NOVARTIS

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey

December 2005

# IMPORTANT

## DRUG WARNING
## AND NEW INFORMATION

Dear Health Care Provider:

Novartis would like to inform you of recent changes to the following sections of the prescribing information (PI) for Clozaril® (clozapine) tablets: BOXED WARNING, WARNINGS, CONTRAINDICATIONS, PRECAUTIONS (Information for Patients and Pharmacokinetic-Related Interactions subsections), and ADVERSE REACTIONS (Post-marketing Clinical Experience subsection)

**MONITORING FREQUENCY**

After reviewing recommendations provided by the Psychopharmacological Drugs Advisory Committee (PDAC) of June 2003 regarding the white blood cell (WBC) monitoring schedule required for all clozapine users, the Food and Drug Administration (FDA) concluded that the current monitoring schedule should be modified. The changes to the monitoring frequency schedule required revisions to the BOXED WARNING (Attachment 1), WARNINGS, and PRECAUTIONS (Information for Patients) sections of the PI. The major changes regarding the frequency and parameters of the monitoring schedule are summarized below:

- Requirement that the absolute neutrophil count (ANC) be determined and reported along with each WBC count.
- New parameters for initiation of Clozaril treatment: WBC $\geq 3500/mm^3$ and ANC $\geq 2000/mm^3$.
- Initiation of monthly monitoring schedule after one year (six months weekly, six months every two weeks) of WBC counts and ANCs in the normal range (WBC $\geq 3500/mm^3$ and ANC $\geq 2000/mm^3$).
- Addition of cautionary language to prescribers describing the increased risk of agranulocytosis in patients who are rechallenged with clozapine following recovery from an initial episode of moderate leukopenia($3000/mm^3 >$ WBC $\geq 2000/mm^3$ and/or $1500/mm^3 >$ANC $\geq 1000/mm^3$). After recovering from such an episode, these patients are now required to undergo weekly monitoring for 12 months if they are re-challenged.

These changes and others are reflected in Table 2 (Attachment 2), which was added to the revised PI. Lastly, modifications to the frequency of monitoring following interruptions in therapy were also revised as reflected in Figure 1 (Attachment 3), which also is included in the revised PI.

Patients receiving Clozaril who are being monitored on the previous schedule of weekly for the first 6 months are to continue this monitoring schedule and report ANCs from this point forward. If WBC $\geq$ 3500/mm$^3$ and ANC $\geq$ 2000/mm$^3$, patients may transition to every 2 weeks monitoring for the next 6 months.

Patients who are currently being monitored on the previous schedule of every other week, are to continue this monitoring schedule for a total of six months and should report ANCs from this point forward. If WBC $\geq$ 3500/mm$^3$ and ANC $\geq$ 2000/mm$^3$, patients may transition to every monthly monitoring.

Health Care Providers are to submit all WBC and ANC values following the discontinuation of Clozaril therapy to the Clozaril National Registry (CNR) for all non-rechallengeable patients (WBC < 2000/mm$^3$ and/or ANC < 1000/mm$^3$), until WBC $\geq$ 3500/mm$^3$ and ANC $\geq$ 2000/mm$^3$.

**DEMENTIA-RELATED PSYCHOSIS**

Recently, the FDA reviewed data related to the use of atypical antipsychotics for the treatment of behavioral symptoms in elderly patients with dementia. They have concluded that the labeling for all atypical antipsychotics should be updated to include information about an increased risk of mortality in elderly patients with dementia-related psychosis. This labeling change is based on a meta analysis of seventeen placebo controlled trials of four atypical antipsychotic drugs (aripiprazole, olanzapine, risperidone, or quetiapine). Because the increase in mortality was consistent across all three relevant chemical classes, the FDA concluded that the effect is likely related to the common pharmacologic effects of all atypical antipsychotics, including those that were not included in the meta-analysis (e.g., Clozaril). The BOXED WARNING section (Attachment 1) of the Clozaril PI was revised to reflect a respective warning. Please be reminded that Clozaril is not approved for use in dementia-related psychosis.

**PARALYTIC ILEUS**

Paralytic ileus has been a listed adverse event associated with Clozaril use as reflected in both the PRECAUTION and ADVERSE REACTIONS sections of the PI. However, based on a review and evaluation of the global post-marketing safety and clinical trial databases for Clozaril, Novartis has concluded that paralytic ileus should be listed as a contraindication in the PI. Thus, the CONTRAINDICATIONS section of the PI was revised accordingly.

**METABOLIC DISORDERS**

Based on data from the global post-marketing safety database, the ADVERSE REACTIONS (Post-Marketing Clinical Experience) section of the PI was revised to reflect

reports of hypercholesterolemia and/or hypertriglyceridemia associated with Clozaril treatment.

**CITALOPRAM**

Following a review of the data from the medical literature as well as data from our global post-marketing safety database, the FDA and Novartis have determined that the conconmitant use of Clozaril and citalopram results in clinically significant elevations of Clozaril blood concentrations. Consequently, the PRECAUTIONS (Pharmacokinetic-Related Interactions) section of the PI was revised to include citalopram.

All patients being treated with Clozaril and their caregivers should be fully informed of all these revisions to the PI that is enclosed in this letter. The revised PI is also conveniently available at http://www.clozaril.com/index.jsp.

Novartis Pharmaceuticals Corporation is committed to providing you with the most current product information available for the management of patients receiving Clozaril. You can facilitate our review and evaluation of adverse events by reporting them. Healthcare professionals should report all serious adverse events suspected to be associated with use of Clozaril to Novartis Pharmaceuticals Corporation, One Health Plaza, East Hanover, New Jersey 07936 or by phone (888) NOW-NOVARTIS or (888-669-6682) or the internet at http://www.novartis.com/contact/en/index.shtml.

Alternatively, this information may be reported to the FDA's MedWatch Reporting System by phone at 1-800-FDA-1088, by fax 1-800-FDA-0178, by mail using the Form 3500 at MedWatch, HF-2, 5600 Fishers Lane, Rockville, MD 20857 or the internet at http://www.accessdata.FDA.gov/scripts/medwatch.

Sincerely,

Alan L. Bess, M.D.
Vice President
Clinical Safety and Epidemiology

Stephen R. Cunningham, M.D., FRCP, FFPM
Vice President
Clinical Development and Medical Affairs

ATTACHMENT 1: Extract of Boxed Warning regarding Agranulocytosis and Dementia-Related Pyschosis:

## WARNING

**AGRANULOCYTOSIS**

**BECAUSE OF A SIGNIFICANT RISK OF AGRANULOCYTOSIS, A POTENTIALLY LIFE-THREATENING ADVERSE EVENT, CLOZARIL® (CLOZAPINE) SHOULD BE RESERVED FOR USE IN (1) THE TREATMENT OF SEVERELY ILL PATIENTS WITH SCHIZOPHRENIA WHO FAIL TO SHOW AN ACCEPTABLE RESPONSE TO ADEQUATE COURSES OF STANDARD ANTIPSYCHOTIC DRUG TREATMENT, OR (2) FOR REDUCING THE RISK OF RECURRENT SUICIDAL BEHAVIOR IN PATIENTS WITH SCHIZOPHRENIA OR SCHIZOAFFECTIVE DISORDER WHO ARE JUDGED TO BE AT RISK OF RE-EXPERIENCING SUICIDAL BEHAVIOR.**

**PATIENTS BEING TREATED WITH CLOZAPINE MUST HAVE A BASELINE WHITE BLOOD CELL (WBC) COUNT AND ABSOLUTE NEUTROPHIL COUNT (ANC) BEFORE INITIATION OF TREATMENT AS WELL AS REGULAR WBC COUNTS AND ANCs DURING TREATMENT AND FOR AT LEAST 4 WEEKS AFTER DISCONTINUATION OF TREATMENT (SEE WARNINGS).**

**CLOZAPINE IS AVAILABLE ONLY THROUGH A DISTRIBUTION SYSTEM THAT ENSURES MONITORING OF WBC COUNT AND ANC ACCORDING TO THE SCHEDULE DESCRIBED BELOW PRIOR TO DELIVERY OF THE NEXT SUPPLY OF MEDICATION (SEE WARNINGS).**

**INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS**

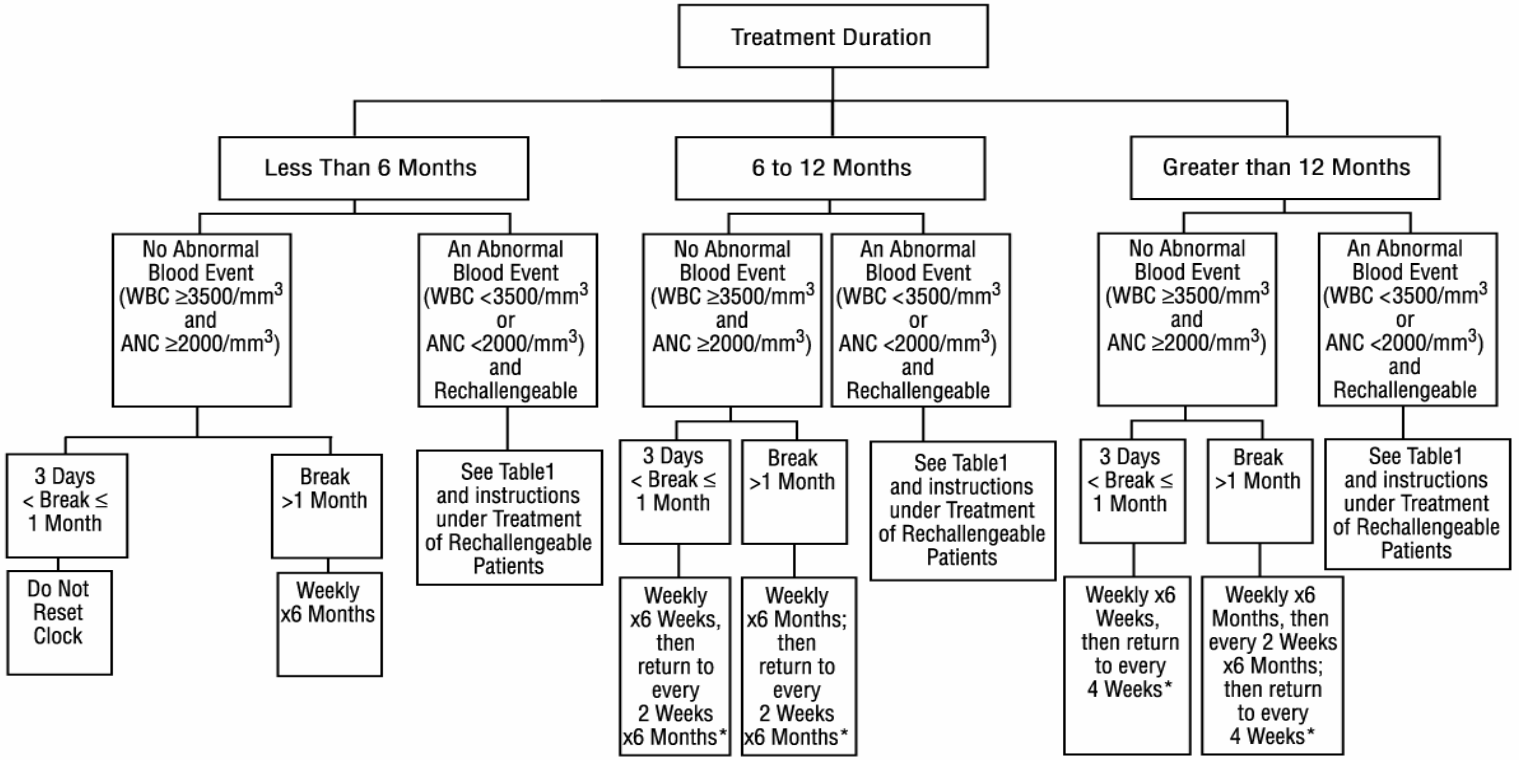
**ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS TREATED WITH ATYPICAL ANTIPSYCHOTIC DRUGS ARE AT AN INCREASED RISK OF DEATH COMPARED TO PLACEBO. ANALYSES OF SEVENTEEN PLACEBO CONTROLLED TRIALS (MODAL DURATION OF 10 WEEKS) IN THESE PATIENTS REVEALED A RISK OF DEATH IN THE DRUG-TREATED PATIENTS OF BETWEEN 1.6 TO 1.7 TIMES THAT SEEN IN PLACEBO-TREATED PATIENTS. OVER THE COURSE OF A TYPICAL 10 WEEK CONTROLLED TRIAL, THE RATE OF DEATH IN DRUG-TREATED PATIENTS WAS ABOUT 4.5%, COMPARED TO A RATE OF ABOUT 2.6% IN THE PLACEBO GROUP. ALTHOUGH THE CAUSES OF DEATH WERE VARIED, MOST OF THE DEATHS APPEARED TO BE EITHER CARDIOVASCULAR (e.g., HEART FAILURE, SUDDEN DEATH) OR INFECTIOUS (e.g., PNEUMONIA) IN NATURE. CLOZARIL (CLOZAPINE) IS NOT APPROVED FOR THE TREATMENT OF PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS.**

**ATTACHMENT 2: Table 1. Frequency of Monitoring based on Stage of Therapy or Results from WBC Count and ANC Monitoring Tests**

| Situation | Hematological Values for Monitoring | Frequency of WBC and ANC Monitoring |
|---|---|---|
| Initiation of therapy | WBC ≥ 3500/mm$^3$<br>ANC ≥ 2000/mm$^3$<br>Note: Do not initiate in patients with 1) history of myeloproliferative disorder or 2) Clozaril® (clozapine) induced agranulocytosis or granulocytopenia | Weekly for 6 months |
| 6 months – 12 months of therapy | All results for<br>WBC ≥ 3500/mm$^3$ and<br>ANC ≥ 2000/mm$^3$ | Every 2 weeks for 6 months |
| 12 months of therapy | All results for<br>WBC ≥ 3500/mm$^3$ and<br>ANC ≥ 2000/mm$^3$ | Every 4 weeks ad infinitum |
| Immature forms present | N/A | Repeat WBC and ANC |
| Discontinuation of Therapy | N/A | Weekly for at least 4 weeks from day of discontinuation or until WBC ≥ 3500/mm$^3$ and ANC > 2000/mm$^3$ |
| Substantial drop in WBC or ANC | Single Drop or cumulative drop within 3 weeks of<br>WBC ≥ 3000/mm$^3$ or<br>ANC ≥ 1500/mm$^3$ | 1. Repeat WBC and ANC<br>2. If repeat values are 3000/mm$^3$ ≤ WBC ≤ 3500/mm$^3$ and ANC < 2000/mm$^3$, then monitor twice weekly |
| Mild Leukopenia<br>---<br>Mild Granulocytopenia | 3500/mm$^3$ > WBC ≥ 3000/mm$^3$<br>and/or<br>2000/mm$^3$ > ANC ≥ 1500/mm$^3$ | Twice-weekly until WBC > 3500/mm$^3$ and ANC > 2000/mm$^3$ then return to previous monitoring frequency |
| Moderate Leukopenia<br>---<br>Moderate Granulocytopenia | 3000/mm$^3$ > WBC ≥ 2000/mm$^3$<br>and/or<br>1500/mm$^3$ > ANC ≥ 1000/mm$^3$ | 1. Interrupt therapy<br>2. Daily until WBC > 3000/mm$^3$ and ANC >1500/mm$^3$<br>3. Twice-weekly until WBC > 3500/mm$^3$ and ANC > 2000/mm$^3$<br>4. May rechallenge when WBC > 3500/mm$^3$ and ANC > 2000/mm$^3$<br>5. If rechallenged, monitor weekly for 1 year before returning to the usual monitoring schedule of every 2 weeks for 6 months and then every 4 weeks ad infinitum |
| Severe Leukopenia<br>---<br>Severe Granulocytopenia | WBC < 2000/mm$^3$<br>and/or<br>ANC < 1000/mm$^3$ | 1. Discontinue treatment and do not rechallenge patient<br>2. Monitor until normal and for at least four weeks from day of discontinuation as follows:<br>• Daily until WBC > 3000/mm$^3$ and ANC > 1500/mm$^3$<br>• Twice weekly until WBC > 3500/mm$^3$ and ANC > 2000/mm$^3$<br>• Weekly after WBC > 3500/mm$^3$ |
| Agranulocytosis | ANC ≤ 500/mm$^3$ | 1. Discontinue treatment and do not rechallenge patient<br>2. Monitor until normal and for at least four weeks from day of discontinuation as follows:<br>• Daily until WBC > 3000/mm$^3$ and ANC > 1500/mm$^3$<br>• Twice weekly until WBC > 3500/mm$^3$ and ANC > 2000/mm$^3$<br>• Weekly after WBC > 3500/mm$^3$ |

## ATTACHMENT 3

**Figure 1. Resuming Monitoring Frequency after Interuption in Therapy.**




*Transitions to reduce frequency of monitoring only permitted if all WBC ≥ 3500 and ANC ≥ 2000.

ATTACHMENT

# CLOZARIL: Starting a Patient

1. Call the CLOZARIL National Registry (CNR) to obtain a rechallenge number and to confirm that you and your pharmacy are registered.
2. Obtain a baseline WBC with ANC from patient. If within normal limits, WBC ≥ 3500/mm³, ANC ≥ 2000/mm³, prescribe CLOZARIL tablets.
3. Submit WBC and ANC information to the registered pharmacy.
4. Please be prepared to provide your DEA # to the CNR when you are registered for the first time.

**For forms, patient enrollment, or medical information call the CLOZARIL National Registry:**

**1-800-448-5938**

**Recommended CLOZARIL®(clozapine) dosage titration at start of therapy[1]**

| Week 1 | am (mg) | hs (mg) | Total (mg) | Week 2 | am (mg) | hs (mg) | Total (mg) |
|---|---|---|---|---|---|---|---|
| Day 1 | 12.5 | 12.5* | 12.5-25 | Day 8 | 50 | 100 | 150 |
| Day 2 | 25 | – | 25 | Day 9 | 100 | 100 | 200 |
| Day 3 | 25 | 25 | 50 | Day 10 | 100 | 100 | 200 |
| Day 4 | 25 | 50 | 75 | Day 11 | 50 | 200 | 250 |
| Day 5 | 50 | 50 | 100 | Day 12 | 50 | 200 | 250 |
| Day 6 | 50 | 75 | 125 | Day 13 | 100 | 200 | 300 |
| Day 7 | 50 | 100 | 150 | Day 14 | 100 | 200 | 300 |

*Optional Subsequent dosage increments should be made no more than once or twice weekly, in increments not to exceed 100 mg.

# CLOZARIL: Managing the Patient

| Current Monitoring Frequency | Eligibility for Monthly Monitoring |
|---|---|
| **Every 2 weeks** (biweekly) for 6 continuous months, following 6 continuous months of weekly monitoring prior to May 12, 2005. | **YES**. Only if all WBC counts ≥ 3000/mm³ (and ANC ≥1500/mm³ if reported) |
| **Every 2 weeks or weekly.** Therapy interrupted after May 12, 2005, due to moderate leukopenia and/or granulocytopenia*, with consecutive monitoring since restart (rechallenge) of therapy. | **NO.** Only after 1 year of continuous weekly monitoring and then 6 months of continuous every two weeks monitoring from the date of restart (rechallenge) with all WBC/ANC above increased monitoring frequency values***. |
| **Weekly** therapy for ≤6 months | **NO**. Patient must have 6 continuous months of weekly monitoring, followed by 6 months of continuous monitoring every two weeks with all WBC/ANC above increased monitoring frequency values**. |
| **Weekly** therapy for ≥6 continuous months, but never monitored biweekly. | **NO.** Patient must have 6 continuous months of monitoring every two weeks with all WBC/ANC above increased monitoring frequency values**. |
| **Increased Monitoring Frequency Requirements** | |
| Patient is currently monitored monthly and experiences a WBC < 3500/mm³ and/or an ANC < 2000/mm³. | Monitoring should be done twice weekly until WBC/ANC values are ≥3500 and ≥ 2000, respectively. The patient can return to monthly blood work. |
| Patient is currently monitored every 2 weeks and experiences a WBC < 3500/mm³ and/or an ANC < 2000/mm³. | Monitoring should be done twice weekly until WBC/ANC values are ≥3500 and ≥2000, respectively. The patient should then be monitored every two weeks for 6 continuous months before progressing to monthly blood work. |
| Patient is currently monitored weekly and experiences a WBC < 3500/mm³ and/or an ANC < 2000/mm³. | Monitoring should be done twice weekly until WBC/ANC values are ≥3500 and ≥2000, respectively. The patient should then be monitored weekly for 6 continuous months before progressing to every two weeks, and then monthly, blood work. |

**Prior to May 12, 2005 values for WBC and ANC counts requiring interruption of therapy were WBC ≤ 3000/mm³ and/or ANC ≤ 1500/mm³. After May 12, 2005 values for counts requiring increased monitoring frequency of therapy are WBC ≤ 3500/ mm³ and/or ANC ≤ 2000mm³, respectively.

Following discontinuation of therapy for any reason, the patient should have WBC and ANC count monitoring once a week for a minimum of 4 weeks. If at the end of 4 weeks WBC < 3500/mm³ and/or ANC < 2000/mm³, weekly monitoring should continue until WBC ≥3500/mm³ and ANC ≥ 2000/mm³.

Clozaril (clozapine) use is associated with a substantial risk of seizure, affected 1% to 2% of patients at low doses (below 300 mg/day), 3% to 4% at moderate doses (300 mg/day to 600 mg/day), and 5% at high doses (600 mg/day to 900 mg/day). Clozaril is contraindicated in patients with paralytic ileus. In clinical trials, Clozaril was associated with a 1% to 2% incidence of agranulocytosis, a potentially fatal blood disorder, which, if caught early, can be reversed. Mandatory monitoring of WBC counts and ANC's and drug dispensing as per the requirements specified in the package insert, provide an efficient means of determining developing agranulocytosis. Analysis of post-marketing safety databases suggests that Clozaril is associated with an increased risk of fatal myocarditis, especially during, but not limited to, the first month of therapy. Orthostatic hypotension may occur in some patients, especially during the initial phases of treatment, and can, in rare cases (approximate incidence of 1/3000), be accompanied by collapse and/or cardiac arrest. Analysis of clinical studies reveal that elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Patients with an established diagnosis of diabetes mellitus who are started on CLOZARIL should be monitored regularly for worsening glucose control (e.g., polydipsia, polyuria, polyphagia, and weakness).

Clozaril® (clozapine) 25mg and 100mg tablets

## Table 1. Frequency of Monitoring based on Stage of Therapy or Results from WBC and ANC Monitoring Tests

| Situation | Hematological Values for Monitoring | Frequency of WBC and ANC Monitoring |
|---|---|---|
| Initiation of therapy | WBC ≥3500/mm³<br>ANC ≥2000/mm³<br>Note: Do not initiate in patients with 1) history of myeloproliferative disorder or 2) Clozaril® (clozapine) induced agranulocytosis or granulocytopenia | Weekly for 6 months |
| 6 months – 12 months of therapy | All results for WBC ≥3500/mm³ and ANC ≥2000/mm³ | Every 2 weeks for 6 months |
| 12 months of therapy | All results for WBC ≥3500/mm³ and ANC ≥2000/mm³ | Every 4 weeks ad infinitum |
| Immature forms present | N/A | Repeat WBC and ANC |
| Discontinuation of Therapy | N/A | Weekly for at least 4 weeks from day of discontinuation or until WBC ≥3500/mm³ and ANC >2000/mm³ |
| Substantial drop in WBC or ANC | Single Drop or cumulative drop within 3 weeks of WBC ≥3000/mm³ or ANC ≥1500/mm³ | 1. Repeat WBC and ANC<br>2. If repeat values are 3000/mm³ ≤WBC ≤3500/mm³ and ANC <2000/mm³, then monitor twice weekly |
| Mild Leukopenia<br>----------<br>Mild Granulocytopenia | 3500/mm³ >WBC ≥3000/mm³<br>---------and/or---------<br>2000/mm³ >ANC ≥1500/mm³ | Twice-weekly until WBC >3500/mm³ and ANC >2000/mm³ then return to previous monitoring frequency |
| Moderate Leukopenia<br>----------<br>Moderate Granulocytopenia | 3000/mm³ >WBC ≥2000/mm³<br>---------and/or---------<br>1500/mm³ >ANC ≥1000/mm³ | 1. Interrupted immediatel.<br>2. Daily until WBC count >3000/mm³ and ANC >1500/mm³<br>3. Twice weekly until WBC >3500/mm³ and ANC >2000/mm³<br>4. May rechallenge when WBC >3500/mm³ ANC >2000/mm³<br>5. If rechallenged, monitor weekly for 1 year before returning to the usual monitoring schedule of every 2 weeks for 6 months and then every 4 weeks ad infinitum. |
| Severe Leukopenia<br>----------<br>Severe Granulocytopenia | WBC <2000/mm³<br>---------and/or---------<br>ANC <1000/mm³ | 1. Discontinue treatment and do not rechallenge patient.<br>2. Monitor until normal and for at least four weeks from day of discontinuation as follows:<br>• Daily until WBC >3000/mm³ and ANC >1500/mm³<br>• Twice weekly until WBC >3500/mm³ and ANC >2000/mm³<br>• Weekly after WBC >3500/mm³ |
| Agranulocytosis | ANC ≤500/mm³ | 1. Discontinue treatment and do not rechallenge patient.<br>2. Monitor until normal and for at least four weeks from day of discontinuation as follows:<br>• Daily until WBC count >3000/mm³ and ANC >1500/mm³<br>• Twice weekly until WBC >3500/mm³ and ANC >2000/mm³<br>• Weekly after WBC >3500/mm³ |

*WBC=white blood cell count; ANC=absolute neutrophil count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