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Novartis Pharmaceuticals Corporation
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Clozaril® (clozapine) Tablets

Briefing Book for Psychopharmacological Drugs Advisory Committee Meeting (June 16, 2003)

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1 Introduction

Clozaril® (clozapine) is an antipsychotic drug that was approved in the United States in 1989. It is chemically classified as a tricyclic dibenzodiazepine derivative and is considered the first in the class of drugs known as 'atypical' antipsychotics. It was classified as an 'atypical' antipsychotic because of its unique dopamine receptor binding profile, its effects on various dopamine mediated behaviors, and the paucity of extrapyramidal side effect, which differentiated it from the 'typical' antipsychotic drugs initially developed to treat schizophrenia (e.g., chlorpromazine and haloperidol).

As previously mentioned, the initial indication for Clozaril was for the treatment of patients with treatment-resistant schizophrenia. This restricted indication was primarily based on the risk/benefit profile considered at the time of approval. The efficacy of Clozaril in the treatment of patients with schizophrenia was well established; however, the risk of developing agranulocytosis that was associated with its use during clinical trials and foreign marketing experience was also well established. Agranulocytosis is clinically defined as the absence of granulocytes, which may lead to serious infections and fatal outcomes. The potential risk to Clozaril-treated patients of developing such a serious complication (i.e., agranulocytosis) was considered high enough compared not only to other antipsychotic drugs but to other drugs on the market at the time to warrant a restricted indication.

The lack of known predictors for patients who will develop agranulocytosis and the overall morbidity and mortality associated with agranulocytosis were the leading reasons why the Food and Drug Administration (FDA) and Novartis Pharmaceuticals Corporation (Novartis) mutually agreed to implement a hematological monitoring system to reduce the risk of agranulocytosis and its serious sequale. The rationale for the frequency of monitoring was based on the premise that a relationship existed between the frequency of monitoring and the probability of early detection of leukopenia. Early detection is considered important because the development of agranulocytosis could be minimized if patients were identified at a point prior to agranulocytosis (e.g., moderate leukopenia; WBC between 2000 and 3000 cells/mm^3). Monitoring on a daily basis was thought to be impractical, but a schedule of weekly monitoring seemed practical and safe. Thus, Novartis developed the Clozaril National Registry (CNR) to ensure weekly monitoring of White Blood Cell (WBC) counts for Clorzaril-treated patients throughout their duration of therapy.

In 1997, following nearly eight years of safe and effective use of Clozaril in the United States, the risk of agranulocytosis associated with Clozaril-therapy was becoming better understood. Importantly, two characteristics were identified:

1. The risk of agranulocytosis was greatest during the first six months of therapy and gradually declines thereafter, but never reaches zero.
2. The number of fatal outcomes was lower than expected.

Given these observations, the possibility of reducing the frequency of monitoring was considered at the 48th meeting (July 14, 1997) of the Psychopharmacological Drugs Advisory Committee (PDAC). Specifically, the following questions were posed to the PDAC:

1. Should the frequency of monitoring be reduced at some time point after initiation of therapy? If so, when and to what frequency?
2. Should monitoring be discontinued at some time point? If so, when?
3. Should monitoring become voluntary?

The PDAC provided the following recommendations to the questions posed at the meeting:

- Monitoring frequency should be reduced after six months to every two weeks.
- Mandatory monitoring should be continued.
- After implementation of the current monitoring system, an evaluation of the impact this frequency of monitoring had on the rate of agranulocytosis should be conducted.

In 1998, Novartis implemented the current monitoring system that was recommended by the PDAC members (i.e., weekly for the first 26 weeks of treatment and every two weeks thereafter). Also, shortly thereafter the first generic version of Clozaril became available in US (note: brand clozapine is referred to as "Clozaril" and generic as "generic clozapine" throughout this document) and patients treated with generic clozapine became subject to the current monitoring system. Manufacturers of generic clozapine are responsible for ensuring adherence to the current monitoring frequency schedule by maintaining a registry database with functionality identical to the CNR. Novartis, however, is responsible for maintaining a database of patients who should not be rechallenged with clozapine ("Non-rechallengable database") and generic manufacturers are responsible for:

1. contacting Novartis prior to initiating patients to cross-check them against the "Non-rechallengable database" and
2. informing Novartis of patients who should be added to this database.

In 2001, the FDA contacted Novartis to follow up on the 1997 PDAC recommendation to evaluate the impact of the current monitoring system on the rate of agranulocytosis and whether further reductions were warranted based on the new data from the CNR.

There were a series of meetings that occurred with the FDA over the next several months regarding the methods of analyses that were eventually agreed upon between the FDA and Novartis and the data from those analyses were summarized and submitted to the FDA in 2002 and 2003. One important milestone that also occurred in late 2002 was the approval of Clozaril for the treatment of recurrent suicidal behavior. Consequently, the number of patients who will be exposed to Clozaril is expected to increase since this new indication allows for the use of Clozaril in patients who are not treatment-resistant, which is a considerably broader group of patients who were not previously exposed to Clozaril.

Following their review of the updated registry data, the FDA informed Novartis that these data should be reviewed by the PDAC, where once again the question of whether to reduce the frequency of monitoring would be discussed.

The data summarized herein were prepared as background information for review and discussion at the PDAC meeting scheduled for June 16, 2003.

2 Monitoring Systems

2.1 Policy and Objectives

The Novartis policy of "No Blood No Drug" is applied globally to all Clozaril-treated patients through national centralized monitoring services, or institutional/physician oversight. Monitoring systems vary somewhat from country to country, however the US, UK and Australian national registries described in this briefing document are representative of Novartis' global monitoring practices.

These 3 registries are identified as follows:

United States: Clozaril National Registry (CNR)

United Kingdom and Ireland: Clozaril Patients Monitoring Service (CPMS)

Australia: Clozaril Patient Monitoring Service (CPMS)

The objective of all monitoring systems is the early detection of moderate leukopenia in order to reduce or prevent the occurrence of severe leukopenia, agranulocytosis and death.

2.2 Limitations

The registry databases were designed for monitoring and not for explanatory assessment. The data for analyses are based on single data entry and are not validated.

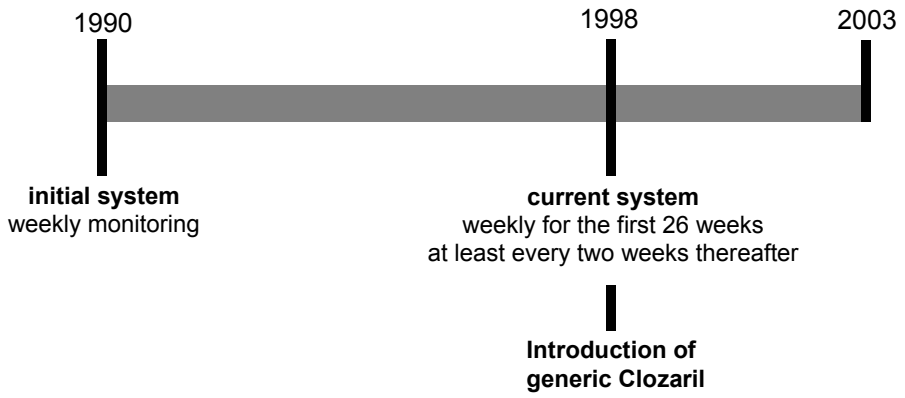
Section 2.3 describes important differences between the three monitoring systems under discussion. These differences limit the ability to compare the results of data analyses between the systems.

2.3 Differences

2.3.1 Historical background

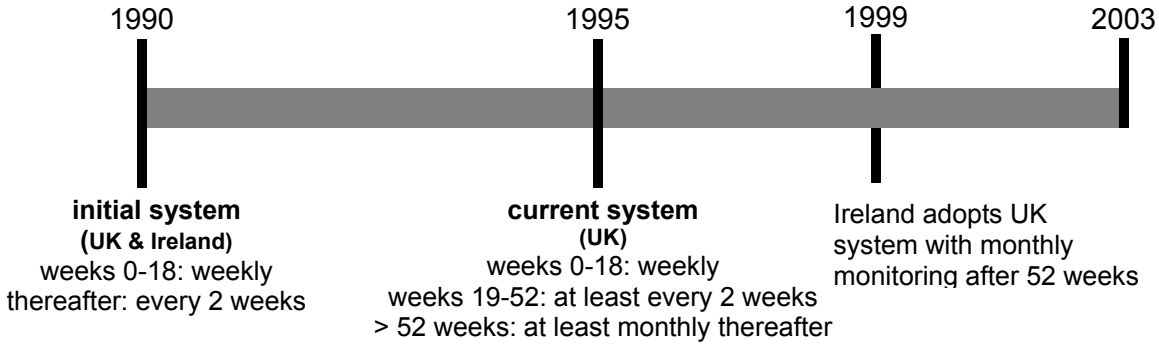
Mandatory hematological monitoring accompanied commercial introduction of Clozaril in the US, UK, and Ireland in 1990 and in Australia in 1992. The initial monitoring frequency and subsequent changes leading to the current systems are summarized in Figures 1-3 below

Figure 1: US changes in CNR monitoring frequency.



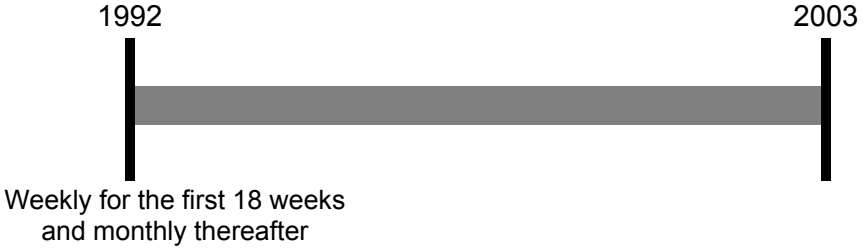
In the US, the initial monitoring system required weekly monitoring for the duration of treatment. In 1998, this requirement was changed to monitoring every 2 weeks after the first 6 months of treatment

Figure 2: UK and Ireland, changes in CPMS monitoring frequency



In the UK and Ireland, the initial monitoring system required weekly monitoring for 18 weeks and then every 2 weeks thereafter. This requirement was changed to monthly monitoring after 52 weeks of treatment in the UK in 1995 and in Ireland in 1999.

Figure 3: Australian CPMS monitoring frequency



In Australia, the monitoring system remains unchanged since its establishment in 1992. Weekly monitoring is required for the first 18 weeks with the option of monthly monitoring thereafter.

2.3.2 Definitions of Leukopenia and Agranulocytosis used in analysis

The terms moderate leukopenia, severe leukopenia and agranulocytosis have been used in the analysis of data from all 3 monitoring systems. Table 1 below shows the definitions of these terms by monitoring system.

Table 1 Definitions of leukopenia and agranulocytosis used in analysis by monitoring system

	US (CNR)	UK(CPMS)	Australia (CPMS)
Moderate leukopenia cells/mm^3	WBC ≤ 3000	WBC ≤ 3000 or ANC < 2000	WBC ≤ 3000
Severe leukopenia cells/mm^3	WBC < 2000	WBC <2000 or ANC <1000	WBC < 2000
Agranulocytosis cells/mm^3	WBC ≤ 1000 or ANC ≤ 500	WBC ≤ 1000 or ANC <500	WBC ≤ 1000 or ANC ≤ 500

The US CNR collects only WBC counts systematically. However, agranulocytosis was defined by absolute neutrophil count (ANC) in 80% of the cases included in the analysis of US data. These cases were identified through Medwatch and other reports received by Novartis Clinical Safety and Epidemiology and eventually entered in to the CNR. The UK and Australian registries routinely collect absolute neutrophil counts and the determination of moderate leukopenia, severe leukopenia and agranulocytosis are often based on these counts.

2.4 Criteria for Action

The three monitoring systems also differ in the action taken at different values for WBC and ANC (Table 2). Most of these differences are subtle but there is one major difference: in the UK and Australia, if the WBC falls below 3000 and/or the ANC is $\leq$ 1500, Clozaril is permanently discontinued and the patient must never be rechallenged. However in the US, Clozaril is only temporarily discontinued at this level (WBC below 3000) and/or an ANC between 1000 and 1500. Furthermore in the US, patients are not permanently discontinued until the WBC falls below 2000 or the ANC falls below 1500.

Across all three countries, patients must meet certain criteria before moving to the next phase of monitoring frequency (e.g., from weekly to bi-weekly monitoring in the US). The qualifying criteria vary somewhat among the three countries and an algorithm showing these criteria is presented in Appendix 6.

Table 2 Registry Criteria for Action

Action	US (CNR)	UK (CPMS)	Australia (CPMS)
Initiation of treatment cells/mm^3	WBC ≥3500	WBC ≥3500 and ANC >2000	WBC ≥3500 and ANC >2000
Twice weekly monitoring cells/mm^3	WBC 3000-3500 and ANC >1500	WBC 3000-3500 and/or ANC1500-2000	WBC ≤3500 and/or ANC1500-2000
Temporary discontinuation cells/mm^3	WBC 2000-3000 and/or ANC 1000-1500	N/A	N/A
Permanent discontinuation. cells/mm^3	WBC <2000 and/or ANC <1000	WBC <3000 and/or ANC ≤1500	WBC <3000 and/or ANC ≤1500

Source: US, UK and Australia Clozaril prescribing information

3 United States

3.1 Methods for Analysis

3.1.1 Patient population

As of September 1, 2001 there were 203,818 patients enrolled in the CNR who provided more than 21 million laboratory records for possible analysis. Given the availability of generic clozapine in the US, Novartis is no longer the sole source of WBC counts for clozapine-treated patients because the CNR was established only for patients treated with Clozaril. Therefore, it was not possible to calculate total patient exposure to clozapine.

In these analyses all patients were classified into nine classes based on their treatment with Clozaril or generic clozapine as described in the following Table 3:

Table 3: Description of patients treated with Clozaril since introduction of generic clozapine.

Patient Type	Treatment initiated with	Treatment continued with	Treatment ended with	Comments
1	Clozaril	Clozaril	Clozaril	CNR has complete record of their WBC.
2	Clozaril	Generic clozapine	Generic clozapine	CNR does not have records of WBC since their switch to Generic clozapine. Total exposure of these patients can not be computed using CNR data.
3	Clozaril	Both Generic clozapine and Clozaril	Clozaril	CNR does not have complete records of WBC since their switch to Generic clozapine.
4	Clozaril	Both Generic clozapine and Clozaril	Generic clozapine	CNR does not have complete records of WBC since their switch to Generic clozapine. Total exposure of these patients cannot be computed using CNR data.
5	Generic clozapine	Generic clozapine	Generic clozapine	CNR does not have records of WBC for these patients. Total exposure of these patients cannot be computed using CNR data.
6	Generic clozapine	Clozaril	Clozaril	CNR does not have complete records of WBC since they started with Generic clozapine. Total exposure of these patients cannot be computed using CNR data.
7	Generic clozapine	Both Generic clozapine and Clozaril	Generic clozapine	CNR does not have complete records of WBC. Total exposure of these patients cannot be computed using CNR data.
8	Generic clozapine	Both Generic clozapine and Clozaril	Clozaril	CNR does not have complete records of WBC. Total exposure of these patients cannot be computed using CNR data.
9	_____	_____	_____	Patients enrolled in CNR, but never treated with Clozaril or had only one WBC entry. Total exposure of these patients cannot be computed using CNR data.

3.1.1.1 Inclusion Criteria

The sole source of data for the data from the US analyses comes from the CNR, subject to the data exclusion criteria mentioned in the following section.

3.1.1.2 Exclusion Criteria

The exclusion criteria for the United States data were as follows:

1. Patients who were enrolled in the CNR, but never started treatment with Clozaril or had only one WBC entry in the database (Table 3: Patient type 9). Approximately 22,000 patients were excluded based on this criterion.

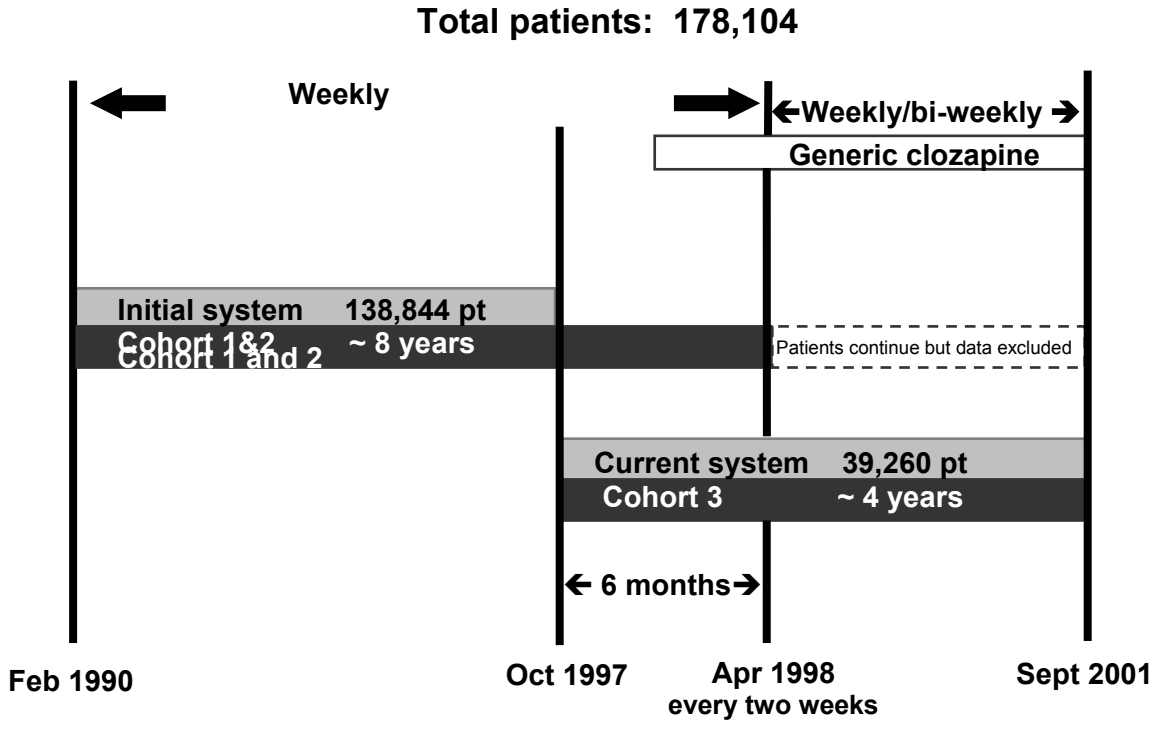
2. Patients who were believed to have started treatment with generic clozapine before any treatment with Clozaril (Table 3: Patient types 5, 6, 7 and 8). Approximately 4,000 patients were excluded based on this criterion.

3. Patients who started Clozaril treatment bit switched to generic clozapine at some point in time(Table 3: Patient types 5, 6, 7 and 8). Data for these patients after treatment with generic clozapine were excluded. Some data from approximately 19,000 patients were excluded based on this criterion.

3.1.1.3 Cohort Definitions

As shown in Figure 4 below, the patients in the CNR were divided into 3 cohorts and are described as follows:

Figure 4: Overview of Cohorts



Cohort 1 (Initial system):

Cohort 1 includes data from approximately 97,000 patients. This cohort represents the group of patients who were included in the briefing book submitted to FDA on May 30, 1997, which was prepared for the Psychopharmacological Drugs Advisory Committee (PDAC) Meeting held on July 14, 1997. This cohort includes all patients who started Clozaril between Feb 5, 1990 and April 30, 1995 (the cut-off date for the 1997 briefing book).

Cohort 2 (Initial system):

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 but before the implementation of the current monitoring system. Therefore, it includes all patients who started Clozaril between April 30, 1995 and October 1, 1997 (six months prior to the introduction of the current monitoring system).

Cohort 3 (Current system):

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 Clozaril (global change) after October 1, 1997 (six months before the introduction of biweekly monitoring option).

For purposes of comparing the initial system with the current system patients were dichotomized into Cohorts 1 and 2 (combined). All relevant data, subject to exclusion criteria 1, 2 and 3 and collected by April 1, 1998 (introduction of bi-weekly monitoring) were used to compute relevant rates and ratios for Cohorts 1 and 2 (combined); all relevant data, subject to exclusion criteria 1, 2 and 3 and collected between April 1, 1998 and September 1, 2001 were used to compute relevant rates and ratios for Cohort 3. Therefore, combined data from Cohorts 1 and 2, also referred to as the "initial monitoring system" cohort, contain information on patients who were subject to weekly monitoring of WBC under the previous monitoring system effective until April 1, 1998. In contrast data from Cohort 3, also referred to as the "current system" cohort contains information on patients who effectively enrolled after October 1, 1997 and follow the current monitoring system in USA with an option to have bi-weekly monitoring after six months of Clozaril treatment.

Estimation of rates under monthly and no-monitoring options were performed for patients in Cohort 3 only.

Table 4 summarizes the disposition of patients described above with the application of the exclusion criteria explained in Section 3.1.1.2

Table 4: Patient disposition

	Number of Patients	
Enrolled in CNR¶	203,818	
Excluded from analysis due to:		
Exclusion Criterion 1	21,743	
Exclusion Criterion 2	3,971	
		Number of patients for whom part of data were excluded due to Exclusion Criterion 3
Included in Analysis:		
All Cohorts	178,104	19,318
Cohort 1	97,485	10,791
Cohort 2	41,359	4,175
Cohort 3	39,260	4,352

Exclusion Citerion 1: Exclude patients who were enrolled in CNR, but never started treatment with clozapine or had only one record of WBC in the database
Exclusion Citerion 2: Exclude patient who started treatment with generic clozapine before any treatment with Clozaril (Patient types 5, 6, 7 and 8)
Exclusion Citerion 3: Patients started on Clozaril, but switched to generic clozapine at some point of time (Patient types 2, 3, and 4) after December 1, 1997. For these patients, exclude all data collected after the first treatment with generic clozapine.

3.1.2 Demographics

Summary statistics of the demographics variables (i.e., age, sex, and race) are provided by cohort and for patients with agranulocytosis, moderate leukopenia and severe leukopenia.

3.1.3 Incidence rates and life table analyses of severe leukopenia and agranulocytosis

Number of cases, total exposure and incidence rates of moderate leukopenia, severe leukopenia and agranulocytosis by cohort, and by treatment duration with Clozaril are provided.

In order to study the trend of agranulocytosis, severe leukopenia and moderate leukopenia over the years, the percent of new patients by calendar year were tabulated along with the corresponding incidence rates of agranulocytosis, severe leukopenia and moderate leukopenia.

Life table analysis method was used for estimating cumulative probability of event incidence rates and hazard rates of agranulocytosis, severe leukopenia and moderate leukopenia by cohort. Yearly conditional risks were tabulated separately for the initial monitoring system (Cohorts 1 and 2) and the current monitoring system (Cohort 3) for the incidence of agranulocytosis and severe leukopenia.

3.1.4 WBC at Time of Discontinuation

The WBC at the time of discontinuation (or interruption of treatment) for each patient was determined as follows:

> For patients in Cohorts 1 and 2, if the time elapsed (gap) between two consecutive WBC counts was greater than 15 days during the entire study period then the patient was considered discontinued (interrupted) Clozaril treatment.
>
> For patients in Cohort 3, if the time elapsed (gap) between two consecutive WBC counts was greater than 15 days during the first six months of therapy or if the gap between WBC counts was greater than 30 days after 6 months of therapy then the patient in Cohort 3 was considered discontinued (interrupted) Clozaril treatment.

The WBC count on the date of first discontinuation was summarized and the time to first discontinuation from baseline was used in computing Kaplan-Meier estimates of probability of discontinuation and presented in a graph.

In addition, patients who discontinued (as defined above) with a WBC value between 3,000 to 6,000 cells/mm^3 were identified and median WBC values were compared for patients in Cohorts 1 and 2 (combined) and Cohort 3.

3.1.5 Projected rates of severe leukopenia and agranulocytosis

Estimation of rates under monthly and no-monitoring options was performed for patients in Cohort 3 only. These rates reflect the estimated of risk for patients in Cohort 3 if they were monitored on a monthly basis or not monitored after their first six months, one year, or two years of treatment with Clozaril. These rates are also referred as projected rates under a less frequent monitoring option in this document.

The method of estimation of these rates of severe leukopenia and agranulocytosis after 6 months (one year and two years) of treatment with Clozaril was similar to the method of estimation of these rates for less frequent monitoring used in the 1997 briefing book submitted to FDA (Appendix 4: Attachment 3).

The duration of prodrome and the rate of decrease in WBC counts (slope) during prodrome were calculated for each patient. The onset of prodrome to moderate leukopenia (WBC ≤3000/mm3) was determined by examining data for WBC counts and determining the date from which the count showed a continual decline until moderate leukopenia developed, allowing for one possible increase in the count during that interval but only to a level that did not exceed the baseline count. The duration of the prodrome was defined as the time from onset to the date of moderate leukopenia (the first day with WBC ≤ 3000/mm3). This definition of the onset of prodrome was adapted from Alvir, et. al. and was used in the briefing document submitted to FDA for the 1997 PDAC meeting regarding Clozaril. The number of patients that would be "caught" or "missed"

to detect at moderate leukopenia under less frequent monitoring were estimated by calculating the number of days it would have taken the patient to reach severe leukopenia from the date of the last WBC count and the rate of decrease (slope) of WBC during prodrome.

The projection of rates of severe leukopenia and agranulocytosis under less frequent monitoring depends on the following four quantities estimated from data collected after six months of treatment:

1. P1 = Probability that a patient will develop severe leukopenia given that the patient was detected ("caught") at moderate leukopenia ($2000/mm^3 < WBC \leq 3000/mm^3$).

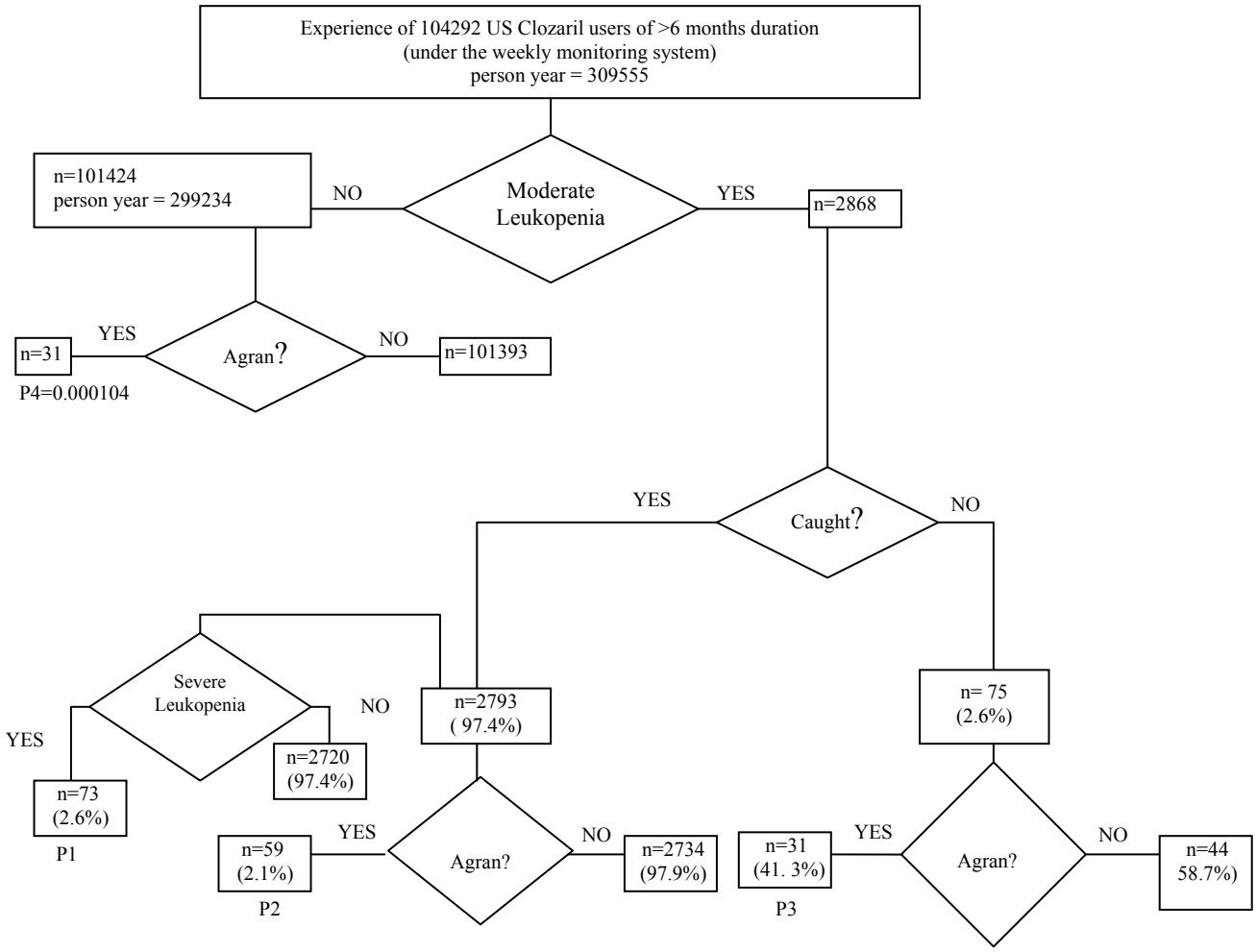
2. P2 = Probability that a patient will develop agranulocytosis given that the patient was detected ("caught") at moderate leukopenia ($2000/mm^3 < WBC \leq 3000/mm^3$).

3. P3 = Probability that a patient will develop agranulocytosis given that the patient was not detected ("missed") at moderate leukopenia (i.e. severe leukopenia, WBC < $2000/mm^3$ by the time of detection).

4. P4 = Incidence rate (per person-year) of agranulocytosis among patients who did not have a WBC ≤ $3000/mm^3$ before developing agranulocytosis. These are the patients who developed agranulocytosis before they met the criteria for moderately leukopenic.

The estimates of these four quantities based on data from Cohort 3 were deemed unreliable since the number of occurrences of agranulocytosis or severe leukopenia in Cohort 3 after six months of treatment was less than 10. These four quantities were estimated using data from Cohorts 1 and 2 during their weekly monitoring of WBC. Estimation of these quantities is demonstrated in Figure 5.

Figure 5: Algorithm for Probabilities



In Cohort 3, the total number of cases of agranulocytosis occurred after six months from start of Clozaril treatment was 10. Three of these cases occurred with less than six months of Clozaril treatment (e.g., a patient was treated for five months with Clozaril and developed agranulocytosis at month 7). These three cases were excluded from the analysis. The total number of severe leukopenia cases observed after six months of treatment under the current monitoring was 9. Finally, the estimation of the rates of agranulocytosis and severe leukopenia utilizing P1-P4 is illustrated in Table 5.

Table 5: Estimation of the number of severe leukopenia and agranulocytosis cases for patients in Cohort 3 after weekly monitoring for six months and monthly thereafter

	Number of Patients with ≥6 months of treatment in Cohort 3	Agranulocytosis rate	Estimated number of agranulocytosis cases	Estimated number of severe leukopenia cases
Moderate under the current monitoring	230			
"Caught" at moderate under monthly monitoring	134	P2=0.021	134*P2=2.83	134*P1=3.5
"Missed" at moderate under monthly monitoring	96	P3=0.413	96*P3=39.68	96
Never moderate under the current monitoring	21974[#]	P4=0.000104	26696*P4=2.78	
Total	22204		45.29	99.5

[#]These patients were treated for 26696 person-years

As seen in Table 5, there were 230 patients within Cohort 3 who developed moderate leukopenia under the current monitoring system. If there were no monitoring of WBC after six months of treatment then all those 230 patients would have continued taking Clozaril even after developing moderate leukopenia. It is expected these patients' WBC counts would continue to decrease at a median rate of 126/mm3 per day (see Post-text Table 3.6-3). Ultimately, all these patients would have developed severe leukopenia. These patients would have considerably higher probability of developing agranulocytosis due to late detection in the absence of monitoring. As mentioned in the 1997 briefing book, 67% of these patients would develop agranulocytosis. Hence under no monitoring option of WBC, the total number of agranulocytosis cases is estimated as 230*.67 + 26696*P4 = 154.1 + 2.8 = 156.9.

3.2 Results from United States

3.2.1 Demographics of patients in the initial monitoring system and the current monitoring system

Within the initial and current monitoring systems, the demographics of all patients, patients with moderate leukopenia, severe leukopenia or agranulocytosis are comparable with respect to sex, age, and race. The percentage of patients with missing information was also similar between these groups. The demographic data for all patients and patients with agranulocytosis are shown in Tables 6 and 7 below. Demographics for patients with moderate or severe leukopenia are presented in Appendix 1 Post-text Tables 3.1-2 and 3.1-3

Table 6: Demographics of all patients in Initial system and Current system

Demographic	Category	Initial system N (%)	Current system N (%)
Sex	Male	79256 (57.1)	22287 (56.8)
	Female	56430 (40.6)	16149 (41.1)
	Missing	3158 (2.3)	824 (2.1)
	Total	138844 (100)	39260 (100)
Age (years)	<= 35	50124 (36.1)	12794 (32.6)
	36 - 50	53225 (38.3)	14808 (37.7)
	51 - 65	17474 (12.6)	6073 (15.5)
	> 65	14863 (10.7)	4761 (12.1)
	Missing	3158 (2.3)	824 (2.1)
	Total	138844 (100)	39260 (100)
	Mean	42.1	43.0
Race	White	95958 (69.1)	24528 (62.5)
	Black	17367 (12.5)	6058 (15.4)
	Hispanic	5819 (4.2)	2014 (5.1)
	Oriental	1725 (1.2)	460 (1.2)
	Other	1578 (1.1)	724 (1.8)
	Missing	16397 (11.8)	5476 (13.9)
	Total	138844 (100)	39260 (100)

Source: Appendix 1, Post-text Table 3.1-1

Table 7: Demographics of patients in Initial system and Current system who developed agranulocytosis

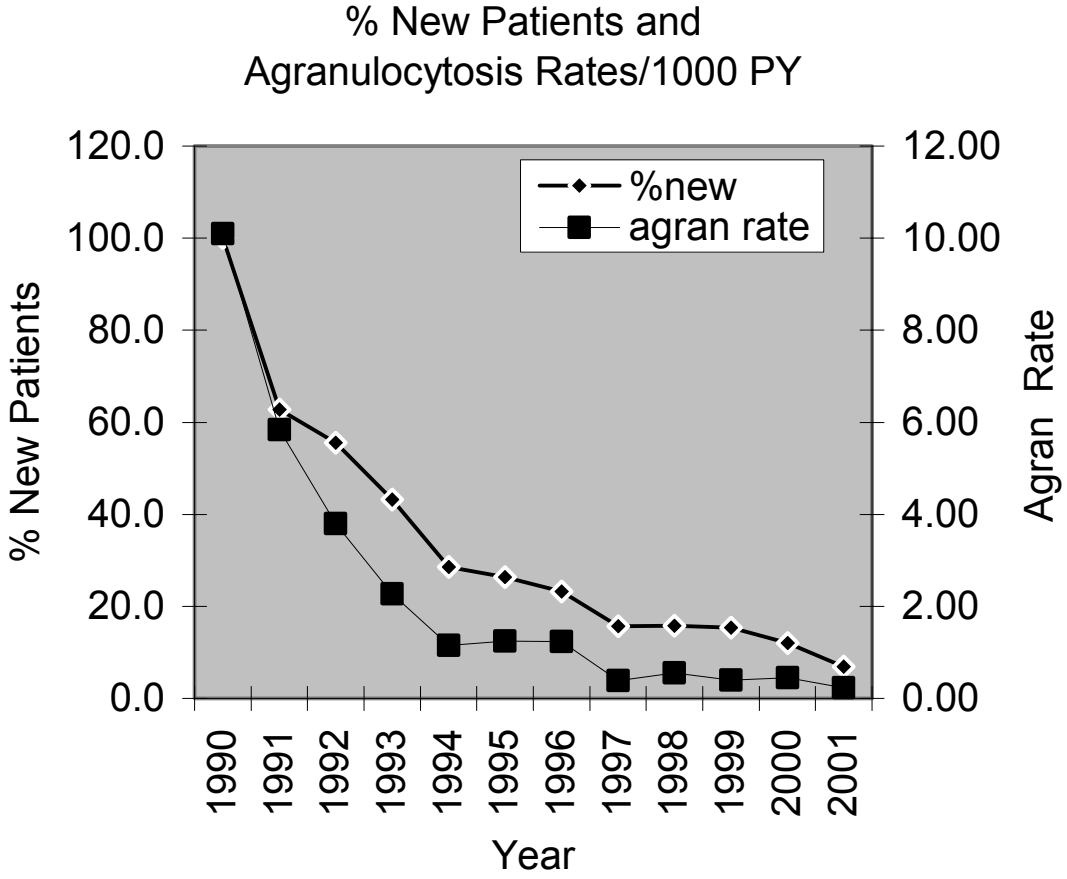
Demographic	Category	Initial system N (%)	Current system N (%)
Sex	Male	283 (54.7%)	31 (55.4%)
	Female	234 (45.3%)	25 (44.6%)
	Total		
Age	<= 35	109 (21.1%)	13 (23.2%)
	36 - 50	200 (38.7%)	18 (32.1%)
	51 - 65	159 (30.8%)	17 (30.4%)
	> 65	49 (9.5%)	8 (14.3%)
	Total	517 (100.0%)	56 (100.0%)
	Mean	46.8	47.7
	SD	13.4	15.4
Race	White	349 (67.5%)	37 (66.1%)
	Black	15 (2.9%)	3 (5.4%)
	Hispanic	24 (4.6%)	4 (7.1%)
	Oriental	3 (0.6%)	0 (0.0%)
	Other	7 (1.4%)	0 (0.0%)
	Missing	119 (23.0%)	12 (21.4%)

Source: Appendix 1, Post-text Table 3.1-4

3.2.2 Incidence of leukopenia and agranulocytosis

Figure 6 below shows that the overall rate of agranulocytosis decreased consistently by calendar year. This decrease may be explained to some extent by the similarly consistent decrease in the proportion of new patients entering the registry overtime.

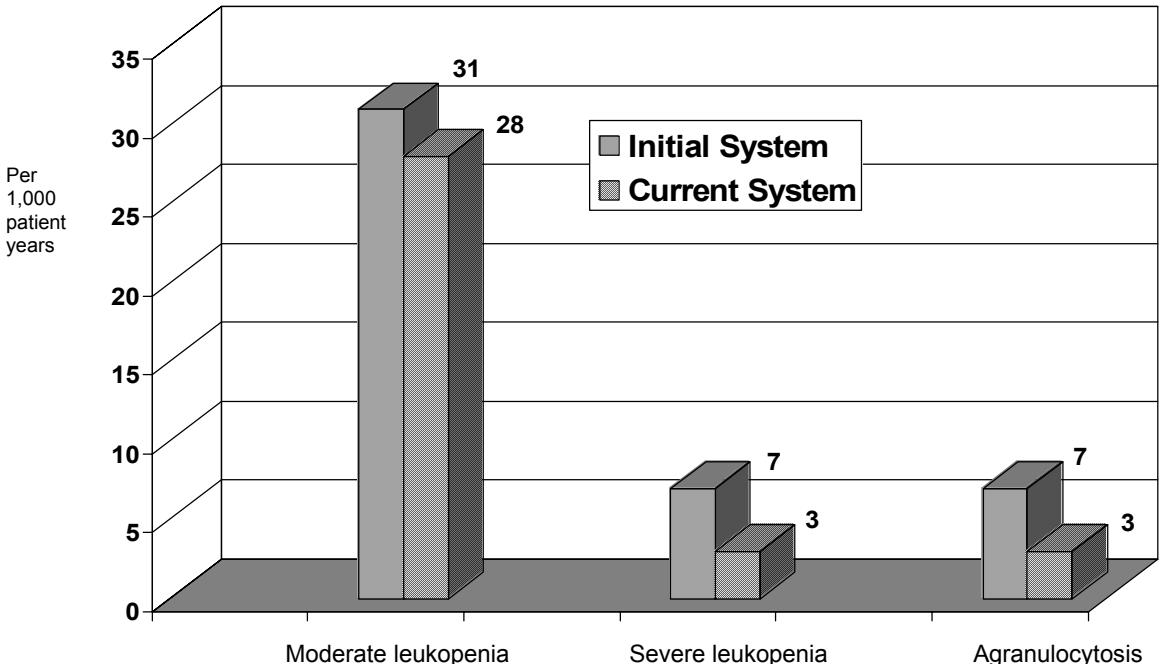
Figure 6: Trend of Agranulocytosis Rate



Source: Clozaril National Registry
Note: All data from all patient included

During the first six months the monitoring frequency was weekly for both the initial and current monitoring systems. The rates of moderate leukopenia was similar for both systems; however, severe leukopenia and agranulocytosis were less under the current monitoring system compared to the initial monitoring system (Figure 7).

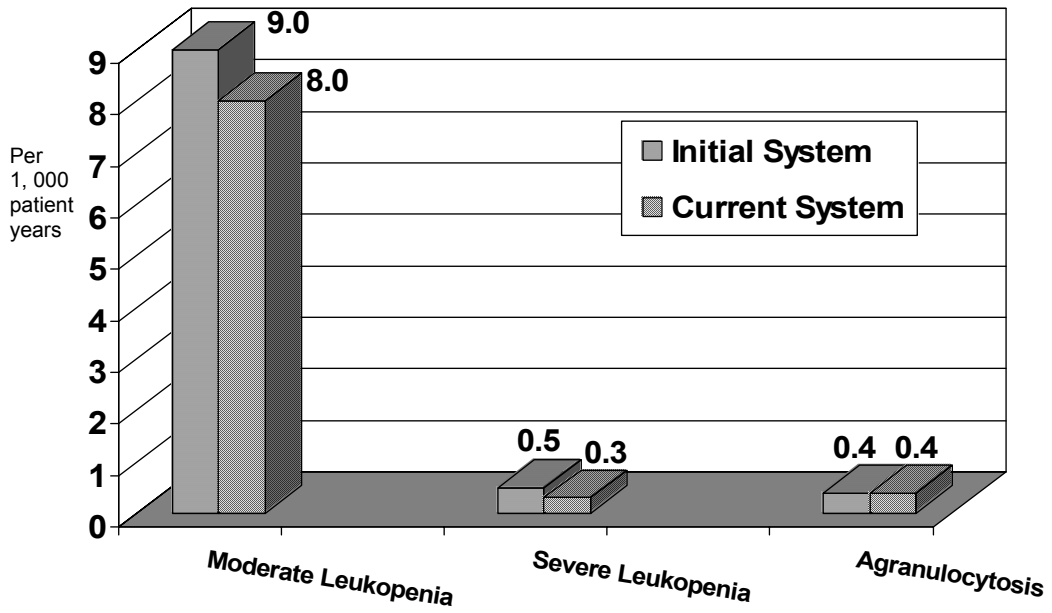
Figure 7: Incidence of moderate leukopenia, severe leukopenia and agranulocytosis during the first 6 months of treatment by monitoring system cohort



Data source: Appendix 1, Post text tables 3.4-1b, 3.3-1b, 3.2-1b

After the first 6 months of treatment, the frequency of monitoring remained weekly under the initial system and changed to bi-weekly under the current system. The rates of moderate leukopenia severe leukopenia and agranulocytosis were less compared to the first six months but similar between the systems (Figure 8).

Figure 8: Incidence of moderate leukopenia, severe leukopenia and agranulocytosis after the first 6 months of treatment by monitoring system cohort

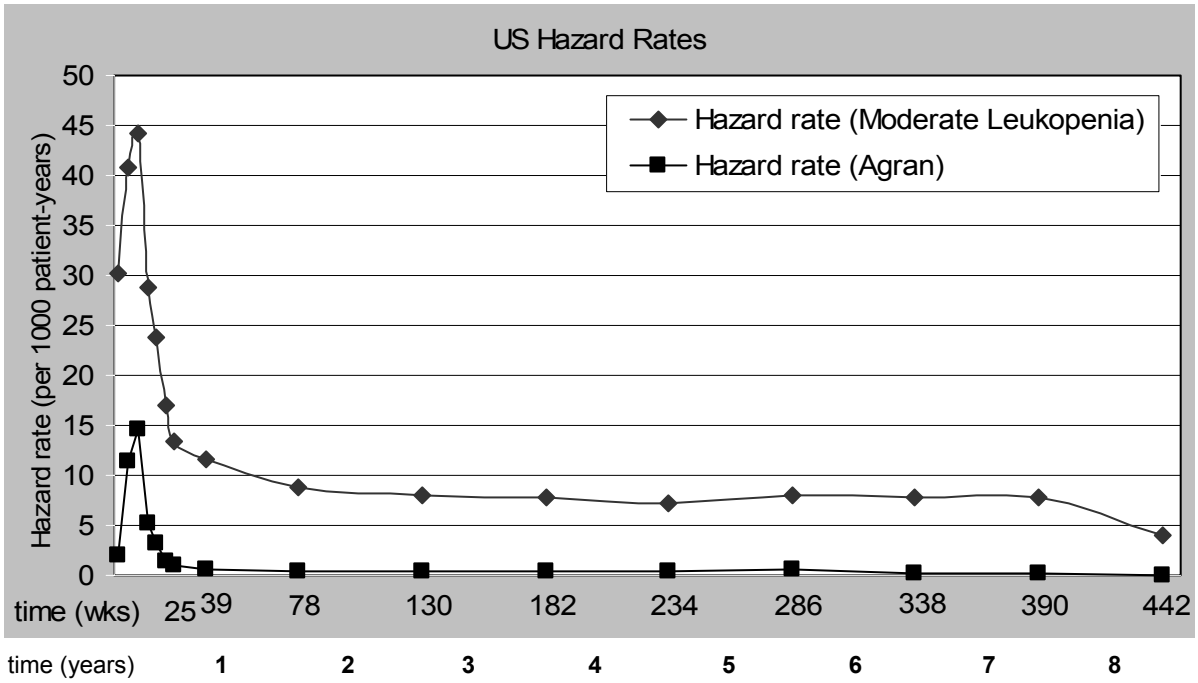


Data source: Appendix 1, Post text tables 3.4-1b, 3.3-1b, 3.2-1b

3.2.3 Risk of moderate leukopenia and agranulocytosis over time

The hazard rate for developing moderate leukopenia or agranulocytosis is greatest during the first 6 months of Clozaril treatment (up to approximately 45/1000 patient-years and 15/1000 patient-years respectively) after which the risk diminishes significantly. The hazard rate begins to stabilize after about 18 months of treatment at approximately 9 per thousand patient-years for moderate leukopenia and approximately 0.3 per thousand patient-years for agranulocytosis (Figure 9).

Figure 9: Hazard rate for moderate leukopenia and agranulocytosis over 8.5 years



Source: Appendix 1, Post-text Tables 3.4-4,3.2-4

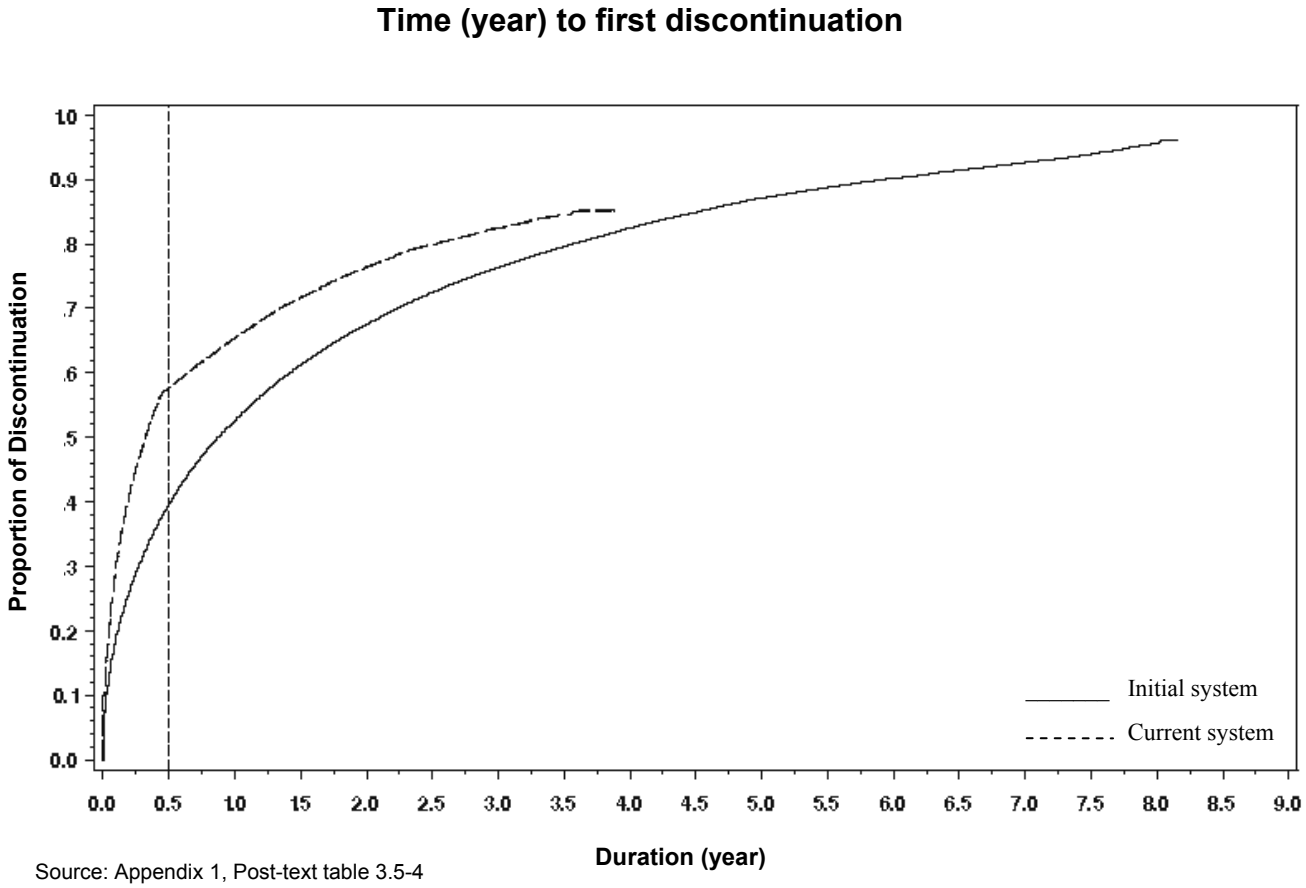
3.2.4 White Blood Cell Count at Time of Discontinuation

There were 110,659 patients defined as patients who discontinued therapy (see Section 3.1.4 for definition). Of these patients, there were 67,883 who discontinued during the first 6 months of therapy and 42,776 who discontinued after 6 months of therapy.

The median white blood cell count at the time of discontinuation for patients in the initial system and current system were 7800 and 7400 cells/mm^3, respectively for patients on therapy for less than or equal to 6 months and 7900 and 7600 cells/mm^3, respectively for patients on therapy for more than 6 months (Appendix 1, Post-text Table 3.5-1). Additionally, there is no clinically meaningful difference between the groups with regard to the distribution (i.e., 5^{th}, 25^{th}, 75^{th}, 95^{th} percentiles) of WBC values at the time of discontinuation. These WBC counts may be high because patients may have been discontinued for any reason (e.g., lost to follow-up) and not for reasons related to abnormal lab values.

Figure 10 shows that 58% of the patients within the current system discontinued therapy within 6 months after initiating therapy. In comparison, 40% of the patients within the initial system discontinued therapy within 6 months after initiating therapy.

Figure 10: Time to first discontinuation



Source: Appendix 1, Post-text table 3.5-4

The WBC values for patients who were discontinued with a WBC value between 3000 and 6000 cells/mm^3 were also evaluated. The value of 3000 cells/mm^3 was chosen because this is the level of WBC counts where patients discontinue from Clozaril treatment and are considered to have developed moderate leukopenia. The upper limit of 6000 cells/mm^3 was chosen because patients who were discontinued with a value above this level would be less likely to have been discontinued for a reason related to an abnormal WBC value and more likely for other reasons (e.g., availability of alternative treatment).

As seen in Table 8 below, the median and mean WBC at the time of discontinuation for patients with a WBC value between 3000 and 6000 in the initial system and the current system were similar for patients on therapy for less than or equal to 6 months and greater than 6 months.

Table 8: White Blood Cell Count (WBC) at time of discontinuation by duration for patients with WBC value between 3000 and 6000 at time of discontinuation by system cohort

WBC (cells/mm3)	≤6 months		>6 months		Total duration of therapy	
	Initial	Current	Initial	Current	Initial	Current
N	9837	4396	7084	712	16921	5108
Median WBC	5300	5300	5400	5300	5300	5300
Mean WBC	5183	5165	5236	5185	5205	5168

Source: Appendix 1, Post-text Table 3.5-2

The proportion of patients who discontinued with values between 3000 and 6000 cells/mm^3 and within each stratum was similar between the groups (Table 9). Over 60% of the patients in both groups discontinued with a WBC value >5000-6000 cells/mm^3 regardless of duration of therapy.

Table 9: Stratified White Blood Cell Count (WBC) at time of discontinuation by duration for patients with WBC value at time of discontinuation by system cohort

WBC (cells/mm3)	Median WBC N (%)					
	≤6 months		>6 months		Total duration of therapy	
	Initial	Current	Initial	Current	Initial	Current
≥3000-4000	3800 649 (7%)	3800 284(6%)	3800 376 (5%)	3800 50 (7%)	3800 1025 (6%)	3800 334 (7%)
>4000-5000	4700 2955 (30%)	4700 1387(32%)	4700 1935 (27%)	4700 216 (30%)	4700 4890 (29%)	4700 1603(31%)
>5000-6000	5600 6233 (63%)	5600 2725 (62%)	5600 4773 (68%)	5600 446 (63%)	5600 11006 (65%)	5600 3171 (62%)

Source: Appendix 1, Post-text Table 3.5-3a, 3.5-3b, 3.5-3c

3.2.5 Fatal Outcomes Related to Agranulocytosis

Overall, there were 22 (4%) fatalities among the 620 patients who developed agranulocytosis. Of these 22 fatalities, 20 (91%) occurred within the first six months of treatment. Two (9%) of the 22

fatalities occurred in patients in the current system cohort and 1 of the 2 occurred during the first 6 months of treatment (see Appendix 5 for narratives regarding these fatal outcomes).

3.2.6 Analysis of Prodrome Period

The rate of decline in WBC from normal to moderate leukopenia was analyzed in patients who subsequently did or did not develop agranulocytosis.

In Appendix 1, Post-text Tables 3.6-1 to 3.6-3 provide summary statistics on the duration of prodrome and the rate of decrease (i.e., slope) of WBC counts during prodrome. The median duration of prodrome for all patients who developed moderate leukopenia in the initial system and the current system appears to be independent of the duration of Clozaril therapy. The median duration of prodrome ranged from 21-25 days and 26-29 days for patients in the initial system cohort and current system cohort, respectively (Appendix 1, Post-text Table 3.6-1) who were treated with Clozaril from >6 months to >2 years of therapy.

Table 10 provides the median slope for patients with moderate leukopenia who did or did not develop agranulocytosis. Patients who developed agranulocytosis during the first 6 months declined faster across both groups than those who did not develop agranulocytosis. Also, patients who did develop agranulocytosis during the first 6 months of therapy in the initial system had a much steeper slope in WBC counts than those in the current system.

Table 10: Median Slope for Patients Who Developed Moderate Leukopenia and Did or Did Not Develop Agranulocytosis

Duration of Therapy	Initial system Median Slope {WBC cells/mm^3 (n)}		Current system Median Slope {WBC cells/mm^3 (n)}	
	Did not Develop Agranulocytosis*	Developed Agranulocytosis **	Did not Develop Agranulocytosis *	Developed Agranulocytosis **
≤6 mos.	150 (1444)	241 (334)	144 (366)	161 (28)
6 mos. – 1 year	135 (563)	244 (19)	126 (87)	71 (1)
1-2 years	161 (743)	150 (32)	121 (77)	None
>2 years	142 (2175)	156 (48)	167 (49)	-

Slope = decrease in WBC/day; *Source: Appendix 1, Post-text Table 3.6-3; **Source: Appendix 1, Post-text Table 3.6-2

3.2.7 Projected Rates

The actual and projected number of cases of severe leukopenia and agranulocytosis under various monitoring frequencies are provided in Table 11 below.

Table 11: Actual and projected number of cases of severe leukopenia and agranulocytosis after weekly monitoring during the first six months of therapy followed by bi-weekly monitoring (Current system cohort)

	Change to bi-weekly monitoring after weekly monitoring for:	Actual Cases Observed under current system	Projected Additional Cases with Monthly Monitoring	Projected Additional Cases with No monitoring
Severe Leukopenia	Six months	9	91	221
	One year	5*	56	123
	Two years	4*	16	46
Agranulocytosis	Six months	7	38	150
	One year	2*	26	86
	Two years	0*	9	34

*Bi-weekly monitoring still occurs (i.e., no change from current monitoring system)
Source: Appendix 1, Post-text Tables 3.6-4 and 3.6-6
Note: The number of severe leukopenia and agranulocytosis cases provided in Table 11 are based, in part, on the calculations shown in Table 5.

As seen in Table 11, if the current monitoring was changed to "monthly monitoring" **after six months** then we would have observed 91 additional cases of severe leukopenia and 38 additional cases of agranulocytosis after **six months of treatment** and 221 and 150 additional, respectively if "no monitoring" was in place. After six months of therapy, bi-weekly monitoring is currently required and the actual observed rate of agranulocytosis is 0.26/1000 person-years. Based on the projections in Table 5, the rate of agranulocytosis would increase to 1.68/1000 person-year if the monitoring frequency after six months of therapy was decreased to monthly intervals and increased to 5.81/1000 person-year if monitoring was discontinued after six months of therapy (Apendix 1, Post-Text Table 3.6-5).

If the current monitoring was changed to "monthly monitoring" **after one year** then we would have observed 56 additional cases of severe leukopenia and 26 additional cases of agranulocytosis after **one year of treatment** and 123 and 86 additional, respectively if "no monitoring" was in place. After six months of therapy, bi-weekly monitoring is currently required and the actual observed rate of agranulocytosis is 0.26/1000 person-years. Based on the projections in Table 5, the rate of agranulocytosis would increase to 1.21/1000 person-year if the monitoring frequency after six months of therapy was decreased to monthly intervals and increased to 3.43/1000 person-year if monitoring was discontinued after one year of therapy (Appendix 1, Post-Text Table 3.6-5).

If the current monitoring was changed to "monthly monitoring" **after two years** then we would have observed 16 additional cases of severe leukopenia and 9 additional cases of agranulocytosis after **two years of treatment** and 46 and 34 additional cases, respectively if "no monitoring" was in place. After six months of therapy, bi-weekly monitoring is currently required and the actual observed rate of agranulocytosis is 0.26/1000 person-years. Based on the projections in

Table 11, the rate of agranulocytosis would increase to 0.6/1000 person-year if the monitoring frequency after six months of therapy was decreased to monthly intervals and increased to 1.52/1000 person-year if monitoring was discontinued after two years of therapy (Appendix 1, Post-Text Table 3.6-5).

3.3 Discussion and Conclusion (United States)

Results of the analyses of US data showed that:

- the rate of agranulocytosis decreased consistently overtime (Figure 9). This decrease may be explained to some extent by the similarly consistent decrease in the percentage of new patients entering the registry by calendar year.
- the demographic characteristics of patients in the initial and current monitoring systems were comparable.
- the rate of moderate leukopenia during and after the first six months of treatment was similar in both monitoring systems
- during the first six months of treatment, the rates of severe leukopenia and agranulocytosis were less in the current monitoring system than in the initial system
- after the first six months of treatment, the rates of severe leukopenia and agranulocytosis were similar in both monitoring systems

The factors responsible for the unexpected decrease in the observed rates of severe leukopenia and agranulocytosis during the first 6 months are unclear. These findings were unexpected because the frequency of monitoring (i.e. weekly) was identical during the first six months for both the initial and current systems. Possible explanations for these unexpected findings are as follows:

- Patients who received generic clozapine were not considered in these analyses when exposure to more than six months of clozapine treatment was known (Section 3.1.1.2; Exclusion Criteria 3). This resulted in an exclusion of data during the period of highest risk for agranulocytosis i.e. the first six months.
- Patients switching to alternative atypical antipsychotics treatments prior to developing severe leukopenia or agranulocytosis.
- The greater proportion of patients who discontinued (Figure 10) during the first six months of therapy under the current monitoring system (58%) compared to the initial monitoring system (40%). This resulted in an exclusion of data during the period of highest risk for agranulocytosis i.e., the first six months.

Overall, the United States data showed that the CNR effectively detects moderate leukopenia, and reduces the occurrence of severe leukopenia, agranulocytosis and death.

The change in monitoring frequency from weekly to every two weeks was not associated with an increase in the rates of moderate leukopenia, severe leukopenia or agranulocytosis.

4 United Kingdom

4.1 Methods for Analysis

4.1.1 Patient Population

Data collected by the Clozaril Patient Monitoring Service (CPMS) from the UK and Ireland between the inception of the registry and April 2002 were used.

4.1.1.1 Inclusion and exclusion criteria.

All patients who received Clozaril in the UK and Ireland were eligible for inclusion in the analysis. As of April 2002, there were 29,298 patients registered and 1,828,832 laboratory records collected in the CPMS.

Consistent with the US analysis, patients who were enrolled in the CPMS, but never started treatment with Clozaril or had only one WBC entry in the database were excluded. It is important to note that generic clozapine is not available in the UK and therefore the exclusion criteria applied in the US (section 3.1.1.2)were not applicable.

Ultimately, 27,894 CPMS registry participants and 1,814,848 laboratory records were included in the analysis.

4.1.2 Cohorts

Patients were divided into the following three cohorts:

- **Initial system:** Included patients enrolled before implementation of the change to monthly monitoring in 1995 (see figure 2). Data beyond the implementation date were excluded.
- **Current system, new patients:** Included patients enrolled one year prior to the implementation of monthly monitoring; therefore being eligible for monthly monitoring at the time of implementation.
- **Current system, old patients:** Included patients from the initial system cohort plus the data that were excluded for these patients as described in bullet 1 above.

For purposes of assessing the impact of the change in the monitoring system that occurred in 1995, data from patients in the "initial system cohort" and "current system, new patients cohort" were compared. The data from the "current system, old patient cohort" helps to distinguish the contribution of change in monitoring schedule protocol and other time related factors to the differences in the incidence rates.

4.1.3 Statistics

Stratified analysis by variables suspected to have an influence in the incidence rate values was conducted i.e. calendar year, treatment duration, and cohort as defined above.

In order to compute confidence intervals for the incidence rates based on person-years, the numerator of the rate was assumed to be a Poisson variable. Since the rates observed are low, this is a reasonable assumption. Exact Poisson limits for counts ≤ 20 and the normal approximation for counts > 20 were used. Tables and Figures present 95% Confidence Intervals. Ninety-five percent confidence intervals for incidence rates were computed using poison approximation (Anders Ahlbom, 1993).

4.2 Results from United Kingdom

4.2.1 Demographics

Within the initial and current monitoring systems, the demographics of all patients, patients with moderate leukopenia, severe leukopenia or agranulocytosis are comparable with respect to sex, age, and race with the exception of patients over 65 years of age who developed severe leukopenia.. The percentage of missing information was also similar between these groups. The demographic data for all patients and patients with agranulocytosis are shown in Tables 12 and 13 below. Demographics for other subgroups are presented in Appendix 2, Post-text Table 4.22.

Table 12: Demographics of all patients in Initial system and Current system

Demographic	Category	Initial system N (%)	Current System N (%)
Gender	Male	4201 (65.0)	14583 (67.9)
	Female	2174 (34.1)	6890 (32.1)
Age at initiation of treatment	≤ 35	3220 (50.5)	11236 (52.3)
	36-50	2208 (34.6)	7053 (32.8)
	51-65	767(12.0)	2627 (12.2)
	>65	180 (2.8)	557 (2.5)
Race	Caucasian	5755 (90.3)	18652 (86.7)
	Afro-Carib	278 (4.3)	1389 (6.5)
	Mixed	112 (1.7)	345 (1.6)
	Oriental	24 (0.4)	90 (0 .4)
	Asian	206 (3.2)	997(4.6)

Source: Appendix 2, Post Text Table 4.22

Table 13: Demographics of all patients with agranulocytosis in Initial system and Current system

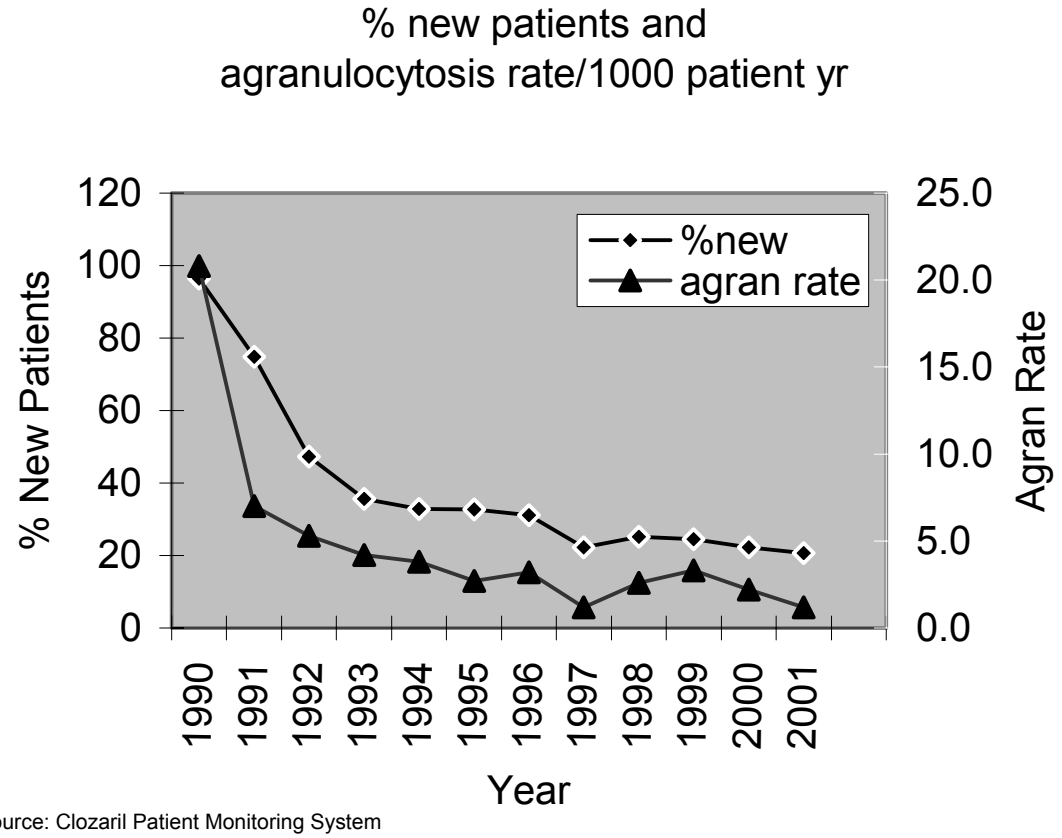
Demographic	Category	Initial system N (%)	Current System N (%)
Gender	Male	28 (58.3)	92 (61.3)
	Female	20 (41.7)	58 (38.7)
Age at initiation of treatment	≤ 35	12 (25.0)	35 (23.3)
	36-50	25 (52.1)	54 (35.0))
	51-65	11 (22.9)	52 (34.7)
	>65	0 (0.00)	9 (6.0)
Race	Caucasian	45 (93.7)	138 (92.0)
	Afro-Carib	1 (2.1)	1 (0.7)
	Mixed	0 (0.0)	2 (1.3)
	Oriental	0 (0.0)	0 (0 .0)
	Asian	2 (4.2)	9 (6.0)

Source: Appendix 2, Post Text Table 4.22

4.2.2 Incidence of leukopenia and agranulocytosis

Figure 11 below shows that the rate of agranulocytosis decreased by calendar year. This decrease may be explained to some extent by the similarly consistent decrease in the percentage of new patients entering the registry by calendar year.

Figure 11: Trend of Agranulocytosis Rate



Source: Clozaril Patient Monitoring System
Note: Included all data from all patients

The rates of moderate leukopenia, severe leukopenia and agranulocytosis observed between weeks 0 and 18 decreased significantly between weeks 19 to 52 and again after 52 weeks under both the initial and current systems. Patients in the current system cohort had a higher incidence of agranulocytosis during monthly monitoring after week 52 than did patients in the initial system cohort during bi-weekly monitoring after week 52, however, this difference was not statistically significant (Table 14).

Table 14 Summary of Results

	Weeks 0-18 Weekly	Weeks 19-52 bi-weekly	Weeks >52 bi-weekly / monthly	
Moderate Leukopenia {per 1,000 pt. yrs. (N)}				
Incidence: pre-1995 (initial system)	105.1 (182)	30.5 (79)	11.8 (77)	
Incidence: patients enrolled post-1995 (current system)	82.5 (482)	20.7 (177)		7.4 (228)
Severe Leukopenia {per 1,000 pt. yrs. (N)}				
Incidence: pre-1995 (initial system)	33.5 (58)	4.3 (11)	2.6 (17)	
Incidence: patients enrolled post-1995 (current system)	31.9 (186)	4.0 (34)		1.9 (58)
Agranulocytosis {per 1,000 pt. yrs. (N)}				
Incidence: pre-1995 (initial system)	24.8 (43)	1.2 (3)	**0.3 (2)**	
Incidence: patients enrolled post-1995 (current system)	20.4 (119)	1.5 (13)		**0.6 (18)**

Source: Appendix 2, Post-text tables 4.5, 4.11 and 4.18

4.3 Discussion and Conclusion (United Kingdom)

The change in monitoring frequency from weekly to bi-weekly monitoring is not associated with an increase in the rates of moderate leukopenia, severe leukopenia or agranulocytosis. Although the change from bi-weekly to monthly monitoring was associated with an increase in the incidence of agranulocytosis, it was not statistically significant.

5 Australia

5.1 Methods for Analysis

From December 1992 to the data cut-off date of April 28, 2003, more than 13,000 patients received Clozaril. If a patient temporarily discontinued Clozaril treatment and then later rechallenged with Clozaril again then that patient's initial enrolment date (entry date) in the database is replaced with the new entry date in the system.

In addition, the start and end date of Clozaril treatment for more than 3,000 patients could not be extracted from the Australian database due to database incompatibility issues. Therefore, these patients were not included in the analysis. Thus, it was not possible to calculate the total exposure time of Clozaril based on the CPMS database in Australia. The exposure time presented in this document is an underestimate of the actual value. Consequently, it was not possible to obtain the exact number of patients with moderate leukopenia, severe leukopenia or agranulocytosis. As a result, all event rates presented in this document should be considered over estimates of the actual rate.

Demographic data are not provided because Australian regulations prohibit the release of information on patients' sex, race or age.

Due to the above mentioned limitations of data from Australia very limited analyses were performed on Australian data. Incidences rate per 1000 person years were computed for 0-18 weeks, 19 to 52 weeks, and greater than 52 weeks (Appendix 3, Post-text Tables 5.1-1, 5.1-2, 5.2-1, 5.2-2, 5.3-1, 5.3-2). No other analyses were performed with Australian data.

5.2 Results from Australia

The rates of moderate leukopenia, severe leukopenia and agranulocytosis observed between weeks 0 and 18 decreased significantly between weeks 19 to 52 and again after 52 weeks.

Table 15: Summary of Results

	Weeks 0-18 Weekly	Weeks 19-52 monthly	Weeks >52 monthly
Moderate Leukopenia {per 1,000 pt. yrs. (N)}	52.5 (165)	11.8 (60)	6.1 (165)
Severe Leukopenia {per 1,000 pt. yrs. (N)}	12.7 (40)	1.6 (8)	0.7 (19)
Agranulocytosis {per 1,000 pt. yrs. (N)}	8.3 (26)	2.2 (11)	0.5 (14)

Source: Appendix 3, Post-text Tables 5.1-2, 5.2-2, 5.3-2

5.3 Discussion and Conclusion (Australian)

The rate of agranulocytosis in Australia after 52 weeks of treatment is similar to the rate observed in the United Kingdom after 52 weeks of treatment.

6 Overall Discussion

Clozaril is recognized, during its long history, as one of the most efficacious anti-psychotics offered to the patients. Today it remains the only drug approved for the treatment of treatment resistant schizophrenia patients as well as for the treatment of recurrent suicidal behavior in patients with schizophrenia and schizoaffective disorder. Since its first introduction in Austria in 1969, it has been marketed in more than 80 countries throughout the world.

Despite such benefits, Clozaril has been associated with a serious risk of agranulocytosis. The incidence rate of agranulocytosis in Europe prior to monitoring was observed to be 1-2% per year. During clinical trials completed prior to approval in the US the rate was 1.3% at 1 year of treatment. Hematological monitoring systems were put in place throughout the world by Novartis to ensure its safe use. The general guidelines of monitoring systems have been:

1) Weekly, biweekly or monthly- monitoring of white blood cell count for early detection of moderate or severe leukopenia or agranulocytosis,
2) Immediate discontinuation of clozapine if severe leukopenia or agranulocytosis is observed,
3) Maintenance of non-rechallengable patient database to ensure exclusion of patients who developed leukopenia or agranulocytosis from re-exposure to clozapine,
4) Adherence to "no blood no drug" policy. These guidelines were developed in cooperation with local health authorities.

Over the years, health authorities have re-evaluated the level of risk based on data from Clozaril national registries and made adjustments to the monitoring frequencies. In the US, such a review took place in 1997 the outcome of which was a change in monitoring frequency from weekly intervals for the entire duration of treatment to weekly monitoring for the first 6 months of treatment followed by monitoring every two weeks thereafter. This new monitoring schedule was initiated in April 1998. The outcome of a similar review of registry data in the UK in 1995 was a change from bi-weekly to monthly monitoring after 52 weeks of Clozaril treatment.

This briefing document is provided to facilitate the PDAC's and FDA's re-evaluation of the current clozapine monitoring guidelines in the US. It contains a summary of the results of analyses submitted to FDA on September, 2002, October, 2002, and February 2003 as well as analyses of data from the UK and Australian registries.

Results of the analyses of US data showed that:

- the rate of agranulocytosis decreased consistently overtime (Figure 9). This decrease may be explained to some extent by the similarly consistent decrease in the percentage of new patients entering the registry by calendar year.
- the demographic characteristics of patients in the initial and current monitoring systems were comparable.

- the rate of moderate leukopenia during and after the first six months of treatment was similar in both monitoring systems
- during the first six months of treatment, the rates of severe leukopenia and agranulocytosis were less in the current monitoring system than in the initial system
- after the first six months of treatment, the rates of severe leukopenia and agranulocytosis were similar in both monitoring systems.

The factors responsible for the unexpected decrease in the observed rates of severe leukopenia and agranulocytosis during the first 6 months are unclear. These findings were unexpected because the frequency of monitoring (i.e. weekly) was identical during the first six months for both the initial and current systems. Possible explanations for these unexpected findings are as follows:

- Patients who received generic clozapine were not considered in these analyses when exposure to more than six months of clozapine treatment was known (Section 3.1.1.2; Exclusion Criteria 3). This resulted in an exclusion of data during the period of highest risk for agranulocytosis i.e. the first six months.
- Patients switching to alternative atypical antipsychotics treatments prior to developing severe leukopenia or agranulocytosis.
- The greater proportion of patients who discontinued (Figure 10) during the first six months of therapy under the current monitoring system (58%) compared to the initial monitoring system (40%). This resulted in an exclusion of data during the period of highest risk for agranulocytosis i.e. the first six months.

The change in the frequency of monitoring in the US was not associated with an increase in fatal outcomes related to agranulocytosis because only one of the fatalities occurred after the first six months of treatment.

Results of the analyses of UK data showed that:

- The rate of agranulocytosis decreased consistently by calendar year (Figure 11). This decrease may be explained to some extent by the similarly consistent decrease in the percentage of new patients entering the registry by calendar year.
- The change from bi-weekly monitoring to at least monthly monitoring after 52 weeks of treatment may have contributed to the observed increase in the rate of agranulocytosis. However, this increased rate does not only reflect the contribution of patients being monitored on a monthly monitoring schedule because some patients continued to be monitored on a weekly or bi-weekly basis. In fact, the incidence rate of agranulocytosis in the group of patients who continued to be monitored on a weekly (4.6/1,000 patient-years) or bi-weekly (0.9/1,000 patient-years) basis after 52 weeks was greater than that of those who were actually monitored on a monthly (0.35/1,000 patient-years) basis (Appendix 2; Post-text table 4.6).

Results of the analyses of Australian data showed that:

- the rates of moderate leukopenia, severe leukopenia and agranulocytosis observed between weeks 0 and 18 decreased significantly between weeks 19 to 52 and again after 52 weeks.

Results of the analyses of data from over 200,000 patients from the US, UK and Australian registries representing over 1 million patient years show that the incidence rates for moderate leukopenia, severe leukopenia and agranulocytosis due to exposure to Clozaril have consistently declined in all 3 countries during the duration of treatment (Table 18) and by calendar year (Figures 6 and 11).

The rates of these dyscrasias appear to be higher in the UK and Australia than in the US, which maybe due to differences in: registry procedures, definitions of events, practice of medicine, availability of generics or other atypical antipsychotics in the market.

Table 16: Incidence of agranulocytosis in US, UK and Australia

	Weeks 0-18 1000 pt/yr (n)	Weeks 19-52 1000 pt/yr (n)	Weeks >52 1000 pt/yr (n)
United States			
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
United Kingdom			
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
Australia			
Agranulocytosis (monitoring frequency)	8.3 (26) weekly	2.2 (11) monthly	0.5 (14) monthly

Source: Appendix 1, Post-text Table 3.2-1c.; Appendix 2, Post-text Table 4.4; Appendix 3, Post-text Table 5.2-2

7 Overall Conclusion

The results of the analyses show that the current monitoring systems in the US, UK and Australia are associated with a very low rate of agranulocytosis and death due to agranulocytosis. Based on these data it may be reasonable to consider a less frequent monitoring schedule in the United States; however, these data do not rule out the possibility that less frequent monitoring may result in an increase in the rate of agranulocytosis. Therefore, it is just as reasonable to consider maintaining the current monitoring system.