

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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DATE: May 19, 2003

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THROUGH: Russell Katz, MD, Division Director  
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TO: Psychopharmacological Drugs Advisory Committee Members

SUBJECT: Overview of the effect of the WBC monitoring schedule on the rate of clozapine-associated agranulocytosis

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## Background

The clinical development program of Clozaril™ (clozapine) identified agranulocytosis (agran) as a serious adverse event associated with the use of the drug. When Clozaril™ was approved for U.S. use on September 26, 1989, the FDA-approved labeling required that the drug only be available through a distribution system that ensured weekly WBC testing prior to the delivery of the next week's supply of medication. The Clozaril National Registry (CNR) collects data from the WBC monitoring system. Previous analyses of the registry data identified that the agran rates decrease substantially after the first six months of therapy. Because of the significant decline in agran risk after six months of use, the question of whether to make changes in the WBC monitoring requirements was taken to the Psychopharmacologic Drugs Advisory Committee (PDAC) in July 1997.

Subsequent to that PDAC meeting, the Agency approved the following changes in WBC monitoring frequency on March 3, 1998:

*“Patients who are being treated with Clozaril (clozapine) must have a baseline white blood cell (WBC) and differential count before initiation of treatment, and a WBC count every week for the first six months. Thereafter, if acceptable WBC counts (WBC greater than or equal to 3,000/mm<sup>3</sup>, ANC ≥ 1500/mm<sup>3</sup>) have been maintained during the first six months of continuous therapy, WBC counts can be monitored every other week. WBC*

*counts must be monitored weekly for at least 4 weeks after the discontinuation of Clozaril (clozapine)."*

The change to biweekly monitoring after six months went into effect on April 1, 1998. With the goal of evaluating the effect of this monitoring schedule change on the rate of agran, the Division met with Novartis in July 2001 to request an analysis of the data from the CNR that had been collected since the initiation of the less frequent monitoring schedule. In March 2002 the Division accepted the sponsor's analysis proposal, and the sponsor's first data analysis was submitted in September 2002.

## **Sponsor's Methods**

Generic clozapine became available in December 1997. Following the introduction of generic clozapine, the sponsor no longer had access to the WBC data for the full population of clozapine users. In order to produce reliable rates of agran from the CNR, the sponsor excluded the following data from their analysis:

1. Exclude all data for patients who were enrolled in CNR but never started treatment with clozapine or had only one record of WBC in the database (Approximately 22,000 patients were excluded).
2. Exclude all data for patients who started treatment with generic clozapine before any treatment with brand Clozaril<sup>®</sup> (Approximately 4,000 patients were excluded).
3. For patients started on brand Clozaril but switched to generic clozapine at some point in time -- exclude all data after the first treatment with generic clozapine (Approximately 19,000 patients were affected by this criterion).

It should be noted that despite the availability of generic clozapine in December 1997, the total numbers of clozapine users in the CNR remained fairly stable for the next two years<sup>1</sup>; in comparison to the number of users in 1997, there were 1% fewer in 1998 and 5% fewer in 1999. The total number of users in 2000 was 15% less than the 1997 value.

For comparison purposes, the sponsor split the CNR data into three cohorts:

### **Cohort 1:**

Cohort 1 includes data from approximately 97,000 patients. This cohort represents the group of patients who were included in the last briefing book submitted (April 28, 1997) to the Agency on frequency of WBC monitoring. It includes all patients who started brand clozapine between Feb 5, 1990 and April 30, 1995 (the cut-off date for that report).

### **Cohort 2:**

Cohort 2 includes data from approximately 41,000 patients. This cohort represents all patients who initiated Clozaril therapy after the April 30, 1995 cut-off mentioned above

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<sup>1</sup> Post-text table 1.1-4; 9/9/2002 submission

but before the implementation of the biweekly monitoring after six months of treatment. It includes all patients who started brand clozapine after April 30, 1995 and before October 1, 1997 (six months before the introduction of biweekly monitoring option).

**Cohort 3:**

Cohort 3 includes data from approximately 39,000 patients. This cohort represents patients who have been monitored according to the current monitoring system. It includes all patients who started brand clozapine after October 1, 1997 (six months before the introduction of biweekly monitoring option).

Although there are patients from cohorts 1 and 2 who continued on clozapine subsequent to the post- 6 month switch from weekly to biweekly monitoring, we requested that the sponsor censor those patients on March 31, 1998 prior to the implementation of the biweekly monitoring. We requested the censoring of those patients to allow for the comparison of the rates of agran from a group monitored on a weekly basis only after six months of therapy to a group of patients monitored on a biweekly basis only after six months of therapy.

In preparation for the July 1997 PDAC meeting, the sponsor used a prediction methodology to project what would happen to the agran rates should the monitoring frequency be decreased at some point. The expectation was that less frequent monitoring would lead to an increase in agran rate. In preparation for the upcoming PDAC meeting, the sponsor planned to again provide projections of what would happen to the agran rates should the monitoring frequency be decreased further. However when the CNR data from cohort 3 was analyzed, this expected rise was not observed. In fact, the agran rate fell by about half between cohort 1 and cohort 3 (see below). As such, the sponsor did not want to provide new projections given that the former ones did not turn out to be valid. The Division encouraged Novartis to explore alternative approaches to modeling the projections. However, because of the limited data that the CNR collects, the sponsor had difficulty identifying with any certainty the reasons for the decline in agran rates where increases had been expected. Thus they provided projections using a very similar methodology to that used in 1997.

The sponsor also submitted agran rates from the Clozaril Patient Monitoring Services (CPMS) in the UK and Australia. Australia has always used a monitoring schedule consisting of weekly monitoring for the first 18 weeks and monthly monitoring thereafter. The UK, until 1995, used weekly monitoring for the first 18 weeks and biweekly monitoring thereafter. In 1995, monthly monitoring after 52 weeks was initiated. Hence, there is “real world” data reflecting the utilization of less frequent monitoring schedules than that used in the US currently.

**Sponsor’s Findings**

The table below summarizes the agran rates in the three cohorts during the first six months and subsequent to the first six months.

	Cohort number*	# of cases/ patient year 0-6 months	Rate /1000 patient year 0-6 months	# of cases/ patient year >6 months	Rate /1000 patient year >6 months
Agranulocytosis (WBC <1000/mm <sup>3</sup> or ANC < 500/mm <sup>3</sup> )	Cohort 1	315/41649	7.56	117/278324	0.42
	Cohort 2	78/16513	4.72	7/31305	0.22
	Cohort 3	46/14152	3.25	10/27020	0.37

\* Cohorts 1 and 2 had weekly monitoring after six months; Cohort 3 had biweekly monitoring after six months.

The sponsor applied to cohort 3 their projections for what would happen to the agran rate if the frequency of monitoring were decreased further (see sections 3.5 and 4.5 of the Hammad and Racoosin 5/19/03 review for details of projection methods and results). If the monitoring schedule was changed from weekly to monthly monitoring or to “no monitoring” after the first six months, the agran rate would be expected to increase to 1.68/ 1000 patient-years or 5.81/ 1000 patient-years, respectively.

The following table shows the agran rates that have been observed in Australia, the UK, and the US, broken out by monitoring schedule. The report recalculated the US data for comparability purposes. The sponsor structured the data from the three countries to reflect the rates in the first 18 weeks, weeks 19-52 and weeks > 52 (so as to match up with the monitoring schedule in the UK).

	<b>Weeks 0-18</b> <b>Rate (# of events)</b>	<b>Weeks 19-52</b> <b>Rate (# of events)</b>	<b>Weeks &gt;52</b> <b>Rate (# of events)</b>
<b>Australian Data</b>			
<b>Agranulocytosis</b> <b>{per 1,000 pt. yrs. (N)}</b>	8.3 (26) weekly	2.2 (11) monthly	0.5 (14) monthly
<b>United Kingdom Data</b>			
<b>Agranulocytosis</b> <b>{per 1,000 pt. yrs. (N)}</b>			
Pre-1995 (monitoring frequency)	24.8 (43) weekly	1.2 (3) bi-weekly	0.3 (2) bi-weekly
Post-1995 (monitoring frequency)	20.4 (119) weekly	1.5 (13) bi-weekly	0.6 (18) monthly
<b>United States Data</b>			
<b>Agranulocytosis</b> <b>{per 1,000 pt. yrs. (N)}</b>			
Pre-1998 (monitoring frequency)	8.8 (366) weekly	0.8 (50) weekly	0.4 (101) weekly
Post-1998 (monitoring frequency)	3.8 (40) weekly	1.0 (14) weekly/bi-weekly	0.1 (2) bi-weekly

## Comment

The CNR data reveal an unexpected secular decrease in the rate of agran occurring during the first six months of clozapine therapy. Despite the same monitoring schedule, those patients initiating clozapine therapy after October 1997 had an agran rate less than half of that of the cohort of patients who initiated clozapine therapy between 1990 and 1995. Several potential explanations have been proposed for this finding, including a higher familiarity of prescribers with clozapine-associated blood dyscrasias, and a suspicion that prescribers temporarily discontinue patients whose WBC counts are trending down towards moderate leukopenia before they actually get there. Reason for discontinuation is not recorded in the CNR, so we can not analyze the WBC at time of discontinuation among the patients who were discontinued for a hematological reason.

Similar to the analysis of the CNR presented to the PDAC in 1997, the current analysis of the CNR shows that the rate of agran drops substantially after the first six months of clozapine therapy, well into the range of agran observed with marketed drugs that do not have mandatory WBC monitoring<sup>2</sup>. The projected expectation in 1997 was that a change of monitoring from weekly to biweekly after six months would increase the agran rate to 0.54/1000 patient years to 0.91/ 1000 patient years. In actuality, the rate has fallen to 0.37/1000 patient years.

There is some “real world” experience with even less frequent monitoring schedules. Since approval in 1992, Australia has utilized a monthly monitoring frequency following the initial high risk 18 weeks; for patients treated for at least 52 weeks, the observed agran rate is 0.5/1000 patient years. In 1995, the UK adopted a monthly monitoring frequency for patients attaining a “stable” WBC count after 52 weeks of therapy. A comparison of biweekly to monthly monitoring after 52 weeks in that system revealed an increase in agran rate from 0.3 to 0.6/1000 patient years; this finding appears consistent with the Australian experience during the same monitoring period (>52 weeks).

The sponsor has proposed that in the US, the WBC monitoring frequency be decreased after one year of clozapine therapy from biweekly to monthly. We pose the following questions to the advisory committee members:

1. Is the sponsor’s proposed change reasonable? If not, would you suggest any alternative changes in monitoring frequency?
2. If the change to monthly monitoring is instituted, should patients have to meet certain “stability” criteria with regard to their WBC counts in order to qualify for the less frequent schedule (similar to the UK system)?

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<sup>2</sup> For example, sulfasalazine has a reported agran rate of 3 cases/1000 person years; mirtazapine has a reported agran rate of 4.5 cases per 1000 person years. See FDA briefing document, Appendix 1 (Racoosin review, July 7, 1997) for details.