FazaClo®
(clozapine, USP) Orally Disintegrating Tablets

Rx only

Prescribing Information

Before prescribing FazaClo® (clozapine, USP), the physician should be thoroughly familiar with the details of this prescribing information.

WARNING

1. AGRANULOCYTOSIS

BECAUSE OF A SIGNIFICANT RISK OF AGRANULOCYTOSIS, A POTENTIALLY LIFE-THREATENING ADVERSE EVENT, CLOZAPINE SHOULD BE RESERVED FOR USE IN THE TREATMENT OF SEVERELY ILL PATIENTS WITH SCHIZOPHRENIA WHO FAIL TO SHOW AN ACCEPTABLE RESPONSE TO ADEQUATE COURSES OF STANDARD ANTIPSYCHOTIC DRUG TREATMENT.

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 COUNTS AND ANCs ACCORDING TO THE SCHEDULE DESCRIBED BELOW PRIOR TO DELIVERY OF THE NEXT SUPPLY OF MEDICATION. (SEE WARNINGS.)

2. SEIZURES

SEIZURES HAVE BEEN ASSOCIATED WITH THE USE OF CLOZAPINE. DOSE APPEARS TO BE AN IMPORTANT PREDICTOR OF SEIZURE, WITH A GREATER LIKELIHOOD AT HIGHER CLOZAPINE DOSES. CAUTION SHOULD BE USED WHEN ADMINISTERING CLOZAPINE TO PATIENTS HAVING A HISTORY OF SEIZURES OR OTHER PREDISPOSING FACTORS. PATIENTS SHOULD BE ADVISED NOT TO ENGAGE IN ANY ACTIVITY WHERE SUDDEN LOSS OF CONSCIOUSNESS COULD CAUSE SERIOUS RISK TO THEMSELVES OR OTHERS. (SEE WARNINGS.)

3. MYOCARDITIS

ANALYSES OF POSTMARKETING SAFETY DATABASES SUGGEST THAT CLOZAPINE IS ASSOCIATED WITH AN INCREASED RISK OF FATAL MYOCARDITIS, ESPECIALLY DURING, BUT NOT LIMITED TO, THE FIRST MONTH OF THERAPY. IN PATIENTS IN WHOM MYOCARDITIS IS SUSPECTED, CLOZAPINE TREATMENT SHOULD BE PROMPTLY DISCONTINUED. (SEE WARNINGS.)

4. OTHER ADVERSE CARDIOVASCULAR AND RESPIRATORY EFFECTS

ORTHOSTATIC HYPOTENSION, WITH OR WITHOUT SYNCOPE, CAN OCCUR WITH CLOZAPINE TREATMENT. RARELY, COLLAPSE CAN BE PROFOUND AND BE ACCOMPANIED BY RESPIRATORY AND/OR CARDIAC ARREST. ORTHOSTATIC HYPOTENSION IS MORE LIKELY TO OCCUR DURING INITIAL TITRATION IN ASSOCIATION WITH RAPID DOSE ESCALATION. IN PATIENTS WHO HAVE HAD EVEN A BRIEF INTERVAL OFF CLOZAPINE (ie, 2 OR MORE DAYS SINCE THE LAST DOSE) TREATMENT SHOULD BE STARTED WITH 12.5 MG ONCE OR TWICE DAILY. (SEE WARNINGS AND DOSAGE AND ADMINISTRATION.)

SINCE COLLAPSE, RESPIRATORY ARREST, AND CARDIAC ARREST DURING INITIAL TREATMENT HAS OCCURRED IN PATIENTS WHO WERE BEING ADMINISTERED BENZODIAZEPINES OR OTHER PSYCHOTROPIC DRUGS, CAUTION IS ADVISED WHEN CLOZAPINE IS INITIATED IN PATIENTS TAKING A BENZODIAZEPINE OR ANY OTHER PSYCHOTROPIC DRUG. (SEE WARNINGS.)

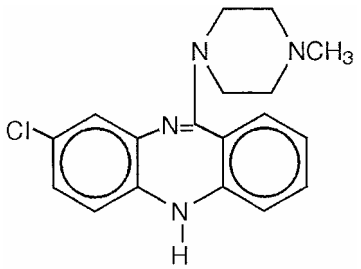
5. INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS TREATED WITH ATYPICAL ANTIPSYCHOTIC DRUGS ARE AT AN INCREASED RISK OF DEATH COMPARED TO PLACEBO. ANALYSES OF 17 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 (eg, HEART FAILURE, SUDDEN DEATH) OR INFECTIOUS (eg, PNEUMONIA) IN NATURE. FAZACLO® (clozapine, USP) IS NOT APPROVED FOR THE TREATMENT OF PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS.

DESCRIPTION

FazaClo® (clozapine, USP), an atypical antipsychotic drug, is a tricyclic dibenzodiazepine derivative, 8-chloro-11-(4-methyl-1-piperazinyl)-5*H*-dibenzo[*b*,*e*][1,4]diazepine.

The structural formula is:



$C_{18}H_{19}ClN_4$ Mol. Wt. 326.83

FazaClo® (clozapine, USP) is available as scored, yellow, orally disintegrating tablets of 25 and 100 mg for oral administration without water.

Each orally disintegrating tablet contains clozapine equivalent to 25 or 100 mg.

25- and 100-mg Orally Disintegrating Tablets

Active Ingredient: clozapine is a yellow, crystalline powder, very slightly soluble in water

Inactive Ingredients: aminoalkyl methacrylate copolymer E, mannitol, aspartame, microcrystalline cellulose, crospovidone, natural and artificial mint flavor, sodium bicarbonate, citric acid, ferric oxide (yellow), and magnesium stearate

THIS PRODUCT CONTAINS ASPARTAME AND IS NOT INTENDED FOR USE BY INFANTS. PHENYLKETONURICS: CONTAINS PHENYLALANINE. Phenylalanine is a component of aspartame. Each 25-mg, orally disintegrating tablet contains 3.1 mg aspartame, thus, 1.74 mg phenylalanine. Each 100-mg, orally disintegrating tablet contains 12.4 mg aspartame, thus, 6.96 mg phenylalanine. The allowable daily intake of aspartame is 50 mg per kilogram of body weight per day. (See PRECAUTIONS, Phenylketonurics.)

CLINICAL PHARMACOLOGY

Pharmacodynamics

FazaClo® (clozapine, USP) is classified as an "atypical" antipsychotic drug because its profile of binding to dopamine receptors and its effects on various dopamine mediated behaviors differ from those exhibited by more typical antipsychotic drug products. In particular, although FazaClo® (clozapine, USP) does interfere with the binding of dopamine at D_1, D_2, D_3, and D_5 receptors, and has a high affinity for the D_4 receptor, it does not induce catalepsy nor inhibit apomorphine-induced stereotypy. This evidence, consistent with the view that FazaClo®

(clozapine, USP) is preferentially more active at limbic than at striatal dopamine receptors, may explain the relative freedom of FazaClo® (clozapine, USP) from extrapyramidal side effects.

FazaClo® (clozapine, USP) also acts as an antagonist at adrenergic, cholinergic, histaminergic, and serotonergic receptors.

Absorption, Distribution, Metabolism, and Excretion

In man, clozapine tablets (25 and 100 mg) are equally bioavailable relative to a clozapine solution. FazaClo® (clozapine, USP) orally disintegrating tablets are bioequivalent to Clozaril® (clozapine) tablets, a registered trademark of Novartis Pharmaceuticals Corporation. Following a dosage of 100 mg b.i.d., the average steady-state peak plasma concentration was 413 ng/mL (range: 132-854 ng/mL), occurring at the average of 2.3 hours (range: 1-6 hours) after dosing. The average minimum concentration at steady state was 168 ng/mL (range: 45-574 ng/mL), after 100-mg b.i.d. dosing. Food does not appear to affect the systemic bioavailability of clozapine. Thus, FazaClo® (clozapine, USP) may be administered with or without food.

Clozapine is approximately 97% bound to serum proteins. The interaction between clozapine and other highly protein-bound drugs has not been fully evaluated but may be important. (See PRECAUTIONS.)

Clozapine is almost completely metabolized prior to excretion and only trace amounts of unchanged drug are detected in the urine and feces. Approximately 50% of the administered dose is excreted in the urine and 30% in the feces. The demethylated, hydroxylated, and *N*-oxide derivatives are components in both urine and feces. Pharmacological testing has shown the desmethyl metabolite (norclozapine) to have only limited activity, while the hydroxylated and *N*-oxide derivatives were inactive.

The mean elimination half-life of clozapine after a single 75-mg dose was 8 hours (range: 4-12 hours), compared to a mean elimination half-life, after achieving steady state with 100-mg b.i.d. dosing, of 12 hours (range: 4-66 hours). A comparison of single-dose and multiple-dose administration of clozapine showed that the elimination half-life increased significantly after multiple dosing relative to that after single-dose administration, suggesting the possibility of concentration-dependent pharmacokinetics. However, at steady state, linearly dose-proportional changes with respect to AUC (area under the curve), peak, and minimum clozapine plasma concentrations were observed after administration of 37.5, 75, and 150 mg b.i.d.

Human Pharmacology

In contrast to more typical antipsychotic drugs, clozapine therapy produces little or no prolactin elevation.

As is true of more typical antipsychotic drugs, clinical electroencephalogram (EEG) studies have shown that clozapine increases delta and theta activity and slows dominant alpha frequencies. Enhanced synchronization occurs; sharp wave activity and spike and wave complexes may also develop. Patients, on rare occasions, may report an intensification of dream activity during

clozapine therapy. REM sleep was found to be increased to 85% of the total sleep time. In these patients, the onset of REM sleep occurred almost immediately after falling asleep.

INDICATIONS AND USAGE

FazaClo® (clozapine, USP) is indicated for the management of severely ill schizophrenic patients who fail to respond adequately to standard drug treatment for schizophrenia. Because of the significant risk of agranulocytosis and seizure associated with its use, FazaClo® (clozapine, USP) should be used only in patients who have failed to respond adequately to treatment with appropriate courses of standard drug treatments for schizophrenia, either because of insufficient effectiveness or the inability to achieve an effective dose due to intolerable adverse effects from those drugs. (See WARNINGS.)

The effectiveness of clozapine in a treatment-resistant schizophrenic population was demonstrated in a 6-week study comparing clozapine and chlorpromazine. Patients meeting DSM-III criteria for schizophrenia and having a mean Brief Psychiatric Rating Scale (BPRS) total score of 61 were demonstrated to be treatment-resistant by history and by open, prospective treatment with haloperidol before entering into the double-blind phase of the study. The superiority of clozapine to chlorpromazine was documented in statistical analyses employing both categorical and continuous measures of treatment effect.

Because of the significant risk of agranulocytosis and seizures, events which both present a continuing risk over time, the extended treatment of patients failing to show an acceptable level of clinical response should ordinarily be avoided. In addition, the need for continuing treatment in patients exhibiting beneficial clinical responses should be periodically reevaluated.

CONTRAINDICATIONS

FazaClo® (clozapine, USP) is contraindicated in patients with a previous hypersensitivity to clozapine or any other component of this drug, in patients with myeloproliferative disorders, uncontrolled epilepsy, paralytic ileus, or a history of clozapine-induced agranulocytosis or severe granulocytopenia. As with more typical antipsychotic drugs, FazaClo® (clozapine, USP) is contraindicated in severe central nervous system (CNS) depression or comatose states from any cause.

FazaClo® (clozapine, USP) should not be used simultaneously with other agents having a well-known potential to cause agranulocytosis or otherwise suppress bone marrow function. The mechanism of clozapine-induced agranulocytosis is unknown; nonetheless, it is possible that causative factors may interact synergistically to increase the risk and/or severity of bone marrow suppression.

WARNINGS

General

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. FAZACLO® (clozapine, USP) IS NOT APPROVED FOR THE TREATMENT OF PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS. (SEE BOXED WARNING.)

AGRANULOCYTOSIS

BECAUSE OF THE SIGNIFICANT RISK OF AGRANULOCYTOSIS, A POTENTIALLY LIFE-THREATENING ADVERSE EVENT (SEE FOLLOWING), FAZACLO® (clozapine, USP) SHOULD BE RESERVED FOR USE IN THE TREATMENT OF SEVERELY ILL PATIENTS WITH SCHIZOPHRENIA WHO FAIL TO SHOW AN ACCEPTABLE RESPONSE TO ADEQUATE COURSES OF STANDARD DRUG TREATMENT FOR SCHIZOPHRENIA, EITHER BECAUSE OF INSUFFICIENT EFFECTIVENESS OR THE INABILITY TO ACHIEVE AN EFFECTIVE DOSE DUE TO INTOLERABLE ADVERSE EFFECTS FROM THOSE DRUGS. CONSEQUENTLY, BEFORE INITIATING TREATMENT WITH FAZACLO® (clozapine, USP), IT IS STRONGLY RECOMMENDED THAT A PATIENT BE GIVEN AT LEAST 2 TRIALS, EACH WITH A DIFFERENT STANDARD DRUG PRODUCT FOR SCHIZOPHRENIA, AT AN ADEQUATE DOSE AND FOR AN ADEQUATE DURATION.

FAZACLO® (clozapine, USP) 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.

AS DESCRIBED IN TABLE 1, PATIENTS WHO ARE BEING TREATED WITH FAZACLO® (clozapine, USP) MUST HAVE A BASELINE WBC COUNT AND ANC BEFORE INITIATION OF TREATMENT, AND A WBC COUNT AND ANC EVERY WEEK FOR THE FIRST 6 MONTHS. THEREAFTER, IF ACCEPTABLE WBC COUNTS AND ANCs (WBC COUNT ≥3500/mm^3 AND ANC ≥2000/mm^3) HAVE BEEN MAINTAINED DURING THE FIRST 6 MONTHS OF CONTINUOUS THERAPY, WBC COUNTS AND ANCs CAN BE MONITORED EVERY 2 WEEKS FOR THE NEXT 6 MONTHS. THEREAFTER, IF ACCEPTABLE WBC COUNTS AND ANCs (WBC COUNT ≥3500/mm^3 AND ANC ≥2000/mm^3) HAVE BEEN MAINTAINED DURING THE SECOND 6 MONTHS OF CONTINUOUS THERAPY, WBC COUNT AND ANC CAN BE MONITORED EVERY 4 WEEKS.

WHEN TREATMENT WITH FAZACLO® (clozapine, USP) IS DISCONTINUED (REGARDLESS OF THE REASON), WBC COUNT AND ANC MUST BE MONITORED

WEEKLY FOR AT LEAST 4 WEEKS FROM THE DAY OF DISCONTINUATION OR UNTIL WBC COUNT ≥3500/mm^3 AND ANC ≥2000/mm^3.

Agranulocytosis

Background

Agranulocytosis, defined as an ANC of less than 500/mm^3, has been estimated to occur in association with clozapine use at a cumulative incidence at 1 year of approximately 1.3%, based on the occurrence of 15 US cases out of 1743 patients exposed to clozapine during its clinical testing prior to domestic marketing. All of these cases occurred at a time when the need for close monitoring of WBC counts was already recognized. Agranulocytosis could prove fatal if not detected early and therapy interrupted. Of the 149 cases of agranulocytosis reported worldwide in association with clozapine use as of December 31, 1989, 32% were fatal. However, few of these deaths occurred since 1977, at which time the knowledge of clozapine-induced agranulocytosis became more widespread, and close monitoring of WBC counts more widely practiced. In the United States, under a weekly WBC count monitoring system with clozapine, there have been 585 cases of agranulocytosis as of August 21, 1997; 19 were fatal (3%). During this period, 150,409 patients received clozapine. A hematologic risk analysis was conducted based upon the available information in the *Clozapine National Registry* for US patients. Based upon a cut-off date of April 30, 1995, the incidence rates of agranulocytosis based upon a weekly monitoring schedule rose steeply during the first two months of therapy, peaking in the third month. Among clozapine patients who continued the drug beyond the third month, the weekly incidence of agranulocytosis fell a substantial degree. After 6 months, the weekly incidence of agranulocytosis declines still further; however, it never reaches zero. It should be noted that any type of reduction in the frequency of monitoring WBC counts may result in an increased incidence of agranulocytosis.

Risk Factors

Experience from clinical development, as well as from examples in the medical literature, suggests that patients who have developed agranulocytosis during FazaClo® (clozapine, USP) therapy are at increased risk of subsequent episodes of agranulocytosis. Analysis of WBC count data from the *Clozapine National Registry* also suggests that patients who have an initial episode of moderate leukopenia (3000/mm^3>WBC count≥2000/mm^3) are at an increased risk of subsequent episodes of agranulocytosis. Except for bone-marrow suppression during initial clozapine therapy, there are no other established risk factors based on worldwide experience for the development of agranulocytosis in association with clozapine use. However, a disproportionate number of the US cases of agranulocytosis occurred in patients of Jewish background compared to the overall proportion of such patients exposed during domestic development of clozapine. Most of the US cases of agranulocytosis occurred within 4-10 weeks of exposure, but neither dose nor duration is a reliable predictor of this problem. Agranulocytosis associated with other antipsychotic drugs has been reported to occur with a greater frequency in women, the elderly, and in patients who are cachectic or have serious underlying medical illness; such patients may

also be at particular risk with FazaClo® (clozapine, USP), although this has not been definitively demonstrated.

WBC Count and ANC Clinical Monitoring Schedule

Table 1 provides a summary of the frequency of monitoring that should occur based on various stages of therapy (eg, initiation of therapy) or results from WBC count and ANC monitoring tests (eg, moderate leukopenia). The text that follows should be consulted for additional details regarding the treatment of patients under the various conditions (eg, severe leukopenia).

Patients should be advised to immediately report the appearance of lethargy, weakness, fever, sore throat, or any other signs of infection occurring at any time during FazaClo® (clozapine, USP) therapy. Such patients should have a WBC count and an ANC performed promptly.

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 Count and ANC Monitoring
Initiation of therapy	WBC count $\geq 3500/mm^3$ and ANC $\geq 2000/mm^3$ Note : Do not initiate in patients with (1) history of myeloproliferative disorder or (2) clozapine-induced agranulocytosis or granulocytopenia.	Weekly for 6 months
6-12 months of therapy	All results for WBC count $\geq 3500/mm^3$ and ANC $\geq 2000/mm^3$	Every 2 weeks for 6 months
12 months of therapy	All results for WBC count $\geq 3500/mm^3$ and ANC $\geq 2000/mm^3$	Every 4 weeks ad infinitum
Immature forms present	N/A	Repeat WBC count and ANC
Discontinuation of Therapy	N/A	Weekly for at least 4 weeks from day of discontinuation or until WBC count $\geq 3500/mm^3$ and ANC $\geq 2000/mm^3$
Substantial drop in WBC count or ANC	Single drop or cumulative drop within 3 weeks of WBC count $\geq 3000/mm^3$ or ANC $\geq 1500/mm^3$	1. Repeat WBC count and ANC 2. If repeat values are $3000/mm^3 \leq$ WBC count $\leq 3500/mm^3$ and ANC $>2000/mm^3$, then monitor twice weekly
Mild leukopenia and/or Mild granulocytopenia	$3500/mm^3 >$ WBC count $\geq 3000/mm^3$ and/or $2000/mm^3 >$ ANC $\geq 1500/mm^3$	Twice weekly until WBC count $>3500/mm^3$ and ANC $>2000/mm^3$ then return to previous monitoring frequency
Moderate leukopenia and/or Moderate granulocytopenia	$3000/mm^3 >$ WBC count $\geq 2000/mm^3$ and/or $1500/mm^3 >$ ANC $\geq 1000/mm^3$	1. Interrupt therapy 2. Daily until WBC count $>3000/mm^3$ and ANC $>1500/mm^3$ 3. Twice weekly until WBC count $>3500/mm^3$ and ANC $>2000/mm^3$ 4. May rechallenge when WBC count $>3500/mm^3$ and ANC $>2000/mm^3$ 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

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 Count and ANC Monitoring**
Severe leukopenia and/or Severe granulocytopenia	WBC count <2000/mm^3 and/or ANC <1000/mm^3	1. Discontinue treatment and do not rechallenge patient 2. Monitor until normal and for at least four weeks from day of discontinuation as follows: • Daily until WBC count >3000/mm^3 and ANC >1500/mm^3 • Twice weekly until WBC count >3500/mm^3 and ANC >2000/mm^3 • Weekly after WBC count >3500/mm^3
Agranulocytosis	ANC <500/mm^3	1. Discontinue treatment and do not rechallenge patient 2. Monitor until normal and for at least four weeks from day of discontinuation as follows: • Daily until WBC count >3000/mm^3 and ANC >1500/mm^3 • Twice weekly until WBC count >3500/mm^3 and ANC >2000/mm^3 • Weekly after WBC count >3500/mm^3
WBC = White blood cell ANC = Absolute neutrophil count		

Decrements in WBC Count and/or ANC

Consult Table 1 above to determine how to monitor patients who experience decrements in WBC count and/or ANC at any point during treatment. Additionally, patients should be carefully monitored for flu-like symptoms or other symptoms suggestive of infection.

Nonrechallengeable Patients

If the total WBC count falls below 2000/mm^3 or the ANC falls below 1000/mm^3, bone-marrow aspiration should be considered to ascertain granulopoietic status and patients should not be rechallenged with FazaClo® (clozapine, USP). Protective isolation with close observation may be indicated if granulopoiesis is determined to be deficient. Should evidence of infection develop, the patient should have appropriate cultures performed and an appropriate antibiotic regimen instituted.

Patients discontinued from clozapine therapy due to significant granulopoietic suppression have been found to develop agranulocytosis upon rechallenge, often with a shorter latency on reexposure. To reduce the chances of rechallenge occurring in patients who have experienced significant bone-marrow suppression during FazaClo® (clozapine, USP) therapy, a single, national master file (ie, Nonrechallengeable Database) is confidentially maintained.

Treatment of Rechallengeable Patients

Patients may be rechallenged with FazaClo® (clozapine, USP) if their WBC count does not fall below 2000/mm^3 and the ANC does not fall below 1000/mm^3. However, analysis of the data from the *Clozapine National Registry* suggests that patients who have an initial episode

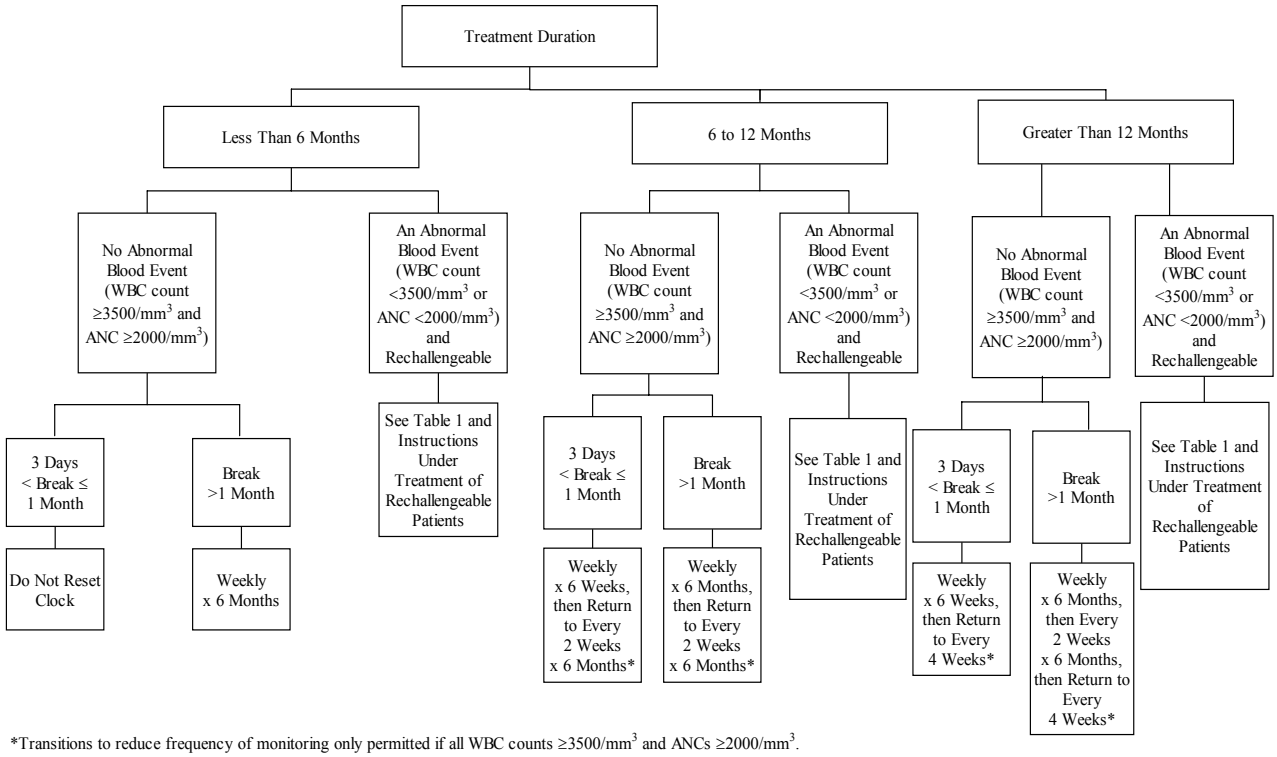
of moderate leukopenia (3000/mm^3>WBC count≥2000/mm^3) have up to a 12-fold increased risk of having a subsequent episode of agranulocytosis when rechallenged as compared to the full cohort of patients treated with clozapine. Although FazaClo® (clozapine, USP) therapy may be resumed if no symptoms of infection develop and when the WBC count rises above 3500/mm^3 and the ANC rises above 2000/mm^3, prescribers are strongly advised to consider whether the benefit of continuing FazaClo® (clozapine, USP) treatment outweighs the increased risk of agranulocytosis.

Analyses of the *Clozapine National Registry* have shown an increased risk of having a subsequent episode of granulopoietic suppression up to a year after recovery from the initial episode. Therefore, as noted in Table 1 above, patients must undergo weekly WBC count and ANC monitoring for one year following recovery from an episode of moderate leukopenia and/or moderate granulocytopenia regardless of when the episode develops. If acceptable WBC counts and ANC (WBC count ≥3500/mm^3 and ANC ≥2000/mm^3) have been maintained during the year of weekly monitoring, WBC counts can be monitored every 2 weeks for the next 6 months. If acceptable WBC counts and ANC (WBC count ≥3500/mm^3 and ANC ≥2000/mm^3) continue to be maintained during the 6 months of every-2-week monitoring, WBC counts can be monitored every 4 weeks thereafter, ad infinitum.

Interruptions in Therapy

Figure 1 provides instructions regarding reinitiating therapy and subsequently the frequency of WBC count and ANC monitoring after a period of interruption.

Figure 1. Resuming Monitoring Frequency After Interruption of Therapy



*Transitions to reduce frequency of monitoring only permitted if all WBC counts ≥3500/mm^3 and ANCs ≥2000/mm^3.

Eosinophilia

In clinical trials, 1% of patients developed eosinophilia, which, in rare cases, can be substantial. If a differential count reveals a total eosinophil count above 4000/mm^3, FazaClo® (clozapine, USP) therapy should be interrupted until the eosinophil count falls below 3000/mm^3.

Seizures

Seizure has been estimated to occur in association with clozapine use at a cumulative incidence at one year of approximately 5%, based on the occurrence of one or more seizures in 61 of 1743 patients exposed to clozapine during its clinical testing prior to domestic marketing (ie, a crude rate of 3.5%). Dose appears to be an important predictor of seizure, with a greater likelihood of seizure at the higher clozapine doses used.

Caution should be used in administering FazaClo® (clozapine, USP) to patients having a history of seizures or other predisposing factors. Because of the substantial risk of seizure associated with clozapine use, patients should be advised not to engage in any activity where sudden loss of consciousness could cause serious risk to themselves or others (eg, the operation of complex machinery, driving an automobile, swimming, climbing, etc.).

Myocarditis

Postmarketing surveillance data from four countries that employ hematological monitoring of clozapine-treated patients revealed: 30 reports of myocarditis with 17 fatalities in 205,493 US patients (August 2001); 7 reports of myocarditis with 1 fatality in 15,600 Canadian patients (April 2001); 30 reports of myocarditis with 8 fatalities in 24,108 UK patients (August 2001); 15 reports of myocarditis with 5 fatalities in 8000 Australian patients (March 1999). These reports represent an incidence of 5.0, 16.3, 43.2, and 96.6 cases/100,000 patient years, respectively. The number of fatalities represent an incidence of 2.8, 2.3, 11.5, and 32.2 cases/100,000 patient years, respectively.

The overall incidence rate of myocarditis in patients with schizophrenia treated with antipsychotic agents is unknown. However, for the established market economies, World Health Organization (WHO), the incidence of myocarditis is 0.3 cases/100,000 patient years and the fatality rate is 0.2 cases/100,000 patient years. Therefore, the rate of myocarditis in clozapine-treated patients appears to be 17-322 times greater than the general population and is associated with an increased risk of fatal myocarditis that is 14-161 times greater than the general population.

The total reports of myocarditis for these four countries were 82, of which 51 (62%) occurred within the first month of clozapine treatment, 25 (31%) occurred after the first month of therapy, and 6 (7%) were unknown. The median duration of treatment was 3 weeks. Of 5 patients rechallenged with clozapine, 3 had a recurrence of myocarditis. Of the 82 reports, 31 (38%) were fatal, and 25 patients who died had evidence of myocarditis at autopsy. These data also suggest that the incidence of fatal myocarditis may be highest during the first month of therapy.

Therefore, the possibility of myocarditis should be considered in patients receiving FazaClo® (clozapine, USP) who present with unexplained fatigue, dyspnea, tachypnea, fever, chest pain, palpitations, other signs or symptoms of heart failure, or electrocardiographic findings such as ST-T wave abnormalities or arrhythmias. It is not known whether eosinophilia is a reliable predictor of myocarditis. Tachycardia, which has been associated with clozapine treatment, has also been noted as a presenting sign in patients with myocarditis. Therefore, tachycardia during the first month of therapy warrants close monitoring for other signs of myocarditis.

Prompt discontinuation of FazaClo® (clozapine, USP) treatment is warranted upon suspicion of myocarditis. Patients with clozapine-related myocarditis should not be rechallenged with FazaClo® (clozapine, USP).

Other Adverse Cardiovascular and Respiratory Effects

Orthostatic hypotension with or without syncope can occur with FazaClo® (clozapine, USP) treatment and may represent a continuing risk in some patients. Rarely (approximately 1 case per 3000 patients), collapse can be profound and be accompanied by respiratory and/or cardiac arrest. Orthostatic hypotension is more likely to occur during initial titration in association with rapid-dose escalation and may even occur on first dose. In one report, initial doses as low as 12.5 mg were associated with collapse and respiratory arrest. When restarting patients who have had even a brief interval off FazaClo® (clozapine, USP) (ie, 2 days or more since the last dose), it is recommended that treatment be reinitiated with one-half of a 25-mg, orally-disintegrating tablet (12.5 mg) once or twice daily. (See DOSAGE AND ADMINISTRATION.)

Some of the cases of collapse/respiratory arrest/cardiac arrest during initial treatment occurred in patients who were being administered benzodiazepines; similar events have been reported in patients taking other psychotropic drugs or even clozapine by itself. Although it has not been established that there is an interaction between FazaClo® (clozapine, USP) and benzodiazepines or other psychotropics, caution is advised when clozapine is initiated in patients taking a benzodiazepine or any other psychotropic drug.

Tachycardia, which may be sustained, has also been observed in approximately 25% of patients taking clozapine, with patients having an average increase in pulse rate of 10-15 bpm. The sustained tachycardia is not simply a reflex response to hypotension and is present in all positions monitored. Either tachycardia or hypotension may pose a serious risk for an individual with compromised cardiovascular function.

A minority of clozapine-treated patients experience ECG repolarization changes similar to those seen with other antipsychotic drugs, including S-T segment depression and flattening or inversion of T-waves, which all normalize after discontinuation of clozapine. The clinical significance of these changes is unclear. However, in clinical trials with clozapine, several patients experienced significant cardiac events, including ischemic changes, myocardial infarction, arrhythmias, and sudden death. In addition, there have been postmarketing reports of congestive heart failure, pericarditis, and pericardial effusions. Causality assessment was difficult in many of these cases because of serious preexisting cardiac disease and plausible

alternative causes. Rare instances of sudden death have been reported in psychiatric patients, with or without associated antipsychotic drug treatment, and the relationship of these events to antipsychotic drug use is unknown.

FazaClo® (clozapine, USP) should be used with caution in patients with known cardiovascular and/or pulmonary disease, and the recommendation for gradual titration of dose should be carefully observed.

Neuroleptic Malignant Syndrome

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias).

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (eg, pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary CNS pathology.

The management of NMS should include (1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, (2) intensive symptomatic treatment and medical monitoring, and (3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

There have been several reported cases of NMS in patients receiving clozapine alone or in combination with lithium or other CNS-active agents.

Tardive Dyskinesia

A syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict at the inception of treatment which patients are likely to develop the syndrome.

There are several reasons for predicting that clozapine may be different from other antipsychotic drugs in its potential for inducing tardive dyskinesia, including the preclinical finding that it has a relatively weak dopamine-blocking effect and the clinical finding of a virtual absence of certain acute extrapyramidal symptoms (eg, dystonia). A few cases of tardive dyskinesia have been

reported in patients on clozapine who had been previously treated with other antipsychotic agents, so that a causal relationship cannot be established. There have been no reports of tardive dyskinesia directly attributable to clozapine alone. Nevertheless, it cannot be concluded without more extended experience that FazaClo® (clozapine, USP) is incapable of inducing this syndrome.

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit partially or completely if antipsychotic drug treatment is withdrawn. Antipsychotic drug treatment itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and, thereby, may possibly mask the underlying process. The effect that symptom suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, FazaClo® (clozapine, USP) should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. As with any antipsychotic drug, chronic FazaClo® (clozapine, USP) use should be reserved for patients who appear to be obtaining substantial benefit from the drug. In such patients, the smallest dose and the shortest duration of treatment should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on FazaClo® (clozapine, USP), drug discontinuation should be considered. However, some patients may require treatment with FazaClo® (clozapine, USP) despite the presence of the syndrome.

Hyperglycemia and Diabetes Mellitus

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including clozapine. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent, hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (eg, obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during

treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

PRECAUTIONS

General

Because of the significant risk of agranulocytosis and seizure, both of which present a continuing risk over time, the extended treatment of patients failing to show an acceptable level of clinical response should ordinarily be avoided. In addition, the need for continuing treatment in patients exhibiting beneficial clinical responses should be periodically reevaluated. Although it is not known whether the risk would be increased, it is prudent to either avoid FazaClo® (clozapine, USP) or use it cautiously in patients with a previous history of agranulocytosis induced by other drugs.

Cardiomyopathy

Cases of cardiomyopathy have been reported in patients treated with clozapine. The reporting rate for cardiomyopathy in clozapine-treated patients in the United States (8.9 per 100,000 person-years) was similar to an estimate of the cardiomyopathy incidence in the US general population derived from the 1999 National Hospital Discharge Survey data (9.7 per 100,000 person-years). Approximately 80% of clozapine-treated patients in whom cardiomyopathy was reported were less than 50 years of age; the duration of treatment with clozapine prior to cardiomyopathy diagnosis varied, but was >6 months in 65% of the reports. Dilated cardiomyopathy was most frequently reported, although a large percentage of reports did not specify the type of cardiomyopathy. Signs and symptoms suggestive of cardiomyopathy, particularly exertional dyspnea, fatigue, orthopnea, paroxysmal nocturnal dyspnea, and peripheral edema should alert the clinician to perform further investigations. If the diagnosis of cardiomyopathy is confirmed, the prescriber should discontinue clozapine unless the benefit to the patient clearly outweighs the risk.

Fever

During FazaClo® (clozapine, USP) therapy, patients may experience transient temperature elevations above 100.4ºF (38ºC), with the peak incidence within the first 3 weeks of treatment. While this fever is generally benign and self-limiting, it may necessitate discontinuing patients from treatment. On occasion, there may be an associated increase or decrease in WBC count. Patients with fever should be carefully evaluated to rule out the possibility of an underlying infectious process or the development of agranulocytosis. In the presence of high fever, the possibility of NMS must be considered. There have been several reports of NMS in patients receiving clozapine, usually in combination with lithium or other CNS-active drugs. (See Neuroleptic Malignant Syndrome under WARNINGS.)

Pulmonary Embolism

The possibility of pulmonary embolism should be considered in patients receiving FazaClo® (clozapine, USP) who present with deep-vein thrombosis, acute dyspnea, chest pain, or with other respiratory signs and symptoms. As of December 31, 1993, there were 18 cases of fatal pulmonary embolism in association with clozapine therapy in users 10-54 years of age. Based upon the extent of use observed in the *Clozapine National Registry*, the mortality rate associated with pulmonary embolus was 1 death per 3450 person-years of use. This rate was about 27.5 times higher than that in the general population of a similar age and gender (95% Confidence Interval; 17.1, 42.2). Deep-vein thrombosis has also been observed in association with clozapine therapy. Whether pulmonary embolus can be attributed to clozapine or some characteristic(s) of its users is not clear, but the occurrence of deep-vein thrombosis or respiratory symptomatology should suggest its presence.

Phenylketonurics

Phenylketonuric patients should be informed that FazaClo® (clozapine, USP) contains phenylalanine (a component of aspartame). Each 25-mg, orally disintegrating tablet contains 1.74 mg phenylalanine. Each 100-mg, orally disintegrating tablet contains 6.96 mg phenylalanine.

Hepatitis

Caution is advised in patients using FazaClo® (clozapine, USP) who have concurrent hepatic disease. Hepatitis has been reported in both patients with normal and preexisting liver function abnormalities. In patients who develop nausea, vomiting, and/or anorexia during FazaClo® (clozapine, USP) treatment, liver function tests should be performed immediately. If the elevation of these values is clinically relevant or if symptoms of jaundice occur, treatment with FazaClo® (clozapine, USP) should be discontinued.

Anticholinergic Toxicity

Eye: Clozapine has potent anticholinergic effects and care should be exercised in using this drug in the presence of narrow-angle glaucoma.

Gastrointestinal: Clozapine use has been associated with varying degrees of impairment of intestinal peristalsis, ranging from constipation to intestinal obstruction, fecal impaction, and paralytic ileus. (See ADVERSE REACTIONS.) On rare occasions, these cases have been fatal. Constipation should be initially treated by ensuring adequate hydration and use of ancillary therapy such as bulk laxatives. Consultation with a gastroenterologist is advisable in more serious cases.

Prostate: Clozapine has potent anticholinergic effects and care should be exercised in using this drug in the presence of prostatic enlargement.

Interference with Cognitive and Motor Performance

Because of initial sedation, FazaClo® (clozapine, USP) may impair mental and/or physical abilities, especially during the first few days of therapy. The recommendations for gradual-dose escalation should be carefully adhered to and patients cautioned about activities requiring alertness.

Use in Patients with Concomitant Illness

Clinical experience with clozapine in patients with concomitant systemic diseases is limited. Nevertheless, caution is advisable in using FazaClo® (clozapine, USP) in patients with renal or cardiac disease.

Use in Patients Undergoing General Anesthesia

Caution is advised in patients being administered general anesthesia because of the CNS effects of clozapine. Check with the anesthesiologist regarding continuation of FazaClo® (clozapine, USP) therapy in a patient scheduled for surgery.

Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe FazaClo® (clozapine, USP):

-Patients who are to receive FazaClo® (clozapine, USP) should be warned about the significant risk of developing agranulocytosis. Patients should be advised to immediately report the appearance of lethargy, weakness, fever, sore throat, malaise, mucous membrane ulceration, or other possible signs of infection. Particular attention should be paid to any flu-like complaints or other symptoms that might suggest infection.

- Patients should be informed that FazaClo® (clozapine, USP) Orally Disintegrating Tablets will be made available only through a special program designed to ensure the required blood monitoring in order to reduce the risk of developing agranulocytosis. Patients should be informed that their WBC count and ANC will be monitored as follows:

    - Weekly blood tests are required for the first 6 months.

    - If acceptable WBC counts and ANCs (WBC count $\geq 3500/mm^3$ and ANC $\geq 2000/mm^3$) have been maintained during the first 6 months of continuous therapy, then WBC counts and ANCs can be monitored every 2 weeks for the next 6 months.

    - Thereafter, if acceptable WBC counts and ANCs have been maintained during the second 6 months of continuous therapy, WBC counts and ANCs can be monitored every 4 weeks.

-Patients should be informed of the significant risk of seizure during FazaClo® (clozapine, USP) treatment, and they should be advised to avoid driving and any other potentially hazardous activity while taking FazaClo® (clozapine, USP).

-Patients with phenylketonuria should be aware that FazaClo® (clozapine, USP) contains phenylalanine (a component of aspartame). (See PRECAUTIONS, Phenylketonurics.)

-Patients should be advised of the risk of orthostatic hypotension, especially during the period of initial dose titration.

-Patients should be informed that if they miss taking FazaClo® (clozapine, USP) for more than 2 days, they should not restart their medication at the same dosage but should contact their physician for dosing instructions.

-Patients should notify their physician if they are taking or plan to take any prescription or over-the-counter drugs or alcohol.

-Patients should notify their physician if they become pregnant or intend to become pregnant during therapy.

-Patients should not breast feed an infant if they are taking FazaClo® (clozapine, USP).

-Patients should be advised that FazaClo® (clozapine, USP) tablets should remain in the unopened blister until immediately before use.

-Patients should be advised that if FazaClo® (clozapine, USP) tablets are split, the half-tablet that is not taken should be destroyed.

Drug Interactions

The risks of using FazaClo® (clozapine, USP) in combination with other drugs have not been systematically evaluated. Concurrent psychopharmaceuticals may affect plasma clozapine levels, thus, plasma concentrations of clozapine may fluctuate, and dosage adjustment may be required to avoid adverse effects or clinical failure.

Pharmacodynamic-Related Interactions

Although the exact mechanism of clozapine-induced agranulocytosis is unknown, the possibility that causative factors may interact synergistically with clozapine to increase the risk and/or severity of bone-marrow suppression warrants consideration. Therefore, FazaClo® (clozapine, USP) should not be used with other agents having a well-known potential to suppress bone-marrow function.

Given the primary CNS effects of clozapine, caution is advised in using it concomitantly with other CNS-active drugs or alcohol.

Orthostatic hypotension in patients taking clozapine can, in rare cases (approximately 1 case per 3000 patients), be accompanied by profound collapse and respiratory and/or cardiac arrest. Some of the cases of collapse/respiratory arrest/cardiac arrest during initial treatment occurred in patients who were being administered benzodiazepines; similar events have been reported in patients taking other psychotropic drugs or even clozapine by itself. Although it has not been established that there is an interaction between clozapine and benzodiazepines or other

psychotropics, caution is advised when clozapine is initiated in patients taking a benzodiazepine or any other psychotropic drug.

FazaClo® (clozapine, USP) may potentiate the hypotensive effects of antihypertensive drugs and the anticholinergic effects of atropine-type drugs. The administration of epinephrine should be avoided in the treatment of drug-induced hypotension because of a possible reverse epinephrine effect.

Pharmacokinetic-Related Interactions

Clozapine is a substrate for many cytochrome P450 isozymes, in particular CYP1A2, CYP2D6, and CYP3A4. The risk of metabolic interactions caused by an effect on an individual isoform is, therefore, minimized. Nevertheless, caution should be used in patients receiving concomitant treatment of FazaClo® (clozapine, USP) with other drugs which are either inhibitors or inducers of these enzymes.

Concomitant administration of drugs known to induce cytochrome P450 enzymes may decrease the plasma levels of clozapine. Phenytoin, nicotine, carbamazepine, and rifampin may decrease FazaClo® (clozapine, USP) plasma levels resulting in a decrease in effectiveness of a previously effective FazaClo® (clozapine, USP) dose.

Concomitant administration of drugs known to inhibit the activity of cytochrome P450 isozymes may increase the plasma levels of clozapine. Cimetidine, caffeine, fluvoxamine, and erythromycin may increase plasma levels of FazaClo® (clozapine, USP), potentially resulting in adverse effects. Although concomitant use of FazaClo® (clozapine, USP) and carbamazepine is not recommended, it should be noted that discontinuation of concomitant carbamazepine administration may result in an increase in FazaClo® (clozapine, USP) plasma levels.

In a study of schizophrenic patients who received clozapine under steady-state conditions, fluvoxamine or paroxetine was added in 16 and 14 patients, respectively. After 14 days of coadministration, mean trough concentrations of clozapine and its metabolites, *N*-desmethylclozapine and clozapine *N*-oxide, were elevated with fluvoxamine by about three-fold compared to baseline concentrations. Paroxetine produced only minor changes in the levels of clozapine and its metabolites. However, other published reports describe modest elevations (less than two-fold) of clozapine and metabolite concentrations when clozapine was taken with paroxetine, fluoxetine, and sertraline. Therefore, such combined treatment should be approached with caution and patients should be monitored closely when FazaClo® (clozapine, USP) is combined with these drugs, particularly with fluvoxamine. A reduced FazaClo® (clozapine, USP) dose should be considered.

A subset (3%-10%) of the population has reduced activity of certain drug metabolizing enzymes such as the cytochrome P450 isozyme CYP2D6. Such individuals are referred to as “poor metabolizers” of drugs such as debrisoquin, dextromethorphan, tricyclic antidepressants, and clozapine. These individuals may develop higher than expected plasma concentrations of clozapine when given usual doses. In addition, certain drugs that are metabolized by this isozyme, including many antidepressants (clozapine, selective serotonin reuptake inhibitors, and others), may inhibit the activity of this isozyme and, thus, may make normal metabolizers

resemble poor metabolizers with regard to concomitant therapy with other drugs metabolized by this enzyme system, leading to drug interaction.

Concomitant use of clozapine with other drugs metabolized by P450 CYP2D6 may require lower doses than usually prescribed for either FazaClo® (clozapine, USP) or the other drug. Therefore, coadministration of FazaClo® (clozapine, USP) with other drugs that are metabolized by this isozyme, including antidepressants, phenothiazines, carbamazepine, and Type 1C antiarrhythmics (eg, propafenone, flecainide, and encainide), or that inhibit this enzyme (eg, quinidine) should be approached with caution.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenic potential was demonstrated in long-term studies in mice and rats at doses approximately 7 times the typical human dose on a mg/kg basis. Fertility in male and female rats was not adversely affected by clozapine. Clozapine did not produce genotoxic or mutagenic effects when assayed in appropriate bacterial and mammalian tests.

Pregnancy Category B

Reproduction studies have been performed in rats and rabbits at doses of approximately 2-4 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to clozapine. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response and in view of the desirability of keeping the administration of all drugs to a minimum during pregnancy, this drug should be used only if clearly needed.

Nursing Mothers

Animal studies suggest that clozapine may be excreted in breast milk and have an effect on the nursing infant. Therefore, women receiving FazaClo® (clozapine, USP) should not breast feed.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Clinical studies of clozapine did not include sufficient numbers of subjects age 65 and over to determine whether they respond differently than younger subjects.

Orthostatic hypotension can occur with clozapine treatment, and tachycardia, which may be sustained, has been observed in about 25% of patients taking clozapine. (See BOXED WARNINGS, Other Adverse Cardiovascular and Respiratory Effects.) Elderly patients, particularly those with compromised cardiovascular functioning, may be more susceptible to these effects.

Also, elderly patients may be particularly susceptible to the anticholinergic effects of clozapine, such as urinary retention and constipation. (See PRECAUTIONS, Anticholinergic Toxicity.)

Dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and concomitant disease or other drug therapy. Other reported clinical experience does suggest that the prevalence of tardive dyskinesia appears to be highest among the elderly, especially elderly women. (See WARNINGS, Tardive Dyskinesia.)

ADVERSE REACTIONS

Associated with Discontinuation of Treatment

Sixteen percent of 1080 patients who received clozapine in premarketing clinical trials discontinued treatment due to an adverse event, including both those that could reasonably be attributed to clozapine treatment and those that might more appropriately be considered intercurrent illness. The more common events considered to be causes of discontinuation included: CNS, primarily drowsiness/sedation, seizures, dizziness/syncope; cardiovascular, primarily tachycardia, hypotension, and ECG changes; gastrointestinal, primarily nausea/vomiting; hematologic, primarily leukopenia/granulocytopenia/agranulocytosis; and fever. None of the events enumerated accounts for more than 1.7% of all discontinuations attributed to adverse clinical events.

Commonly Observed

Adverse events observed in association with the use of clozapine in clinical trials at an incidence of greater than 5% were: CNS complaints, including drowsiness/sedation, dizziness/vertigo, headache, and tremor; autonomic nervous system complaints, including salivation, sweating, dry mouth, and visual disturbances; cardiovascular findings, including tachycardia, hypotension, and syncope; gastrointestinal complaints, including constipation and nausea; and fever. Complaints of drowsiness/sedation tend to subside with continued therapy or dose reduction. Salivation may be profuse, especially during sleep, but may be diminished with dose reduction.

Incidence in Clinical Trials

The following table enumerates adverse events that occurred at a frequency of 1% or greater among clozapine patients who participated in clinical trials. These rates are not adjusted for duration of exposure.

Treatment-Emergent Adverse Experience Incidence Among Patients Taking Clozapine in Clinical Trials (N = 842) (percentage of patients reporting)

Body System Adverse Event[a]	Percent
Central Nervous System	
Drowsiness/Sedation	39
Dizziness/Vertigo	19
Headache	7
Tremor	6
Syncope	6
Disturbed Sleep/Nightmares	4
Restlessness	4
Hypokinesia/Akinesia	4
Agitation	4
Seizures (convulsions)	3[b]

Rigidity	3
Akathisia	3
Confusion	3
Fatigue	2
Insomnia	2
Hyperkinesia	1
Weakness	1
Lethargy	1
Ataxia	1
Slurred Speech	1
Depression	1
Epileptiform Movements/Myoclonic Jerks	1
Anxiety	1
Cardiovascular	
Tachycardia	25[b]
Hypotension	9
Hypertension	4
Chest Pain/Angina	1
ECG Change/Cardiac Abnormality	1
Gastrointestinal	
Constipation	14
Nausea	5
Abdominal Discomfort/Heartburn	4
Nausea/Vomiting	3
Vomiting	3
Diarrhea	2
Liver Test Abnormality	1
Anorexia	1
Urogenital	
Urinary Abnormalities	2
Incontinence	1
Abnormal Ejaculation	1
Urinary Urgency/Frequency	1
Urinary Retention	1
Autonomic Nervous System	
Salivation	31
Sweating	6
Dry Mouth	6
Visual Disturbances	5
Integumentary (skin)	
Rash	2
Musculoskeletal	
Muscle Weakness	1
Pain (back, neck, legs)	1
Muscle Spasm	1
Muscle Pain, Ache	1
Respiratory	
Throat Discomfort	1
Dyspnea, Shortness of Breath	1
Nasal Congestion	1
Hemic/Lymphatic	
Leukopenia/Decreased WBC Count/Neutropenia	3
Agranulocytosis	1[b]
Eosinophilia	1
Miscellaneous	
Fever	5
Weight Gain	4
Tongue Numb/Sore	1

[a]Events reported by at least 1% of clozapine patients are included.
[b]Rate based on population of approximately 1700 exposed during premarket clinical evaluation of clozapine.

Other Events Observed During the Premarketing Evaluation of Clozapine

This section reports additional, less frequent adverse events which occurred among the patients taking clozapine in clinical trials. Various adverse events were reported as part of the total experience in these clinical studies; a causal relationship to clozapine treatment cannot be

determined in the absence of appropriate controls in some of the studies. The table above enumerates adverse events that occurred at a frequency of at least 1% of patients treated with clozapine. The list below includes all additional adverse experiences reported as being temporally associated with the use of the drug which occurred at a frequency less than 1%, enumerated by organ system.

Central Nervous System: loss of speech, amentia, tics, poor coordination, delusions/ hallucinations, involuntary movement, stuttering, dysarthria, amnesia/memory loss, histrionic movements, libido increase or decrease, paranoia, shakiness, Parkinsonism, and irritability

Cardiovascular System: edema, palpitations, phlebitis/thrombophlebitis, cyanosis, premature ventricular contraction, bradycardia, and nose bleed

Gastrointestinal System: abdominal distention, gastroenteritis, rectal bleeding, nervous stomach, abnormal stools, hematemesis, gastric ulcer, bitter taste, and eructation

Urogenital System: dysmenorrhea, impotence, breast pain/discomfort, and vaginal itch/infection

Autonomic Nervous System: numbness, polydypsia, hot flashes, dry throat, and mydriasis

Integumentary (skin): pruritus, pallor, eczema, erythema, bruise, dermatitis, petechiae, and urticaria

Musculoskeletal System: twitching and joint pain

Respiratory System: coughing, pneumonia/pneumonia-like symptoms, rhinorrhea, hyperventilation, wheezing, bronchitis, laryngitis, and sneezing

Hemic and Lymphatic System: anemia and leukocytosis

Miscellaneous: chills/chills with fever, malaise, appetite increase, ear disorder, hypothermia, eyelid disorder, bloodshot eyes, and nystagmus

Postmarketing Clinical Experience

Postmarketing experience has shown an adverse experience profile similar to that presented above. Voluntary reports of adverse events temporally associated with clozapine not mentioned above that have been received since market introduction and that may have no causal relationship with the drug include the following:

Central Nervous System: delirium, EEG abnormal, exacerbation of psychosis, myoclonus, overdose, paresthesia, possible mild cataplexy, and status epilepticus

Cardiovascular System: atrial or ventricular fibrillation and periorbital edema

Gastrointestinal System: acute pancreatitis, dysphagia, fecal impaction, intestinal obstruction/paralytic ileus, and salivary gland swelling

Hepatobiliary System: cholestasis, hepatitis, jaundice

Hepatic System: cholestasis

Urogenital System: acute interstitial nephritis and priapism

Integumentary (skin): hypersensitivity reactions: photosensitivity, vasculitis, erythema multiforme, and Stevens-Johnson Syndrome

Musculoskeletal System: myasthenic syndrome and rhabdomyolysis

Respiratory System: aspiration and pleural effusion

Hemic and Lymphatic System: deep-vein thrombosis, elevated hemoglobin/hematocrit, ESR increased, pulmonary embolism, sepsis, thrombocytosis, and thrombocytopenia

Vision Disorders: narrow-angle glaucoma

Miscellaneous: creatine phosphokinase elevation, hyperglycemia, hyperuricemia, hyponatremia, and weight loss

DRUG ABUSE AND DEPENDENCE

Physical and psychological dependence have not been reported or observed in patients taking clozapine.

OVERDOSAGE

Human Experience

The most commonly reported signs and symptoms associated with clozapine overdose are: altered states of consciousness, including drowsiness, delirium, and coma; tachycardia; hypotension; respiratory depression or failure; and hypersalivation. Aspiration pneumonia and cardiac arrhythmias have also been reported. Seizures have occurred in a minority of reported cases. Fatal overdoses have been reported with clozapine, generally at doses above 2500 mg. There have also been reports of patients recovering from overdoses well in excess of 4 g.

Management of Overdose

Establish and maintain an airway; ensure adequate oxygenation and ventilation. Activated charcoal, which may be used with sorbitol, may be as or more effective than emesis or lavage and should be considered in treating overdosage. Cardiac and vital signs monitoring are recommended along with general symptomatic and supportive measures. Additional surveillance should be continued for several days because of the risk of delayed effects. Avoid epinephrine and derivatives when treating hypotension and quinidine and procainamide when treating cardiac arrhythmia.

There are no specific antidotes for FazaClo® (clozapine, USP). Forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit.

In managing overdosage, the physician should consider the possibility of multiple-drug involvement.

Up-to-date information about the treatment of overdose can often be obtained from a certified Regional Poison Control Center. Telephone numbers of certified Regional Poison Control Centers are listed in the *Physicians' Desk Reference*®, a registered trademark of Thomson PDR.

DOSAGE AND ADMINISTRATION

Administration

FazaClo® (clozapine, USP) rapidly disintegrates after placement in the mouth. The FazaClo® (clozapine, USP) Orally Disintegrating Tablet should be left in the unopened blister until time of use. The orally disintegrating tablet should not be pushed through the foil. Just prior to use, peel the foil from the blister and gently remove the orally disintegrating tablet. Immediately place the tablet in the mouth and allow to disintegrate and swallow with saliva. No water is needed to take FazaClo® (clozapine, USP).

Upon initiation of FazaClo® (clozapine, USP) therapy, up to a 1-week supply of additional FazaClo® (clozapine, USP) orally disintegrating tablets may be provided to the patient to be held for emergencies (eg, weather, holidays).

Initial Treatment

It is recommended that treatment with FazaClo® (clozapine, USP) begin with one-half of a 25-mg, orally disintegrating tablet (12.5 mg) once or twice daily. The remaining one-half tablet should be destroyed. The dosing should be continued with daily dosage increments of 25-50 mg/day, if well-tolerated, to achieve a target dose of 300-450 mg/day by the end of 2 weeks. Subsequent dosage increments should be made no more than once or twice weekly, in increments not to exceed 100 mg. Cautious titration and a divided dosage schedule are necessary to minimize the risks of hypotension, seizure, and sedation.

In the multicenter study that provides primary support for the effectiveness of clozapine in patients resistant to standard drug treatment for schizophrenia, patients' doses were titrated during the first 2 weeks up to a maximum dose of 500 mg/day on a t.i.d. basis. Subsequent dosage increments were then dosed in a total daily dose range of 100-900 mg/day on a t.i.d. basis, with clinical response and adverse effects as guides to correct dosing.

Therapeutic Dose Adjustment

Daily dosing should continue on a divided basis as an effective and tolerable dose level is sought. While many patients may respond adequately at doses between 300-600 mg/day, it may be necessary to raise the dose to the 600-900 mg/day range to obtain an acceptable response. (Note: In the multicenter study providing the primary support for the superiority of clozapine in treatment-resistant patients, the mean and median clozapine doses were both approximately 600 mg/day.)

Because of the possibility of increased adverse reactions at higher doses, particularly seizures, patients should ordinarily be given adequate time to respond to a given dose level before escalation to a higher dose is contemplated. Clozapine can cause EEG changes, including the occurrence of spike and wave complexes. It lowers the seizures threshold in a dose-dependent manner and may induce myoclonic jerks or generalized seizures. These symptoms may be likely to occur with rapid-dose increase and in patients with preexisting epilepsy. In this case, the dose should be reduced and, if necessary, anticonvulsant treatment initiated.

Dosing should not exceed 900 mg/day.

Because of the significant risk of agranulocytosis and seizure, events which both present a continuing risk over time, the extended treatment of patients failing to show an acceptable level of clinical response should ordinarily be avoided.

Maintenance Treatment

While the maintenance effectiveness of clozapine in schizophrenia is still under study, the effectiveness of maintenance treatment is well established for many other drugs used to treat schizophrenia. It is recommended that responding patients be continued on FazaClo® (clozapine, USP), but at the lowest level needed to maintain remission. Because of the significant risk associated with the use of FazaClo® (clozapine, USP), patients should be periodically reassessed to determine the need for maintenance treatment.

Discontinuation of Treatment

In the event of planned termination of FazaClo® (clozapine, USP) therapy, gradual reduction in dose is recommended over a 1-2 week period. However, should a patient's medical condition require abrupt discontinuation (eg, leukopenia), the patient should be carefully observed for the recurrence of psychotic symptoms and symptoms related to cholinergic rebound such as headache, nausea, vomiting, and diarrhea.

Reinitiation of Treatment in Patients Previously Discontinued

When restarting patients who have had even a brief interval off FazaClo® (clozapine, USP) (ie, 2 days or more since the last dose), it is recommended that treatment be reinitiated with one-half of a 25-mg, orally disintegrating tablet (12.5 mg) once or twice daily. The remaining one-half tablet should be destroyed. (See WARNINGS.) If that dose is well tolerated, it may be feasible to titrate patients back to a therapeutic dose more quickly than is recommended for initial treatment. However, any patient who has previously experienced respiratory or cardiac arrest with initial dosing but was then able to be successfully titrated to a therapeutic dose should be retitrated with extreme caution after even 24 hours of discontinuation.

Certain additional precautions seem prudent when reinitiating treatment. The mechanisms underlying clozapine-induced adverse reactions are unknown. It is conceivable, however, that reexposure of a patient might enhance the risk of an untoward event's occurrence and increase its severity. Such phenomena, for example, occur when immune-mediated mechanisms are responsible. Consequently, during the reinitiation of treatment, additional caution is advised.

Patients discontinued for WBC counts below 2000/mm^3 or an ANC below 1000/mm^3 must *not* be restarted on FazaClo® (clozapine, USP). (See WARNINGS.)

HOW SUPPLIED

FazaClo® (clozapine, USP) is available as 25- and 100-mg round, yellow, orally disintegrating tablets with a score on one side.

FazaClo® (clozapine, USP) Orally Disintegrating Tablets

25 mg

5/16-inch diameter tablet debossed with "A01" on one side and with a score on the opposite side.

Packages of 48: 8 cards, 6 non child-resistant blisters per card..... NDC 68322-001-01
Packages of 96: 16 cards, 6 non child-resistant blisters per card..... NDC 68322-001-02
Packages of 100: 100 child-resistant blisters..... NDC 68322-001-04

100 mg

1/2-inch diameter tablet debossed with "A02" on one side and with a score on the opposite side.

Packages of 48: 8 cards, 6 non child-resistant blisters per card..... NDC 68322-002-01
Packages of 96: 16 cards, 6 non child-resistant blisters per card..... NDC 68322-002-02
Packages of 100: 100 child-resistant blisters..... NDC 68322-002-04

Store and Dispense

Store FazaClo® (clozapine, USP) at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). (See *USP* Controlled Room Temperature.) Protect from moisture. The patient should be instructed not to remove the orally disintegrating tablet from the blister until the patient is ready to consume the tablet.

FazaClo® (clozapine, USP) must remain in the sealed blister until used by the patient. Drug dispensing should not ordinarily exceed a weekly supply. If a patient is eligible for WBC count and ANC testing every 2 weeks, then a two-week supply of FazaClo® (clozapine, USP) can be dispensed. If a patient is eligible for WBC count and ANC testing every 4 weeks, then a 4-week supply of FazaClo® (clozapine, USP) can be dispensed. Dispensing should be contingent upon the WBC count and ANC testing results.

Manufactured for

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