

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
75417

MEDICAL REVIEW

CONSULTATIVE REVIEW AND EVALUATION OF CLINICAL DATA

Clinical Reviewer: Gregory M. Dubitsky, M.D.
HFD-120

Material Reviewed: Consultation Request from the Office of
Generic Drugs (HFD-600) RE: Mylan brand
of clozapine (ANDA 75-417)

Date Received: April 1, 1999

Date Reviewed: April 13, 1999

I. Background

Mylan Pharmaceuticals, Inc., has submitted ANDA 75-417 to the Office of Generic Drugs (OGD) for the approval of a generic formulation of clozapine, an atypical antipsychotic agent for the treatment of treatment-refractory schizophrenic patients.

Clozapine has been marketed in the U.S. since 1990 by Novartis as Clozaril under NDA 19-758. A generic formulation manufactured by Zenith Goldline Pharmaceuticals was approved in November 1997 under ANDA 74-949 and was launched shortly thereafter.

Since clozapine has demonstrated the potential to cause agranulocytosis, both marketed products are distributed under a mandatory system to insure regular monitoring of white blood cell counts in all patients receiving this treatment. Mylan has proposed a distribution/WBC monitoring system to be implemented with the launch of their product, which they have designated as the Clozapine Patient Protection Program (CPPP). This consultation request seeks the evaluation of the CPPP by the Division of Neuropharmacological Drug Products (HFD-120).

This review conveys my comments regarding the CPPP.

II. Materials Reviewed

The following materials, provided by OGD as part of the consultation request package, were reviewed:

- 1) OGD reviewer's comments.
- 2) Mylan CPPP summary (pages 95-108).
- 3) CPPP Flowcharts (pages 109-117).
- 4) Reminder Forms A-E (pages 118-122).
- 5) Report Forms A-E (pages 123-127).
- 6) Registration and Reporting Forms A-D (pages 128-131).
- 7) Mylan CPPP Development Document (Draft) (pages 132-150).

III. Comments on Mylan CPPP

In general, the Mylan CPPP appears to parallel the distribution systems in place for the Novartis and Zenith Goldline products and should be adequate to minimize the risk of agranulocytosis with Mylan clozapine. However, there are a few specific points that merit attention:

1) The brief discussion of the independent quality assurance committee on page 98 of the CPPP summary does not adequately describe the composition, role, and functioning of this body. This information should be provided.

2) One area in which the CPPP differs from the other two systems is in allowing Mylan clozapine to be dispensed to patients switched from another formulation without obtaining signatures from the pharmacist or physician, as discussed on pages 98 and 99 of the CPPP summary. Given the provisions that the pharmacy must have been registered with the CPPP beforehand, that the patient is already being treated with a clozapine product as part of another treatment group, and that registration documentation, except for signatures, must be completed before the next supply of Mylan clozapine is dispensed, this deviation does not seem objectionable.

3) Page 101 of the CPPP summary contains the statement "Any patient whose therapy has been interrupted must begin a new six month cycle of weekly WBC count monitoring." In the context of Mylan's definition of "interrupted therapy" on page 97, which requires that an abnormal blood event have occurred, this is true. However, using a broader definition, if the interruption in treatment was not related to a blood event, this would not be consistent with current labeling for clozapine products. Specifically, within the first six months of treatment, if there were no abnormal blood events and the treatment interruption was not longer than one month, the six month "clock" need not be reset. Also, after the first six months, if there were

no abnormal blood events and the interruption was not longer than one year, biweekly monitoring may continue. The flowcharts on pages 113 and 115 do make this distinction between "interrupted therapy" and "break," respectively. It is recommended that this distinction also be made in the CPPP summary for clarity.

4) Mylan's system for monitoring compliance with the CPPP and taking action in instances of non-compliance should be described.

5) Mylan's plan for auditing the distribution of clozapine by wholesalers to pharmacies should be described.

6) I agree with the remaining comments from the OGD reviewer (under comment 2: b., c., e., f., g., and h.)

IV. Conclusions and Recommendations

It is my recommendation that the sponsor be requested to respond to items 1), 3), 4), 5), and 6) above. Otherwise, the Mylan CPPP appears to be adequate.

jsl

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