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## Clozaril<sup>®</sup> (clozapine) Tablets

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

Appendix 4: Method for Estimating the Rates of Agranulocytosis and Severe Leukopenia if the Current Bi-weekly Monitoring Option of WBC Counts After Six Months of Treatment with Clozaril is Changed to a Less Frequent Monitoring Option

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## Introduction

On October 15, 2002 Novartis and the Food and Drug Administration (FDA) met to discuss the planned Advisory Committee meeting regarding the frequency of monitoring for Clozaril-treated patients. During this meeting, the FDA requested that we develop a model that would estimate the incidence of agranulocytosis if monitoring were reduced in frequency or discontinued. The recommendation was to develop a model that was similar to the one that was outlined in the Briefing Book for the Psychopharmacological Drugs Advisory Committee held on July 14, 1997, which was submitted on April 28, 1997 (NDA No. 19-758).

This analysis plan is being provided as a supplement to our monitoring frequency analysis plan that was submitted on November 5, 2001 (NDA No. 19-758).

## Principle

The method that will be used to estimate the rates of agranulocytosis and severe leukopenia if the current bi-weekly monitoring of white blood cell counts (WBC) that occurs after 6 months of treatment with Clozaril is changed to monthly or no-monitoring is based on the methods outlined in the above-mentioned briefing book. The rates will be estimated for patients in Cohort 3 only who are defined in our monitoring frequency analysis plan (Attachment 1) referenced above.

## Data

All relevant data from Cohorts 1 and 2 who are defined in our monitoring frequency analysis plan (Attachment 1) referenced above will be used to compute relevant rates and ratios mentioned in Figure C (Attachment 2). All relevant data from Cohort 3, subject to exclusion criteria 1, 2, and 3 and data cut-off date of September 1, 2001 will be used for projection of rates for patients in this cohort.

## Method

**Step 1:** Combined data from Cohorts 1 and 2 contains information on Clozaril-treated patients who experienced weekly WBC monitoring. These data will be used to update Figure C. Figure C provides estimates of various probabilities that will be used in the following steps for estimation of rates under less frequent monitoring options.

**Step 2:** The number of patients in Cohort 3 that would be “caught” or “missed” under less frequent monitoring will be estimated using the method described on pages 169-170 of the above-mentioned briefing book (Attachment 3).

**Step 3:** The projected number of cases of agranulocytosis and severe leukopenia will be estimated following the method used in Table D, page 33 of the above-mentioned briefing book (Attachment 4). The estimated probabilities obtained in Step 1 and the estimated number of cases “caught” and “missed” in Step 2 will be used in computation of rates.

**Step 4:** Finally, Tables similar to Tables E, F, G, and H, pages 34-37 of the above-mentioned briefing book (Attachment 5) will be produced for monthly or no-monitoring of WBC after six months, one year, and two years of Clozaril treatment.

**Attachment 1**

**Definitions of Cohorts 1-3**



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**Attachment 2**

**Figure C**



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**Attachment 3**

**Pages 169-170**



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**Attachment 4**

**Table D**



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**Attachment 5**

**Tables E and F**



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**Tables G and H**



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