October 23, 2002

CDER Psychopharmacologic Drugs Advisory Committee
Sandra Titus, Ph.D., Executive Secretary
HFD-21

Re: Application Number S047:
Supplemental Drug Application from Novartis

Dear Dr. Titus:

We have learned that a FDA panel will review a supplemental application from Novartis for the use of clozapine as first line treatment for patients with schizophrenia or schizoaffective disorder at high risk of suicide on November 4 between 8am-4:30pm at the Holiday Inn, 2 Montgomergy Village Ave, Gaithersburg MD. At that time the panel will discuss the findings of the 2-year InterSePT study. That is of great interest to us since a member of our family has been successfully treated for schizophrenia with clozapine for over the past decade.

We have been told that clozapine reduced suicide attempts to a substantially greater degree than olanzapine. If that is correct and if the FDA approves a new label that indicates this new advantage, then it is likely that the clinical use of clozapine in the United States will expand.

If that is the case, an issue that is necessarily tied to the use of clozapine should also be reviewed. That issue is the rigorous hematological monitoring program that is mandatory for patients to receive the medication. When the FDA approved clozapine for use in the USA in 1990, Sandoz and the FDA mandated the previously mentioned hematological surveillance program for schizophrenic patients treated with clozapine. Weekly complete blood counts were performed to determine the concentration of blood neutrophils in the patient. The essence of the monitoring system was as follows.

1. The numbers of white blood cells are monitored during the initial months of therapy for early detection of severe neutropenia.
2. Clozapine is immediately discontinued if a severe neutropenia occurs.
3. In the event of a clozapine -induced agranulocytosis (< 500 neutrophils/mm^3), clozapine is not re-administered to the patient.
4. If hematological monitoring is not conducted, the patient is not permitted to receive the drug.

During the first few years of the hematological monitoring program in the USA, about three percent of schizophrenic patients treated with clozapine became neutropenic (1). Data from 11,555 patients treated during February 1990 through April 1991 were analyzed by survival analysis to determine the incidence of agranulocytosis and the effects of potential risk factors. Agranulocytosis developed in 73 patients, two of whom died from infections. Agranulocytosis occurred in 61 patients within three months after they began treatment. The cumulative incidence of agranulocytosis was 0.80 percent (95 percent confidence interval, 0.61 to 0.99) at 1 year and

0.91 percent (95 percent confidence interval, 0.62 to 1.20) at 1.5 years. The risk of agranulocytosis increased with age and was higher among women.

The following data recorded in the Clozaril® (clozapine) National Registry for the USA reflected the extent of use of the drug between February 1990 and August 21, 1997 and the risk for hematological side effects between February 1990 and April 30, 1995 (2).

1. 150,409 patients were treated with clozapine between February 1990 and August 21, 1997.
2. Based on a cut-off date of April 30, 1995, clozapine-induced neutropenias began to surface in the first two months of therapy.
3. The peak of new cases occurred at three months of treatment.
4. Afterwards, the frequency of clozapine-induced neutropenias fell steeply so that at 6 months the weekly incidence of agranulocytosis was reduced to 3 per 1000 patient years.

After 6 months of drug exposure, the weekly incidence of agranulocytosis continued to fall but did not reach zero. Nevertheless, if a neutropenia did not develop during the first six months of treatment, the chance of developing a drug-induced neutropenia thereafter was remote.

Based upon the last reported analysis, Novartis (the pharmaceutical firm that purchased the commercial rights to the drug from Sandoz) and the FDA decided to alter the hematological monitoring program in 1998. All new patients who were treated with clozapine would have weekly blood counts as before. Patients who had not developed a neutropenia during the first six months of therapy would have the frequency of blood counts reduced to once every two weeks.

The current hematological monitoring program is complex, but a few of the more important aspects are as follows.

1. The drug is precluded for the following populations.
   a. Those taking another agent that has a high propensity for causing neutropenias.
   b. Individuals who are neutropenic.
   c. Patients with a myeloproliferative disease.
   d. Patients with a history of epilepsy
   e. Patients with severe CNS depression or coma.
2. All new patients must have weekly blood counts. Patients who had not developed a neutropenia during the first six months of therapy have the frequency of blood counts reduced to once every two weeks.
3. The drug is stopped if the total blood leukocyte count falls below $3000/mm^3$, the blood neutrophil count falls below $1500/mm^3$, or the blood eosinophil count is above $4000/mm^3$.
4. In those patients that develop an agranulocytosis, more intensive hematological monitoring is required until the neutropenia is resolved.

Only two possible late-onset cases of agranulocytosis due to clozapine have been reported in the medical literature since then (3,4). A 41-year-old male had been treated with clozapine for 89 months when neutropenia developed. It was not established whether the neutropenia was due to clozapine or to a second 5-HT2 –blocking anti-psychotic agent, resperidone, that had been introduced shortly before the neutropenia developed. The second patient was a 28-year-old male who developed agranulocytosis after three years of clozapine therapy and two months after interferon-α was begun to treat a chronic hepatitis C infection. It was unclear whether one or

both agents caused the neutropenia. The viral infection itself could have also been responsible for the neutropenia (5).

In view of the last data analysis provided by Novartis, it appears that the frequency of complete blood counts and hence of venipunctures in the current hematological monitoring program are excessive. Well over a year ago, we requested the FDA to obtain an updated analysis of the hematological monitoring data from Novartis. Furthermore, if the data are similar to those from the last analysis, we will continue to urge the FDA to further reduce the frequency of complete blood counts in patients on clozapine for a year who have not developed a clozapine-induced neutropenia.

To our knowledge, an update from Novartis has not been received. Dr. Steven K. Galson, the Deputy Center Director at FDA, indicated about a month ago that because of the new prescription user fee bill the FDA would devote more efforts to risk management plans across the Center. He added that since clozapine was one of the priorities, he was asking for additional analyses and information concerning the hematological monitoring program in order for him to reply formally to our previous request concerning this problem.

Thus, it would be most appropriate to remind the officials at Novartis before and during the meeting in November of the pressing need to update the hematological monitoring program data if they have not done so already. If the updated data indicate that the risk of a drug-induced neutropenia after several months of therapy is no greater than that found with many common medications for which hematological monitoring is not required, then the frequency of monitoring should be reduced. This would provide substantial savings in time, money, and other resources and a reduction in the pain and inconvenience due to the many venipunctures required in the present monitoring program.

Unfortunately, we are unable to attend the meeting in November because of the short notice concerning the date of the meeting. Nevertheless, we urge you to consider the matter of the hematological monitoring program when you meet with the representatives of Novartis on November 4. Before then you may wish to not only consult with them but also with Dr. Galson in your agency.

If you desire any other information from us regarding this matter, let one of us know.

Sincerely,

Lynn Goldman, M.D.
Professor
Johns Hopkins Bloomberg School
of Public Health
Baltimore, Maryland
lgoldman@jhsph.edu

Daniel Goldman, M.D
President
Expert Health Data Programming, Inc.
Austin, Texas
dgoldman@ehdp.com

David Goldman, M.D.
Director. Laboratory of Neurogenetics
National Institute on Alcohol Abuse and Alcoholism
Rockville, Maryland
dgneuro@mail.nih.gov

Armond S Goldman, M.D.
Emeritus Professor
University of Texas Medical Branch
Galveston, Texas
agoldman@utmb.edu or
agoldman@cvtv.net

References

1. Alvir JM, Lieberman JA, Safferman AZ, Schwimmer JL, Schaaf JA. .Clozapine-induced agranulocytosis. Incidence and risk factors in the United States. N Engl J Med 1993; 329:162-167.
2. Physician's Desk Reference. 2001; pp 2155-2158.
3. Patel NC, Dorson PG, Bettinger TL. Sudden late onset of clozapine-induced agranulocytosis. Ann Pharmacother. 2002;36:1012-1015.
4. Schafer M, Schmidt F, Grunze H, Laakmann G, Loeschke K. Interferon alpha-associated agranulocytosis during clozapine treatment. Case report and status of current knowledge. Nervenarzt. 2001;72:872-875.
5. Vande Stouwe RA, Attia AA, Karanas A, Ciavarella D, Grieco MH. 1983. Transient agranulocytosis associated with non-A, non-B hepatitis. *Gastroenterology* **85**(1): 186-189.