to ensure adherence to the ICH Tripartite Guideline for Good Clinical Practice (1997), relevant sections of the Code of Federal Regulations (including parts 50 and 56), and the Declaration of Helsinki (2000).

D. Evaluation of Financial Disclosure

Neal R. Cutler, M.D., President and CEO of Alamo Pharmaceuticals, certified that, as the sponsor of the

⁶ Patients #806, 809, and 811.

submitted study, he has not entered into any financial arrangement with any investigator listed on the submitted Form FDA 3454 (6/02) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a).⁷ He also certified that each listed investigator required to disclose a proprietary interest in the product or significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. He further certified that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

VI. Review of Efficacy

Study CS-001-2002 was not designed to evaluate the efficacy of clozapine DT. No other clinical efficacy data was reviewed in conjunction with this NDA.

VII. Integrated Review of Safety

A. Methodology of the Safety Review

Safety data in this NDA derives from study CS-001-2002 and the sponsor's literature review.

Study CS-001-2002 was not designed to permit an evaluation of the comparative safety of clozapine DT versus Clozaril. The number of patients was small (N=36), the clozapine DT treatment phase was brief (6.5 days), all patients received Clozaril for varying durations prior to clozapine DT exposure, and the crossover design makes attribution of safety findings to a particular product very difficult in patients who received both products. Furthermore, since Clozaril and clozapine DT appear to be bioequivalent, it is very unlikely that the safety profiles would differ to any appreciable extent with the exception of possible oral irritation associated with clozapine DT.

Thus, this safety review will be abbreviated compared to that conducted for most NDA's and will focus on: 1) any serious adverse experiences (i.e., deaths, non-fatal serious adverse events, and adverse events that led to premature discontinuation) that might suggest a particular

⁷ The listed investigators include the principal investigator (Michelle Middle) and the five co-investigators listed in Appendix 16.1.4 of the study report.

hazard related to clozapine DT treatment and 2) the potential for oral irritation with clozapine DT.

Important safety findings from the sponsor's literature review are also summarized.

B. Safety Findings

1. Deaths

No deaths were reported in study CS-001-2002.

2. Non-Fatal Serious Adverse Events^a

There was one patient with a non-fatal serious adverse event.

Patient #809 was a 47 year old female of mixed racial origin who completed the Clozaril titration period and Period I (clozapine DT). She was withdrawn during Period II after receiving Clozaril for 5.5 days when she was hospitalized for a subacute small bowel obstruction. She reportedly had symptoms consistent with a subacute small bowel obstruction in the four week period prior to initiating study treatment. This patient underwent a laparotomy, which revealed multiple fibrotic adhesions which produced a band obstruction around loops of small intestine. These were surgically released and this serious adverse experience resolved.

This event is unlikely to be related to clozapine exposure from either formulation.

3. Dropouts due to Adverse Events

In addition to patient #809, there were two other patients who dropped out due to adverse experiences.

Patient #806 was a 29 year old male of mixed racial origin who completed the Clozaril titration period and was withdrawn during period I after he had received Clozaril for 1.5 days in that phase. The reason for withdrawal was elevated liver enzymes. There were no associated symptoms

^a Seriousness was defined in accordance with 21 CFR 312.32(a).

(anorexia, nausea, vomiting, or jaundice). This finding resolved. Pertinent laboratory data are summarized below.⁹

	Date					
SGOT	20	81	222	168	80	19
SGPT	20	199	520	471	314	38
T.Bili	10	10	10	10	-	-
AlkPhos	61	66	-	79	-	-

This patient may have experienced an early stage of clozapine-induced hepatitis, which was aborted with discontinuation of treatment. This possibility is described in Clozaril labeling under PRECAUTIONS. This patient did not receive clozapine DT.

Patient #811 was a 48 year old female of mixed racial origin who finished the Clozaril titration period and was withdrawn in Period I after 6.5 days of Clozaril treatment due to hyperthermia. The day prior to dropout, her temperature was 99.3°F and the WBC count was 7,700/cmm (neutrophil count=6,300). No clear symptoms of infection were noted. Three days later (2 days after dropout), her temperature was 102.2°F and the WBC count had decreased to 4,200/cmm (neutrophil count=2,180). She was treated with Augmaxil (a penicillin combination) and other medications. The hyperthermia and decreased WBC count subsequently resolved.

It has been reported that 10 to 15% of patients who begin treatment with clozapine experience an increase in body temperature (usually 1 to 2°F) between the fifth and fifteenth day of treatment, after which the temperature normalizes.¹⁰ This patient experienced substantial drops in total WBC and neutrophil counts at about the same time as she experienced an increase in body temperature. The source of the fever is not clear from available documentation although antibiotics were begun, suggesting the possibility of an infection, and the fever resolved. It is quite possible that clozapine produced the drops in

⁹ Clozaril titration was begun on 4/5/02. The final dose of Clozaril was taken 4/11/02. Corresponding normal ranges and units are as follows: SGOT and SGPT 0-35 U/L, total bilirubin 5.1-17 µmol/L, and alkaline phosphatase 30-120 U/L.

¹⁰ Davis JM, Barter JT, Kane JM: Antipsychotic Drugs. In *Comprehensive Textbook of Psychiatry/V*, H Kaplan and B Saddock, editors. Williams and Wilkins, Baltimore, 1989.

blood cell counts and, conceivably, these in turn increased vulnerability to infection. The associations between clozapine and leukopenia as well as clozapine and fever are adequately labeled. This patient did not receive clozapine DT.

4. Oral Irritation

On the first, third, and seventh day of each of the two randomized treatment periods, the patient's oral cavity was assessed for local irritation immediately prior to the morning dose of study medication and at 0.5 hours after the morning dose. If irritation was present at 0.5 hours post-dose, follow-up assessments were conducted at 1 and 2 hours post-dose. If irritation persisted beyond two hours, the patient was to be withdrawn from the study. At each assessment, the presence or absence of oral irritation was documented in the CRF. If present, the location, degree, and extent of irritation were to be described. No signs of irritation were noted in any patient at any timepoint.

Salivary hypersecretion can be an indication of oral irritation. However, since this event is commonly reported with clozapine therapy, it is not useful as an indicator of local irritation in study CS-001-2002.¹¹

The listing of adverse event verbatim terms from AE.xpt was searched for any other events that suggested oral irritation. Nine such events in nine patients were identified and are listed below.

<u>Patient #</u>	<u>Adverse Event (verbatim term)</u>
801	Tongue laceration
802	Tongue laceration
807	Tongue feels swollen
808	Tongue feels thick
816	Thickness of tongue
818	Bitter taste in mouth
821	Thickness of tongue
825	Dryness of oropharynx
829	Pharyngitis

¹¹ Salivary hypersecretion was reported by 5 (15%) patients during treatment with clozapine DT and 8 (22%) patients during randomized treatment with Clozaril; 21 (58%) of all patients reported this event during the initial titration with Clozaril.

The onset of seven of these events occurred on Clozaril treatment. Of the remaining two events, one (bitter taste in mouth in Patient #818) occurred only on the first day of treatment of clozapine DT and the other (thickness of tongue in Patient #821) occurred four days after completing study treatment.

5. Published Literature Findings

The sponsor's literature review and search revealed no safety information specific to clozapine DT nor new safety findings associated with clozapine which warrant a change to Clozaril labeling at this time.

It should be noted, however, that the Division issued a letter on 9-11-03 to Novartis Pharmaceuticals, the sponsor of Clozaril, requesting that information relevant to hyperglycemia and diabetes with clozapine be added as a WARNING to Clozaril labeling. This request should also apply to the labeling for clozapine DT.

Also, changes to the required frequency for WBC monitoring and a new requirement for absolute neutrophil count monitoring with Clozaril treatment are under consideration by the Division pursuant to a meeting of the Psychopharmacological Drugs Advisory Committee on 6-16-03. Any such changes for Clozaril should also be implemented for clozapine DT.

C. Adequacy of Patient Exposure and Safety Assessments

As a 505(b)(2) application, the safety assessment of clozapine DT relies on the safety experience with clozapine, which has been marketed in numerous foreign countries and for over a decade in the U.S.

D. Assessment of Data Quality and Completeness

There were some minor problems noted with the completeness of the Narrative Summaries and with the coding of adverse events (see section V.B). However, these deficiencies do not appreciably impact on the limited assessment of safety based on study CS-001-2002.

E. Summary of Important Safety Findings

This review revealed no safety concerns which would preclude the approval of clozapine FDT or new safety issues that would require a change to the labeling of clozapine products except as noted in section VII.B.5 above.

VIII. Proposed Registry and WBC Monitoring System

The sponsor has proposed a patient registry protocol to insure that patients who receive clozapine FDT undergo appropriate WBC monitoring.¹² This proposal includes a description of the plan, flowcharts for registration and WBC monitoring, and forms to be completed by the physician and pharmacist.

In summary, this protocol mandates registration of all such patients as well as the prescribing physician and dispensing pharmacist for each patient, known here as the affiliated treatment pair. The physician and pharmacist must certify that they understand the hematological risks associated with clozapine therapy and agree to abide by monitoring requirements. All patients who begin treatment with clozapine FDT will be cross-checked prior to clearance with the _____

_____ maintained by Novartis Pharmaceuticals, to insure that they are eligible to receive a clozapine product. Likewise, any patient who becomes non-rechallengeable while taking clozapine FDT (i.e., total WBC count less than $2000/\text{mm}^3$ or absolute neutrophil count less than $1000/\text{mm}^3$) is to be immediately reported by the physician to the registry, which will then notify the _____. The registry protocol requires WBC monitoring every 1 or 2 weeks, in accordance with Clozaril labeling, and prohibits dispensation of clozapine FDT to any patient in the absence of an acceptable WBC count. A Coordinating Center will be established to provide registration services, assistance to all registered parties, and to manage registry data collection and provide quality control and registry auditing. The Coordinating Center will also assist patients who changing healthcare providers and traveling out of the area.

Overall, the proposed registry protocol appears acceptable. However, there are a number of minor issues that should be

¹² See volume 1.29.

addressed by the sponsor prior to implementation of the clozapine DT registry. These are discussed below, with reference to the appropriate page number in volume 1.29.

Page 12: Since physicians who register to prescribe clozapine DT 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 _____ diagnosis of schizophrenia may receive clozapine DT. 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." It is recommended that the qualifier _____ be deleted.

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.

Page 13: Also under Exclusion Criteria, current labeling does not contraindicate use in patients with severe hepatic, renal, or cardiac disease. This criterion should be deleted.

Page 13: The first paragraph in section 7.3.1 indicates that clozapine DT 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. The sponsor should consider an accommodation for military physicians.

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.

Page 20: The process for transferring patients who have received another clozapine formulation to clozapine DT is not entirely clear. Section 7.9 indicates that such patients may be switched to clozapine DT 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.

The following points require clarification in the protocol:

- 1) 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.
- 2) 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 clozapine DT. This should be explained in the protocol.
- 3) According to the Physician Enrollment Form and the Pharmacy/Pharmacist Enrollment Form, the physician agrees not to prescribe clozapine DT and the pharmacist agrees not to dispense clozapine DT 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 clozapine DT 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.

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 clozapine **ODT** are not delivered to non-registered pharmacies.

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.

IX. Dosing, Regimen, and Administration Issues

There is one issue regarding the administration of clozapine **ODT** that merits further emphasis in labeling. Patients who divide the scored clozapine **ODT** tablets should be advised to discard the half-tablet that is not consumed to avoid the possibility that patients may attempt to store the extra half until the next dose. Given the likelihood of degradation of the product outside a sealed blister secondary to moisture, such storage should be highly discouraged. Also, the half-tablet should be disposed of in a way that prevents the accidental ingestion by a child or animal. This advice should be included in labeling as suggested in section XI below.

X. Use in Special Populations

This NDA provides no information about the use of clozapine **ODT** in special populations.

XI. Review of Proposed Labeling

The labeling proposed by the sponsor very closely parallels the approved labeling for Clozaril.¹³ Important differences are discussed.

The proposed labeling indicates that the trade name for clozapine DT is _____ . As we have indicated to the sponsor, this name is unacceptable. Labeling will need to utilize an acceptable trade name throughout.

A prefatory section entitled "Attention Pharmacists, Prescribing Physicians, and Patients" is included in the proposed labeling but is not found in Clozaril labeling. This section essentially summarizes information already in labeling regarding the risk of agranulocytosis and the WBC monitoring requirement. It also includes contact information for individuals who wish to reach the sponsor. Although this section is not needed, I have no strong objection to including it.

Under DESCRIPTION, the last paragraph indicates that this product contains aspartame and contains information for phenylketonurics. The Chemistry Reviewer was consulted on this information and indicated that it is acceptable.

Under WARNINGS/Other Adverse Cardiovascular and Respiratory Effects, the fourth sentence in the penultimate paragraph mentions _____

_____ These events have been deleted from Clozaril labeling and may be omitted here.

Under PRECAUTIONS, there is a paragraph entitled "Hyperglycemia." The Division, in a 9-11-03 letter to Novartis Pharmaceuticals, has requested that Clozaril labeling be amended to replace this paragraph with a new, more strongly worded section under WARNINGS as follows:

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 Clozaril. Assessment of the relationship between atypical antipsychotic use and

¹³ Alamo's proposed labeling is found in volume 1.1.

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. J

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.

This change should be implemented in the labeling for clozapine DT.

The PRECAUTIONS section contains a paragraph entitled "Phenylketonurics." This paragraph meets the requirements of 21 CFR 201.21(c).

Gregory M. Dubitsky, M.D.
September 27, 2003

cc: NDA 21-590
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this page is the manifestation of the electronic signature.

/s/

Greg Dubitsky
9/27/03 07:59:23 PM
MEDICAL OFFICER

Thomas Laughren
11/14/03 09:17:36 AM
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I agree that this NDA is approvable; see memo
to file for more detailed comments.--TPL