CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

019758Orig1s036

Trade Name:	CLOZARIL
Generic or Proper Name:	(clozapine)
Sponsor:	Novartis
Approval Date:	August 19, 1998

CENTER FOR DRUG EVALUATION AND RESEARCH

019758Orig1s036

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

019758Orig1s036

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-758/SLR-036

Novartis
Attention: Susan Witham
59 Route 10
East Hanover, NJ 07936

AUG 19 1998

Dear Ms. Witham:

Please refer to your supplemental new drug application dated November 20, 1997, received November 24, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Clozaril (clozapine) tablets.

We acknowledge receipt of your submission dated July 1, 1998. Your submission of July 1, 1998, constituted a full response to our April 17, 1998 action letter.

This supplemental new drug application provides for the following labeling changes:

1. PRECAUTIONS section -- A cautionary statement regarding concurrent use of Clozaril and selective serotonin reuptake inhibitors (SSRI's) was added. As agreed in the telephone conversation of August 7, 1998, between yourself and Steve Hardeman, of this Division, we have amended the SSRI cautionary statement to read as follows:

   "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 Clozaril (clozapine) is combined with these drugs, particularly with fluvoxamine. A reduced Clozaril (clozapine) dose should be considered."

2. CONTRAINDICATIONS section -- Added statement that use in patients with a previous hypersensitivity to clozapine or any other component of the drug is contraindicated.

3. WARNINGS section -- Added to Agranulocytosis subsection statistics for experience in the U.S. with Clozaril-associated agranulocytosis.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and

effective for use as recommended in the submitted labeling (November 20, 1997).

Accordingly, the supplemental application is approved effective on the date of this letter. The above revisions are terms of the approval. Marketing the product before making the revisions, exactly as requested, in the product's final printed labeling (FPL) may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 19-758/SLR-036." Approval of this submission by FDA is not required before the labeling is used.

If additional information relating to the safety or effectiveness of this drug becomes available before we receive the final printed labeling, revision of that labeling may be required.

If a letter communicating important information about this drug product (i.e., a "Dear Healthcare Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Steve Hardeman, R.Ph., Regulatory Management Officer, at (301) 594-5533.

Sincerely,

8/18/98

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

cc:
Archival NDA 19-758
HFD-120/Div. Files
HFD-120/Hardeman/Dubitsky/Laughren
HF-2/MedWatch (with labeling)
HFD-002/ORM (with labeling)
HFD-101/ADRA (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613/OGD (with labeling)
HFD-95/DDMS (with labeling)
HFD-810/DNDC Division Director
DISTRICT OFFICE

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Final: August 11, 1998

APPROVAL (AP)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

019758Orig1s036

OTHER ACTION LETTERS

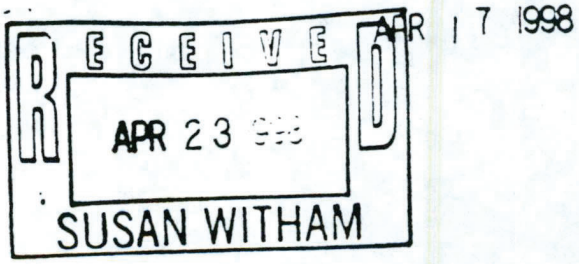
DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administrat
Rockville MD 20857

NDA 19-758 / SLR-036

Novartis Pharmaceuticals Corporation
Attention: Susan Witham
59 Route 10
East Hanover, NJ 07936



APR 17 1998

Dear Ms. Witham:

Please refer to your supplemental new drug application of November 20, 1997, received November 24, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Clozaril (clozapine) tablets.

The supplemental application provides for revised labeling as follows:

1. PRECAUTIONS section – As requested in Division's letter of July 9, 1997, a cautionary statement regarding concurrent use of Clozaril and selective serotonin reuptake inhibitors (SSRI's) was added.

2. CONTRAINDICATIONS section -- Added statement that use in patients with a previous hypersensitivity to clozapine or any other component of the drug is contraindicated.

3. WARNINGS section -- Added to Agranulocytosis subsection statistics for experience in the U.S. with Clozaril-associated agranulocytosis.

We have completed the review of this supplemental application and it is approvable. However, your proposed precautionary statement implicitly includes paroxetine and sertraline, even though we are not aware of any direct evidence for an interaction with these two drugs. Please submit for our review any data supporting clinically significant interactions between clozapine and either of these two drugs. Alternatively, we propose the following language for this statement:

> "Elevated serum levels of clozapine have been observed when Clozaril (clozapine) is administered with the selective serotonin reuptake inhibitors (SSRI's) fluoxetine and fluvoxamine. Therefore, such combined treatment should be approached with caution and patients should be monitored closely when Clozaril (clozapine) is combined with either of these drugs. A reduced Clozaril (clozapine) dose should be considered. Although direct evidence for interactions with two other SSRI's, paroxetine and sertraline, and clozapine is not available, an interaction may be predicted, given that all the SSRI's have some potential for CYP2D6 inhibition, the likely mechanism for this interaction. Therefore, similar caution is indicated in co-administration of either of these two SSRI's with clozapine."

Once a labeling agreement is reached, it will be necessary for you to submit final printed labeling (FPL) identical in content to the agreed upon language. Please submit 20 copies of the final printed labeling, ten of which are individually mounted on heavy-weight paper or similar material. In addition, all previous revisions as reflected in the most recently approved package inserts must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

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

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the application.

This change may not be implemented until you have been notified in writing that this supplemental application is approved.

If you have any questions, please contact Steven D. Hardeman, R.Ph., Project Manager, at (301) 594-5533.

Sincerely yours,

Thomas P. Laughren, MD
for

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

References

		Page No.
1.	Allen L., Tejera C. Treatment of clozapine-induced obsessive-compulsive symptoms with sertraline. *American Journal of Psychiatry*. July 1994, 151:7, p. 1096-1097.	006
2.	Pinninti N. R., de Leon J. Interaction of sertraline with clozapine. *Journal of Clinical Psychopharmacology*. April 1997, 17:2, p. 119-120.	008
3.	Wetzel H., Anghelescu I., Szegedi A., Wiesner J., Weigmann H., Harter S., Hiemke C. Pharmacokinetic interactions of clozapine with selective serotonin reuptake inhibitors: differential effects of fluvoxamine and paroxetine in a prospective study. *Journal of Clinical Pharmacology*. February 1998, 18:1, p. 2-9.	010
4.	Joos A. A., Konig F., Frank U.G., Kaschka W. P., Morike K. E., Ewald R. Dose-dependent pharmacokinetic interaction of clozapine and paroxetine in an extensive metabolizer. *Pharmacopsychiatry*. November 1997, 30:6, p. 266-270.	018
5.	Centorrino F., Baldessarini R. J., Frankenburg F. R., Kando J., Volpicelli S. A., Flood J. G. Serum levels of clozapine and norclozapine in patients treated with selective serotonin reuptake inhibitors. *American Journal of Psychiatry*. June 1996, 153:6, p. 820-822.	023
6.	Taylor D., Pharmacokinetic interactions involving clozapine. *British Journal of Psychiatry*. August 1997, 171, p. 109-112.	026
7.	Edge S. C., Markowitz J. S., Devane C. L., Clozapine drug-drug interactions: a review of the literature. *Human Psychopharmacology*. 1997, 12:1, p. 5-20.	030
8.	Chong S. A., Tan C. H., Lee H. S. Worsening of psychosis with clozapine and selective serotonin reuptake inhibitor combination: two case reports. *Journal of Clinical Pharmacology*. February 1997, 17:1, p. 68-69.	046

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

019758Orig1s036

CLINICAL REVIEW(S)

JUL 30 1998

Review and Evaluation of Clinical Data
NDA # 19-758

Sponsor:	Novartis
Drug:	Clozaril (clozapine)
Indication:	Schizophrenia
Material Submitted:	Amendment to a Pending Supplement (SLR-036)
Correspondence Date:	July 1, 1998
Date Received:	July 6, 1998

I. Background

The sponsor submitted a supplement (SLR-036) on 11/20/97 to add the following to Clozaril labeling:

- contraindicated use of Clozaril in patients with hypersensitivity to clozapine or other components of the drug product.
- updated statistics regarding U.S. experience with Clozaril-associated agranulocytosis.
- precautionary statement regarding the concurrent use of Clozaril with SSRI's.

These changes were reviewed (see my 12/16/97 Review and Evaluation of Clinical Data) and deemed acceptable with the exception of the statement about the potential interaction between Clozaril and SSRI's. This change was first requested by the Division based on a literature report of elevated clozapine levels when clozapine and fluoxetine were co-administered and a second report of elevated clozapine concentrations when clozapine and fluvoxamine were given together (see our 7/9/97 letter to Novartis).

Since reasonable evidence for an interaction between clozapine and either sertraline or paroxetine was not known to exist, I objected to extending this statement to all SSRI's and preferred to restrict the precaution to fluvoxamine and fluoxetine.[1]

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[1] In fact, our latest letter to Novartis (4/17/98) suggested language that acknowledged the possibility of an interaction between Clozaril and all four SSRI's since they all had some potential to inhibit CYP2D6.

The sponsor has conducted a recent literature search and has submitted a series of published papers which, they claim, do indicate the possibility of an interaction with paroxetine and sertraline.

II. Summary of Submitted Literature

Copies of relevant literature articles are provided under the "Published Literature" tab of this submission. This comprises eight articles:

- two prospective studies.
- four anecdotal reports.
- two review papers.

Of the two studies, the more adequately designed study examined the effects of fluvoxamine and paroxetine on clozapine pharmacokinetics within subjects (i.e., using a crossover design).[2] This revealed a clear elevation of clozapine (and metabolite) concentrations when fluvoxamine was added to clozapine but no substantial effect of paroxetine on clozapine pharmacokinetics.

The second study examined four parallel groups of patients treated with clozapine alone, clozapine + sertraline, clozapine + fluoxetine, and clozapine + paroxetine.[3] Results suggest a modest increase in mean clozapine and norclozapine levels with each SSRI plus clozapine versus clozapine alone. However, mean increases in clozapine levels were much smaller than those observed with fluvoxamine and clozapine co-administration in the above described study (i.e., three-fold elevation). Differences between the SSRI's were minor and sample sizes were inadequate to permit statistical comparisons for each SSRI. Clozapine levels, adjusted for weight-corrected daily dose, increased by about 40% in all SSRI groups.

The literature review articles reflect clear evidence to support a significant interaction between fluvoxamine and clozapine, with some evidence of a less marked interaction between clozapine and the other three SSRI's, suggesting a possible role of CYP2D6.

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[2] Wetzel H, et al. J Clin Psychopharmacol 1998;18:2-9.
[3] Centorrino F, et al. Am J Psychiatry 1996;153:820-822.

The case reports, taken together, do not provide persuasive evidence of an interaction with sertraline or paroxetine.

III. Conclusions/Recommendations

It seems clear that fluvoxamine produces clinically significant elevations in serum clozapine levels. Evidence demonstrating that fluoxetine, paroxetine, and sertraline can do likewise is less consistent and weaker. Even one of the studies that prompted our original request that this precaution include fluoxetine showed a smaller mean increase in clozapine levels (+76%)[4] when given with fluoxetine compared to observed elevations when fluvoxamine was given with clozapine in the Wetzel study (mean increase of three-fold with up to six-fold elevations).

Nonetheless, elevations of this magnitude may be clinically important and, given that the 1996 Centorrino study showed elevations of about 40%, I do not object to including all four SSRI's in the precaution. However, I also feel that it would be useful for the prescriber to know that the degree of clozapine level elevation consequent to combining fluvoxamine and clozapine is likely to be appreciably greater than that with the addition of fluoxetine, paroxetine, or sertraline. This may be an important consideration for clozapine patients who are candidates for the addition of an SSRI to their treatment regimen for whatever reason. Accordingly, I propose the following statement for labeling:[5]

"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

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[4] Centorrino F, et al. Am J Psychiatry 1994;151:123-125.

[5] This statement includes specific mention of the Wetzel study which, by virtue of its prospective design and larger sample size, is felt to supersede the Hiemke report of fluvoxamine/clozapine interactions, which we referenced in our original letter to Novartis.

sertraline. Therefore, such combined treatment should be approached with caution and patients should be monitored closely when Clozaril® (clozapine) is combined with these drugs, particularly with fluvoxamine. A reduced Clozaril® (clozapine) dose should be considered."

Based on the submitted data, I feel that this proposal most accurately depicts the interaction potential between clozapine and SSRI's in a manner that will be useful to the prescribing clinician.

Gregory M. Dubitsky, M.D.
July 30, 1998

7-30-98

cc: NDA# 19-758
HFD-120 (Div. File)
HFD-120/GDubitsky
/TLaughren
/SHardeman

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

019758Orig1s036

ADMINISTRATIVE AND CORRESPONDENCE DOCUMENTS

facsimile
TRANSMITTAL

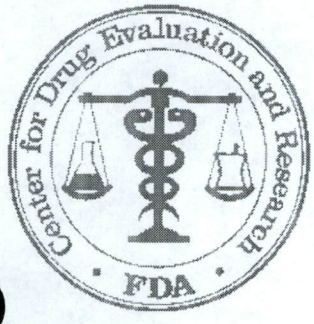
To: Sue Witham
Sponsor: Novartis
Fax #: (973) 781- 6325
Re: Labeling Supplement SLR-036 (amendment dated July 1, 1998)
Date: 8/7/98
Pages: 1

Sue -- Drs. Dubitsky and Laughren feel that the following proposed labeling most accurately depicts the interaction potential between clozapine and SSRI's in a manner that will be useful to the prescribing clinician. If we can agree on this change, I will get an approval letter in the mail (as opposed to another approvable action).

> "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 Clozaril (clozapine) is combined with these drugs, particularly with fluvoxamine. A reduced Clozaril (clozapine) dose should be considered."

(Susan Witham)
Sponsor agreed via telephone and mail that above labeling is acceptable. Will generate approval letter

S Hardeman
8/7/98



From the desk of...
CDR Steven D. Hardeman, R.Ph.
Project Manager
Division of Neuropharmacological Drug Products / HFD-120
Food and Drug Administration
Rockville, Maryland 20857

301-594-5533
Fax: 301-594-2859

cc: N19-758 /SLR-036
DIV File
Laughren/Dubitsky/Hardeman

Distribution List: T. Koestler, R. Brezin, Mgr(s).*
1* Witham
Date: 7/14/97

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-758

Novartis Pharmaceuticals Corporation
Attention: Susan Witham
59 Route 10
East Hanover, NJ 07936

JUL 9 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

JUL 06 1998

RECEIVED HFD-120

Dear Ms. Witham:

Please refer to your new drug application for Clozaril (clozapine) tablets.

We have recently completed a review of package insert 30118906, dated March 1997, and the published medical literature to evaluate cases of specific drug interactions associated with clozapine treatment.

Based upon our review, we are requesting that you amend the Clozaril labeling by adding the following paragraph under the PRECAUTIONS, Drug Interactions subsection:

> "Elevated serum levels of clozapine have been observed when clozapine is administered with fluoxetine and with fluvoxamine. Therefore, such combined treatment should be approached with caution and a reduced clozapine dose should be considered."

The rationale for the addition is based on the following two literature reports:

1. In a study comparing 17 patients receiving clozapine alone to 6 patients receiving the combination of clozapine and fluoxetine (Centorino et al., Am J Psychiatry 1994:151:123-125), mean steady-state clozapine serum concentrations corrected for dose were 76% higher among the patients receiving the combination; clozapine metabolite levels were also increased.

2. Elevated levels of clozapine have been reported when clozapine and fluvoxamine are co-administered (Hiemke C, et al. Elevated Levels of Clozapine in Serum After Addition of Fluvoxamine [letter] J Clin Psychopharm 1994; 14(4):279-281).

Please submit final printed labeling exactly as specified above in the form of a "SPECIAL SUPPLEMENT - CHANGES BEING EFFECTED" as described under 21 CFR 314.70(c). Please incorporate all previous revisions as reflected in the most recently approved package insert. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

Please submit twenty copies of the final printed labeling, ten of which are individually mounted on heavy weight paper or similar material.

We request that these changes be made with the next printing, but not later than 6 months from the date of this letter.

If you have any questions, please contact Steve Hardeman, R.Ph., Project Manager, at (301) 594-5533.

Sincerely yours,

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