CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-590

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA:	21590 (012)
Brand Name:	FAZACLO
Generic Name:	Clozapine
Type of Dosage Form:	Orally Disintegrating Tablets
Strengths:	25 mg, 100 mg
Indications:	Schizophrenia
Type of Submission:	Complete Response to Approvable Letter
Sponsor:	Alamo Pharmaceuticals
Submission Dates:	December 10, 2003
Assigned Date:	January 26, 2004
OCPB Division:	DPE-I
OND Division:	Division of Neuropharmacological Drug Products HFD-120
OCPB Reviewer:	Sally Usdin Yasuda, MS, PharmD
OCPB Team Leader:	Ramana Uppoor, PhD

1 Executive Summary

This review evaluates the Sponsor's response to the recommendations made by the Office of Clinical Pharmacology and Biopharmaceutics (OCPB) in the approvable action letter for NDA 21590.

In the review of the original NDA (see OCPB review of 11/12/03), the Office of Clinical Pharmacology and Biopharmaceutics recommended the following:

- A change in the *in vitro* dissolution specification
- Specific revisions of the proposed label's text

The Sponsor has provided responses as follows:

- The Sponsor has changed the dissolution specification as recommended. The dissolution method and specification are as follows:

USP Apparatus	[redacted]
Rotation Speed:	[redacted]
Volume:	900 ml
Medium:	[redacted]
Tolerance:	Q= — in 15 minutes

- The sections Sponsor's "Track-Change Version" that include the Clinical Pharmacology and Drug Interactions are included in the Appendix of this review. The Sponsor has made most of the changes recommended in the Clinical Pharmacology sections of the labeling. The exceptions are as follows:

CLINICAL PHARMACOLOGY

Absorption, Distribution Metabolism, and Excretion (See Attachment 5 of Submission, page 7)

The Sponsor replaced some pharmacokinetic values (p. 7, track change version of label in Attachment 5 of submission) appropriately to reflect the average peak (C_{max}) steady state values. (The values previously presented were steady state C_{avg}, although the text stated that they were average peak steady state values). Presentation of average t_{max} as mean values (proposed by Sponsor) rather than median (as proposed by the Agency) is acceptable.

The Sponsor inserted the following statement in the last line of the 6th paragraph in Attachment 5, page 7 in the track-change version of the package insert: "while hydroxylated and N-oxide derivatives were inactive". OCPB did not intend to delete this statement, and its inclusion is consistent with the labeling for Clozaril. This change is acceptable.

Pharmacokinetic-Related Interactions (See Attachment 5 of Submission, page 17)

Carbamazepine (paragraph 2 of the section on pharmacokinetic-related interactions)

The Sponsor has deleted carbamazepine from a list of drugs that may decrease plasma levels of clozapine by inducing P450. The potential for a carbamazepine/clozapine interaction is alluded to in a subsequent paragraph ("Although concomitant use ... is not recommended, it should be noted that discontinuation of concomitant carbamazepine administration may result in an increase in FAZACLO... plasma levels"). However, the label (consistent with the Clozaril label) does not state that carbamazepine is a P450 inducer, and does not state the consequences of adding carbamazepine to a clozapine regimen.

There is some published primary literature in which an approximately 50% reduction of clozapine concentrations was observed in combination with carbamazepine.[1,2] Jerling et al[1] evaluated results from a therapeutic drug monitoring service that identified 124 patients taking clozapine alone and 17 taking it in combination with carbamazepine. Patients taking carbamazepine had lower clozapine concentrations than did those on monotherapy, despite higher mean daily doses. The mean concentration/dose was 0.78 ng/ml/mg/day on monotherapy and 0.39 ng/ml/mg/day on carbamazepine, and concentration in the latter group was inversely proportional to carbamazepine dose. Tiihonen et al[2] switched patients from a combination of clozapine and carbamazepine taken at stable doses for 8 weeks to a combination of clozapine and oxcarbazepine (not a P450 inducer) for 8 weeks. (Other concomitant

medications given to the patients in the study are not considered to be inducers or inhibitors of P450). During the carbamazepine period, the plasma concentrations were a mean of 47% lower (range 29-82%) than during the oxcarbazepine period, supporting the ability of carbamazepine to induce clozapine metabolism.

Inclusion of carbamazepine in the paragraph regarding P450 inducers would be consistent with the labeling for carbamazepine (Tegretol), and there is some evidence to support it. We suggest maintaining this statement in the label.

Fluvoxamine (paragraph 3 of the section on pharmacokinetic-related interactions)

The sponsor has deleted a mention of fluvoxamine, in attachment 5, page 17 of the track change version in the present submission, from a list of drugs known to inhibit the activity of P450, although the fluvoxamine/clozapine interaction is described later in more detail. The rationale for removing it is consistency with the Clozaril label. Inclusion of fluvoxamine in that list of drugs may be helpful to the practicing physician when focusing on the section of the label about drugs inhibiting P450. We suggest keeping fluvoxamine in the list.

1.1 Recommendations

The Office of Clinical Pharmacology and Biopharmaceutics (OCPB) has the following recommendations.

1) The proposed *in vitro* dissolution specification is acceptable.
2) OCPB recommends maintaining carbamazepine in the list of inducers and fluvoxamine in the list of inhibitors in the labeling.
3) The remainder of the labeling changes are acceptable.

Please forward to the Sponsor the recommendations above and the rationale for including carbamazepine and fluvoxamine in the labeling.

Sally Usdin Yasuda, MS, PharmD
Reviewer, Neuropharmacological Drug Section, DPE I
Office of Clinical Pharmacology and Biopharmaceutics

Concurrence: Ramana Uppoor, PhD
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Office of Clinical Pharmacology and Biopharmaceutics

cc: HFD-120 NDA 21-590
CSO/ S. Hardeman
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/TL Biopharm/R. Uppoor
HFD-860 /DD DPE1/M. Mehta, C. Sahajwalla

2 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

Withheld Track Number: Clin Pharm/Bio- 1

References

1. Jerling M, Lindstrom L, Bondesson U, Bertillson L. Fluvoxamine inhibition and carbamazepine induction of the metabolism of clozapine: evidence from a therapeutic drug monitoring service.
   Ther Drug Monit. 1994; 16: 368-74.
2. Tiihonen J, Vartiainen H, Hakola P. Carbamazepine-induced changes in plasma levels of neuroleptics. Pharmacopsychiatry. 1995; 28: 26-8.

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/s/

Sally Yasuda
2/3/04 12:25:13 PM
BIOPHARMACEUTICS

Ramana S. Uppoor
2/3/04 12:31:39 PM
BIOPHARMACEUTICS

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
REVIEW

NDA: 21-590	Submission Date(s): January 30, 2003 March 28, 2003 June 11, 2003 July 23, 2003
Brand Name	Fazaclo™ orally disintegrating tablets
Generic Name	Clozapine Orally Disintegrating Tablets
Reviewer	Carol Noory
Team Leader	Ramana Uppoor
OCPB Division	HFD-860
OND Division	Neuropharm HFD-120
Sponsor	Alamo Pharmaceutical , LLC Beverly Hills, CA 90211
Submission Type; Code	Original NDA 505(b)(2)
Formulation; Strength(s)	Orally Disintegrating Tablets, 25 and 100 mg
Indication	Management of schizophrenia
Related INDs/NDAs	IND: 61-484

I. Executive Summary

Alamo Pharmaceuticals has developed a new, orally disintegrating tablet that provides a pharmaceutical alternative to Clozaril® immediate-release conventional tablets. The Fazaclo™ orally disintegrating tablets are formulated to disintegrate once exposed to fluid, such as saliva. The tablets are then easily swallowed. The sponsor proposes to market the orally disintegrating tablets in strengths of 25 mg and 100-mg, which are formulated to be bioequivalent to the reference listed drug, Clozaril® (NDA 19-758) which is manufactured by Novartis.

This application includes no clinical trials, however, the bioequivalence and clinical safety of Fazaclo™ were investigated in a multiple dose, steady-state in vivo study conducted in patients comparing the 100 mg clozapine orally disintegrating tablet (ODT) to a 100 mg Clozaril® tablet both administered with water. The firm developed a suitable dissolution procedure using the 100 mg orally disintegrating tablet. Comparative dissolution profiles were evaluated for both the 25-mg and the 100-mg ODT in three media to support a biowaiver for the 25-mg ODT. Since patients are titrated with a starting dose of 12.5 mg, the half and whole tablet profiles were evaluated in three media. Literature was submitted to indicate that kinetics of clozapine are linear

at steady-state. The sponsor is relying on the Agency's findings of safety and efficacy for Clozaril® Tablets, USP, originally approved in 1989.

The clinical pharmacology and biopharmaceutics section of this application is acceptable based on the following:

1. The firm has demonstrated that the highest proposed strength (100 mg) of Clozapine orally disintegrating tablet was bioequivalent to the approved 100-mg Clozaril® reference product manufactured by Novartis.
2. A waiver for the lower strength 25-mg tablet was requested and found acceptable based on formulation proportionality and similarity of the dissolution profiles compared to the 100-mg biobatch tablets in three media.
3. An in vitro disintegration study at the pH of saliva demonstrated that the product disintegrated in 29 seconds (n=18; RSD=7).
4. An appropriate dissolution study was conducted. The study tested two USP dissolution apparati and four media.
5. Half versus whole 25-mg tablets have similar release characteristics and the tablets can be divided in half at the score for titrating the patients with a starting dose of 12.5 mg.
6. A DSI inspection of the study sites for study CS-001-2002 found no violations at the clinical site. Violations found at the analytical site were adequately addressed by the firm. The data for study CS-001-2002 is acceptable.

Comments:

1. The sponsor's proposed dissolution method is acceptable. However, the dissolution specification is not acceptable. After evaluation of all of the dissolution data submitted, it appears that the ODT can meet a tighter specification. The agency recommended dissolution procedure, based on the data submitted, is the Paddle apparatus,— rpm with 900 mL of pH — acetate buffer as the medium. The Q value based on individual tablet data should be — in — minutes.

Labeling Comments:

1. Changes in the labeling are shown in the Clinical Pharmacology Section of the label (pages 19-20).
2. Toxicology statements should be reviewed by a toxicologist prior to inclusion in the label. All clinical information should be reviewed by a medical reviewer prior to including this in the label.

II. Recommendation

1. The Office of Clinical Pharmacology and Biopharmaceutics has reviewed NDA 21-590 and finds the clinical pharmacology and biopharmaceutics section acceptable if the dissolution comment and the above labeling comments are appropriately addressed. The sponsor's proposed dissolution specification,Q value of — in — minutes, is not acceptable. The following dissolution method and specification is recommended based on the data evaluated.

USP Apparatus .
Rotation speed:
Volume: 900 mL
Medium: pH
Tolerance: Q = in minutes

This recommendation, the labeling comments and the edited label (pages 19-20) should be forwarded to the sponsor.

An OCPB briefing was held on November 6, 2003.

A. Carol Noory
Division of Pharmaceutical Evaluation I

RD:
FT: Initialed by Ramana Uppoor, Ph.D.

cc list: NDA 21-590; HFD-860: (Noory, Uppoor, Sahajwalla, Mehta); CDER Central Document Room

III. Table of Contents

IV. Summary of CPB Findings

Clozapine is classified as an atypical antipsychotic drug currently approved for oral administration and marketed by Novartis under the brand name Clozaril®. Clozapine is

indicated for the management of severely ill schizophrenic patients who fail to respond adequately to standard antipsychotic drug treatment. Clozaril® was approved by the FDA on September 26, 1989.

Alamo Pharmaceutical has developed a new orally disintegrating dosage form of clozapine that provides a pharmaceutical alternative to the traditional dosing of tablets with water. The orally disintegrating tablet disintegrates in the oral cavity when exposed to fluid, such as saliva, and can be easily swallowed. Alamo Pharmaceutical proposes to market the orally disintegrating tablets in 25 and 100 mg strengths, which are formulated to be bioequivalent to Clozaril® Tablets manufactured by Novartis. Upon disintegration of Fazaclo™, the taste-masked particles will remain intact and no dissolution will take place in the oral cavity. The drug particles are coated and formulated not to dissolve at the pH of saliva (5.8-7.1) to assure adequate taste masking. Therefore there will be no exposure of clozapine to the oral mucosa.

The current application includes no clinical trials but does include one multiple dose, steady-state ***in vivo*** bioequivalence study in patients comparing the 100-mg clozapine orally disintegrating tablet to a 100-mg Clozaril® tablet. The clinical efficacy and safety of the drug are based on the clinical information from the original NDA for Clozaril® Tablets, USP (NDA 19-758), originally approved in 1989. A dissolution procedure was developed and dissolution studies comparing the 25-mg Clozapine orally disintegrating tablet to the 100-mg clozapine orally disintegrating tablet were performed using three media. Since the patient is titrated with a starting dose of 12.5 mg, the half and whole 25-mg orally disintegrating tablets were tested using the paddle method, ——— and three media. The submission contains the following information supporting approval of the NDA:

1. **Bioequivalence Study (Study CS-001-2002) "A steady-state bioequivalence study comparing 100-mg clozapine orally disintegrating tablets (TEST) and 100-mg Clozaril® (REFERENCE) in schizophrenic patients."**
   The sponsor conducted a steady state bioequivalence study in South Africa comparing 100-mg clozapine orally disintegrating tablets (Fazaclo™) to 100-mg Clozaril® tablets in schizophrenic patients. Both clozapine and its major metabolite, desmethylclozapine (norclozapine) were measured. The pharmacokinetic parameters measured include C^{ss}_{max}, C^{ss}_{min}, $AUC_{0\text{-}12\ h}$, T_{max}, $t\ ½$, and percent fluctuation. Log transformed AUC, C^{ss}_{max}, and C^{ss}_{min}, were analyzed using analysis of variance and 90% confidence interval. The results, C^{ss}_{max} (90.9%-105%), C^{ss}_{min} (96.6%-110%), $AUC_{0\text{-}12\ h}$ (94.4%-104%) based on the parent clozapine moiety demonstrates the bioequivalence of 100-mg Fazaclo™ to 100-mg of Clozaril® in schizophrenic patients under steady-state conditions.
2. **Literature Study**
   - The Fazaclo™ 505(b)(2) NDA clinical information is supported by way of reference to the approved NDA for Clozaril™ (N19-758) and certain pertinent literature regarding the use of clozapine in the treatment of schizophrenia. Fifteen references were cited.

3. **Waiver for a biostudy of the lower strength, 25-mg tablet**
A biowaiver was requested for the lower strength ODT based on steady-state linear kinetics, formulation proportionality and the in vitro dissolution f2 comparison, which were similar in three dissolution media. This waiver is acceptable based on criteria stated in the FDA guidance, "Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations". This guidance states that "when the drug product is in the same dosage form, but in a different strength, and is proportionally similar in its active and inactive ingredients, an in vivo BE demonstration of one or more lower strengths can be waived based on dissolution tests and an in vivo study on the highest strength."

4. **Dissolution Studies**
   - Study RA 2002-100

An in vitro evaluation of the current USP procedure for clozapine tablets demonstrated that this method was not acceptable for the ODT. The firm studied the dissolution profiles of the Clozapine orally disintegrating tablets (100-mg) in four media of different pH using USP Apparatus — USP Apparatus — Method) was found acceptable.

   - Study RA 2003-146

The sponsor compared the 25-mg to the 100-mg tablets using three media (pH 1.2, 4.5 and 6.8). All profiles were similar in all media which supports the request for a waiver of the lower strength (25-mg tablet).

   - Study RA 2003-104

The firm compared the 25-mg ODT broken in half at the score to the whole tablet of the same lot. The results indicate that the 25 mg scored tablets can be broken in half for initially titrating the patient using a 12.5 mg starting dose. If needed, the 100-mg tablet can also be divided at the score.

5. **Labeling**

The Labeling includes a warning to alert phenylketonuric patients that the product contains a sweetener containing phenylalanine. Other labeling comments need to be forwarded to the sponsor (see pages 19-20).

Conclusion:

The firm has demonstrated the steady-state bioequivalence of a new dosage form of Clozapine 100-mg orally disintegrating tablet taken with water, to the approved 100-mg immediate release clozapine tablet, Clozaril®, manufactured by Novartis. A waiver for an in vivo study demonstrating the bioequivalence of the 25-mg ODT compared to the 100-mg ODT is acceptable. To support the absorption, distribution, metabolism and elimination portion of the label, the firm also submitted a literature search that was reviewed. The firm has tested the dissolution of the 100-mg ODT compared to the 25-mg ODT, and half tablets vs. whole 25-mg orally disintegrating tablets have been tested in three media of different pH using the USP Paddle method at —. The sponsor's proposed dissolution method of USP Apparatus — 900 mL of acetate buffer pH is acceptable. However, the specification (Q value) of — in — minutes is not acceptable. The following dissolution method and specification is recommended based on individual tablet data evaluated.

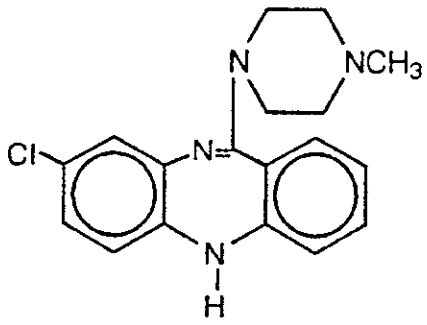
USP Apparatus	
Rotation speed:	
Volume:	900 mL
Medium:	
Tolerance:	Q = ___ in ___ minutes (individual sampling)

V. QBR

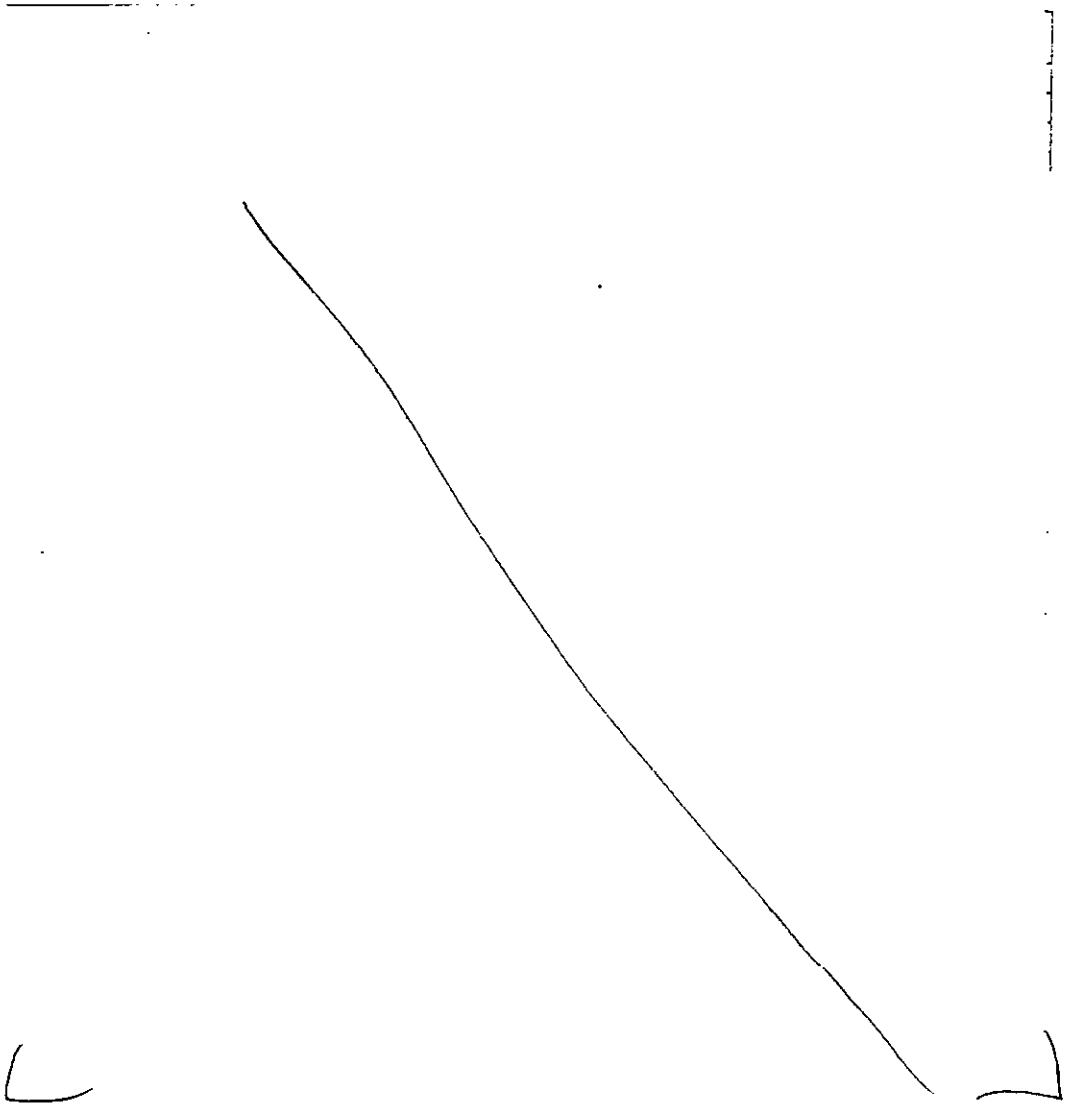
A. General Attributes

A.1. What are the chemical and physical-chemical properties of the drug substance and the formulation of the drug product?

Clozapine, USP is a yellow crystalline powder that is very slightly soluble in water. Clozapine, an atypical antipsychotic drug, is a tricyclic dibenzodiazepine derivative, 8-chloro-11-(4-methyl-1-piperazinyl)-5H-dibenzo *[b,e]* [1,4] diazepine. The structural formula is:



$C_{18}H_{19}ClN_4$ Mol. wt. 326.83



B. Clinical Pharmacology

B. 1. What are the pharmacokinetics of clozapine?

The sponsor summarized the pharmacology studies submitted in NDA 19-758. Additional statements were extracted from journal articles.

B.1.1. Clozaril® Label:

- Clozapine is classified as an 'atypical' antipsychotic drug because its profile of binding to dopamine receptors and its effects on various dopamine mediated behaviors differ from those exhibited by more typical antipsychotic drug products. In particular, although clozapine does interfere with the binding of dopamine at D_1, D_2, D_3 and D_5 receptors, and has a high affinity for the D_4 receptor, it does not induce catalepsy nor inhibit apomorphine-induced stereotypy.
- The view that clozapine is preferentially more active at limbic than at striatal dopamine receptors, may explain the relative freedom of clozapine from extrapyramidal side effects.

- In man, clozapine tablets (25 mg and 100 mg) are equally bioavailable relative to a clozapine solution. Following a dosage of 100 mg b.i.d., the average steady state peak plasma concentration was 319 ng/mL (range: 102-771 ng/mL), occurring at the average of 2.5 hours (range: 1-6 hours) after dosing. The average minimum concentration at steady state was 122 ng/mL (range: 41-343 ng/mL), after 100 mg b.i.d. dosing. Food does not appear to affect the systemic bioavailability of clozapine. Thus, TRADE NAME™ (Clozapine, USP) may be administered with or without food.
- Clozapine is approximately 97% bound to serum proteins. The interaction between clozapine and other highly protein-bound drugs has not been fully evaluated but may be important.
- Clozapine is almost completely metabolized prior to excretion and only trace amounts of unchanged drug are detected in the urine and feces. Approximately 50% of the administered dose is excreted in the urine and 30% in the feces. The demethylated, hydroxylated and N-oxide derivatives are components in both urine and feces. Pharmacological testing has shown the desmethyl metabolite (norclozapine) to have only limited activity.
- The mean elimination half-life of clozapine after a single 75 mg dose was 8 hours (range: 4-12 hours), compared to a mean elimination half-life, after achieving steady state with 100 mg b.i.d. dosing, of 12 hours (range: 4-66 hours). A comparison of single-dose and multiple-dose administration of clozapine showed that the elimination half-life increased significantly after multiple dosing relative to that after single-dose administration, suggesting the possibility of concentration dependent pharmacokinetics. However, at steady state, linearly dose-proportional changes with respect to AUC (area under the curve), peak and minimum clozapine plasma concentrations were observed after administration of 37.5 mg, 75 mg, and 150 mg b.i.d.
- In contrast to more typical antipsychotic drugs, clozapine therapy produces little or no prolactin elevation.
- As is true of more typical antipsychotic drugs, clinical EEG studies have shown that clozapine increases delta and theta activity and slows dominant alpha frequencies. Enhanced synchronization occurs, and sharp wave activity and spike and wave complexes may also develop. Patients, on rare occasions, may report an intensification of dream activity during clozapine therapy. REM sleep was found to be increased to 85% of the total sleep time. In these patients, the onset of REM sleep occurred almost immediately after falling asleep.
- **Pharmacodynamic-related Interactions:** Although the exact mechanism of clozapine induced agranulocytosis is unknown; nonetheless, the possibility that causative factors may interact synergistically with clozapine to increase the risk and/or severity of bone marrow suppression warrants consideration. Therefore, TRADE NAME™ (Clozapine, USP) should not be used with other agents having a well-known potential to suppress bone marrow function.
- Given the primary CNS effects of clozapine, caution is advised in using it concomitantly with other CNS-active drugs or alcohol.
- Orthostatic hypotension in patients taking clozapine can, in rare cases (approximately 1 case per 3,000 patients), be accompanied by profound collapse and respiratory and/or cardiac arrest. Some of the cases of collapse/respiratory arrest/cardiac arrest during initial treatment occurred in patients who were being administered benzodiazepines; similar events have been reported in patients taking other psychotropic drugs or even clozapine by itself. Although it has not been established that there is an interaction between clozapine and benzodiazepines or other psychotropics, caution is advised when clozapine is initiated in patients taking a benzodiazepine or any other psychotropic drug.
- TRADE NAME™ (Clozapine, USP) may potentiate the hypotensive effects of antihypertensive drugs and the anticholinergic effects of atropine-type drugs. The administration of epinephrine should be avoided in the treatment of drug induced hypotension because of a possible reverse epinephrine effect.

- **Pharmacokinetic-related Interactions:** Clozapine is a substrate for many cytochrome P450 isozymes, in particular 1A2, 2D6, and 3A4. The risk of metabolic interactions caused by an effect on an individual isoform is therefore minimized. Nevertheless, caution should be used in patients receiving concomitant treatment with other drugs which are either inhibitors or inducers of these enzymes.

- Concomitant administration of drugs known to induce cytochrome P450 enzymes may decrease the plasma levels of clozapine. Phenytoin, nicotine, carbamazepine,[1] and rifampin may decrease TRADE NAME™ (Clozapine, USP) plasma levels, resulting in a decrease in effectiveness of a previously effective TRADE NAME™ (Clozapine, USP) dose.
- Concomitant administration of drugs known to inhibit the activity of cytochrome P450 isozymes may increase the plasma levels of clozapine. Cimetidine, caffeine, and erythromycin may increase plasma levels of TRADE NAME™ (Clozapine, USP), potentially resulting in adverse effects. Although concomitant use of TRADE NAME™ (Clozapine, USP) and carbamazepine is not recommended, it should be noted that discontinuation of concomitant carbamazepine administration may result in an increase in TRADE NAME™ (Clozapine, USP) plasma levels.
- In a study of schizophrenic patients who received clozapine under steady state conditions, fluvoxamine or paroxetine was added in 16 and 14 patients, respectively. After 14 days of co-administration, mean trough concentrations of clozapine and its metabolites, N-desmethylclozapine and clozapine N-oxide, were elevated with fluvoxamine by about three-fold compared to baseline concentrations.
- Paroxetine produced only minor changes in the levels of clozapine and its metabolites. However, other published reports describe modest elevations (less than two-fold) of clozapine and metabolite concentrations when clozapine was taken with paroxetine, fluoxetine, and sertraline. Therefore, such combined treatment should be approached with caution and patients should be monitored closely when TRADE NAME™ (Clozapine, USP) is combined with these drugs, particularly with fluvoxamine. A reduced TRADE NAME™ (Clozapine, USP) dose should be considered.
- A subset (3%-10%) of the population has reduced activity of certain drug metabolizing enzymes such as the cytochrome P450 isozyme 2D6. Such individuals are referred to as "poor metabolizers" of drugs such as debrisoquin, dextromethorphan, the tricyclic antidepressants, and clozapine. These individuals may develop higher than expected plasma concentrations of clozapine when given usual doses. In addition, certain drugs that are metabolized by this isozyme, including many antidepressants (clozapine, selective serotonin reuptake inhibitors, and others), may inhibit the activity of this isozyme, and thus may make normal metabolizers resemble poor metabolizers with regard to concomitant therapy with other drugs metabolized by this enzyme system, leading to drug interaction.
- Concomitant use of clozapine with other drugs metabolized by cytochrome P450 2D6 may require lower doses than usually prescribed for either clozapine or the other drug. Therefore, co-administration of clozapine with other drugs that are metabolized by this isozyme, including antidepressants, phenothiazines, carbamazepine, and Type 1C antiarrhythmics (e.g., propafenone, flecainide and encainide), or that inhibit this enzyme (e.g., quinidine), should be approached with caution.

B.1.2. Journal articles:

1. "Clinical Pharmacodynamics and Pharmacokinetics of Antimanic and Mood-Stabilizing Medications."; Keck PE and McElroy SL; J Clin Psychiatry; 63:4; (2002) 3-11.

The following statements are derived from this article:

- One mechanism of clozapine's antimanic activity may be through the antagonism of D_2 receptors.
- Clozapine binds to serotonin receptors, 5-$HT_{1A,1C}$, 5-$HT_{2A,2C}$, 5-HT_3, and 5-HT_6, as well as α_1- and α_2-adrenergic and H_1 and M1 receptors.[1]
- Clozapine's serotonergic and α2-adrenergic effects may confer antidepressant activity. Its α1 antagonism is associated with orthostatic effects, H1 antagonism with sedative and appetite stimulating effects, and M1 antagonism with anticholinergic side effects.
- At high plasma concentrations, the norclozapine metabolite was found to be potentially toxic to hematopoietic precursors, while the hydroxylated and N-oxide derivatives of clozapine are inactive.

- The pharmacokinetics of clozapine were shown to vary with age, gender, smoking habits, and concurrent medication. It has been noted that smoking has a greater effect on plasma clozapine concentrations in men than women. Also, women and elderly patients have a slower clearance of clozapine.

This article combines information from a MEDLINE search augmented by a manual search of bibliographies and a review of textbooks to identify articles regarding the clinical pharmacology of clozapine among other antimanic and/or mood stabilizing drugs. A review of the reference material is required to determine the appropriateness of these statements. The statement "At high plasma concentrations, this (norclozapine) metabolite was found to be potentially toxic to hematopoietic precursors." should be removed from the label until evaluated by a Pharm/Tox reviewer. It appears this information was gathered in the rat. Since most of the statements add only limited information and are not supported by data they should be removed from the label.

2. "Modafinil-Associated Clozapine Toxicity."; John Dequardo, MD; letter to editor, Am J Psyciatry 159:7 (July 2002) 1243-1244.
The following statements are derived from this article:

- Clozapine undergoes extensive hepatic metabolism, principally by N-oxidation, N-demethylation, and hydroxylation. Norclozapine is the major metabolite of clozapine. Clozapine is primarily metabolized by CYP2C19 and CYP3A4, with lesser involvement of CYP2C9, CYP2D6, and CYP1A2.
- In a case study, the combination of modafinil and clozapine resulted in a plasma clozapine level increase from 761 to 1400 ng mL. The patient's symptoms of unsteady gait and hypoxemia resolved immediately with discontinuation of clozapine and modafinil. The patient was restarted on clozapine without additional complications.

This is a letter to the editor describing the emergence of clozapine toxicity after modafinil was added to a patient's drug regimen. There is not sufficient data to support these statements in the labeling. They should be removed.

3. "Evidence from a Population Pharmacokinetic Analysis for a Major Effect of CYP1A2 Activity on Inter- and Intra-individual Variations of Clozapine Clearance." Dailly E, Urien S, Chanut E, Claudel B, Guerra N, Fernandez C, Jolliet P, and Bourin M; Progress in Neuro-Psychopharmacology and Biological Psychiatry; 26 (2002) 699-703.
The following statements are derived from this article:

- A linear relationship between clozapine clearance and CYP1A2 activity was noted in one study.

This is a cohort study of 23 patients suffering from schizophrenia and being treated in three different psychiatric centers. This statement should be removed for lack of appropriate supporting data.

4. "Clozapine Pharmacokinetics in Children and Adolescents with Childhood-Onset Schizophrenia."; Frazier JA, Cohen, LG, Jacobsen L, Grothe D, Flood J,

Basdessarini, RJ, Piscitelli S, Kim GS and Rapoport JL; J Clin Psychopharmacology 23:1 (Feb. 2003) 87-91.
The following statements are derived from this article:

- In a published study with 6 pediatric and adolescent patients with childhood-onset schizophrenia between the ages of 9-16 years of age, dose-normalizing concentrations of clozapine did not vary with age and were similar to reported adult values. No age-related differences were seen in the serum concentrations, AUC, or clearance measurements in this small sample population. However, gender differences were observed with girls having higher AUC values for norclozapine and clozapine-N-oxide than boys. No gender differences were seen in estimated clearance for clozapine, norclozapine, and clozapine-N-oxide.

This study is supported by an NIH grant and is approved by the National Institute of Mental Health Internal Review Board. Although the data is generated on a small number of subjects, the trial appears to be well-controlled. The statement can remain in the label. One of the recommendations drawn from the study was that the "AUC of norclozapine was higher in comparison to the clozapine (especially in females) and that the clozapine serum assays in youth be standardized to clozapine + norclozapine rather that to clozapine which is typically used in adults." This measurement is used as a prediction for response. NIH currently measures both clozapine plus norclozapine as part of its in-patient protocol in children. This recommendation should be evaluated by a medical officer. At this point, since there is no established relationship between clozapine plus norclozapine concentrations and efficacy and/or toxicity, this statement should not be put in the label.

5. "Therapeutic Drug Monitoring of Clozapine Relapse-a Retrospective Study of Routine Clinical Data". Ulrich S, Baumann B, Wolf R, Lehmann D, Peters B, Bogerts B and Meyer FP; Int J of Clin Pharm and Ther; 41:1 (2003) 3-13.
The following statements are derived from this article:

- In a published clinical study with 86 patients, clozapine plasma levels were analyzed to provide additional data on the therapeutic window for clozapine during maintenance treatment in evaluating potential for relapses or intoxications. Clozapine levels between 50-250 ng mL were suggested as sufficient if given with other effective, concurrent, antipsychotic medication. Serum levels of clozapine less than 50 ng mL were found to be related to relapse regardless of concurrent psychotropic drugs. In cases where there were no concurrent psychotropic drugs, serum levels of clozapine less than 250 ng mL were observed to be associated with relapse. The risk of relapse was low for serum levels of clozapine greater than 250 ng mL irrespective of concurrent psychotropic drugs. The risk of intoxication was observed to be increased with serum levels greater than 750 ng mL.

This study was conducted at the Psychiatric Clinic, University Hospital in Magdelburg Germany and other local clinics. Pharmacokinetic interactions relative to serum levels per dose were analyzed by multiple regression with gender, age, use of tobacco, and several types of concurrent medications as

independent variables. Data concerning body weight, and liver and renal function were not included in the analysis. Since the underlying data is unavailable for review at this point, the information from this study should not be used in the label.

6. "Obesity Related Metabolic Abnormalities During Antipsychotic Drug Administration: Mechanisms, Management and Research Perspectives." Baptista T, Kin NMKNY, Beaulieu S and Baptista EA; Pharmacopsychiatry (2002) 205-219.
   The following statements are derived from this article:
   - Clozapine may result in excessive body-weight gain. This gain in weight may be related to increased appetite that is due to drug interaction with the brain monoaminergic and cholinergic systems. In a published paper, it was shown that patients with schizophrenia manifest a significantly high prevalence of diabetes with clozapine treatment by inducing both glucose dysregulation and dyslipidemia. Sudden body-weight gain, insulin resistance, increased appetite, and related endocrine changes may also be involved in the development of glucose intolerance and dyslipidemia in these predisposed individuals. Patients should be informed of these potential effects.

   This article focuses on proposing a unified theory to explain excessive body weight gain and metabolic dysfunction on the interaction of atypical antipsychotic drugs with brain neurotransmitters involved in appetite regulation. The article is based on a review of the literature. This statement deals with the clinical aspects of the drug and should be reviewed by a medical reviewer.

7. Relation of Blood Counts During Clozapine Treatment to Serum Concentrations of Clozapine and Nor-Clozapine."; Oyewumi LK, Cernovsky ZZ; Freeman DJ and Streiner D; The Canadian J of Phychiatry; 47:3 (April 2002) 257-261.
   The following statements are derived from this article:

   - In a published report, clozapine-induced agranulocytosis was shown to have a delayed onset. Approximately 76% of cases occur between Weeks 4 and 18 of therapy, with peak incidence at Week 10. An 8-week study was conducted to determine the risk of developing clozapine-induced agranulocytosis with initiation of clozapine therapy by measuring different blood parameters. In this published study, the white blood cell, red blood cell, neutrophil, and lymphocyte counts, or changes in the hemoglobin and hematocrit showed no significant changes within 8 weeks of clozapine treatment at therapeutic dosages. Only a few weak correlations were found between these hematological parameters and the measures of serum clozapine and norclozapine. The mechanism of clozapine-induced hematotoxicity at the therapeutic dosage range is probably not by direct toxicity of clozapine or norclozapine to the blood cells or their precursors. The study's findings suggest that, under normal clinical conditions, clozapine and norclozapine are not directly responsible for clozapine-induced agranulocytosis. It was postulated that the formation of cytotoxic nitrenium ion from clozapine by neutrophils may be responsible for clozapine-induced agranulocytosis, whether by direct toxicity or through an immune-mediated mechanism.

   This was a prospective, longitudinal study of 37 patients being treated with clozapine. Samples were taken for 4-8 weeks. Analysis of variance showed no sign of change in the observed mean white blood count, red blood count, neutrophils and lymphocytes counts or in hemoglobin and hematocrit. This

statement deals with the clinical aspects of the drug and should be reviewed by a medical reviewer.

8. "Neutropenia in a patient treated with Clozapine in Combination with Other Psychotropic Drugs." Senechal A, Landry P, Deschamps R, and Lessard M; Encephal 28:6 (Nov-Dec 2002) 567-569.
The following statements are derived from this article:

    - Neutropenia has been reported in a few cases with the addition of new mediations to clozapine therapy, including paroxetine, risperidone, trimethoprim-sulfamethoxazole, haloperidol, divaplproex, and erythromycin.

    This statement is based on the experiences of a single patient, but noted that additional cases of neutropenia had been received. This statement deals with the clinical aspects of the drug and should be reviewed by a medical reviewer.

9. "Serum Glucose and Lipid Changes During the Course of Clozapine Treatment: the Effect of Concurrent β-adrenergic Antagonist Treatment. Schizophrenia Research; 59 (2002) 49-57.

    The following statements are derived from this article:

    - Significant increases in serum triglycerides, total cholesterol, and glucose levels were observed in association with clozapine therapy. Combination therapy with β-adrenergic receptor antagonists (propranolol and atenolol) may have additive effects on serum lipids resulting in clozapine-associated weight gain.

    This study, conducted by the University of Maryland Psychiatric Research Center, examined the effects of long-term clozapine treatment given concurrently with β-adrenergic antagonists and clozapine induced weight gain on serum glucose and lipid measurements. Fifty patients participated in the study. This statement deals with the clinical aspects of the drug and should be reviewed by a medical reviewer.

10. "The Effect of Orlistat on Plasma Levels of Psychotropic Drugs in Patients with Long Term Psychopharmacotherapy." Hilger E, Quiner S, Ginzel I, Walter H, Saria L and Barnas C. J of Clin Psychopharmacology; 22:1 (Feb 2002) 68-70.
The following statements are derived from this article:

    - Plasma levels of clozapine in psychiatric patients receiving orlistat, an antiobesity drug, had no clinically relevant changes in plasma concentrations over an 8-week period.

    This study was conducted by the University of Vienna in Austria. Eight psychiatric patients who had gained weight because of long-term Psychopharmacotherapy treatment were enrolled in the study. Only two of these patients were taking clozapine. There is insufficient information of no interaction to make a label claim and the statement should be removed from the label.

11. Clinical Significance of Pharmacokinetic Interactions Between Antiepileptic and Psychotropic Drugs." Spina E and Perucca E; Epilepsia 43:2 (2002) 37-44.
The following statements are derived from this article:

- Concomitant administration of drugs known to induce cytochrome P450 enzymes may decrease the plasma levels of clozapine. Phenytoin, nicotine, carbamazepine, and rifampin may decrease TRADE NAME™ (Clozapine, USP) plasma levels, resulting in a decrease in effectiveness of a previously effective TRADE NAME™ (Clozapine, USP) dose
- Antiepileptic drugs, such as carbamazepine, phenytoin, and barbiturates, stimulate oxidative biotransformation and, thus, may potentially reduce the plasma concentrations of clozapine. In several case studies, addition of carbamazepine decreased clozapine plasma concentration.

This study was conducted by the Institute of Pharmacology, University of Messina, Italy. This study is a review of the available literature on the pharmacokinetic interactions between psychotropic agents and antiepileptic drugs. This information is already in the label, and this additional statement will not add much to the label. It should be removed..

12. Tobacco and Cannabis Smoking Cessation can Lead to Intoxication with Clozapine or Olanzapine." Zullino DF, Delesser D, Eap CB, Preisig M and Baumann P. Int Clin Psychopharmacology. 17 (2002) 141-143.
The following statements are derived from this article:

- Plasma levels of clozapine are lower in smokers than in nonsmokers, which is mainly due to induction of CYP1A2 by some smoke constituents. Smoking cessation in patients treated with antipsychotic drugs that are CYP1A2 substrates may result in increased plasma levels of the drug.

This study was conducted by the University in Lausanne, Switzerland. The study evaluates the effects of tobacco and marijuana cessation on the clozapine levels of one patient. Sufficient data is not available to support this label claim. The statement should be removed from the label.

13. "Toxic Interaction between Risperidone and Clozapine: A Case Report." Kontaxakis VP, Havaki-Kontaxaki BJ, Stamouli SS and Christodoulou GN. Progress in Neuro-Psychopharmacology & Biological Psychiatry 26 (2002) 407-409.
The following statements are derived from this article:

- A toxic interaction between risperidone and clozapine was observed in a first-episode schizophrenic patient. The patient developed a neurotoxin syndrome characterized as mild NMS after clozapine (100 mg day) was added to a regimen of risperidone (16 mg day). The NMS symptomatology subsided only by drug discontinuation and supportive care. The patient was successfully restarted on clozapine monotherapy without further complications.

This study was conducted by the University of Athens in Athens, Greece. A case report for one patient is presented. Sufficient data is not available to support this

label claim. The statement should be removed from the label until reviewed by the Medical reviewer.

14. "Comments on In vitro and In vivo Studies of Fluvoxamine-Clozapine Interaction." Oleson OV and Linnet K (letter to editor) J Clin Psychopharmacology; 22:5 (Oct 2002) 527-528.
The following statements are derived from this article:

- Fluvoxamine strongly inhibits the N-demethylation of clozapine. When fluvoxamine was administered to patients receiving clozapine at steady-state levels, there was a highly variable, but marked increase in plasma clozapine concentrations with a corresponding reduction in the total elimination clearance of clozapine.

This study was done by the University Hospital in Risskov, Denmark. The authors comment on in vivo and in vitro study results using fluvoxamine and clozapine. Information regarding fluvoxamine is currently in the Clozaril® label. This additional statement does not add to the label and should be removed.

B.2. What are the dose and dosing regimen and are there any unresolved dosing or administration issues?

The dose and dosing regimen are the same as labeled for Clozaril®. Clozapine orally disintegrating tablets are designed to be bioequivalent to Clozaril® tablets of the same strength. Clozapine is initially titrated beginning with a starting dose of 12.5 mg once or twice a day by mouth. The total daily dose is increased by increments of 25-50 mg per day, if well tolerated, to achieve a target dose of 300-450 mg/day by the end of two weeks. There are no unresolved dosing issues.

B.3. The Dose and Administration section of the label states: "Initial treatment is recommended to begin with ½ of a 25 mg tablet once or twice daily and then continue with daily dosage increments of 25-50 mg/day, if well tolerated, to achieve a target dose of 300-450 mg/day by the end of week two." Has the ability to divide the tablet in half been evaluated?

The firm conducted a dissolution study comparing the half 25-mg tablet to the whole 25-mg tablet. The results (Table 2) indicate that the tablets can be reasonably divided.

TABLE 2: HALF VS. WHOLE 25 MG FAZACLO TABLETS

Whole	Mean	84	98	101	102	104
	%RSD	5.2	3.5	4.3	9.0	3.0
	Range					
Half	Mean	86	99	102	105	104
	%RSD	11.5	11.0	11.2	11.1	11.1
	Range					
F2=85						

B.4. Are the pharmacokinetic parameters linear at steady-state?

The labeling of Clozaril® states that a comparison of single-dose and multiple-dose administration of clozapine showed that the elimination half-life increased significantly after multiple dosing relative to that after single-dose administration, suggesting the possibility of concentration dependent pharmacokinetics. However, at steady state, linearly dose-proportional changes with respect to AUC (area under the curve), peak and minimum clozapine plasma concentrations were observed after administration of 37.5 mg, 75 mg, and 150 mg b.i.d.

B.5. Was a waiver for a pediatric trial granted?

No. The sponsor requested a pediatric waiver, but this was not granted. The pediatric requirement was deferred until after the NDA is approved. The firm must submit a proposal for a pediatric trial to be conducted in Phase IV. The agency will require a clinical trial in adolescents.

C. General Biopharmaceutics

C.1. Was bioequivalence demonstrated for the new orally disintegrating tablet when compared to the conventional dosage form, Clozaril®?

Yes, the in vivo study (CS-00102002) submitted by the sponsor supports the claim of bioequivalence between the 100-mg orally disintegrating tablet and the 100-mg Clozaril® tablet based on the parent drug. The 90% confidence intervals are summarized in the following table:

Statistical Analyses of Clozapine Pharmacokinetic Parameters Following Administration of 100 mg b.i.d. of Clozaril® (Treatment A) or 100 mg b.i.d. of Clozapine ODT (Treatment B) in Schizophrenic Patients.

Parameter	Geometric Mean		Ratio of Means (%)[a]	90% Confidence Interval[b]
	Clozaril® (Treatment A)	Clozapine ODT (Treatment B)		
Clozapine				
Steady State Populations				
C_{max}^{ss} (ng/mL)	386.5	379.5	97.6%	90.9%-105%
C_{min}^{ss} (ng/mL)	137.8	141.5	103%	96.6%-110%
$AUC_{\tau 0-12h}$ (ng.hr/mL)	2849	2836	99.2%	94.4%-104%

C.2. Are the 25 and 100 mg orally disintegrating clozapine tablets bioequivalent to each other?

Yes, a biowaiver was requested for the lower strength based on formulation proportionality and dissolution similarity. This was supported by the in vitro dissolution f2 comparisons, which were similar in three media using the chosen dissolution procedure. The biowaiver is acceptable and the 25 and 100 mg orally disintegrating tablets are deemed bioequivalent to each other as suggested in the FDA guidance,

"Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations".

C.3. What is the effect of food on the bioavailability of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal type?

The labeling for Clozaril® states that "food does not appear to affect the systemic bioavailability". Since Clozapine 100-mg ODT are bioequivalent to Clozaril® 100-mg tablets, food effects are not likely to occur for the clozapine ODT and the same statement can be included in Clozapine ODT label.

C.4. The product is designed to disintegrate in the mouth within seconds, allowing it to be swallowed without water. What are the dosing recommendations, if any, regarding administration of the product without water?

Clozapine orally disintegrating tablets disintegrate in the mouth. The drug particles are coated and formulated not to dissolve at the pH of saliva (pH 5.8-7.1) in order to assure adequate taste masking. There should be no exposure of clozapine to the oral mucosa. The product may be swallowed without water, however, without in vivo data, a specific label claim stating that the clozapine ODT can be taken without water cannot be allowed in the label.

C.5. Was a disintegration test added to assure that the orally disintegrating tablets disintegrate in the pH of saliva?

Yes, an in vitro disintegration test was conducted in addition to a dissolution specification to insure that the tablets disintegrate in the pH of saliva. The product disintegrates in 29 seconds.

C.6. What is the in vivo relationship of the proposed to-be-marketed formulation to the pivotal clinical trial formulation?

The formulation to be marketed is identical to the formulation used in the pivotal clinical trial.

C.7. Are the Sponsor's proposed dissolution medium and specifications acceptable?

The sponsor's proposed dissolution method and tolerance uses the ——— method at—— —— with 900 mL acetate buffer, pH — and a tolerance specification of Q= —— in —— ——— The dissolution method proposed is acceptable. However, the dissolution specification should be tightened. The dissolution data submitted indicates that the ODT can meet a more stringent requirement. Based on the data submitted, the agency recommended dissolution test and specification is ——— 900 mL pH ——— as the medium, and "Q" value of — in— minutes.

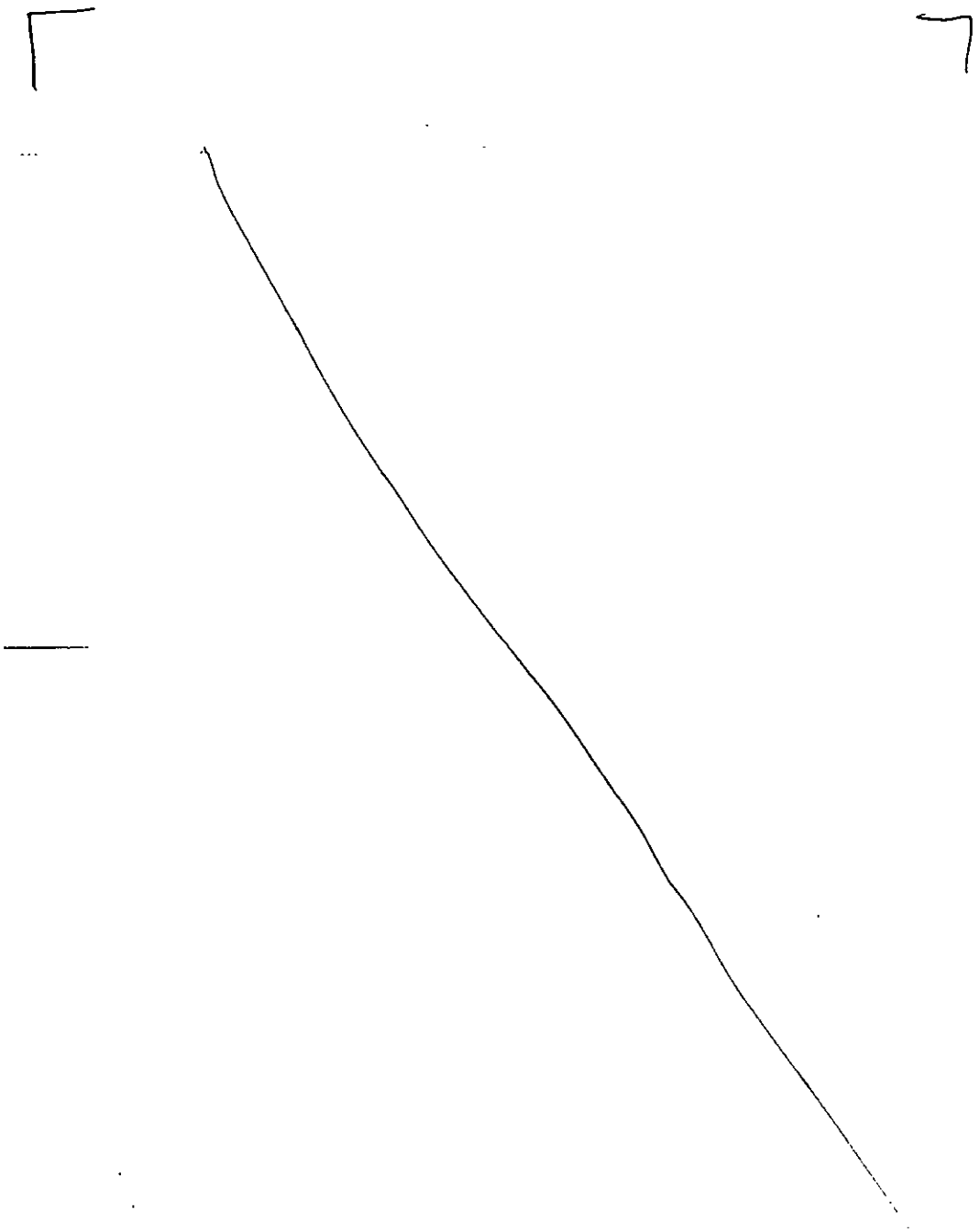
D. Analytical

D.1. Were the correct moieties identified and properly measured?

Yes, pharmacological testing has shown that the desmethyl metabolite has only limited activity, while the hydroxylated and N-oxide derivatives were inactive. Clozapine and

desmethylclozapine (norclozapine) were evaluated in the bioequivalence study, although bioequivalence is solely based on parent clozapine.

D.2. What bioanalytical methods are used to assess concentrations?



D.3. Was the possible interaction of aspartame with the inactive ingredients in clozapine orally disintegrating tablets studied?
Yes, Report RA 2002-46 assesses the interactions of clozapine orally disintegrating tablet ingredients with aspartame. This study was submitted to chemistry for review.

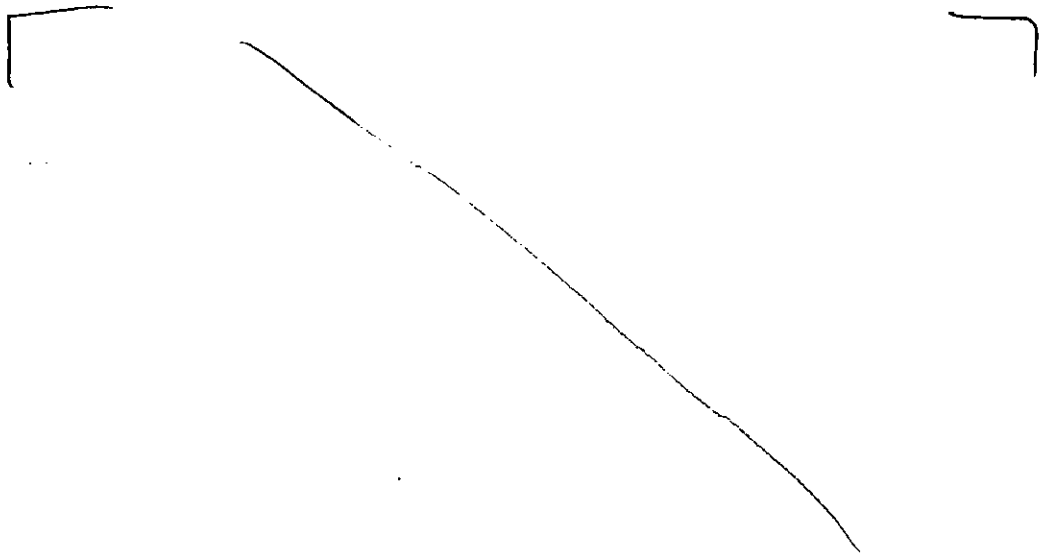
D.4. What information is available to assure that both the analytical assay and the clinical study were performed according to current GMPs and GCPs?
An Establishment Inspection was requested for both the analytical site and the clinical site.

D.5. Did the Establishment Inspection report reveal any deficiencies that may affect the outcome of the bioequivalence study submitted by the firm?
Yes, the Establishment Inspection of the analytical site made 9/25 to 9/26, 2003, in ——— for study CS-001-2002, did reveal deficiencies that may affect the outcome of the bioequivalence study submitted by the firm. The firm adequately responded to these deficiencies in their letter dated 10/17/2003. There were no deficiencies noted at the clinical site in South Africa (6/30-7/4/2003).

VI. Clinical Pharmacology Labeling

CLINICAL PHARMACOLOGY

Pharmacodynamics



2 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

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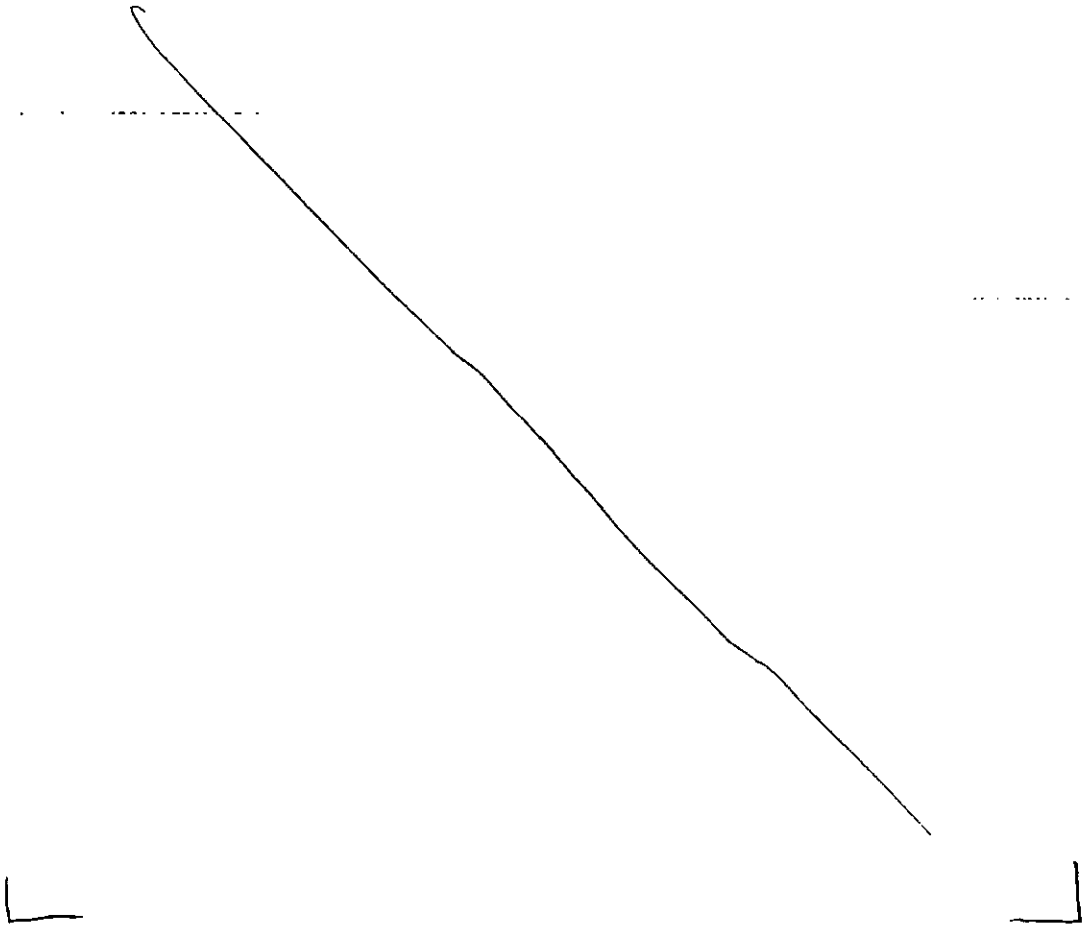


General labeling comments:

A large portion of the label is taken from the label for Clozaril®. Toxicity statements made in the proposed Clozapine ODT label should be reviewed by a Pharm/Tox reviewer prior to being placed in the label. Clinical information should be reviewed by a Medical reviewer prior to being placed in the label. The study in children and young adolescents bases the observation on a limited number of subjects; however, the study appears to be well controlled and may be the only indication of the pharmacokinetics of clozapine in children. Other additions to the label are from limited data, or information reviewed from other articles and data to support the claim in the label is not available for review. These statements should be deleted.

VII. Appendix

A. Individual Study Reviews

A.1. Study No. CS-001-2002

Title:
A Steady State Bioequivalence Study Comparing 100-mg Clozapine Orally Disintegrating Tablets (TEST) and 100-mg Clozaril® Tablets (REFERENCE) in Schizophrenic Patients.

Investigator:

Objective:
The objective of the study was to determine the bioequivalence of 100-mg clozapine orally disintegrating tablet to 100-mg Clozaril® following b.i.d. doses in schizophrenic patients.

Formulations:

- Treatment A (Test Product) Clozapine orally disintegrating 100 mg tablet manufactured by ——— · Lot RK0101A, Expiry Date: November 2002, (——tablet batch); assay=
- Treatment B (Reference Product) Clozaril® 100-mg Immediate-Release tablet, Manufactured by Novartis, lot 209E2127, Expiry Date: August 2004, commercial batch; assay= ———

Study Dates:
Start Date: March 22, 2002
Ending Date: July 25, 2002

Study design:
This was Phase 1, randomized, open-label, multiple dose, two-way crossover study in schizophrenic patients. Thirty-six (36) eligible patients between the ages of 18 and 59 years with a diagnosis of chronic schizophrenia in a residual phase or in remission (according to ——' criteria) were included in the study.
The study is a multiple-dose, randomized, two-way crossover study comparing equal 100-mg doses of Clozapine ODTs and Clozaril® Tablets in schizophrenic patients. The rationale for performing this study in patients rather than healthy volunteers is based on safety concerns. The patients (36) were randomized to one of the two groups (A and B). An initial 5-day titration period preceded the first treatment. Each patient was taken off of medication 3 days prior to the titration phase. During the titration period, Clozaril® was administered at 0800 and 1600 hours in increasing doses from 25 mg (12.5 mg b.i.d.) on Day 1 to 150 mg (75 mg b.i.d.) on day 5. After the titration period, the total daily dose of

either Clozaril® or Fazaclo™ was dosed at 100 mg b.i.d. at 0800 and 1600 hours for a period of 6 days. On day 12 and 19 only the morning dose was administered. There was no wash out period between treatments. The following dosing schedule was used:

Table A.1.1 : Dosing Schedule

Group	Titration Phase	Treatment Phase	
Group A	up to 75 mg of Clozaril® b.i.d.	100 mg Clozapine ODT, b.i.d.	100 mg Clozaril® tablet b.i.d.
Group B	up to 75 mg of Clozaril® b.i.d.	100 mg Clozaril® tablet b.i.d.	100 mg Clozapine ODT, b.i.d.

Psychiatric Assessment

The psychiatrist assessed the condition of each patient at baseline and discharge using a Clinical Global Impression (CGI) scale. The same psychiatrist made both assessments. Baseline evaluation was performed within three days prior to the first dose on Day 1.

Patient demographics

The following table shows the demographics of the patients in each leg of the study.

Table A.1.2: Patient Demographics

	Statistic	Clozaril/Clozapine	Clozapine/Clozaril	All
Age	N	18	18	36
	Arithmetic Mean	39.6	40.1	39.8
	Median	40	41.5	41.5
	SD	10.2	8.8	9.4
	Min	24	25	21
	Max	54	56	56
Sex	Male	12 (66.7%)	11 (61.1%)	23 (63.9%)
	Female	6 (33.3%)	7 (38.7%)	13 (36.1%)
Race	White	3 (16.7%)	2 (11.1%)	5 (13.9%)
	Black	1 (5.6%)	2 (11.1%)	3 (8.3%)
	Asian	0 (0%)	0 (0%)	0 (0%)
	Mixed Origin	14 (77.8%)	14 (77.8%)	
	Other	0 (0%)	0 (0%)	0 (0%)
Body Frame	Small	5 (27%)	5 (27%)	10 (27.8%)
	Medium	12 (66.7%)	11 (61.1%)	23 (63.9)
	Large	1 (5.6%)	2 (11.1%)	3 (8.3%)
Height (cm)	N	18	18	36
	Arithmetic Mean	165.1	166.2	165.7
	Median	166.5	164	165
	SD	11.1	8.8	9.9
	Min	143	153	143
	Max	192	186	192
Weight (kg)	N	18	18	36
	Arithmetic Mean	63.47	64.82	64.15
	Median	61.55	64.30	63.50
	SD	10.38	9.83	9.99
	Min	47.2	48.4	47.2
	Max	85.8	79.1	85.8
Weight within range	Yes	17 (94.4%)	18 (100%)	35 (97.2%
	No	1 (5.6%)	0 (0%)	1 (2.8%)
Drink Alcohol	Yes	11 (61.1%)	11 (61.1%)	22 (61.1%)

Table A.1.2: Patient Demographics				
	Statistic	Clozaril/Clozapine	Clozapine/Clozaril	All
	No	7 (38.9%)	7 (38.9%)	14 (38.9%)
No. of drinks/week	N	11	11	22
	Arithmetic Mean	2.5	1.5	2.0
	Median	1.0	1.0	1.0
	SD	2.0	0.7	1.6
	Min	1	1	1
	Max	6	3	6
Smoker	Yes	15 (83.3%)	14 (77.8%)	29 (80.6%)
	Ex-Smoker	0 (0%)	0 (0%)	0 (0%)
	No	3 (16.7%)	4 (22.2%)	7 (19.4%)
No. of Cigarettes-cigars/day	N	15	13	28
	Arithmetic Mean	8.6	9.2	8.9
	Median	5.0	8.0	6.0
	SD	7.8	6.0	6.9
	Min	2	1	1
	Max	30	20	30
No. of pipes of tobacco /day	N	1	4	5
	Arithmetic Mean	3.0	3.8	3.6
	Median	3.0	3.5	3.0
	SD	.	1.7	1.5
	Min	3	2	2
	Max	3	6	6
No. of drinks containing caffeine consumer per day	N	18	18	36
	Arithmetic Mean	2.2	2.7	2.5
	Median	2.0	2.0	2.0
	SD	1.1	1.3	1.2
	Min	1	1	1
	Max	4	6	6
Type of Schizophrenia	Disorganized	1 (5.6%)	1 (5.6%)	2 (5.6%)
	Catatonic	0 (0%)	0 (0%)	0 (0%)
	Paranoid	8 (44.4%)	5 (27.8%)	13 (36.1%)
	Residual	8 (44.4%)	10 (55.6%)	18 (50%)
	Undifferentiated	1 (5.6%)	2(11.1%)	3 (8.3%)

Sample Collection:

Blood samples were collected from each subject at 0.0 (pre-dose), just prior to the morning dose, on days 9, 10, 11, 12, 16, 17, 18 and 19 for measurement of trough levels. Additionally, on Days 12 and 19, blood samples were taken just prior to the morning dose (0h) and at 0.5,1, 1.5, 2, 2.5, 3, 4, 6, 9, and 12 hours post dose. On Day 19, additional blood samples (10 mL) were taken at 16, 24, 36, 48, and 72 hours after the morning dose.

Analytical Method Performance

Samples

Approximately 10 mL of venous blood was collected from each patient at predetermined times [redacted]. All samples were stored and shipped at [redacted] until time of processing. A total of 1122 samples were tested. Samples were analyzed by subject and in ascending order of sampling time.

Standards

[redacted]

Method

[redacted]

constituents.

Assay Performance

For [redacted] analytical runs [redacted] runs for desmethylclozapine), the overall imprecision (%CV) of QC values was no greater than [redacted] at all [redacted] concentrations levels for both compounds. The accuracy (%RE) at all [redacted] QC concentrations for both compounds ranged from [redacted] The overall means of the correlation coefficients (r) for all analytical runs were [redacted] for clozapine and desmethylclozapine, respectively. The assay validation package is included in the Appendix. The analytical parameters are summarized in the following Table A.1.3 .

Table A.1.3: Analytical Method Parameters

Parameter	Number of results	strength	Clozapine	Desmethylclozapine
Mass Spec Range Monitored			[redacted]	
Matrix				
Standard Range				
Lower Limit of Quantitation (LOQ)				
Extraction Dates				
Standard correlation coefficient (SD)	N=10/9.			
Percent recovery	N=6 QC samples			

Precision (%CV)	N=10 QC samples
Accuracy (%RE)	N=10 QC samples
Precision (%CV)	N=5 Calibration standards
Accuracy (%RE)	N=5 Calibration standards

An example of a typical chromatogram is shown in the Figure below.

Chromatogram of Clozapine in Plasma (Blank with Internal Standard)

Pharmacokinetic Results:

A 12-hour pharmacokinetic profile (pre-dose, at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 9, and 12 hours post-dose) for both the parent drug and its desmethyl metabolite was determined after each 6.5-day treatment period. On Day 19, additional blood samples were taken at 16, 24, 36, 48 and 72 hours after the AM dose. These additional samples following the last dose were used to more accurately determine the elimination half-life. C_{trough} was also assessed just prior to AM dose on Days 9-12 (Period I) and Days 16-19 (Period II). The steady state clozapine and desmethyl clozapine pharmacokinetic parameters evaluated were $C^{ss}_{average}$, C^{ss}_{max}, C^{ss}_{min}, $AUC_{0\text{-}12h}$, T_{max}, $t_{1/2}$ and percent fluctuation [=100*(C^{ss}_{max} - C^{ss}_{min})/ $C^{ss}_{average}$]. The log transformed AUC, C_{ssmax} and C_{ssmin} data were analyzed statistically using analysis of variance and 90% confidence interval.

Steady state conditions for clozapine and desmethylclozapine were assessed by comparing the trough concentration on the day of pharmacokinetic profile (Days 12 and 19) with the trough concentration collected on the previous day (Days 11 and 18, respectively). Changes in plasma concentration in excess of 30% were considered to be indicative of lack of steady state. If a patient was found not to be at steady state during one period, then he/she was dropped from statistical analysis for both the periods. Assessment of steady state conditions was conducted separately for clozapine and desmethylclozapine.

Of the thirty-six patients enrolled in this study, three patients withdrew from the study due to adverse events and were excluded from pharmacokinetic analysis. Thirty patients were assessed to be at steady-state for clozapine and desmethylclozapine.

Results:

A summary of clozapine and desmethylclozapine pharmacokinetic parameters by treatment is presented in Table A.1.5. Mean concentration plots of clozapine (Figure A.1.2) and desmethylclozapine (Figure A.1.3) are presented below.

Table A.1.5. Mean (%CV) Clozapine Pharmacokinetic Parameters Following Administration of 100 mg b.i.d. of Clozaril® (Treatment A) or 100 mg b.i.d. of Clozapine ODT (Treatment B) in Schizophrenic Patients.

Parameter	Completer Population (N=33)		Steady State Population (N=30)	
	Clozaril® (Treatment A)	Clozapine ODT (Treatment B)	Clozaril® (Treatment A)	Clozapine ODT (Treatment B)
Clozapine				
Tmax (hr)[a]	2.0 (0.5-4)	2.0 (1-6)	2.0 (0.5-4)	2.0 (1-6)
C_{max}^{ss} (ng/mL)	455.5 (50)	439.7 (47)	438.1 (52)	412.7 (40)
C_{min}^{ss} (ng/mL)	177.0 (68)	176.2 (68)	169.6 (71)	167.7 (65)
C_{avg} (ng/mL)	286.9 (55)	275.1 (52)	273.6 (57)	262.2 (48)
AUC_{0-12h} (ng.hr/mL)	3443 (55)	3301 (52)	3283 (57)	3146 (48)
T1/2 (hr)	17.6 (30)[b]	17.7 (52)[c]	17.0 (32)[d]	18.0 (53)[e]

% Fluc	104.6 (33)	103.9 (36)	105.9 (33)	102.1 (36)
Desmethylclozapine				
Tmax (hr)[a]	2.0 (0.5-9)	2.5 (1-9)	2.0 (0.5-9)	2.5 (1-9)
C_{max}[ss] (ng/mL)	177.6 (47)	174.2 (45)	182.3 (47)	179.7 (44)
C_{min}[ss] (ng/mL)	113.0 (63)	111.6 (64)	117.0 (63)	115.4 (63)
C_{avg} (ng/mL)	147.99 (55)	144.0 (54)	152.0 (55)	148.0 (54)
$AUC_{(0-12h)}$ (ng.hr/mL)	1775 (55)	1727 (54)	1824 (55)	1776 (54)
T1/2 (hr)	22.2 (31)[b]	22.9 (63)[c]	22.5 (30)[f]	23.1 (66)[g]
% Fluc	50.5 (39)	51.1 (44)	49.9 (41)	51.4 (45)

[a] Median (range) presented for tmax; [b]N=18; [c]N=15; [d]N=16; N=14; N=17; [g]N=13

Figure 1 Mean Plasma Concentrations of Clozapine for Completer Population Following Administration of 100 mg b.i.d. of Clozaril® (Treatment A) or 100 mg b.i.d. of Clozapine ODT (Treatment B) in Schizophrenic Patients

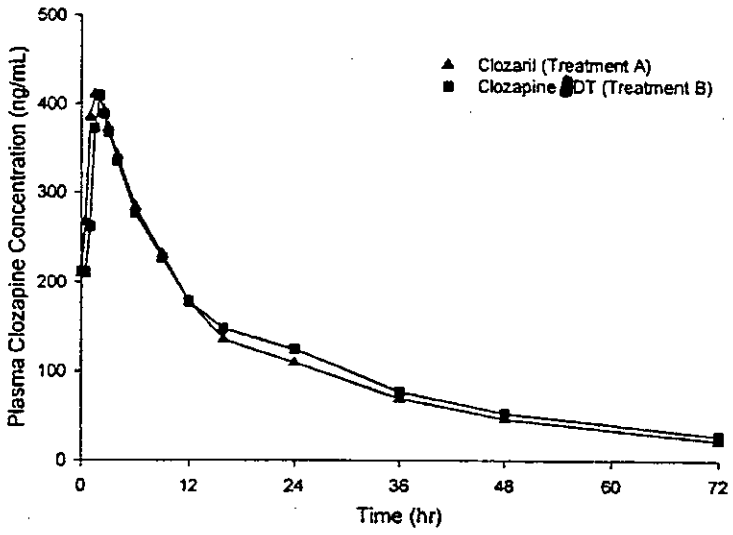
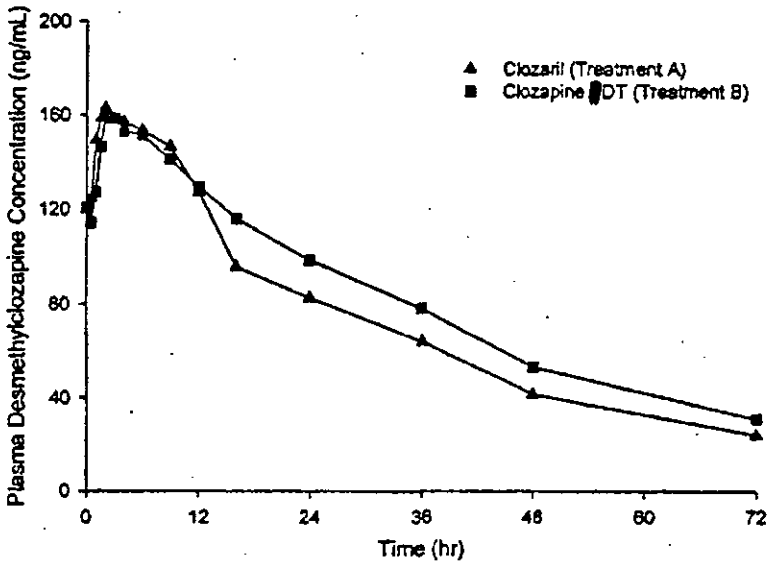


Figure 2 Mean Plasma Concentrations of desmethylclozapine for Completer Population Following Administration of 100 mg b.i.d. of Clozaril® (Treatment A) or 100 mg b.i.d. of Clozapine ODT (Treatment B) in Schizophrenic Patients



A summary of the results from statistical analyses of clozapine pharmacokinetic parameters is presented in Table A.1.6.

Table A.1.6. Statistical Analyses of Clozapine and Desmethylclozapine Pharmacokinetic Parameters Following Administration of 100 mg b.i.d. of Clozaril® (Treatment A) or 100 mg b.i.d. of Clozapine ODT (Treatment B) in Schizophrenic Patients.

Parameter	Geometric Mean		Ratio of Means (%)[a]	90% Confidence Interval[b]
	Clozaril® (Treatment A)	Clozapine ODT (Treatment B)		
Clozapine				
Completer Population				
C_{max}^{ss} (ng/mL)	403.3	398.3	97.6%	90.6%-105%
C_{min}^{ss} (ng/mL)	144.8	146.7	101%	92.6%-111%
$AUC_{(0-12h)}$ (ng.hr/mL)	2994	2944	97.6%	91.2%-104%
Steady State Populations				
C_{max}^{ss} (ng/mL)	386.5	379.5	97.6%	90.9%-105%
C_{min}^{ss} (ng/mL)	137.8	141.5	103%	96.6%-110%

$AUC_{(0-12h)}$ (ng.hr/mL)	2849	2836	99.2%	94.4%-104%
Desmethylclozapine				
Completer Population				
C_{max}^{ss} (ng/mL)	160.8	160.3	99.1%	94.7%-104%
C_{min}^{ss} (ng/mL)	95.4	95.5	99.7%	93.3%-107%
$AUC_{(0-12h)}$ (ng.hr/mL)	1558	1542	98.4%	93.5%-104%
Steady State Populations				
C_{max}^{ss} (ng/mL)	165.0	166.1	99.7%	94.9%-105%
C_{min}^{ss} (ng/mL)	98.8	99.2	99.6%	92.6%-107%
$AUC_{(0-12h)}$ (ng.hr/mL)	1598	1585	98.3%	93.0%-104%

[a] Ratio of Clozapine ODT/Clozaril®

[b] 90% confidence interval for the ratio of means as percent of Clozaril® geometric mean

Study Conclusions

Mean plasma concentrations of clozapine were superimposable following the administration of Clozaril® and Clozapine ODT. The pharmacokinetic parameters of clozapine were similar for the two populations: Completer and Steady State. Following the administration of either Clozaril® or Clozapine ODT, clozapine was absorbed with median tmax of 2.0 hours. Clozapine plasma concentrations declined with a terminal t ½ of approximately 17 to 18 hours. The t ½ was independent of treatment.

The pharmacokinetic parameters, C_{max}^{ss}, C_{min}^{ss}, and $AUC^{(0-12h)}$ of Clozapine ODT treatment were within 5% of the Clozaril® treatment for the Completer and Steady State Populations. For both the analysis populations, Completers and Steady State, the ratio of the geometric means was close to 100%, and the 90% confidence intervals for the geometric mean ratio were within the target limits of 80%-125%. There was no statistically significant difference in Tmax between the two treatments. Pharmacokinetic parameters of desmethylclozapine were similar for the Completer population and the Steady State population. Following the administration of either Clozaril® or Clozapine ODT, desmethylclozapine appeared in plasma with a median tmax of 2.5 hours. Desmethylclozapine plasma concentrations declined with a terminal t ½ of approximately 22 to 23 hours.

The 100 mg Clozapine Orally Disintegrating Tablet was bioequivalent to 100 mg Clozaril® following multiple (b.i.d.) doses in schizophrenic patients based on 90% confidence interval of ratio of geometric means of clozapine, which were within the target limits of 80% to 125%. Desmethylclozapine, a metabolite of clozapine, was also bioequivalent between the two treatments.

Adverse Events

Both treatments were tolerated similarly. All patients experienced drug-related adverse events during the period of dose titration of Clozaril® treatment. The incidence of drug-related adverse events was lower during the treatment periods (approximately 60% of patients) and was similar between treatments. The nature and incidence of adverse events was similar between treatment groups. Some adverse events were expected to occur in >5% of patients during treatment with Clozaril® because they had been reported frequently in previous studies. These adverse events were central nervous system complaints, including drowsiness/sedation, dizziness/vertigo, headache, tremor, and syncope, autonomic nervous system complaints, including salivation, sweating, dry mouth and visual disturbances; cardiovascular findings, including tachycardia and hypotension; gastrointestinal complaints, including constipation and nausea; and miscellaneous complaints, including abnormal dreams and fever. There were no unexpected adverse events.

B. Dissolution studies

1. Evaluation of the USP monograph method for clozapine tablets:
Samples: Fazaclo 100 mg Lot RK0101A (registration lot used in the bioequivalence study)

Method:

Time:

Results:

2. Study RA-2002-100: Development of Dissolution Parameters for Clozapine Orally Disintegrating Tablet.

Samples: Lot RK0101A (100 mg tablet used in the clinical bioequivalence trial)

Once it was determined that the USP monograph method was not appropriate, further

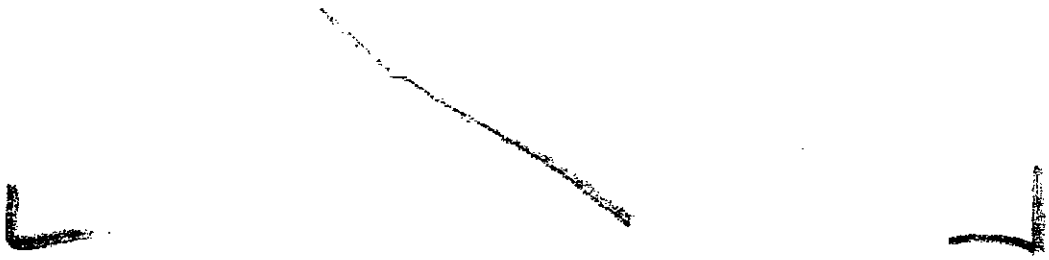
2 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

Withheld Track Number: Clin Pharm/Bio- 3



Comment

The firm has proposed the following dissolution method and specification for the OD Fazaclo® tablets:

Apparatus [redacted]
Speed of Rotation: [redacted]
Media: [redacted]
Volume: 900 mL
Sampling time: [redacted] minutes
Tolerance: Q= [redacted] at [redacted] minutes

Conclusions

The dissolution studies accomplish three objectives. First an appropriate dissolution procedure was developed for the 100-mg orally disintegrating tablet. Secondly, the dissolution of the 25mg mint-flavored orally disintegrating tablet was compared to the 100-mg strength using the USP apparati and several media ranging from pH [redacted] The information from this study is used to support the waiver for a bioequivalence study of the 25 mg strength. Finally, the half 25-mg tablet was compared to the whole 25 mg scored tablet to assure the accuracy of the tablet splitting. The data evaluated indicate that the orally disintegrating tablet can meet the following specification.

Agency Recommended Dissolution Method and Specifications:

USP [redacted] Apparatus [redacted]
900 mL [redacted]
Q= [redacted] dissolved in [redacted] minutes

C. Analytical Method Validation

An LC-MS/MS procedure has been developed for the quantitation of clozapine and desmethylclozapine in EDTA human plasma. Clozapine, desmethylclozapine and the internal standard clozapine-

A small amount of the sample was separated on an HPLC system, and quantitated on a . The transition ions were monitored for clozapine, desmethylclozapine, and clozapine respectively. Clozapine and desmethylclozapine in human plasma have a lower limit of quantitation of of plasma.

The method was validated for specificity, linearity, recovery, and stability using prepared standards and quality control samples in plasma. Standards were of clozapine and desmethylclozapine per mL of plasma. Quality Control Samples were with clozapine and desmethylclozapine at The Internal Standard was added at a concentration of of plasma. Concentrations of analytes in replicates of each level of quality control sample were determined from the standard curve. standard curves were assayed over a period of clozapine and desmethylclozapine at were assessed. During the validation, quality control samples were stored in a freezer set at

Intra-batch Precision and Accuracy of Quality Control Samples (n=6) was determined by analyzing replicates in a single batch. The clozapine and desmethylclozapine concentrations for each sample were from the standard curve.

Inter-batch Precision and Accuracy of Calibration Standards and Quality Control Samples were determined in separate curves over days.

Specificity was evaluated by analyzing aliquots from lots of blank human plasma. No peaks were found, indicating that there is no interference from endogenous plasma constituents.

Linearity of clozapine and desmethylclozapine in human plasma ranged from The internal standard used was clozapine prepared at Linearity was demonstrated by analyzing plasma at of clozapine and desmethylclozapine per mL of plasma.

Recovery of clozapine and desmethylclozapine were determined by comparing the responses of plasma with of clozapine and desmethylclozapine per mL of plasma to unextracted standards prepared at the same levels. Overall recovery of internal standard was

Stability of solutions of the analytical standard in methanol was assessed by comparing the area of freshly prepared standard solutions to the area counts of standard solutions that had been stored at

Stability of QC samples left at ambient temperature for was assessed.

Stability of Extracted Quality Control Samples was assessed by

Stability of Unextracted Quality Control Samples was determined by analyzing two sets of quality control samples. One of the replicates was left on the

Freeze/Thaw Stability of Unextracted Quality Control Samples was determined by analyzing one set of samples after one freeze-thaw cycle and another set after freeze-thaw cycles.

Long Term Stability of Quality Control Samples (n=6) was assessed by analyzing QC samples stored in a freezer for The samples were then extracted and analyzed.

A summary of the validation study results are given in the following two tables.

Stability

Analytical Method Parameters				
Parameter	**Number of results**	**strength**	**Clozapine**	**Desmethylclozapine**
Selectivity			No interference	No interference
Internal Standard Concentration:				
Lower Limit of Quantitation				
Standard correlation coefficient	N=5			
Percent recovery	N=6 QC samples			
Precision (%CV)	N=6 QC samples			
Intrabatch Accuracy (%RE)	N=6 QC samples			
Precision (%CV)	N=5 Calibration standards			
Intrabatch Accuracy (%RE)	N=5 Calibration standards			

Analysis

The chromatograms were integrated using _____ software, part of the _____ data system. A weighted [$(1/X^2)$ where x= concentration] linear regression analysis was used to calculate the slopes, intercepts and correlation coefficients. Weighted linear regression is the method of choice for mass spectrometry. The concentrations of clozapine and desmethylclozapine were then calculated by the following formula, where r is the ratio of the compound peak area to the internal standard peak area.

$$(x) = \frac{r - (v\text{-intercept})}{\text{slope}}$$

Conclusion

The validation report data demonstrates that the procedure for the determination of clozapine and desmethylclozapine in human plasma is specific, accurate, and reproducible. The data also demonstrates that the method can be used to measure clozapine and desmethylclozapine in human plasma in the range of _____

22 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

Withheld Track Number: Clin Pharm/Bio- 64

E. Filing Memo

Filing Memo

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-590	Brand Name	Clozapine Orally Disintegrating Tablets
OCPB Division (I, II, III)	I	Generic Name	Clozapine
Medical Division	Neuropharm	Drug Class	Antipsychotic
OCPB Reviewer	Carol Noory	Indication(s)	Management of schizophrenia
OCPB Team Leader	Ramana Uppoor	Dosage Form	Orally disintegrating tablets 25 mg and 100 mg
		Dosing Regimen	Starting dose of 12.5 mg b.i.d., titrated to 300-450 mg day
Date of Submission	1/31 03	Route of Administration	Oral
Estimated Due Date of OCPB Review		Sponsor	Alamo Pharmaceutical LLC
PDUFA Due Date		Priority Classification	Standard
Division Due Date			

Clozapine Orally Disintegrating Tablets , 25 mg and 100 mg tablets, were developed to be equivalent to the RLD, Clozaril® manufactured by Novartis The firm submitted a steady state BE study in patients (2 way crossover) comparing the highest strength to the RLD. Dissolution data for clozapine was submitted for the 25 mg and 100 mg tablets using the ——— apparatus ——————— The data indicates that the profiles are similar in the dissolution media, pH ——————— The firm submitted literature showing that the pharmacokinetics of clozapine in rats are linear at steady state. A waiver was requested for the 25 mg strength based on dissolution similarity in pH ——————— and formulation proportionality of both the active and inactive ingredients. The sponsor proposed dissolution specifications is the same as the USP specification for Clozaril.

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary				
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
1. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Health Volunteers-				
single dose:				
multiple dose:				

Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	1	1		Steady-state comparing 100 mg ODT to RLD in patients
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:	X	3	3	
(IVIVC):				
Bio-waiver request based on BCS				Lower strength
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	X	15	15	
Total Number of Studies		4	4	
Filability and QBR comments				

	"X" if yes	Comments
Application filable ?	X	This submission contains results from 1 in-vivo study: 1) Pivotal BE study using the 100 mg strength to compare the proposed orally disintegrating dosage form to the marketed immediate release dosage form 2) Dissolution study comparing the rapidly dissolving 100 mg tablet and 25 mg tablet. 3) Literature showing that clozapine follows linear kinetics at steady-state in rats. 4) PK data stored electronically
Comments sent to firm ?		1. Dissolution data for the dissolution study comparing 25 and 100 mg ODTs should be provided on 12 individual tablets in three media (e.g. pH 1.2, 4.5 and 6.8). [redacted] is formulated not to dissolve at the pH of saliva (5.8-7.1) this will be demonstrated by this testing. Dissolution data was submitted using only the [redacted] method 2. A dissolution development report showing that the [redacted] is the best discriminatory method for this product should be submitted. 3. The dosage and administration section of the proposed label recommends titrating from 12.5 mg t.i.d. Since the 25 mg ODT is a scored tablet and needs to be split to obtain the starting dose, in vitro dissolution profiles comparing the [redacted] vs. whole tablet for the 25 mg strength should be provided. Individual data (N=12) should be submitted in three media. Samples should be tested at 5 minute intervals. Due to the nature of the rapidly disintegrating tablets, in conducting this dissolution study, the firm should treat the tablets in the same manner as recommended to the patient. All dissolution data (Comments 1, 2 and 3) should be submitted within 3 months. 4. The Pharmacokinetic and Drug Interaction Section of the label should be updated with any additional information available from published literature.
QBR questions (key issues to be considered)	I. Is the proposed rapidly dissolving formulation of clozapine 100-mg tablet bioequivalent to the marketed 100-mg immediate release Clozaril™ product? II. Are the kinetics of clozapine linear at steady-state? III. Is there a need for a food effect study and a PK study with and without water? IV. Can a waiver for in-vivo BE study be granted for the 25 mg strengths based on sponsor's argument of compositional proportionality and dissolution similarity? V. Are the dissolution specifications appropriate?	
Other comments or information not included above		
Primary reviewer Signature and Date	Carol A. Noory 3/6/03	
Secondary reviewer Signature and Date		

CC: NDA 21-950, HFD-850(Lee), HFD-120(Hardeman), HFD-860(Uppoor, Mehta, Sahajwalla), CDR (B. Murphy)

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

/s/

Carol Noory
11/12/03 03:14:57 PM
BIOPHARMACEUTICS

Ramana S. Uppoor
11/12/03 03:24:27 PM
BIOPHARMACEUTICS
Label comments in DFS show our final version - the track changes seem to have disappeared upon conversion to PDF in DFS. Label with track changes sent to Steve Hardeman and Dr. Tom Laughren.