1 INDICATIONS AND USAGE

1.1 Treatment-Resistant Schizophrenia

Clozapine tablets are indicated for the treatment of severely ill patients with schizophrenia who fail to respond adequately to standard antipsychotic treatment. Because of the risks of severe neutropenia and of seizure associated with their use, clozapine tablets should be used only in patients who have failed to respond adequately to standard antipsychotic treatment (see Warnings and Precautions [5.1, 5.5]).

The effectiveness of clozapine tablets in treatment-resistant schizophrenia was demonstrated in a 6-week randomized, double-blind, active-controlled study comparing clozapine tablets and chlorpromazine in patients who had failed to respond to other antipsychotics (see Clinical Studies [14.1]).

1.2 Reduction in the Risk of Recurrent Suicidal Behavior in Schizophrenia or Schizoaffective Disorder

Clozapine tablets are indicated for reducing the risk of recurrent suicidal behavior and/or suicide in patients with schizophrenia or schizoaffective disorder who are judged to be at risk for suicide (see Warnings and Precautions [5.1]).

2 DOSAGE AND ADMINISTRATION

2.1 Required Laboratory Testing Prior to Initiation and During Therapy

Prior to initiating treatment with clozapine tablets, a baseline ANC must be obtained. The baseline ANC must be at least 1500/μL for the general population; and must be at least 1000/μL for patients with documented Benign Ethnic Neutropenia (BEN). During treatment, patients must have regular ANC monitoring. Advise patients to immediately report symptoms consistent with severe neutropenia or infection (e.g., fever, weakness, lethargy, or sore throat) (see Dosage and Administration [2.1] and Warnings and Precautions [5.1]).

Because of the risk of severe neutropenia, clozapine is available only through a restricted program under a Risk Evaluation Mitigation Strategy (REMS) called the Clozapine REMS Program (see Warnings and Precautions [5.2]).

Orthostatic Hypotension, Bradycardia, Syncope

Orthostatic hypotension, bradycardia, syncope, and cardiac arrest have occurred with clozapine treatment. The risk is highest during the initial titration period, particularly with rapid dose escalation. These reactions can occur with the first dose, with doses as low as 12.5 mg per day. Initiate treatment at 12.5 mg once or twice daily; titrate slowly; and use divided dosages. Use clozapine cautiously in patients with cardiovascular or cerebrovascular disease or conditions predisposing to hypotension (e.g., dehydration, use of antihypertensive medications) (see Dosage and Administration [2.2, 2.5], Warnings and Precautions [5.3]).

Seizures

Seizures have occurred with clozapine treatment. The risk is dose-related. Initiate treatment at 12.5 mg, titrate gradually, and use divided dosing. Use caution when administering clozapine to patients with a history of seizures or other predisposing risk factors for seizure (CNS pathology, medications that lower the seizure threshold, alcohol abuse). Caution patients about engaging in any activity where sudden loss of consciousness could cause serious risk to themselves or others (see Dosage and Administration [2.2], Warnings and Precautions [5.5]).

Myocarditis, Cardiomyopathy and Mitral Valve Incompetence

Fatal myocarditis and cardiomyopathy have occurred with clozapine treatment. Discontinue clozapine and obtain a cardiac evaluation upon suspicion of these reactions. Generally, patients with clozapine-related myocarditis or cardiomyopathy should not be rechallenged with clozapine. Consider the possibility of myocarditis or cardiomyopathy if chest pain, tachycardia, palpitations, dyspnea, fever, flu-like symptoms, hypotension, or ECG changes occur (see Warnings and Precautions [5.6]).

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Clozapine is not approved for use in patients with dementia-related psychosis (see Warnings and Precautions [5.7]).
CLOZAPINE TABLETS

2.7 Renal or Hepatic Impairment or CYP2D6 Poor Metabolizers
It may be necessary to reduce the clozapine tablets dose in patients with significant renal or hepatic impairment, or in CYP2D6 poor metabolizers [see Use in Specific Populations (8.6, 8.7)].

3 DOSAGE FORMS AND STRENGTHS
Clozapine tablets are available as 25 mg, 50 mg, 100 mg, and 200 mg pale-yellow tablets with a score on one side.

4 CONTRAINDICATIONS
4.1 Hypersensitivity
Clozapine tablets are contraindicated in patients with a history of serious hypersensitivity to clozapine (e.g., photosensitivity, vasculitis, erythema multiforme, or Stevens-Johnson Syndrome) or any other component of clozapine tablets [see Adverse Reactions (6.2)].

5 WARNINGS AND PRECAUTIONS

5.1 Severe Neutropenia

Background
Clozapine can cause neutropenia (a low absolute neutrophil count (ANC)), defined as a reduction below pre-treatment normal levels of blood neutrophils. The ANC is usually available as a component of the complete blood count (CBC), including differential, and is more relevant to drug-induced neutropenia than is the white blood cell (WBC) count. The ANC may also be calculated using the following formula: ANC equals the total WBC count multiplied by the total percentage of neutrophils obtained from the differential (neutrophil “segs” plus neutrophil “bands”). Other granulocytes (basophils and eosinophils) contribute minimally to neutropenia and their measurement is not necessary [see Adverse Reactions (6.2)]. Neutropenia may be mild, moderate, or severe (see Tables 2 and 3). To improve and standardize understanding, “severe neutropenia” replaces the previous terms severe leukopenia, severe granulocytopenia, or agranulocytosis.

Severe neutropenia, ANC less than (<) 500/μL, occurs in a small percentage of patients taking clozapine and is associated with an increase in the risk of serious and potentially fatal infections. Risk of neutropenia appears greatest during the first 18 weeks on treatment and then declines. The mechanism by which clozapine causes neutropenia is unknown and is not dose-dependent.

Two separate management algorithms are provided below, the first for patients in the general population, and the second for patients identified to have baseline neutropenia.

Clozapine Treatment and Monitoring in the General Patient Population (see Table 2)

Obtain a CBC, including the ANC value, prior to initiating treatment with clozapine to ensure the presence of a normal baseline neutrophil count (equal to or greater than 1500/μL) and to permit later comparisons. Patients in the general population with an ANC equal to or greater than (≥)1500/μL are considered within normal range (Table 2) and are eligible to initiate treatment. Weekly ANC monitoring is required for all patients during the first 6 months of treatment. If a patient’s ANC remains equal to or greater than 1500/μL for the first 6 months of treatment, monitoring frequency may be reduced to every 2 weeks for the next 6 months. If the ANC remains equal to or greater than 1500/μL for the second 6 months of continuous therapy, ANC monitoring frequency may be reduced to once every 4 weeks thereafter.

Table 2: Clozapine Treatment Recommendations Based on Absolute Neutrophil Count (ANC) Monitoring for the General Patient Population

<table>
<thead>
<tr>
<th>ANC Level</th>
<th>Clozapine Treatment Recommendations</th>
<th>ANC Monitoring</th>
</tr>
</thead>
</table>
| Normal range (<1500/μL)  | • Initiate treatment  
|                      | • If treatment interrupted:  
|                      | - ≤ 30 days, continue monitoring as before  
|                      | - > 30 days, monitor as if new patient  
|                      | • Discontinuation for reasons other than neutropenia  | • See Section 2.4 |
| Mild Neutropenia (1000 to 1499/μL)  | • Continue treatment  | • Three times weekly until ANC ≥1500/μL  
|                                          | • Once ANC ≥1500/μL, return to patient’s last “Normal Range” ANC monitoring interval2 | |
| Moderate Neutropenia (500 to 999/μL)  | • Recommend hematology consultation  
|                                          | • Interrupt treatment for suspected clozapine-induced neutropenia  
|                                          | • Resume treatment once ANC >1000/μL  | • Daily until ANC ≥1000/μL, then  
|                                          | • Three times weekly until ANC >1500/μL  
|                                          | • Once ANC >1500/μL, check ANC weekly for 4 weeks, then return to patient’s last “Normal Range” ANC monitoring interval2 |
| Severe Neutropenia (less than 500/μL)  | • Recommend hematology consultation  
|                                          | • Interrupt treatment for suspected clozapine-induced neutropenia  
|                                          | • Do not rechallenge unless prescriber determines benefits outweigh risks  | • Daily until ANC ≥1000/μL, then  
|                                          | • Three times weekly until ANC >1500/μL  
|                                          | • If patient rechallenged, resume treatment as a new patient under “Normal Range” monitoring once ANC ≥1500/μL  |

1. Confirm all initial reports of ANC less than 1500/μL with a repeat ANC measurement within 24 Hours
2. If clinically appropriate

Clozapine Treatment and Monitoring in Patients with Benign Ethnic Neutropenia (see Table 3)

Benign ethnic neutropenia (BEN) is a condition observed in certain ethnic groups whose average ANC values are lower than “standard” laboratory ranges for neutrophils. It is most commonly observed in individuals of African descent (approximate prevalence of 25 to 50%), some Middle Eastern ethnic groups, and in other non-Caucasian ethnic groups with darker skin. BEN is more common in men. Patients with BEN have normal hematopoietic stem-cell number and myeloid maturation, are healthy, and do not suffer from repeated or severe infections. They are not at increased risk for developing clozapine-induced neutropenia. Additional evaluation may be needed to determine if baseline neutropenia is due to BEN. Consider hematology consultation before initiating or during clozapine treatment as necessary.

Patients with BEN require a different ANC algorithm for clozapine management due to their lower baseline ANC levels. Table 3 provides guidelines for managing clozapine treatment and ANC monitoring in patients with BEN.

Table 3: Patients with Benign Ethnic Neutropenia (BEN): Clozapine Treatment Recommendations Based on Absolute Neutrophil Count (ANC) Monitoring

<table>
<thead>
<tr>
<th>ANC Level</th>
<th>Treatment Recommendations</th>
<th>ANC Monitoring</th>
</tr>
</thead>
</table>
| Normal BEN Range (Established ANC baseline ≥1000/μL)  | • Obtain at least two baseline ANC levels before initiating treatment  
|                      | • If treatment interrupted:  
|                      | - ≤ 30 days, continue monitoring as before  
|                      | - > 30 days, monitor as if new patient  | • Weekly from initiation to 6 months  
|                      | • Discontinuation of treatment for reasons other than neutropenia  | • See Section 2.4 |
| BEN Neutropenia 500 to 999/μL  | • Recommend hematology consultation  
|                                          | • Continue treatment  | • Three times weekly until ANC ≥ 1000/μL  
|                                          |                      | • Once ANC > 1000/μL or at patient’s known baseline  
|                                          |                      | • Check ANC weekly for 4 weeks, then return to patient’s last “Normal BEN Range” ANC monitoring interval2 |
| BEN Severe Neutropenia less than 500/μL  | • Recommend hematology consultation  
|                                          | • Interrupt treatment for suspected clozapine-induced neutropenia  | • Daily until ANC ≥500/μL, then  
|                                          | • Do not rechallenge unless prescriber determines benefits outweigh risks  | • Three times weekly until ANC ≥ patient’s baseline  
|                                          |                      | • If patient rechallenged, resume treatment as a new patient under “Normal Range” monitoring once ANC ≥1000/μL or at patient’s baseline  |

1. Confirm all initial reports of ANC less than 1500/μL with a repeat ANC measurement within 24 Hours
2. If clinically appropriate
CLOzapine Tablets

5.6 Myocarditis, Cardiomyopathy and Mitral Valve Incompetence
Myocarditis and cardiomyopathy have occurred with the use of clozapine. These reactions can be fatal. Discontinue clozapine and obtain a cardiac evaluation upon suspicion of myocarditis or cardiomyopathy. Generally, patients with a history of clozapine-associated myocarditis or cardiomyopathy should not be rechallenged with clozapine. However, if the benefit of clozapine treatment is judged to outweigh the potential risks of recurrent myocarditis or cardiomyopathy, the clinician may consider rechallenge with clozapine in consultation with a cardiologist, after a complete cardiac evaluation, and under close monitoring.

Consider the possibility of myocarditis or cardiomyopathy in patients receiving clozapine who present with chest pain, dyspnea, persistent tachycardia at rest, palpitations, fever, flu-like symptoms, hypotension, other signs or symptoms of heart failure, or electrocardiographic findings (low voltages, ST-T abnormalities, arrhythmias, right axis deviation, and poor R wave progression). Myocarditis most frequently presents within the first 2 months of clozapine treatment. Symptoms of cardiomyopathy are less common than myocarditis; however, cardiomyopathy has been reported to occur up to 8 weeks after initiation of treatment. However, myocarditis and cardiomyopathy can occur at any period during treatment with clozapine. It is common for nonspecific flu-like symptoms such as malaise, myalgia, pleuritic chest pain, and low-grade fevers to precede more overt signs of heart failure. Typical laboratory findings include elevated troponin I or T, and can resolve without intervention. There are reports of successful rechallenge at an increased risk of death. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death 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 rate of death in the clozapine group appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality in this population. The extent to which the findings of increased mortality in observational studies can be attributed to the antipsychotic drug or to some characteristic(s) of the patients is not clear. Clozapine is not approved for the treatment of patients with dementia-related psychosis [see Boxed Warning].

5.7 Increased Mortality in Elderly Patients with Dementia-Related Psychosis
Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death as compared to placebo. In one of the most comprehensive reviews of mortality studies in the literature, the rate of death of all causes in patients treated with atypical antipsychotics was about 1.9 times the rate of death of those in the placebo group, while the rate of death of all causes in patients treated with conventional antipsychotics was about 1.8 times the rate of death of those in the placebo group. The increased mortality in patients treated with conventional antipsychotics was observed regardless of age or sex; the cause of death was not specifically addressed but was often described as a cardiovascular issue, including congestive heart failure, in patients treated with clozapine.

Cardiogenic shock and sudden cardiac death have been reported in association with clozapine. However, if the benefit of clozapine treatment is judged to outweigh the potential risks of recurrent cardiogenic shock or sudden cardiac death, the clinician may consider rechallenge with clozapine in consultation with a cardiologist, after a complete cardiac evaluation, and under close monitoring.

If a cause of eosinophilia unrelated to clozapine is identified (e.g., asthma, allergies, collagen vascular disease, parasitic infections, and specific neoplasms), treat the underlying cause and continue clozapine. Clozapine-related eosinophilia has also occurred in the absence of organ involvement and eosinophil count decreases should be based on the overall clinical assessment, in consultation with an internist or hematologist.

5.9 QT Interval Prolongation
QT prolongation, Torsade de Pointes, and other life-threatening ventricular arrhythmias, cardiac arrest, and sudden death have occurred with clozapine treatment. When prescribing clozapine, consider the presence of additional risk factors for QT prolongation and serious cardiovascular reactions. Conditions that increase these risks include the following: history of QT prolongation, long QT syndrome, family history of long QT syndrome or sudden cardiac death, significant cardiac arrhythmia, recent myocardial infarction, uncompensated heart failure, treatment with other medications that cause QT prolongation, treatment with medications that inhibit the metabolism of clozapine, and electrolyte abnormalities. Prior to initiating treatment with clozapine, perform a careful physical examination, medical history, and concomitant medication history. Consider obtaining a baseline ECG and serum chemistry panel. Correct electrolyte abnormalities. Discontinue clozapine if the QTc interval exceeds 500 msec. If patients experience symptoms consistent with Torsades de Pointes, or other arrhythmias (e.g., syncope, presyncope, diziness, or palpitations), obtain a cardiac evaluation and discontinue clozapine.

5.8 Eosinophilia
Eosinophilia, defined as a blood eosinophil count of greater than 700/μL, has occurred with clozapine treatment. In clinical trials, approximately 1% of patients developed eosinophilia. Clozapine-related eosinophilia usually occurs during the first month of treatment. In some patients, it has been associated with myocardiitis, pancreatitis, hepatitis, colitis, and nephritis. Such organ involvement can be consistent with a histologically documented hypersensitivity syndrome (DRESS), also known as drug induced hypersensitivity syndrome (DIHS). If eosinophilia develops during clozapine treatment, evaluate promptly for signs and symptoms of systemic reactions, such as rash or other allergic symptoms, myocarditis, or other organ-specific disease associated with eosinophilia. If clozapine-related systemic disease is suspected, discontinue clozapine.

If a cause of eosinophilia unrelated to clozapine is identified (e.g., asthma, allergies, collagen vascular disease, parasitic infections, and specific neoplasms), treat the underlying cause and continue clozapine. Clozapine-related eosinophilia has also occurred in the absence of organ involvement and eosinophil count decreases should be based on the overall clinical assessment, in consultation with an internist or hematologist. Discontinue clozapine if the QTc interval exceeds 500 msec. If patients experience symptoms consistent with Torsades de Pointes, or other arrhythmias (e.g., syncope, presyncope, diziness, or palpitations), obtain a cardiac evaluation and discontinue clozapine.
Use caution when administering concomitant medications that prolong the QT interval or inhibit the metabolism of clozapine tablets. Drugs that cause QT prolongation include: specific antipsychotics (e.g., ziprasidone, iloperidone, chlorpromazine, thioridazine, mesoridazine, droperidol, pimozide), specific antibiotics (e.g., erythromycin, gatifloxacin, moxifloxacin, sparfloxacin), Class 1A antiarrhythmic medications (e.g., quinidine, procaainamide) or Class III antiarrhythmics (e.g., amiodarone, sotalol), and others (e.g., pentamidine, levomefentanyl, levomefentanyl, halofantrine, melflufen, dolasetron mesylate, procainamide or tacrolimus). Clozapine is primarily metabolized by CYP isoenzymes 1A2, 2C9, and 3A4. Concomitant treatment with inhibitors of these enzymes can increase the concentration of clozapine tablets [see Drug Interactions (7.1) and Clinical Pharmacology (12.3)]. Hypokalemia and hypomagnesemia increase the risk of QT prolongation. Hypokalemia can result from diuretic therapy, diarrhea, and other causes. Use caution when treating patients at risk for significant electrolyte disturbance, particularly hypokalemia. Obtain baseline measurements of serum potassium and magnesium levels, and periodically monitor electrolytes. Correct electrolyte abnormalities before initiating treatment with clozapine.

### 5.10 Metabolic Changes

Atypical antipsychotic drugs, including clozapine, have been associated with metabolic changes that can increase cardiovascular and cerebrovascular risk. These metabolic changes include hyperglycemia, dyslipidemia, and body weight gain. While atypical antipsychotic drugs may produce some metabolic changes, each drug in the class has its own specific risk profile.

#### Hyperglycemia and Diabetes Mellitus

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar nonketotic 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 confounding factors, the relationship between atypical antipsychotic use and hyperglycemia-related adverse reactions is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent, hyperglycemia-related adverse reactions in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse reactions in patients treated with atypical antipsychotics are not available. Patients with an established diagnosis of diabetes mellitus who are started on clozapine should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., 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.

In a pooled data analysis of 8 studies in adult subjects with schizophrenia, the mean changes in fasting glucose concentration in the clozapine and chlorpromazine groups were +11 mg/dL and +4 mg/dL, respectively. A higher proportion of the clozapine group demonstrated categorical increases from baseline in fasting glucose concentrations, compared to the chlorpromazine group (Table 4). The clozapine doses were 100 to 900 mg per day (mean modal dose: 512 mg per day). The maximum clozapine dose was 1800 mg per day (mean modal dose: 1029 mg per day). The median duration of exposure was 42 days for clozapine and chlorpromazine.

#### Table 4: Categorical Changes in Fasting Glucose Level in Studies in Adult Subjects with Schizophrenia

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>Category Change (at least once) from baseline</th>
<th>Treatment Arm</th>
<th>N</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting Glucose</td>
<td>Normal (&lt; 100 mg/dL) to High (≥ 126 mg/dL)</td>
<td>Clozapine</td>
<td>198</td>
<td>53 (27)</td>
</tr>
<tr>
<td></td>
<td>borderle (100 to 125 mg/dL) to High (≥ 126 mg/dL)</td>
<td>Chlorpromazine</td>
<td>135</td>
<td>14 (10)</td>
</tr>
</tbody>
</table>

#### Dyslipidemia

Undesirable alterations in lipids have occurred in patients treated with atypical antipsychotics, including clozapine. Clinical monitoring, including baseline and periodic follow-up lipid evaluations in patients using clozapine, is recommended. In a pooled data analysis of 10 studies in adult subjects with schizophrenia, clozapine treatment was associated with increases in serum total cholesterol. No data were collected on LDL and HDL cholesterol. The mean increase in total cholesterol was 13 mg/dL in the clozapine group and 15 mg/dL in the chlorpromazine group. In a pooled data analysis of 2 studies in adult subjects with schizophrenia, clozapine treatment was associated with increases in fasting serum triglyceride. The mean increase in fasting triglyceride was 71 mg/dL (54%) in the clozapine group and 39 mg/dL (35%) in the chlorpromazine group (Table 5). In addition, clozapine treatment was associated with categorical increases in serum total cholesterol and triglyceride, as illustrated in Table 6. The proportion of patients with categorical increases in total cholesterol or fasting triglyceride increased with the duration of exposure. The median duration of clozapine and chlorpromazine exposure was 45 days and 38 days, respectively. The clozapine dose range was 100 mg to 900 mg daily; the maximum chlorpromazine dose was 1800 mg daily.

#### Table 5: Mean Changes in Total Cholesterol and Triglyceride Concentration in Studies in Adult Subjects with Schizophrenia

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>Baseline total cholesterol concentration (mg/dL)</th>
<th>Change from baseline mg/dL (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine</td>
<td>184</td>
<td>+13 (7)</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>182</td>
<td>+15 (8)</td>
</tr>
</tbody>
</table>

#### Table 6: Categorical Changes in Lipid Concentrations in Studies in Adult Subjects with Schizophrenia

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Treatment Arm</th>
<th>N</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triglycerides (fasting)</td>
<td>Increase by ≥ 50 mg/dL</td>
<td>Clozapine</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Normal (&lt; 150 mg/dL) to High (≥ 200 mg/dL)</td>
<td>Chlorpromazine</td>
<td>7</td>
</tr>
</tbody>
</table>

#### Table 7: Mean Change in Body Weight (kg) by Duration of Exposure from Studies in Adult Subjects with Schizophrenia

<table>
<thead>
<tr>
<th>Weight change from baseline</th>
<th>Clozapine (N = 669)</th>
<th>Olanzapine (N = 442)</th>
<th>Chlorpromazine (N = 155)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 weeks</td>
<td>+0.9</td>
<td>+0.7</td>
<td>+0.8</td>
</tr>
<tr>
<td>(Day 11 to 17)</td>
<td></td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>4 weeks</td>
<td>+0.7</td>
<td>+1.9</td>
<td>+1.8</td>
</tr>
<tr>
<td>(Day 21 to 35)</td>
<td></td>
<td>8</td>
<td>17</td>
</tr>
<tr>
<td>8 weeks</td>
<td>+1.9</td>
<td>+2.8</td>
<td>+3.1</td>
</tr>
<tr>
<td>(Day 49 to 63)</td>
<td></td>
<td>13</td>
<td>16</td>
</tr>
<tr>
<td>12 weeks</td>
<td>+2.8</td>
<td>+5.7</td>
<td>+5.7</td>
</tr>
<tr>
<td>(Day 70 to 98)</td>
<td></td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>24 weeks</td>
<td>+0.6</td>
<td>+3.7</td>
<td>+3.7</td>
</tr>
<tr>
<td>(Day 154 to 182)</td>
<td></td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>48 weeks</td>
<td>+3.7</td>
<td>+13.7</td>
<td>+13.7</td>
</tr>
<tr>
<td>(Day 322 to 350)</td>
<td></td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>

#### Weight Gain

Weight gain has occurred with the use of antipsychotics, including clozapine. Monitor weight during treatment with clozapine. Table 7 summarizes the data on weight gain by the duration of exposure pooled from 11 studies with clozapine and active comparators. The median duration of exposure was 609, 728, and 42 days, in the clozapine, olanzapine, and chlorpromazine group, respectively.

#### Table 8: Proportion of Adult Subjects in Schizophrenia Studies with Weight Gain ≥ 7% Relative to Baseline Body Weight

<table>
<thead>
<tr>
<th>Weight change</th>
<th>Clozapine</th>
<th>Olanzapine</th>
<th>Chlorpromazine</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>669</td>
<td>442</td>
<td>155</td>
</tr>
</tbody>
</table>

#### Table 9: Proportion of Adult Subjects in Schizophrenia Studies with Weight Gain ≥ 7% Relative to Baseline Body Weight

<table>
<thead>
<tr>
<th>Weight change</th>
<th>Clozapine</th>
<th>Olanzapine</th>
<th>Chlorpromazine</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>669</td>
<td>442</td>
<td>155</td>
</tr>
</tbody>
</table>

#### 5.11 Neuroleptic Malignant Syndrome

Antipsychotic drugs including clozapine can cause a potentially fatal symptom complex referred to as Neuroleptic Malignant Syndrome (NMS). Clinical manifestations of NMS include hyperpyrexia, muscle rigidity, altered mental status, and autonomic
instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias). Associated findings can include elevated creatine phosphokinase (CPK), myoglobinuria, rhabdomyolysis, and acute renal failure. The diagnostic evaluation of patients with this syndrome is complicated. It is important to consider the presence of other serious medical conditions (e.g., severe neutropenia, infection, heat stroke, primary CNS pathology, central anticholinergic toxicity, extrapyramidal symptoms, and drug fever). 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 comorbid medical conditions. There is no general agreement about specific pharmacological treatments for NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. NMS can recur. Monitor closely if restarting treatment with antipsychotics. NMS has occurred with clozapine monotherapy and with concomitant CNS-activating medications, including lithium.

5.12 Hepatotoxicity
Severe, life threatening, and in some cases fatal hepatotoxicity including hepatic failure, hepatic necrosis, and hepatitis have been reported in post marketing studies in patients treated with clozapine [see Adverse Reactions (6.2)]. Monitor for the appearance of signs and symptoms of hepatotoxicity such as fatigue, malaise, anorexia, nausea, jaundice, bilirubinemia, coagulopathy, and hepatic encephalopathy. Perform serum tests for liver injury and consider permanently discontinuing treatment if hepatitis or transaminase elevations combined with other systemic symptoms are due to clozapine.

5.13 Fever
During clozapine therapy, patients have experienced transient, clozapine-related fever. The peak incidence is within the first 3 weeks of treatment. While this fever is generally benign and self-limited, it may necessitate discontinuing treatment. The fever was found with an increase in core temperature in WBC count. Carefully evaluate patients with fever to rule out severe neutropenia or infection. Consider the possibility of NMS [see Warnings and Precautions (5.11)].

5.14 Pulmonary Embolism
Pulmonary embolism and deep-vein thrombosis have occurred in patients treated with clozapine tablets. Consider the possibility of pulmonary embolism in patients who present with deep-vein thrombosis, acute dyspnea, chest pain, or with other respiratory signs and symptoms. Whether pulmonary embolus and deep-vein thrombosis can be attributed to clozapine or some characteristic(s) of patients is not clear.

5.15 Anticholinergic Toxicity
Clozapine has potent anticholinergic effects. Treatment with clozapine can result in CNS and peripheral anticholinergic toxicity. Use with caution in the presence of narrow-angle glaucoma, concomitant anticholinergic medications, prostatic hypertrophy, or other conditions in which anticholinergic effects can lead to significant adverse reactions. Treatment with clozapine can result in gastrointestinal adverse reactions, including constipation, intestinal obstruction, fecal impaction, and paralytic ileus. Such adverse reactions are due to clozapine.

5.16 Interference with Cognitive and Motor Performance
Clozapine can cause sedation and impairment of cognitive and motor performance. Caution patients about operating hazardous machinery, including automobiles, until they are reasonably certain that clozapine does not affect them adversely. These reactions may be dose-related. Consider reducing the dose if they occur.

5.17 Tardive Dyskinesia
Tardive dyskinesia (TD) has occurred in patients treated with antipsychotic drugs, including clozapine. The syndrome consists of potentially irreversible, involuntary, dyskinetic movements. The risk of TD and the likelihood that it will become irreversible are believed to increase with greater durations of treatment and higher total cumulative doses. However, the syndrome can develop after relatively brief treatment periods at low doses. Prescribe clozapine in a manner that is most likely to minimize the risk of developing TD. Use the lowest effective dose and the shortest duration of treatment consistent with the patient’s needs. Consider discontinuing treatment if TD occurs. However, some patients may require treatment with clozapine despite the presence of the syndrome. There is no known treatment for TD. However, the syndrome may remit partially or completely if treatment is discontinued. Antipsychotic treatment, itself, may suppress (or partially suppress) the signs and symptoms, and it has the potential to mask the underlying process. The effect of symptom suppression on the long-term course of TD is unknown.

5.18 Cerebrovascular Adverse Reactions
In controlled trials, elderly patients with dementia-related psychosis treated with some atypical antipsychotics had an increased risk (compared to placebo) of cerebrovascular adverse reactions (e.g., stroke, transient ischemic attack), including fatalities. The mechanism for this increased risk is not known. An increased risk cannot be excluded for clozapine or other antipsychotics or other patient populations. Clozapine should be used with caution in patients with risk factors for cerebrovascular adverse reactions.

5.19 Recurrence of Psychosis and Cholinergic Rebound after Abrupt Discontinuation of Clozapine
If abrupt discontinuation of clozapine is necessary (because of severe neutropenia or another medical condition, for example) [see Dosage and Administration (2.4), Warnings and Precautions (5.1)], monitor carefully for the recurrence of psychotic symptoms and adverse reactions related to cholinergic rebound, such as profuse sweating, headache, nausea, vomiting and diarrhea.

6 ADVERSE REACTIONS
The following adverse reactions are discussed in more detail in other sections of the labeling:

- Severe Neutropenia [see Warnings and Precautions (5.1)].
- Orthostatic Hypotension, Bradycardia, and Syncope [see Warnings and Precautions (5.3)].
- Falls [see Warnings and Precautions (5.4)].
- Seizures [see Warnings and Precautions (5.5)].
- Myocarditis, Cardiomyopathy and Mitral Valve Incompetence [see Warnings and Precautions (5.6)].
- Increased Mortality in Elderly Patients with Dementia-Related Psychosis [see Warnings and Precautions (5.7)].
- Eosinophilia [see Warnings and Precautions (5.8)].
- Intestinal Prolongation [see Warnings and Precautions (5.9)].
- Metabolic Changes (Hyperglycemia and Diabetes Mellitus, Dyslipidemia, and Weight Gain) [see Warnings and Precautions (5.10)].
- Neuroleptic Malignant Syndrome [see Warnings and Precautions (5.11)].
- Hepatotoxicity [see Warnings and Precautions (5.12)].
- Fever [see Warnings and Precautions (5.13)].
- Pulmonary Embolism [see Warnings and Precautions (5.14)].
- Anticholinergic Toxicity [see Warnings and Precautions (5.15)].
- Interference with Cognitive and Motor Performance [see Warnings and Precautions (5.16)].
- Tardive Dyskinesia [see Warnings and Precautions (5.17)].
- Cerebrovascular Adverse Reactions [see Warnings and Precautions (5.18)].
- Recurrence of Psychosis and Cholinergic Rebound after Abrupt Discontinuation [see Warnings and Precautions (5.19)].

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice. The most commonly reported adverse reactions (≥ 5%) across clozapine clinical trials were: CNS reactions, including sedation, dizziness/vertigo, headache, and tremor; cardiovascular reactions, including tachycardia, hypotension, and syncope; autonomic nervous system reactions, including hypersalivation, sweating, dry mouth, and visual disturbances; gastrointestinal reactions, including constipation and nausea; and fever. Table 9 summarizes the most commonly reported adverse reactions (≥ 5%) in clozapine-treated patients (compared to chlorpromazine-treated patients) in the pivotal, 6 week, randomized, chlorpromazine-controlled trial in Treatment-Resistant Schizophrenia.

Table 9: Common Adverse Reactions (≥ 5%) in the 6 Week, Randomized, Chlorpromazine-controlled Trial in Treatment-Resistant Schizophrenia

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Clozapine (N = 126) (%)</th>
<th>Chlorpromazine (N = 142) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sedation</td>
<td>21</td>
<td>13</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>17</td>
<td>11</td>
</tr>
<tr>
<td>Constipation</td>
<td>16</td>
<td>12</td>
</tr>
<tr>
<td>Dizziness</td>
<td>14</td>
<td>16</td>
</tr>
<tr>
<td>Hypotension</td>
<td>13</td>
<td>38</td>
</tr>
<tr>
<td>Fever (hypothermia)</td>
<td>13</td>
<td>4</td>
</tr>
<tr>
<td>Hypersalivation</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>Headache</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>5</td>
<td>20</td>
</tr>
</tbody>
</table>

Table 10 summarizes the adverse reactions reported in clozapine-treated patients at a frequency of 2% or greater across all clozapine studies (excluding the 2 year InterSePT™ Study). These rates are not adjusted for duration of exposure.

Table 10: Adverse Reactions (≥ 2%) Reported in Clozapine-treated Patients (N = 842) Across All Clozapine Studies (excluding the 2 year InterSePT™ Study)

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse Reaction*</th>
<th>Clozapine N = 842 Percentage of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central Nervous System</td>
<td>Drowsiness/Sedation</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td>Dizziness/Vertigo</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>Headache</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Tremor</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Syncope</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Disturbed Sleep/Nightmares</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Restlessness</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Hypokinesia/Akinisia</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Agitation</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Seizures (convulsions)</td>
<td>3'</td>
</tr>
</tbody>
</table>
|              | Rigidity         | 3                        | continued
CLOZAPINE TABLETS

7.2 Potential for Clozapine to Affect Other Drugs

CYP1A2 Inhibitors

Concomitant use of clozapine tablets and CYP1A2 inhibitors can increase plasma levels of clozapine, potentially resulting in adverse reactions. Reduce the clozapine tablets dose to one-third of the original dose when clozapine tablets are coadministered with CYP1A2 inhibitors (e.g., fluvoxamine, ciprofloxacin, cimetidine). The clozapine tablets dose should be increased to the original dose when coadministration of strong CYP1A2 inhibitors is discontinued [see Dosage and Administration (2.6), Clinical Pharmacology (12.3)]. Use caution and monitor patients closely when using such inhibitors. Consider reducing the clozapine tablets dosage if necessary [see Dosage and Administration (2.6)].

CYP2D6 and CYP3A4 Inhibitors

Concomitant treatment with clozapine tablets and CYP2D6 or CYP3A4 inhibitors (e.g., cimetidine, escitalopram, erythromycin, paroxetine, bupropion, fluoxetine, quinidine, d氯zoxetin, terbinafine, or sertraline) can increase clozapine levels and lead to adverse reactions [see Clinical Pharmacology (12.3)]. Use caution and monitor patients closely when using such inhibitors. Consider reducing the clozapine tablets dosage if necessary [see Dosage and Administration (2.6)].

7.3 Potential for Other Drugs to Affect Clozapine

Class effect: Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and at higher doses of first generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of clozapine. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Central Nervous System

Dizziness, somnolence, sedation, confusion, agitation, voiding disturbance, and ataxia.

Cardiovascular System

Tachycardia, hypotension, hypertension, and bradycardia.

Adverse Reaction*  Clozapine N = 842  Olanzapine N = 477

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<th>Adverse Reaction</th>
<th>Clozapine % Reporting</th>
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Table 11 summarizes the most commonly reported adverse reactions (≥ 10% of the clozapine or olanzapine group) in the InterSePT™ Study. This was an adequate and well-controlled, two-year study evaluating the efficacy of clozapine relative to olanzapine in reducing the risk of suicidal behavior in patients with schizophrenia or schizoaffective disorder. The rates are not adjusted for duration of exposure.

Table 11: Incidence of Adverse Reactions in Patients Treated with Clozapine or Olanzapine in the InterSePT™ Study (≥ 10% in the clozapine or olanzapine group)

Dystonia

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8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

Risk Summary

There are no adequate or well-controlled studies of clozapine in pregnant women. Reproduction studies have been performed in rats and rabbits at doses up to 0.4 and 0.9 times, respectively, the maximum recommended human dose (MRHD) of 900 mg/day on a mg/m² body surface area basis. The studies revealed no evidence of impaired fertility or harm to the fetus due to clozapine. Because animal reproduction studies are not always predictive of human response, clozapine tablets should be used during pregnancy only if clearly needed.

Clinical Considerations

Consider the risk of exacerbation of psychosis when discontinuing or changing treatment with antipsychotic medications during pregnancy and postpartum. Consider early screening for gestational diabetes for patients treated with antipsychotic medications (see Warnings and Precautions (5.10)). Neonates exposed to antipsy- chotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. Monitor neonates for symptoms of agitation, hyperto- nia, hypotonia, tremor, somnolence, respiratory distress, and feeding difficulties. The severity of complications can vary from self-limited symptoms to some neonates requiring intensive care unit support and prolonged hospitalization.

Animal Data

In embryofetal developmental studies, clozapine had no effects on maternal parameters, litter sizes, or fetal parameters when administered orally to pregnant rats and rabbits during the period of organogenesis at doses up to 0.4 and 0.9 times, respectively, the MRHD of 900 mg/day on a mg/m² body surface area basis. In peri/postnatal developmental studies, pregnant female rats were administered clozapine over the last third of pregnancy and until day 21 postpartum. Observations were made on fetuses at birth and during the postnatal period; the offspring were allowed to reach sexual maturity and mated. Clozapine caused a decrease in maternal body weight but had no effects on litter size or body weights of either F1 or F2 generations at doses up to 0.4 times the MRHD of 900 mg/day on a mg/m² body surface area basis.

8.3 Nursing Mothers

Clozapine is present in human milk. Because of the potential for serious adverse reactions in nursing infants from clozapine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Patients

There have not been sufficient numbers of geriatric patients in clinical studies utilizing clozapine to determine whether those over 65 years of age differ from younger subjects in their response to clozapine. Orthostatic hypotension and tachycardia can occur with clozapine treatment (see Boxed Warning and Warnings and Precautions (5.3)). Elderly patients, particularly those who are symptomatic and who have compromised cardiovascular functioning, may be more susceptible to these effects.

Elderly patients may be particularly susceptible to the anticholinergic effects of clozapine, such as urinary retention and constipation (see Warnings and Precautions (15.2)). Carefully select clozapine doses in elderly patients, taking into consideration their greater frequency of decreased hepatic, renal, or cardiac function, as well as other concomitant disease and other drug therapy. Clinical experience suggests that the prevalence of tardive dyskinesia appears to be highest among the elderly; especially elderly women (see Warnings and Precautions (5.4)).

8.6 Patients with Renal or Hepatic Impairment

Dose reduction may be necessary in patients with significant impairment of renal or hepatic function. Clozapine concentrations may be increased in these patients, because clozapine is almost completely metabolized and then excreted (see Dosage and Administration (2.7), Clinical Pharmacology (12.3)).

8.7 CYP2D6 Poor Metabolizers

Dose reduction may be necessary in patients who are CYP2D6 poor metabolizers. Clozapine concentrations may be increased in these patients, because clozapine is almost completely metabolized and then excreted (see Dosage and Administration (2.7), Clinical Pharmacology (12.3)).

8.8 Hospice Patients

For hospice patients (i.e., terminally ill patients with an estimated life expectancy of six months or less), the prescriber may reduce the ANC monitoring frequency to once every 6 months, after a discussion with the patient and his/her caregiver. Individual treatment decisions should weigh the importance of monitoring ANC in the context of the need to control psychiatric symptoms and the patient’s terminal illness.

10 OVERDOSE

10.1 Overdose Experience

The most commonly reported signs and symptoms associated with clozapine overdose are: sedation, delirium, coma, tachycardia, hypotension, respiratory depression or failure, and hyperthermia. There are reports of aspiration pneumonia, cardiac arrhythmias, and seizure. 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.

10.2 Management of Overdose

For the most up-to-date information on the management of clozapine overdose, contact a certified Regional Poison Control Center (1-800-222-1222). Telephone numbers of certified Regional Poison Control Centers are listed in the Physicians’ Desk Reference®. Establish and maintain an airway; ensure adequate oxygenation and ventilation. Monitor cardiac status and vital signs. Use general symptomatic and supportive measures. There are no specific antidotes for clozapine.

In managing overdose, consider the possibility of multiple-drug involvement.

11 DESCRIPTION

Clozapine tablets USP, an atypical antipsychotic drug, is a tricyclic dibenzoazepine derivative. The chemical name of clozapine, USP is 8-chloro-11-(4-methyl-1-piperazinyl)-5H-dibenzo[b,e] [1,4] diazepine and it has the following structural formula:

![Clozapine Structural Formula](image)

Clozapine, USP is a yellow, crystalline powder, very slightly soluble in water. Each tablet, for oral administration, contains 25 mg, 50 mg, 100 mg, or 200 mg clozapine, USP. In addition, each tablet contains the following inactive ingredients: colloidal silicon dioxide, corn starch, magnesium stearate, povidone, pregelatinized corn starch, and talc. Additionally, the 25 mg and 100 mg tablets contain lactose monohydrate and the 50 mg and 200 mg tablets contain anhydrous lactose and croscpovidone.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of clozapine is unknown. However, it has been proposed that the therapeutic efficacy of clozapine in schizophrenia is mediated through antagonism of the dopamine type 2 (D2) and the serotonin type 2A (5-HT2A) receptors. Clozapine tablets also act as an antagonist at adrenergic, cholinergic, histaminergic and other dopaminergic and serotonergic receptors.

12.2 Pharmacodynamics

Clozapine demonstrated binding affinity to the following receptors: histamine H1 (Kᵢ 1.1 nM), adrenergic α1 (Kᵢ 1.6 nM), serotonin 5-HT2A (Kᵢ 4 nM), serotonin 5-HT2C (Kᵢ 5.4 nM), muscarinic M1 (Kᵢ 6.2 nM), serotonin 5-HT6 (Kᵢ 6.3 nM), serotonin 5-HT7 (Kᵢ 9.3 nM), dopamine D1 (Kᵢ 24 nM), dopamine D2 (Kᵢ 90 nM), dopamine D3 (Kᵢ 1.1 nM), dopamine D4 (Kᵢ 160 nM), dopamine D5 (Kᵢ 270 nM), dopamine D6 (Kᵢ 454 nM), and dopamine D7 (Kᵢ 555 nM).

Clozapine causes little or no prolactin elevation.

Clinical electroencephalogram (EEG) studies demonstrated 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 have reported 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.

12.3 Pharmacokinetics

Absorption

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 Drug Interactions (7)).

Metabolism and Excretion

Clozapine is almost completely metabolized prior to excretion, and only trace amounts of unchanged drug are detected in the urine and feces. Clozapine is a substrate for many cytochrome P450 isozymes, in particular CYP1A2, CYP2D6, and CYP3A4. 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 to 12 hours), compared to a mean elimination half-life of 12 hours (range: 4 to 66 hours), after achieving steady state with 100 mg twice daily dosing.

A comparison of single-dose and multiple-dose administration of clozapine demonstrated 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, approximately doubling the dosage (e.g., from 37.5 to 75 mg twice daily) increased the mean elimination half-life from 8 hours to 12 hours (range: 5 to 22 hours).
CLOZAPINE TABLETS

Drug-Drug Interaction Studies

Fluvoxamine
A pharmacokinetic study was conducted in 16 schizophrenic patients who received clozapine under steady-state conditions. After coadministration of fluvoxamine for 14 days, mean trough concentrations of clozapine and its metabolites, N-desmethyl-clozapine and clozapine-N-oxide, were elevated about three-fold compared to base-line steady-state concentrations. Paroxetine, Fluoxetine, and Sertraline
In a study of schizophrenic patients (n = 14) who received clozapine under steady-state conditions, coadministration of 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.

Specific Population Studies
Renal or Hepatic Impairment
No specific pharmacokinetic studies were conducted to investigate the effects of renal or hepatic impairment on the pharmacokinetics of clozapine. Higher clozapine plasma concentrations are likely in patients with significant renal or hepatic impairment when given usual doses.

CYP2D6 Poor Metabolizers
A subset (3% to 10%) of the population has reduced activity of CYP2D6 (CYP2D6 poor metabolizers). These individuals may develop higher than expected plasma concentrations of clozapine when given usual doses.

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenesis
No carcinogenic potential was demonstrated in long-term studies in mice and rats at doses up to 0.3 times and 0.4 times, respectively, the maximum recommended human dose (MRHD) of 900 mg/day on a mg/m² body surface area basis.

Mutagenesis
Clozapine was not genotoxic when tested in the following gene mutation and chromosomal aberration tests: the bacterial Ames test, the in vitro mammalian V79 Chinese hamster cells, the in vitro unscheduled DNA synthesis in rat hepatocytes or the in vivo micronucleus assay in mice.

Impairment of Fertility
Clozapine had no effect on any parameters of fertility, pregnancy, fetal weight or postnatal development when administered orally to male rats 70 days before mating and to female rats for 14 days before mating at doses up to 0.4 times the MRHD of 900 mg/day on a mg/m² body surface area basis.

14 CLINICAL STUDIES
14.1 Treatment-Resistant Schizophrenia
The efficacy of clozapine in treatment-resistant schizophrenia was established in a multicenter, randomized, double-blind, active-controlled (chlorpromazine) study in patients with a DSM-III diagnosis of schizophrenia who had inadequate responses to at least 3 different antipsychotics (from at least 2 different chemical classes) during the preceding 5 years. The antipsychotic trials must have been judged adequate; the antipsychotic dosages must have been equivalent to or greater than 1000 mg per day of chlorpromazine for a period of at least 6 weeks, each without significant reduction of symptoms. There must have been no period of good functioning within the preceding 5 years. Patients must have had a baseline score of at least 45 on the investigator-rated Brief Psychiatric Rating Scale (BPRS). On the 18-item BPRS, 1 indicates the absence of symptoms, and 7 indicates severe symptoms; the maximum potential total BPRS score is 126. At baseline, the mean BPRS score was 61. In addition, patients must have had a score of at least 4 on at least two of the following four individual BPRS items: conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content. Patients must have had a Clinical Global Impressions–Severity Scale score of at least 4 (moderately ill).

In the prospective, lead-in phase of the trial, all patients (N = 305) initially received single-blind treatment with haloperidol (the mean dose was 61 mg per day) for 6 weeks. More than 80% of patients completed the 6 week trial. Patients with an inadequate response to haloperidol (n = 268) were randomized to double-blind treatment with clozapine (N = 126) or chlorpromazine (N = 142). The maximum daily clozapine dose was 900 mg; the mean daily dose was 600 mg. The maximum daily chlorpromazine dose was 1800 mg; the mean daily dose was 1200 mg.

The primary endpoint was treatment response, predefined as a decrease in BPRS score of at least 20% and a Clinical Global Impressions–Severity Scale score of at least 4 (moderately ill). The mean change in total BPRS score was -16 and -5 in the clozapine and chlorpromazine groups, respectively; the mean change, expressed as a percentage, in the 4 key BPRS items was -5 and -2 in the clozapine and chlorpromazine group, respectively, and the mean change in CGI-S score was -1.2 and -0.4, in the clozapine and chlorpromazine group, respectively. These changes in the clozapine group were statistically significantly greater than in the chlorpromazine group (p = 0.001 in each analysis).

14.2 Recurrent Suicidal Behavior in Schizophrenia or Schizoaffective Disorder
The effectiveness of clozapine in reducing the risk of recurrent suicidal behavior was assessed in the International Suicide Prevention Trial (InterSePT™). This was a prospective, randomized, open-label, active-controlled, multicenter, international, parallel-group comparison of clozapine versus olanzapine (Zyprexa®) in 956 patients with schizophrenia or schizoaffective disorder (DSM-IV) who were judged to be at risk for recurrent suicidal behavior. Only about one-fourth of these patients (27%) were considered resistant to standard antipsychotic drug treatment. To enter the trial, patients must have met 1 of the following criteria:
- They had attempted suicide within the three years prior to their baseline evaluation.
- They had been hospitalized to prevent a suicide attempt within the three years prior to their baseline evaluation.
- They demonstrated moderate-to-severe suicidal ideation with a depressive component within one week prior to their baseline evaluation.
- They demonstrated moderate-to-severe suicidal ideation accompanied by command hallucinations to do self-harm within one week prior to their baseline evaluation.

Dosing regimens for each treatment group were determined by individual investigators and were individualized by patient. Dosing was flexible, with a dose range of 200 to 900 mg/day for clozapine and 5 to 20 mg/day for olanzapine. For the 956 patients who received clozapine or olanzapine in this study, there was extensive use of concomitant psychotropics; 64% with antipsychotics, 65% with anxiolytics, 53% with antidepressants, and 28% with mood stabilizers. There was significantly greater use of concomitant psychotropic medications among the patients in the olanzapine group.

The primary efficacy measure was time to (1) a significant suicide attempt, including a completed suicide; (2) hospitalization due to imminent suicide risk, including increased level of surveillance for suicidality for patients already hospitalized; or (3) worsening of suicidality severity as demonstrated by “much worsening” or “very much worsening” from baseline in the Clinical Global Impression of Severity of Suicidality as assessed by the Blinded Psychiatrist (CGI-S-S-SP) scale. A determination of whether or not a reported event met criterion 1 or 2 above was made by the Suicide Monitoring Board (SMB), a group of experts blinded to patient data.

A total of 980 patients were randomized to the study and 956 received study medication. Sixty-two percent of the patients were diagnosed with schizophrenia, and the remainder (38%) were diagnosed with schizoaffective disorder. Only about one-fourth of the total patient population (27%) was identified as “treatment-resistant” at baseline. There were more males than females in the study (61% of all patients were male). The mean age of patients entering the study was 37 years of age (range 18 to 69). Most patients were Caucasian (71%); 15% were Black, 1% were Asian, and 13% were classified as being of “other” races.

Patients treated with clozapine had a statistically significant longer delay in the time to recurrent suicidal behavior in comparison with olanzapine. This result should be interpreted only as evidence of the effectiveness of clozapine in delaying time to recurrent suicidal behavior and not a demonstration of the superior efficacy of clozapine over olanzapine.

The probability of experiencing (1) a significant suicide attempt, including a completed suicide, or (2) hospitalization because of imminent suicide risk, including increased level of surveillance for suicidality for patients already hospitalized, was lower for clozapine patients than for olanzapine patients at Week 104: clozapine 24% versus olanzapine 32%; 95% CI of the difference: 2%, 14% (Figure 1).

Figure 1: Cumulative Probability of a Significant Suicide Attempt or Hospitalization to Prevent Suicide in Patients with Schizophrenia or Schizoaffective Disorder at High Risk of Suicidality

16 HOW SUPPLIED/STORAGE AND HANDLING
16.1 How Supplied
Clozapine Tablets USP are available as pale yellow, round tablets, debossed “Ivax hourglass logo” and “4399” on one side and “25” and a bisect on the other side, containing 50 mg clozapine, USP.

NDC 0093-4399-01 50 mg packaged in unit-dose boxes of 100 tablets
NDC 0093-4399-05 25 mg packaged in bottles of 100 tablets
NDC 0093-4399-93 25 mg packaged in bottles of 500 tablets

Clozapine Tablets USP are available as pale yellow, round, flat-faced, beveled-edge tablets, debossed “Ivax hourglass logo” and “4404” on one side and “50” and a bisect on the other side, containing 50 mg clozapine, USP.

NDC 0093-4404-01 50 mg packaged in bottles of 100 tablets
NDC 0093-4404-05 25 mg packaged in bottles of 500 tablets
NDC 0093-4404-93 25 mg packaged in unit-dose boxes of 100 tablets
Instruct patients (and caregivers) beginning treatment with clozapine about the following issues:

- Discuss the following issues with patients and caregivers:
  - Severe Neutropenia:
    - Instruct patients (and caregivers) beginning treatment with clozapine about the risk of developing severe neutropenia and infection.
    - Inform patients to immediately report to their physician any symptom or sign of infection (e.g., flu-like illness; fever; lethargy; general weakness or malaise; mucus membrane ulceration; skin, pharyngeal, vaginal, urinary, or pulmonary infection; or extreme weakness or lethargy) occurring at any time during clozapine therapy, to aid in evaluation for neutropenia and to institute prompt and appropriate management [see Warnings and Precautions (5.1), (5.11), and (5.13)].
  - An ANC is required every 2 weeks for the next 6 months if an acceptable ANC is maintained during the first 6 months of continuous therapy.
  - An ANC is required once every 4 weeks thereafter if an acceptable ANC is maintained during the second 6 months of continuous therapy.

- Clozapine is available only through a restricted program called the Clozapine REMS Program designed to ensure the required blood monitoring, in order to reduce the risk of developing severe neutropenia. Advise patients and caregivers of the importance of having blood tested as follows:
  - Weekly blood tests are required for the first 6 months.
  - An ANC is required every 2 weeks for the next 6 months if an acceptable ANC is maintained during the first 6 months of continuous therapy.
  - An ANC is required once every 4 weeks thereafter if an acceptable ANC is maintained during the second 6 months of continuous therapy.

- Orthostatic Hypotension, Bradycardia, and Syncope: Inform patients and caregivers about the risk of orthostatic hypotension and syncope, especially during the period of initial dose titration. Instruct them to strictly follow the clinician’s instructions for dosage and administration. Advise patients to consult their clinician immediately if they feel faint, lose consciousness or have signs or symptoms suggestive of bradycardia or arrhythmia [see Dosage and Administration (2.2) and Warnings and Precautions (5.3)].

- Seizures: Inform patients and caregivers about the significant risk of seizure during clozapine treatment. Caution them about driving and any other potentially hazardous activity while taking clozapine [see Warnings and Precautions (5.5)].

- QT Interval Prolongation: Advise patients to consult their clinician immediately if they feel faint, lose consciousness or have signs or symptoms suggestive of arrhythmia. Instruct patients not to take clozapine with other drugs that cause QT interval prolongation. Instruct patients to inform their clinicians that they are taking clozapine before any new drug [see Warnings and Precautions (5.5) and Drug Interactions (7.1)].

- Metabolic Changes (hyperglycemia and diabetes mellitus, dyslipidemia, weight gain): Educate patients and caregivers about the risk of metabolic changes and the need for specific monitoring. The risks include hyperglycemia and diabetes mellitus, dyslipidemia, weight gain, and cardiovascular reactions. Educate patients and caregivers about the symptoms of hyperglycemia (high blood sugar) and diabetes mellitus (e.g., polydipsia, polyuria, polyphagia, and weakness). Monitor all patients for these symptoms. Patients who are diagnosed with diabetes or have risk factors for diabetes (obesity, family history of diabetes) should have their fasting blood glucose monitored before beginning treatment and periodically during treatment. Patients who develop symptoms of hyperglycemia should have assessments of fasting glucose. Clinical monitoring of weight is recommended [see Warnings and Precautions (5.10)].

- Interference with Cognitive and Motor Performance: Because clozapine may have the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that clozapine therapy does not affect them adversely [see Warnings and Precautions (5.16)].

- Missed Doses and Re-initiating Treatment: Inform patients and caregivers that if the patient misses taking clozapine for more than 2 days, they should not restart their medication at the same dosage but should contact their physician for dosing instructions [see Dosage and Administration (2.5) and Warnings and Precautions (5.1, 5.3)].
WARNINGS AND PRECAUTIONS

- Severe Neutropenia: Clozapine can cause severe neutropenia, which can lead to serious and fatal infections. Patients initiating or continuing treatment with Clozapine ODT must have a baseline blood absolute neutrophil count (ANC) measured before treatment initiation and regular ANC monitoring during treatment (2.1, 5.1).
- Clozapine ODT is available only through a restricted program called the Clozapine REMS (5.2).
- Orthostatic Hypotension, Bradycardia, and Syncope: Risk is dose-related. Starting dose is 12.5 mg. Titrate gradually and use divided dosages (2.2, 2.6, 5.3).
- Seizure: Risk is dose-related. Titrate gradually and use divided doses. Use with caution in patients with history of seizure or risk factors for seizure (2.2, 5.5).
- Myocarditis and Cardiomyopathy: Can be fatal. Discontinue and obtain cardiac evaluation if findings suggest these cardiac reactions (5.6).
- Increased Mortality in Elderly Patients with Dementia-Related Psychosis: Clozapine ODT is not approved for this condition (5.7).

INDICATIONS AND USAGE

- WITH DEMENTIA-RELATED PSYCHOSIS
- CARDIOMYOPATHY; INCREASED MORTALITY IN ELDERLY PATIENTS

WARNINGS AND PRECAUTIONS

- Severe Neutropenia: Clozapine can cause severe neutropenia, which can lead to serious and fatal infections. Patients initiating or continuing treatment with Clozapine ODT must have a baseline blood absolute neutrophil count (ANC) measured before treatment initiation and regular ANC monitoring during treatment (2.1, 5.1).
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- Seizure: Risk is dose-related. Titrate gradually and use divided doses. Use with caution in patients with history of seizure or risk factors for seizure (2.2, 5.5).
- Myocarditis and Cardiomyopathy: Can be fatal. Discontinue and obtain cardiac evaluation if findings suggest these cardiac reactions (5.6).
- Increased Mortality in Elderly Patients with Dementia-Related Psychosis: Clozapine ODT is not approved for this condition (5.7).

Dosage and Administration

- Starting Dose: 12.5 mg once daily or twice daily (2.3).
- Use caution titration and divided dosage schedule (2.3, 5.3).
- Titration: increase the total daily dosage in increments of 25 mg to 50 mg per day, if well-tolerated (2.3).
- Target dose: 300 mg to 450 mg per day, in divided doses, by the end of 2 weeks (2.3).
- Subsequent increases: increase in increments of 100 mg or less, once or twice weekly (2.3).
- Maximum daily dose: 900 mg (2.3).
- Tablets rapidly disintegrate after placement in the mouth and may be chewed if well-tolerated (2.3).

Dosage Forms and Strengths

Orally disintegrating tablets: 12.5 mg, 25 mg, 100 mg, 150 mg and 200 mg (3).

Contraindications

- Known serious hypersensitivity to clozapine or any other component of Clozapine ODT (4.1).

Full Prescribing Information: Contents

1.1 Treatment-Resistant Schizophrenia
1.2 Risk in the Risk of Recurrent Suicidal Behavior in Schizophrenia or Schizoaffective Disorder
2.1 Required Laboratory Testing Prior to Initiation and During Therapy
2.2 Important Administration Instructions
2.3 Dosing Information
2.4 Maintenance Treatment
2.5 Discontinuation of Treatment
2.6 Re-Initiation of Treatment
2.7 Dosage Adjustments with Concomitant use of CYP1A2, CYP2D6, CYP3A4 Inhibitors or CYP1A2, CYP3A4 Inducers
2.8 Renal or Hepatic Impairment or CYP2D6 Poor Metabolizers

Adverse Reactions

Most common adverse reactions (65%) were: CNS reactions (sedation, diziness/ vertigo, headache, and tremor); cardiovascular reactions (tachycardia, hypotension, and syncope); autonomic nervous system reactions (hypersalivation, sweating, dry mouth, and visual disturbances); gastrointestinal reactions (constipation and nausea); and fever (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Jazz Pharmaceuticals, Inc., at 1-800-520-5568 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Drug Interactions

- Concomitant use of Strong CYP1A2 Inhibitors: Reduce Clozapine ODT dose to one third when coadministered with strong CYP1A2 inhibitors (e.g., fluvoxamine, ciprofloxacin, enoxacin) (2.7, 7.1).
- Concomitant use of Strong CYP3A4 Inhibitors is not recommended (2.7, 7.1).

Adverse Reactions

Use in Specific Populations

- Nursing Mothers: Discontinue drug or discontinue nursing, taking into consideration importance of drug to mother (8.3).

See 17 for PATIENT COUNSELING INFORMATION.

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CLOZAPINE ODT (Orally Disintegrating Tablets) for oral use

10 OVERDOSAGE
10.1 Overdose Experience
10.2 Management of Overdosage

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

FULL PRESCRIBING INFORMATION

WARNING: SEVERE NEUTROPHENIA; ORTHOSTATIC HYPOTENSION, BRADYCARDIA, AND SYNCOPE; SEIZURE; MYOCARDITIS AND CARDIOMYOPATHY; INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

Severe Neutropenia

Clozapine has caused severe neutropenia, defined as an absolute neutrophil count (ANC) less than 500/µL. Severe neutropenia can lead to serious infection and death. Prior to initiating treatment with Clozapine ODT a baseline ANC must be obtained and repeated weekly until ANC is ≥ 1500/µL or is sufficient to support clinical response. The ANC must be ≥ 1000/µL for patients with documented Benign Ethnic Neutropenia (BEN). During treatment, patients must have regular ANC monitoring. Advise patients to immediately report symptoms consistent with severe neutropenia or infection (e.g., fever, weakness, lethargy, or sore throat) [see Dosage and Administration (2.1) and Warnings and Precautions (5.1)]. Because of the risk of severe neutropenia, Clozapine ODT is available only through a restricted program under a Risk Evaluation Mitigation Strategy (REMS) called the Clozapine REMS Program (see Warnings and Precautions (5.2)). Orthostatic Hypotension, Bradycardia, Syncope

Orthostatic hypotension, bradycardia, syncope, and cardiac arrest have occurred with clozapine treatment. The risk is highest during the initial titration period, particularly with rapid dose escalation. These reactions can occur with the first dose, with doses as low as 12.5 mg per day. Initiate treatment at 12.5 mg once or twice daily; titrate slowly; and use divided dosages. Use clozapine cautiously in patients with cardiovascular or cerebrovascular disease or conditions predisposing to hypotension (e.g., dehydration, use of antihypertensive medications) [see Dosage and Administration (2.3, 2.6) and Warnings and Precautions (5.3)].

Seizures

Seizures have occurred with clozapine treatment. The risk is dose-related. Initiate treatment at 12.5 mg, titrate gradually, and use divided dosing. Use caution when administering clozapine to patients with a history of seizures or other predisposing risk factors for seizure (CNS pathology, medications that lower the seizure threshold, alcohol abuse). Caution patients about engaging in any activity where sudden loss of consciousness could cause physical injury to themselves or others [see Dosage and Administration (2.3), Warnings and Precautions (5.5)].

Myocarditis and Cardiomyopathy

FATAL myocarditis and cardiomyopathy have occurred with clozapine treatment. Discontinue clozapine and obtain a cardiac evaluation upon suspicion of these reactions. Generally, patients with clozapine-related myocarditis or cardiomyopathy should not be rechallenged with clozapine. Consider the possibility of myocarditis or cardiomyopathy if chest pain, tachycardia, palpitations, dyspnea, fever, flu-like symptoms, hypotension, or ECG changes occur [see Warnings and Precautions (5.6)]. Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Clozapine ODT is not approved for use in patients with dementia-related psychosis [see Warnings and Precautions (5.7)].

1 INDICATIONS AND USAGE

1.1 Treatment-Resistant Schizophrenia

Clozapine ODT is indicated for the treatment of severely ill patients with schizophrenia who fail to respond adequately to standard antipsychotic treatment. Because of the risks of severe neutropenia and of seizure associated with its use, Clozapine ODT should be used only in patients who have failed to respond adequately to standard antipsychotic treatment [see Warnings and Precautions (5.1, 5.5)]. The effectiveness of clozapine in treatment-resistant schizophrenia was demonstrated in a 6-week, randomized, double-blind, active-controlled study comparing clozapine and chlorpromazine in patients who had failed other antipsychotics [see Clinical Studies (14.1)].

1.2 Reduction in the Risk of Recurrent Suicidal Behavior in Schizophrenia or Schizoaffective Disorder

Clozapine ODT is indicated for reducing the risk of recurrent suicidal behavior in patients with schizophrenia or schizoaffective disorder who are judged to be at chronic risk for re-experiencing suicidal behavior, based on history and recent clinical state. Suicidal behavior refers to actions by a patient that put him/herself at risk for death. Suicidal behavior refers to actions by a patient that put him/herself at risk for death. [see Clinical Studies (14.2)].

2 DOSAGE AND ADMINISTRATION

2.1 Required Laboratory Testing Prior to Initiation and During Therapy

Prior to initiating treatment with Clozapine ODT, a baseline ANC must be obtained. The baseline ANC must be at least 1500/µL for the general population, and at least 1000/µL for patients with documented Benign Ethnic Neutropenia (BEN). To continue treatment, the ANC must be monitored regularly [see Warnings and Precautions (5.1)].

2.2 Important Administration Instructions

Clozapine orally disintegrating tablets should be immediately placed in the mouth after removing the tablet from the blister pack or bottle. The tablet disintegrates rapidly after placement in the mouth. The tablets can be allowed to disintegrate, or they may be chewed. They may be swallowed with saliva. No water is necessary for administration.

The orally disintegrating tablets in a blister pack should be left in the unopened blister until the time of use. Just prior to use, peel the foil from the blister and gently remove the orally disintegrating tablet. Do not push the tablets through the foil, because this could damage the tablet.

2.3 Dosing Information

The starting dose is 12.5 mg once daily or twice daily. The total daily dose can be increased in increments of 25 mg to 50 mg per day, if well-tolerated, to achieve a target dose of 300 mg to 450 mg per day (administered in divided doses) by the end of 2 weeks. Subsequently, the dose can be increased once weekly or twice weekly, in increments of up to 100 mg. The maximum dose is 900 mg per day. To minimize the risk of orthostatic hypotension, bradycardia, and syncope, it is necessary to use this low starting dose, gradual titration schedule, and divided dosages [see Warnings and Precautions (5.3)].

Clozapine ODT can be taken with or without food [see Pharmacokinetics (12.3)].

2.4 Maintenance Treatment

Generally, patients responding to Clozapine ODT should continue maintenance treatment on their effective dose beyond the acute episode.

2.5 Discontinuation of Treatment

Method of treatment discontinuation will vary depending on the patient’s last ANC:

- See Tables 2 or 3 for appropriate ANC monitoring based on the level of neutropenia if abrupt treatment discontinuation is necessary because of moderate to severe neutropenia.
- Reduce the dose gradually over a period of 1 to 2 weeks if termination of Clozapine ODT therapy is planned and there is no evidence of moderate to severe neutropenia.
- For abrupt clozapine discontinuation for a reason unrelated to neutropenia, continue the existing ANC monitoring is recommended for general population patients until their ANC is ≥1500/µL and for BEN patients until their ANC is ≥1000/µL or above their baseline.
- Additional ANC monitoring is required for any patient reporting onset of fever (temperature of 38.5°C or 101.3°F or greater) during the 2 weeks after discontinuation [see Warnings and Precautions (5.1)].
- Monitor all patients carefully for the recurrence of psychotic symptoms and sympotoms related to cholinergic rebound such as profuse sweating, headache, nausea, vomiting, and diarrhea.

2.6 Re-initiation of Treatment

When restarting Clozapine ODT in patients who have discontinued Clozapine ODT (i.e., 2 days or more since the last dose), re-initiate with 12.5 mg once daily or twice daily. This is necessary to minimize the risk of hypotension, bradycardia, and syncope [see Warnings and Precautions (5.2)]. If that dose is well-tolerated, the dose may be increased to the previously therapeutic dose more quickly than recommended for initial treatment.

2.7 Dose Adjustments with Concomitant use of CYP1A2, CYP2D6, CYP3A4 Inhibitors or CYP1A2, CYP3A4 Inducers

Dose adjustments may be necessary in patients concomitantly taking: strong CYP1A2 inhibitors (e.g., fluvoxamine, ciprofloxacin, or enoxacin); moderate or weak CYP1A2 inhibitors (e.g., oral contraceptives, or caffeine); CYP2D6 or CYP3A4 inhibitors (e.g., cimetidine, escitalopram, erythromycin, paroxetine, bupropion, fluoxetine, quinidine, valproate, trazodone, or sertraline); CYP3A4 inducers (e.g., phenytoin, carbamazepine, St. John’s wort, and rifampin); or CYP1A2 inducers (e.g., tobacco smoking) (Table 1) [see Drug Interactions (7)].

Table 1: Dosage Adjustment in Patients Taking Concomitant Medications

<table>
<thead>
<tr>
<th>Co-medications</th>
<th>Scenarios</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initiating Clozapine ODT while taking a co-medication</td>
<td>Adding a co-medication while taking Clozapine ODT</td>
</tr>
</tbody>
</table>

| Strong CYP1A2 Inhibitors | Use one third of the dose. | Increase Clozapine ODT dose based on clinical response. |

continued
CLOZAPINE ODT (Orally Disintegrating Tablets) for oral use

Co-medications | Scenarios
--- | ---
Moderate or Weak CYP1A2 Inhibitors | Monitor for adverse reactions. Consider reducing the Clozapine ODT dose if necessary.
CYP2D6 or CYP3A4 Inhibitors | Monitor for lack of effectiveness. Consider increasing Clozapine ODT dose if necessary.
Strong CYP3A4 Inducers | Concomitant use is not recommended. However, if the inducer is necessary, it may be necessary to increase the Clozapine ODT dose. Monitor for decreased effectiveness.
Moderate or Weak CYP1A2 or CYP3A4 Inducers | Monitor for decreased effectiveness. Consider increasing the Clozapine ODT dose if necessary.

2.8 Renal or Hepatic Impairment or CYP2D6 Poor Metabolizers
It may be necessary to reduce the Clozapine ODT dose in patients with significant renal or hepatic impairment, or in CYP2D6 poor metabolizers [see Use in Specific Populations (8.6, 8.7)].

3 DOSAGE FORMS AND STRENGTHS
Clozapine ODT is available as 12.5 mg, 25 mg, 100 mg, 150 mg and 200 mg round, yellow, orally disintegrating tablets.

4 CONTRAINDICATIONS

4.1 Hypersensitivity
Clozapine ODT is contraindicated in patients with a history of serious hypersensitivity to clozapine (e.g., photosensitivity, vasculitis, erythema multiforme, or Stevens-Johnson Syndrome) or any other component of Clozapine ODT [see Adverse Reactions (6.2)].

5 WARNINGS AND PRECAUTIONS

5.1 Severe Neutropenia

Background
Clozapine ODT can cause neutropenia (a low absolute neutrophil count [ANC]), defined as a reduction below pre-treatment normal levels of blood neutrophils. The ANC is usually available as a component of the complete blood count (CBC), including differential, and is more relevant to drug-induced neutropenia than is the white blood cell (WBC) count. The ANC may also be calculated using the following formula: ANC equals the Total WBC count multiplied by the total percentage of neutrophils obtained from the differential (neutrophil “segs” plus neutrophil “bands”). Other granulocytes (basophils and eosinophils) contribute minimally to neutropenia and their measurement is not necessary [see Adverse Reactions (6.2)]. Neutropenia may be mild, moderate, or severe (see Tables 2 and 3). To improve and standardize understanding, “severe neutropenia” replaces the previous terms severe leukopenia, severe granulocytopenia, or agranulocytosis.

Severe neutropenia, ANC less than (<) 500/μL, occurs in a small percentage of patients taking Clozapine ODT and is associated with an increase in the risk of serious and potentially fatal infections. Risk of neutropenia appears greatest during the first 18 weeks on treatment and then declines. The mechanism by which Clozapine ODT causes neutropenia is unknown and is not dose-dependent. Two separate management algorithms are provided below, the first for patients in the general population, and the second for patients identified to have baseline neutropenia.

Clozapine ODT Treatment and Monitoring in the General Patient Population (see Table 2)

Obtain a CBC, including the ANC value, prior to initiating treatment with Clozapine ODT to ensure the presence of a normal baseline neutrophil count (equal to or greater than 1500/μL) and to permit later comparisons. Patients in the general population with an ANC equal to or greater than (>1500/μL) are considered within normal range (Table 2) and are eligible to initiate treatment. Weekly ANC monitoring is required for all patients during the first 6 months of treatment. If a patient’s ANC remains equal to or greater than 1500/μL for the first 6 months of treatment, monitoring frequency may be reduced to every 2 months. If the next ANC remains equal to or greater than 1500/μL for the second 6 months of continuous therapy, ANC monitoring frequency may be reduced to once every 4 weeks thereafter.

Table 2: Clozapine ODT Treatment Recommendations Based on Absolute Neutrophil Count (ANC) Monitoring for the General Patient Population

<table>
<thead>
<tr>
<th>ANC Level</th>
<th>Clozapine ODT Treatment Recommendations</th>
<th>ANC Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal range (&gt;1500/μL)</td>
<td>• Initiate treatment</td>
<td>• Weekly from initiation to 6 months</td>
</tr>
<tr>
<td></td>
<td>• If treatment interrupted: &lt;30 days, continue monitoring as before</td>
<td>• Every 2 weeks from 6 to 12 months</td>
</tr>
<tr>
<td></td>
<td>&gt;30 days, monitor as if new patient</td>
<td>• Monthly after 12 months</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mild Neutropenia (1000 to 1499/μL)*</th>
<th>• Discontinuation for reasons other than neutropenia</th>
<th>• See Section 2.4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Continue treatment</td>
<td></td>
</tr>
</tbody>
</table>

Table 3: Patients with Benign Ethnic Neutropenia (BEN): Clozapine ODT Treatment Recommendations Based on Absolute Neutrophil Count (ANC) Monitoring

<table>
<thead>
<tr>
<th>ANC Level</th>
<th>Treatment Recommendations</th>
<th>ANC Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal BEN Range (Established ANC baseline &gt;1000/μL)</td>
<td>• Obtain at least two baseline ANC levels before initiating treatment</td>
<td>• Weekly from initiation to 6 months</td>
</tr>
<tr>
<td></td>
<td>• If treatment interrupted: &lt;30 days, continue monitoring as before</td>
<td>• Every 2 weeks from 6 to 12 months</td>
</tr>
<tr>
<td></td>
<td>&gt;30 days, monitor as if new patient</td>
<td>• Monthly after 12 months</td>
</tr>
<tr>
<td></td>
<td>• Discontinuation of treatment for reasons other than neutropenia</td>
<td>• See Section 2.4</td>
</tr>
</tbody>
</table>

| BEN Neutropenia (500 to 999/μL)* | • Recommend hematology consultation | • Three times weekly until ANC >1000/μL or at patient’s known baseline |
| | | • Once ANC >1000/μL, check ANC weekly for 4 weeks, then return to patient’s last “Normal Range” ANC monitoring interval** |
| | • Continue treatment | |

* Confirm all initial reports of ANC less than 1500/μL with a repeat ANC measurement within 24 hours.
** If clinically appropriate
5.6 Myocarditis and Cardiomyopathy
Myocarditis and cardiomyopathy have occurred with the use of clozapine. These reactions can be fatal. Discontinue Clozapine ODT and obtain a cardiac evaluation upon suspicion of myocarditis or cardiomyopathy. Generally, patients with a history of clozapine-associated myocarditis or cardiomyopathy should not be rechallenged with Clozapine ODT. However, before Clozapine ODT treatment is judged to outweigh the potential risks of recurrent myocarditis or cardiomyopathy, the clinician may consider rechallenge with Clozapine ODT in consultation with a cardiologist, after a complete cardiac evaluation, and under close monitoring. Consider the possibility of myocarditis or cardiomyopathy in patients receiving Clozapine ODT who present with chest pain, dyspnea, persistent tachycardia at rest, palpitations, fever, flu-like symptoms, hypotension, other signs or symptoms of heart failure, or electrocardiographic findings (low voltages, ST-T abnormalities, arrhythmias, right axis deviation, and poor R wave progression). Myocarditis most frequently presents within the first two months of clozapine treatment. Symptoms of cardiomyopathy are generally reported within 5 years of the onset of clozapine-associated myocarditis and usually after 8 weeks of treatment. However, myocarditis and cardiomyopathy can occur at any period during treatment with Clozapine ODT. It is common for nonspecific flu-like symptoms such as malaise, myalgia, pleuritic chest pain, and low-grade fevers to precede more overt signs of heart failure. Typical laboratory findings include elevated liver transaminases, BNP, and hyperviscosity. Treatment consists of immediate withdrawal of Clozapine ODT and initiation of C-reactive protein (CRP). Chest roentgenogram may demonstrate cardiac silhouette enlargement, and cardiac imaging (echocardiogram, radionuclide studies, or cardiac catheterization) may reveal evidence of left ventricular dysfunction.

5.7 Increased Mortality in Elderly Patients with Dementia-Related Psychosis
The risk of death in patients with dementia-related psychosis treated with antipsychotic drugs is unknown. A post-marketing observational study of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. 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. Observational studies suggest that, similar to atypical antipsychotics, treatment with conventional antipsychotic drugs may increase mortality in older patients, for whom the cause-specific mortality in observational studies may be attributed to the antipsychotic drug as opposed to some other characteristic(s) of the patients is not clear. Clozapine ODT is not approved for the treatment of patients with dementia-related psychosis [see Boxed Warning].

5.8 Eosinophilia
Eosinophilia, defined as a blood eosinophil count of greater than 700/μL, has occurred with clozapine treatment. In clinical trials, approximately 1% of patients developed eosinophilia. Clozapine-related eosinophilia usually occurs during the first month of treatment. In some patients, it has been associated with myocarditis, pancreatitis, hepatitis, or death related to eosinophilia. Such organ involvement is inconsistent with the drug reaction with eosinophilia and systemic symptoms syndrome (DRESS), also known as drug induced hypersensitivity syndrome (DIHS). If eosinophilia develops during Clozapine ODT treatment, evaluate promptly for signs and symptoms of systemic reactions, such as rash or other allergic symptoms, myocarditis, or other organ involvement. In the absence of organ involvement, the clinician may consider discontinuing Clozapine ODT immediately.

If a cause of eosinophilia unrelated to clozapine is identified (e.g., asthma, allergies, collagen vascular disease, parasitic infections, and specific neoplasms), treat the underlying cause and continue Clozapine ODT. Do not discontinue Clozapine ODT in the absence of organ involvement and can resolve without intervention. There are reports of successful rechallenge after discontinuation of clozapine, without recurrence of eosinophilia. In the absence of organ involvement, continue Clozapine ODT under careful monitoring. If the total eosinophil count continues to increase over several weeks in the absence of systemic disease, the decision to interrupt Clozapine ODT therapy and rechallenge after the eosinophil count decreases should be based on the overall clinical assessment, in consultation with an internist or hematologist.

5.9 QT Interval Prolongation
QT prolongation, Torsades de Pointes and other life-threatening ventricular arrhythmias, sudden death, and sudden death associated with drug use have occurred with clozapine treatment. When prescribing Clozapine ODT, consider the presence of additional risk factors for QT prolongation and serious cardiovascular reactions. Conditions that increase these risks include the following: history of QT prolongation, long QT syndrome, family history of long QT syndrome, female sex, hormonal contraceptives, class 1A and class 1B antiarrhythmic agents, hypokalemia, hypomagnesemia, concomitant use of medications that prolong QT interval or inhibit the metabolism of Clozapine ODT, and electrolyte abnormalities. Prior to initiating treatment with Clozapine ODT, perform a careful physical examination, including a family history and concomitant medication history, and baseline electrocardiogram (ECG) and serum chemistry panel. Correct electrolyte abnormalities. Discontinue Clozapine ODT if the QTc interval exceeds 500 msec. If patients experience symptoms consistent with Torsades de Pointes or other arrhythmias (e.g., syncope, presyncope, dizziness, or palpitations), obtain a cardiac evaluation and discontinue Clozapine ODT. Use caution when administering concomitant medications that prolong the QT interval or inhibit the metabolism of Clozapine ODT. Drugs that cause QT prolongation include: specific antipsychotics (e.g., ziprasidone, iloperidone, chlorpromazine, thioridazine, mesoridazine, droperidol, pimozide), specific antibiotics (e.g., erythromycin, gatifloxacin, moxifloxacin, sparfloxacin), Class 1A antiarrhythmic medications (e.g.,
CLOZAPINE ODT (Orally Disintegrating Tablets) for oral use

quintidine, procainamide) or Class III antarrhythmics (e.g., amiodarone, sotalol), and others (e.g., pantoprazole, levomethadyl acetate, methadone, halofantrine, mefloquine, dolasetron mesylate, propocul or tacrolimus). CLOZAPINE ODT is primarily metabolized by CYP isozymes 1A2, 2D6, and 3A4. Concomitant treatment with inhibitors of these enzymes can increase the concentration of CLOZAPINE ODT (see Drug Interactions (7.1) and Clinical Pharmacology (12.3)).

Hypokalemia and hypomagnesemia increase the risk of QT prolongation. Hypokalemia can result from diuretic therapy, diarrhea, and other causes. Use caution when treating patients at risk for significant electrolyte disturbance, particularly hypokalemia. Obtain baseline measurements of serum potassium and magnesium levels, and periodically monitor electrolytes. Correct electrolyte abnormalities before initiating treatment with CLOZAPINE ODT.

5.10 Metabolic Changes

Atypical antipsychotic drugs, including CLOZAPINE ODT, have been associated with metabolic changes that can increase cardiovascular and cerebrovascular risk. These metabolic changes include hyperglycemia, dyslipidemia, and body weight gain. While atypical antipsychotic drugs may produce some metabolic changes, each drug in the class has its own specific risk profile.

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 ODT. 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 reactions is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent, hyperglycemia-related adverse reactions in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse reactions in patients treated with atypical antipsychotics are not available.

Patients with an established diagnosis of diabetes mellitus who are started on CLOZAPINE ODT should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., 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.

In a pooled data analysis of 8 studies in adult subjects with schizophrenia, the mean changes in fasting glucose concentration in the clozapine and chlorpromazine groups were 0.1 mmol/L (7 mg/dL) and 0.0 mmol/L (4 mg/dL), respectively. A higher proportion of the clozapine group demonstrated categorical increases from baseline in fasting glucose concentrations, compared to the chlorpromazine group (Table 4). The clozapine doses were 100-900 mg per day (mean modal dose: 512 mg per day). The maximum mean changes in fasting glucose concentration in the clozapine and chlorpromazine group demonstrated categorical increases from baseline in fasting glucose level. The median duration of exposure was 42 days and 38 days, respectively. The maximum mean changes in fasting glucose concentration in the clozapine and chlorpromazine group was 45 days and 42 days, respectively.

The metabolic changes include hyperglycemia, dyslipidemia, and body weight gain. These metabolic changes can increase cardiovascular and cerebrovascular risk. These metabolic changes are associated with increases in serum total cholesterol and triglyceride, as illustrated in Table 6. The proportion of patients with categorical increases in total cholesterol or fasting triglyceride increased with the duration of exposure. The median duration of clozapine and chlorpromazine exposure was 45 days and 38 days, respectively. The maximum mean changes in fasting glucose concentration in the clozapine and chlorpromazine group was 45 days and 42 days, respectively. The maximum mean changes in fasting glucose concentration in the clozapine and chlorpromazine group was 45 days and 42 days, respectively.

5.11 Neuroleptic Malignant Syndrome

Antipsychotic drugs including CLOZAPINE ODT can cause a potentially fatal symptom complex referred to as Neuroleptic Malignant Syndrome (NMS). Clinical manifestations of NMS include hyperpyrexia, muscle rigidity, altered mental status, and autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias). Associated findings can include elevated creatine phosphokinase (CPK), myoglobinuria, rhabdomyolysis, and acute renal failure.

Table 5: Mean Changes in Total Cholesterol and Triglyceride Concentration in Studies in Adult Subjects with Schizophrenia

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>Baseline Total Cholesterol Concentration (mg/dL)</th>
<th>Change from Baseline mg/dL (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine (N=334)</td>
<td>184</td>
<td>+13 (7)</td>
</tr>
<tr>
<td>Chlorpromazine (N=185)</td>
<td>182</td>
<td>+15 (8)</td>
</tr>
<tr>
<td>Baseline Triglyceride Concentration (mg/dL)</td>
<td>Change from Baseline mg/dL (%)</td>
<td></td>
</tr>
<tr>
<td>Clozapine (N=6)</td>
<td>130</td>
<td>+71 (54)</td>
</tr>
<tr>
<td>Chlorpromazine (N=7)</td>
<td>110</td>
<td>+39 (35)</td>
</tr>
</tbody>
</table>

Table 6: Categorical Changes in Lipid Concentrations in Studies in Adult Subjects with Schizophrenia

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>Category Change (at least once) from Baseline</th>
<th>Treatment Arm</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Cholesterol (random or fasting)</td>
<td>Increase by ≥40 mg/dL</td>
<td>Clozapine</td>
<td>334 (111 (33)</td>
</tr>
<tr>
<td>Normal (&lt;200 mg/dL to High (≥240 mg/dL) to High (≥240 mg/dL)</td>
<td>Increase by ≥50 mg/dL</td>
<td>Clozapine</td>
<td>222 (18 (8)</td>
</tr>
<tr>
<td>Triglycerides (fasting)</td>
<td>Normal (&lt;150 mg/dL) to High (≥200 mg/dL)</td>
<td>Clozapine</td>
<td>4 (0 (0)</td>
</tr>
<tr>
<td>Borderline (≥150 mg/dL) to &lt;200 mg/dL to High (≥200 mg/dL)</td>
<td>Borderline (≥150 mg/dL)</td>
<td>Clozapine</td>
<td>6 (2 (33)</td>
</tr>
</tbody>
</table>

Table 7: Mean Change in Body Weight kg by duration of exposure from studies in adult subjects with schizophrenia

<table>
<thead>
<tr>
<th>Weight Gain</th>
<th>Clozapine (N=669)</th>
<th>Olanzapine (N=442)</th>
<th>Chlorpromazine (N=155)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 weeks (Day 11 - 17)</td>
<td>6.0</td>
<td>+0.9</td>
<td>+0.7</td>
</tr>
<tr>
<td>4 weeks (Day 21 - 35)</td>
<td>23.0</td>
<td>+0.7</td>
<td>8.0</td>
</tr>
<tr>
<td>8 weeks (Day 49 - 63)</td>
<td>12.0</td>
<td>+1.9</td>
<td>13.0</td>
</tr>
<tr>
<td>12 weeks (Day 70 - 98)</td>
<td>17.0</td>
<td>+2.8</td>
<td>5.0</td>
</tr>
<tr>
<td>24 weeks (Day 154 - 182)</td>
<td>42.0</td>
<td>-0.6</td>
<td>12.0</td>
</tr>
<tr>
<td>48 weeks (Day 322 - 350)</td>
<td>3.0</td>
<td>+3.7</td>
<td>3.0</td>
</tr>
</tbody>
</table>

Table 8 summarizes pooled data from 11 studies in adult subjects with schizophrenia demonstrating weight gain of 7% of body weight relative to baseline. The median duration of exposure was 609, 728, and 42 days, in the clozapine, olanzapine, and chlorpromazine group, respectively.
The diagnostic evaluation of patients with this syndrome is complicated. It is important to consider the presence of other serious medical conditions (e.g., severe neutropenia, infection, heat stroke, primary CNS pathology, central anticholinergic toxicity, extrapyramidal symptoms, and drug fever).

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 co-morbid medical conditions. There is no general agreement about specific pharmacological treatments for NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. NMS can recur. Monitor closely if restarting treatment with antipsychotics.

5.12 Heparin Toxicity
Severe, life-threatening, and in some cases fatal heparin toxicity including heparin-induced thrombocytopenia, and heparin neutralizing antibodies have been reported in patients treated with clozapine [see Adverse Reactions (6.2)]. Monitor for the appearance of signs and symptoms of heparin toxicity such as fatigue, malaise, anorexia, nausea, jaundice, bilirubinemia, coagulopathy, and hepatic encephalopathy. Perform serum tests for liver injury and consider permanently discontinuing treatment if hepatitis or transaminase elevations combined with other systemic symptoms are due to clozapine.

5.13 Fever
During clozapine therapy, patients have experienced transient, clozapine-related fever. The peak incidence is within the first 3 weeks of treatment. While this fever is generally benign and not related to treatment, it may necessitate discontinuing treatment. The fever can be associated with an increase or decrease in WBC count. Carefully evaluate patients with fever to rule out severe neutropenia or infection. Consider the possibility of NMS [see Warnings and Precautions (5.11)].

5.14 Pulmonary Embolism
Pulmonary embolism and deep vein thrombosis have occurred in patients treated with clozapine. Consider the possibility of pulmonary embolism in patients who present with deep vein thrombosis, acute dyspnea, chest pain, or with other respiratory signs and symptoms. Whether pulmonary embolus and deep vein thrombosis can be attributed to clozapine or some characteristic(s) of patients is not clear.

5.15 Anticholinergic Toxicity
Clozapine ODT has potent anticholinergic effects. Treatment with Clozapine ODT can result in CNS and peripheral anticholinergic toxicity. Use with caution in the presence of narrow-angle glaucoma, concomitant anticholinergic medications, prostatic hypertrophy, or other conditions in which anticholinergic effects can lead to significant and life-threatening adverse events.

Treatment with Clozapine ODT can result in gastrointestinal adverse reactions, including constipation, intestinal obstruction, fecal impaction, and paralytic ileus. Such reactions can be 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.

5.16 Interference with Cognitive and Motor Performance
Clozapine ODT can cause sedation and impairment of cognitive and motor performance. Caution patients about operating hazardous machinery, including automobiles, until they are reasonably certain that Clozapine ODT does not affect them adversely. These reactions may be dose-related. Consider reducing the dose if they occur.

5.17 Tardive Dyskinesia
Tardive dyskinesia (TD) has occurred in patients treated with antipsychotic drugs, including Clozapine ODT. The syndrome consists of potentially irreversible, involuntary, dyskinetic movements of the orofacial region and extremities. The risk of TD and the likelihood that it will become irreversible are believed to increase with greater durations of treatment and higher total cumulative doses. However, the syndrome can develop after relatively brief treatment periods at low doses. Prescribe Clozapine ODT in a manner that is most likely to minimize the risk of developing TD. Use the lowest effective dose and the shortest duration necessary to control symptoms. Periodically assess the need for continued treatment. Consider discontinuing treatment if TD occurs. However, some patients may require treatment with Clozapine ODT despite the presence of the syndrome.

There is no known treatment for TD. However, the syndrome may remit partially or completely if treatment is discontinued. Antipsychotic treatment, itself, may suppress or (partially suppress) the signs and symptoms, and it has the potential to mask the underlying process. The effect of symptom suppression on the long-term course of TD is unknown.

5.18 Patients with Phenylketonuria
Phenylketonuric patients should be informed that Clozapine ODT contains phenylalanine (a component of asparagine). Each 12.5 mg, orally disintegrating tablet contains 0.87 mg phenylalanine. Each 25 mg, orally disintegrating tablet contains 1.74 mg phenylalanine. Each 100 mg, orally disintegrating tablet contains 6.96 mg phenylalanine. Each 150 mg, orally disintegrating tablet contains 10.44 mg phenylalanine. Each 200 mg, orally disintegrating tablet contains 13.92 mg phenylalanine.

5.19 Cerebrovascular Adverse Reactions
In controlled trials, elderly patients with dementia-related psychosis treated with some atypical antipsychotics had an increased risk (compared to placebo) of cerebrovascular adverse reactions (e.g., stroke, transient ischemic attack), including fatalities. The mechanism for this increased risk is not known. An increased risk cannot be predicted for Clozapine ODT or other antipsychotics or other patient populations. Clozapine ODT should be used with caution in patients with risk factors for cerebrovascular adverse reactions.

5.20 Recurrence of Psychosis and Cholinergic Rebound after Abrupt Discontinuation of Clozapine ODT
If abrupt discontinuation of Clozapine ODT is necessary (because of severe neutropenia or another medical condition, for example) [see Dosage and Administration (2.4), Warnings and Precautions (5.1)], monitor carefully for the recurrence of psychotic symptoms and adverse reactions related to cholinergic rebound, such as profuse sweating, headache, nausea, vomiting, and diarrhea.

6 ADVERSE REACTIONS
The following adverse reactions are discussed in more detail in other sections of the labeling:

- Severe Neutropenia [see Warnings and Precautions (5.1)].
- Orthostatic Hypotension, Bradycardia, and Syncope [see Warnings and Precautions (5.3)].
- Falls [see Warnings and Precautions (5.4)].
- Seizures [see Warnings and Precautions (5.5)].
- Myocarditis and Cardiomyopathy [see Warnings and Precautions (5.6)].
- Increased Mortality in Elderly Patients with Dementia-Related Psychosis [see Warnings and Precautions (5.7)].
- Eosinophilia [see Warnings and Precautions (5.8)].
- QT Interval Prolongation [see Warnings and Precautions (5.9)].
- Metabolic Changes (Hyperglycemia and Diabetes Mellitus, Dyslipidemia, and Weight Gain) [see Warnings and Precautions (5.10)].
- Neuroleptic Malignant Syndrome [see Warnings and Precautions (5.11)].
- Heparin Toxicity [see Warnings and Precautions (5.12)].
- Fever [see Warnings and Precautions (5.13)].
- Pulmonary Embolism [see Warnings and Precautions (5.14)].
- Anticholinergic Toxicity [see Warnings and Precautions (5.15)].
- Interference with Cognitive and Motor Performance [see Warnings and Precautions (5.16)].
- Tardive Dyskinesia [see Warnings and Precautions (5.17)].
- Patients with Phenylketonuria [see Warnings and Precautions (5.18)].
- Cerebrovascular Adverse Reactions [see Warnings and Precautions (5.19)].
- Recurrence of Psychosis and Cholinergic Rebound after Abrupt Discontinuation [see Warnings and Precautions (5.20)].

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The most commonly reported adverse reactions (≥5%) across clozapine clinical trials were somnolence, dizziness/vertigo, headache, and tremor; cardiovascular reactions, including tachycardia, hypotension, and syncope; autonomic nervous system reactions, including hypersalivation, sweating, dry mouth, and visual disturbances; gastrointestinal reactions, including constipation and nausea; and fever. Table 9 summarizes the most commonly reported adverse reactions (≥5%) in clozapine-treated patients (compared to chlorpromazine-treated patients) in the pivotal, 6-week, controlled trial in treatment-resistant schizophrenia.

Table 9: Common Adverse Reactions (≥5%) in the 6-Week, Randomized, Chlorpromazine-controlled Trial in Treatment-Resistant Schizophrenia

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Clozapine (N=126) (%)</th>
<th>Chlorpromazine (N=142) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sedation</td>
<td>21</td>
<td>14</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>17</td>
<td>11</td>
</tr>
<tr>
<td>Constipation</td>
<td>16</td>
<td>12</td>
</tr>
<tr>
<td>Dizziness</td>
<td>14</td>
<td>16</td>
</tr>
<tr>
<td>Hypertension</td>
<td>13</td>
<td>38</td>
</tr>
<tr>
<td>Fever (hyperthermia)</td>
<td>13</td>
<td>4</td>
</tr>
<tr>
<td>Hypersalivation</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>Headache</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>5</td>
<td>20</td>
</tr>
</tbody>
</table>

Table 10 summarizes the adverse reactions reported in clozapine-treated patients at a frequency of 2% or greater across all clozapine studies (excluding the 2-year InterSePT™ Study). These rates are not adjusted for duration of exposure.

Table 10: Adverse Reactions (≥ 2%) Reported in Clozapine-treated Patients (N=842) across all Clozapine Studies (excluding the 2-year InterSePT™ Study)

<table>
<thead>
<tr>
<th>Body System</th>
<th>Clozapine N=842 Percentage of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central Nervous System</td>
<td>Drowsiness/Sedation</td>
</tr>
<tr>
<td></td>
<td>Dizziness/Vertigo</td>
</tr>
<tr>
<td></td>
<td>Headache</td>
</tr>
<tr>
<td></td>
<td>Tremor</td>
</tr>
<tr>
<td></td>
<td>Syncope</td>
</tr>
<tr>
<td></td>
<td>Disturbed Sleep/Nightmares</td>
</tr>
<tr>
<td></td>
<td>Restlessness</td>
</tr>
</tbody>
</table>

continued
CLOZAPINE ODT (Orally Disintegrating Tablets) for oral use

**Table 11. Incidence of Adverse Reactions in Patients Treated with Clozapine or Olanzapine in the InterSePT™ Study (<10% in the clozapine or olanzapine group)**

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse Reaction</th>
<th>Clozapine N = 479</th>
<th>Olanzapine N = 477</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Central Nervous System</strong> continued</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypokinesia/Akinetia</td>
<td>4</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Agitation</td>
<td>4</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Seizures (conversions)</td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Rigidity</td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Akathisia</td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Confusion</td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td><strong>Cardiovascular System</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tachycardia</td>
<td>25†</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td>9</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>4</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td><strong>Gastrointestinal System</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>14</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>5</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Abdominal Discomfort/Heartburn</td>
<td>4</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Nausea/Vomiting</td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>3</td>
<td>3</td>
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</tr>
<tr>
<td>Diarrhea</td>
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<tr>
<td><strong>Urogenital System</strong></td>
<td></td>
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<tr>
<td>Urinary Abnormalities</td>
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<td><strong>Autonomic Nervous System</strong></td>
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</tr>
<tr>
<td>Salivation</td>
<td>31</td>
<td>25†</td>
<td></td>
</tr>
<tr>
<td>Sweating</td>
<td>6</td>
<td>3</td>
<td></td>
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<tr>
<td>Dry Mouth</td>
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<td>3</td>
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</tr>
<tr>
<td>Visual Disturbances</td>
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<td>3</td>
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<td><strong>Skin and Appendages</strong></td>
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<td>Skin Rash</td>
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<td><strong>Hemic/Lymphatic System</strong></td>
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<tr>
<td>Leukopenia/Decreased WBC/Neutropenia</td>
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<td>2</td>
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<td><strong>Miscellaneous</strong></td>
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</tr>
<tr>
<td>Fever</td>
<td>5</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Weight Gain</td>
<td>4</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

1 Rate based on population of approximately 1700 exposed during premarket clinical evaluation of clozapine.

Table 11 summarizes the most commonly reported adverse reactions (>10% of the clozapine or olanzapine group) in the InterSePT™ Study. This was an adequate and well-controlled, two-year study evaluating the efficacy of clozapine relative to olanzapine in reducing the risk of suicidal behavior in patients with schizophrenia or schizoaffective disorder. The rates are not adjusted for duration of exposure.

**Adverse Reactions**

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>Clozapine % Reporting</th>
<th>Olanzapine % Reporting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salivary hypersecretion</td>
<td>48%</td>
<td>6%</td>
</tr>
<tr>
<td>Somnolence</td>
<td>46%</td>
<td>25%</td>
</tr>
<tr>
<td>Weight increased</td>
<td>31%</td>
<td>33%</td>
</tr>
<tr>
<td>Dizziness (excluding vertigo)</td>
<td>27%</td>
<td>12%</td>
</tr>
<tr>
<td>Constipation</td>
<td>25%</td>
<td>10%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>20%</td>
<td>33%</td>
</tr>
<tr>
<td>Nausea</td>
<td>17%</td>
<td>10%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>17%</td>
<td>9%</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>14%</td>
<td>8%</td>
</tr>
</tbody>
</table>

**Drug Interactions**

7. **DRUG INTERACTIONS**

7.1 **Potential for Other Drugs to Affect Clozapine ODT**

Clozapine is a substrate for many cytochrome P450 isozymes, in particular CYP1A2, CYP3A4, and CYP2D6. Use caution when administering Clozapine ODT concomitantly with drugs that are inducers or inhibitors of these enzymes.

**CYP1A2 Inhibitors**

Concomitant use of Clozapine ODT and CYP1A2 inhibitors can increase plasma levels of clozapine, potentially resulting in adverse reactions. Reduce the Clozapine ODT dose to one third of the original dose when Clozapine ODT is coadministered with strong CYP1A2 inhibitors (e.g., fluvoxamine, ciprofloxacin, or enoxacin). The Clozapine ODT dose should be increased to the original dose when coadministration of strong CYP1A2 inhibitors is discontinued [see Dosage and Administration (2.7), Clinical Pharmacology (12.3)].

**CYP3A4 Inducers**

Concomitant treatment with Clozapine ODT and CYP3A4 inducers (e.g., simvastatin, lovastatin, fenofibrate, erythromycin, diltiazem, or clozapine) can increase plasma levels of clozapine, potentially resulting in adverse reactions. Reduce the Clozapine ODT dose if used concomitantly with these inhibitors. Consider reducing the Clozapine ODT dosage if necessary [see Dosage and Administration (2.7)].

7.2 **Potential for Clozapine ODT to Affect Other Drugs**

Concomitant use of Clozapine ODT with other drugs metabolized by CYP2D6 can increase levels of these CYP2D6 substrates. Use caution when coadministering Clozapine ODT with other drugs that are metabolized by CYP2D6. It may be necessary to use lower doses of such drugs than usually prescribed. Such drugs include specific antidepressants, phenothiazines, carbamazepine, and other 5-HT2C antagonists (e.g., propafenone, flecainide, and encainide).
CLOZAPINE ODT (Orally Disintegrating Tablets) for oral use

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

Risk Summary

There are no adequate or well-controlled studies of clozapine in pregnant women. Reproduction studies have been performed in rats and rabbits at doses up to 0.4 and 0.9 times, respectively, the maximum recommended human dose (MRHD) of 900 mg/day on a mg/m² body surface area basis. The studies revealed no evidence of impaired fertility or harm to the fetus due to clozapine. Because animal reproduction studies are not always predictive of human response, Clozapine ODT should be used during pregnancy only if clearly needed.

Clinical Considerations

Consider the risk of exacerbation of psychosis when discontinuing or changing treatment with antipsychotic medications during pregnancy and postpartum. Consider early screening for gestational diabetes for patients treated with antipsychotic medications (see Warnings and Precautions (5.17)).

8.2 Lactation

Breastfeeding is not recommended because of the potential for serious adverse reactions in nursing infants from clozapine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.3 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.4 Geriatric Use

There have been insufficient numbers of geriatric patients in clinical studies utilizing Clozapine ODT to determine whether those over 65 years of age differ from younger subjects in their response to Clozapine ODT. Orthostatic hypotension and tachycardia can occur with clozapine treatment (see Boxed Warning and Warnings and Precautions (5.3)). Elderly patients, particularly those with compromised cardiovascular functioning, may be more susceptible to these effects.

Elderly patients may be particularly susceptible to the anticholinergic effects of clozapine, such as urinary retention and constipation (see Warnings and Precautions (5.15)). Carefully select Clozapine ODT doses in elderly patients, taking into consideration their greater frequency of decreased hepatic, renal, or cardiac function, as well as their generally decreased sensitivity to adverse reactions compared to younger subjects in their response to Clozapine ODT.

8.5 Patients with Renal or Hepatic Impairment

Dose reduction may be necessary in patients with significant impairment of renal or hepatic function. Clozapine concentrations may be increased in these patients, because clozapine is almost completely metabolized and then excreted (see Dosage and Administration (2.8), Clinical Pharmacology (12.3)).

8.6 CYP2D6 Poor Metabolizers

Dose reduction may be necessary in patients who are CYP2D6 poor metabolizers. Clozapine concentrations may be increased in these patients, because clozapine is almost completely metabolized and then excreted (see Dosage and Administration (2.8), Clinical Pharmacology (12.3)).

8.7 Hospice Patients

For hospice patients (i.e., terminally ill patients with an estimated life expectancy of 6 months or less), the prescriber may reduce the ANC monitoring frequency to once every 6 months, after a discussion with the patient and his/her caregiver. Individual treatment decisions should weigh the importance of monitoring ANC in the context of the need to control psychosomatic symptoms and the patient's terminal illness.

10 OVERDOSE

10.1 Overdosage Experience

The most commonly reported signs and symptoms associated with clozapine overdose are: sedation, delirium, coma, tachycardia, hypotension, respiratory depression or failure, and hypersalivation. There are reports of aspiration pneumonia, cardiac arrhythmias, and seizure. 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.

10.2 Management of Overdose

For the most up-to-date information on the management of Clozapine ODT overdosage, contact a certified Regional Poison Control Center (1-800-222-1222). Telephone numbers of certified Regional Poison Control Centers are listed in the Physicians' Desk Reference®, a registered trademark of PDR Network. Establish and maintain an airway; ensure adequate oxygenation and ventilation. Monitor cardiac status and vital signs. Use general symptomatic and supportive measures. There are no specific antidotes for Clozapine ODT.

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

11 DESCRIPTION

Clozapine ODT, an atypical antipsychotic drug, is a tricyclic dibenzodiazepine derivative, 5-(4-methyl-1-piperazinyl)-5H-dibenzo[b,e][1,4]diazepine.

The structural formula is:

C18H19ClN4     Mol. wt. 326.83

Clozapine ODT is available as yellow, orally disintegrating tablets of 12.5, 25 mg, 100 mg, 150 mg and 200 mg for oral administration without water. Clozapine ODT may be chewed.

Each orally disintegrating tablet contains clozapine equivalent to 12.5, 25 mg, 100 mg, 150 mg and 200 mg.

The active component of Clozapine ODT is clozapine. The remaining components are aspartame, microcrystalline cellulose, croscarmellose sodium, corn starch, and magnesium stearate.

PHENYLKETONURICS: CONTAINS PHENYLALANINE. [see Warnings and Precautions (5.18)]. Phenylalanine is a component of aspartame. Each 12.5 mg, orally disintegrating tablet contains 1.6 mg aspartame, thus, 0.87 mg phenylalanine. 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. Each 150 mg, orally disintegrating tablet contains 18.6 mg aspartame, thus, 10.44 mg phenylalanine. Each 200 mg, orally disintegrating tablet contains 24.8 mg aspartame, thus, 13.92 mg phenylalanine. The allowable daily intake of aspartame is 50 mg per kilogram of body weight per day.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of clozapine is unknown. However, it has been proposed that the therapeutic efficacy of clozapine in schizophrenia is mediated through antagonism of the dopamine type 2 (D2) and the serotonin type 2A (5-HT 2A) receptors.

Clozapine ODT also acts as an antagonist at adrenergic, cholinergic, histaminergic and other dopaminergic and serotoninergic receptors.

12.2 Pharmacodynamics

Clozapine demonstrated binding affinity to the following receptors: histamine H1, alpha 1-adrenergic, adenosine A 1, N-methyl-D-aspartate (NMDA), serotonin 5-HT 2A, serotonin 5-HT 2C (K 5.4 nM), muscarinic M 1 (K 8.2 nM), serotonin 5-HT 3, serotonin 5-HT 4 (K 9.4 nM), dopamine D 1 (K 24 nM), adenosine A 1 (K 90 nM), serotonin 5-HT 1D (K 95 nM), serotonin 5-HT 7, dopamine D 2 (K 120 nM), dopamine D 3 (K 160 nM), dopamine D 4 (K 270 nM), dopamine D 5 (K 454 nM), and dopamine D 6 (K 555 nM).

Clozapine causes little or no prolactin elevation.

Clinical electroencephalogram (EEG) studies demonstrated 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 have reported an intensification of dream activity during clozapine therapy. REM sleep has been shown to be increased to 85% of the total sleep time. In these patients, the onset of REM sleep occurred almost immediately after falling asleep.

12.3 Pharmacokinetics

Absorption

In man, clozapine tablets (25 mg and 100 mg) are equally bioavailable relative to a clozapine solution. Clozapine ODT is 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: 132-854 ng/mL), after 100 mg b.i.d. dosing.

A comparative bioequivalence/bioavailability study was conducted in 32 patients (with schizophrenia or schizoaffective disorder) comparing FazaClo® 200 mg tablets + to 2 × FazaClo® 100 mg tablets (the approved reference product) under fasted conditions. The study also evaluated the effect of food and chewing on the pharmacokinetics of the 200 mg tablet. Under fasted conditions, the mean AUC 0-8 of clozapine for the 200 mg tablets were equivalent to those of the 2 × 100 mg tablets. The mean C 0-8 of clozapine for FazaClo® 200 mg tablets was 85% that for 2 × 100 mg FazaClo® tablets. This decrease in C 0-8 of FazaClo® 200 mg tablets is not clinically significant.
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For FazaClo® 200 mg tablets, food significantly increased the Cmax of clozapine by 21%. However, this increase is not clinically significant. The mean AUC, and Cmax values of clozapine under fed conditions were equivalent to those under fasted conditions. Food delayed clozapine absorption by 1.5 hours, from a median Tmax of 2.5 hours while the AUC, and Cmax values were similar between the chewed and non-chewed conditions.

In a food-effect study, a single dose of FazaClo® (clozapine) orally disintegrating tablets 12.5 mg was administered to healthy volunteers under fasting conditions and after a high-fat meal. When FazaClo® was administered after a high fat meal, the Cmax of both clozapine and its active metabolite, desmethylclozapine, were decreased by approximately 20%, compared to administration under fasting conditions, while the AUC values were unchanged. This decrease in Cmax is not clinically significant. Therefore, Clozapine orally disintegrating tablets can be taken without regard to meals.

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 Drug Interactions (7)).

Metabolism and Excretion

Clozapine is almost completely metabolized prior to excretion, and only trace amounts of unchanged drug are detected in the urine and feces. Clozapine is a substrate for many cytochrome P450 isozymes, in particular CYP1A2, CYP2D6, and CYP3A4. Approximately 50% of the administered dose is excreted in the urine and 30% in the feces. The hydroxylated, N-dealkylated, and N-dealkylated N-oxide derivatives are 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 of 12 hours (range: 4-66 hours), after achieving steady-state with 100 mg twice daily dosing.

A comparison of single-dose and multiple-dose administration of clozapine demonstrated 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, approximately dose-proportional changes with respect to AUC (area under the curve), peak, and minimum clozapine concentrations were observed after administration of 37.5, 75, and 150 mg twice daily.

Drug-Drug Interaction Studies

Pharmacokinetics

A pharmacokinetic study was conducted in 16 schizophrenic patients who received clozapine under steady-state conditions. After coadministration of fluvoxamine for 14 days, mean trough concentrations of clozapine and its metabolites, N-desmethylclozapine and clozapine-N-oxide, were elevated about three-fold compared to baseline steady-state concentrations.

Paroxetine, Fluoxetine, and Sertraline

In a study of schizophrenic patients (n=14) who received clozapine under steady-state conditions, coadministration of 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.

Specific Population Studies

Renal or Hepatic Impairment

In specific pharmacokinetic studies were conducted to investigate the effects of renal or hepatic impairment on the pharmacokinetics of clozapine. Higher clozapine plasma concentrations are likely in patients with significant renal or hepatic impairment when given usual doses.

CYP2D6 Poor Metabolizers

A subset (3%-10%) of the population has reduced activity of CYP2D6 (CYP2D6 poor metabolizers). These individuals may develop higher than expected plasma concentrations of clozapine when given usual doses.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

No carcinogenic potential was demonstrated in long-term studies in mice and rats at doses up to 0.3 times and 0.4 times, respectively, the maximum recommended human dose (MRHD) of 900 mg/day on a mg/m² body surface area basis.

Mutagenesis

Clozapine was not genotoxic when tested in the following gene mutation and chromosomal aberration tests: the bacterial Ames test, the in vitro mammalian V79 in Chinese hamster cells, the in vitro unscheduled DNA synthesis in rat hepatocytes, or the in vivo micronucleus assay in mice.

Impairment of Fertility

Clozapine had no effect on any parameters of fertility, pregnancy, fetal weight, or postnatal development when administered orally to male rats 70 days before mating and to female rats for 14 days before mating at doses up to 0.4 times the MRHD of 900 mg/day on a mg/m² body surface area basis.

14 CLINICAL STUDIES

14.1 Treatment-Resistant Schizophrenia

The efficacy of clozapine in treatment-resistant schizophrenia was established in a multicenter, randomized, double-blind, active-controlled (chlorpromazine) study in patients with a DSM-III diagnosis of schizophrenia who had inadequate responses to at least 3 different antipsychotics (from at least 2 different chemical classes) during the preceding 5 years. The antipsychotic trials must have been judged adequate; the antipsychotic dosages must have been equivalent to or greater than 1000 mg per day of chlorpromazine for a period of at least 6 weeks, each without significant reduction of symptoms. There must have been no period of good functioning within the preceding 5 years. Patients must have a CGI baseline ≥45 on the investigator-rated Brief Psychiatric Rating Scale (BPRS). On the 18-item BPRS, 1 indicates the absence of symptoms, and 7 indicates severe symptoms; the maximum potential total BPRS score is 126. At baseline, the mean BPRS score was 61. In addition, patients must have had a score of at least 4 on at least two of the following four individual BPRS items: conceptual disorganization, hallucinatory behavior, and unusual thought content. Patients must have had a Clinical Global Impressions – Severity Scale score of at least 4 (moderately ill). In the prospective, lead-in phase of the trial, all patients (N=305) initially received single-blind treatment with haloperidol (the mean dose was 41.1 mg/day per week) for at least 6 weeks. More than 80% of patients completed the Week 6 trial. Patients with an inadequate response to haloperidol (N=268) were randomized to double-blind treatment with clozapine (N=126) or chlorpromazine (N=142). The maximum daily clozapine dose was 900 mg; the mean daily dose was 600 mg. The maximum daily chlorpromazine dose was 1800 mg; the mean daily dose was ≥1200 mg. The primary endpoint was treatment response, predefined as a decrease in BPRS score of at least 20% and either (1) a CGI-S score of ≤3 (mildly ill), or (2) a BPRS score of ≤35, at the end of 6 weeks of treatment. Approximately 88% of patients from the clozapine and chlorpromazine groups completed the 6-week trial. At the end of six weeks, 30% of patients from the chlorpromazine group and 40% from the clozapine group responded to treatment. The difference was statistically significant (p<0.001). The mean change in total BPRS score was -16.5 in the clozapine and chlorpromazine group, respectively; the mean change in the 4 key BPRS item scores was -5 and -2 in the clozapine and chlorpromazine group, respectively; and the mean change in CGI-S was -1.2 and -0.4, in the clozapine and chlorpromazine group, respectively. These changes in the clozapine group were statistically significantly greater than in the chlorpromazine group (p<0.001 in each analysis).

14.2 Recurrent Suicidal Behavior in Schizophrenia or Schizoaffective Disorder

The effectiveness of clozapine in reducing the risk of recurrent suicidal behavior was demonstrated in the International Suicide Prevention Trial (ITST), a group of experts blinded to patient data. Patients with schizophrenia or schizoaffective disorder (DSM-IV) who were judged to be at risk for recurrent suicidal behavior were randomized (SMB), a group of experts blinded to patient data. Patients must have met one of the following criteria:

• They had attempted suicide within the three years prior to their baseline evaluation.
• They had been hospitalized to prevent a suicide attempt within the three years prior to their baseline evaluation.
• They demonstrated moderate-to-severe suicidal ideation with a depressive component within one week prior to their baseline evaluation.
• They demonstrated moderate-to-severe suicidal ideation accompanied by command hallucinations to do self-harm within one week prior to their baseline evaluation.

Due to the potential for each treatment to be potentially fatal, for each treatment, FazaClo® was administered after a high fat meal, and individuals by individual patient. Dosing was flexible, with a dose range of 200–900 mg/day for clozapine and 5–20 mg/day for olanzapine. For the 956 patients who received clozapine or olanzapine in this study, there was extensive use of concomitant psychotropic medications: 56% with antipsychotics, 53% with antidepressants, and 28% with mood stabilizers. There was significantly greater use of concomitant psychotropic medications among the patients in the olanzapine group. The primary efficacy measure was time to (1) a significant suicide attempt, including a com-risk of suicide, (2) hospitalization due to imminent suicide risk, including increased level of surveillance for suicidality for patients already hospitalized; or (3) worsening of suicidal symptoms, and after a high fat meal. When FazaClo® was administered after a high fat meal, the Cmax of both clozapine and its active metabolite, desmethylclozapine, were decreased by approximately 20%, compared to administration under fasting conditions, while the AUC values were unchanged. This decrease in Cmax is not clinically significant. Therefore, Clozapine orally disintegrating tablets can be taken without regard to meals.

The probability of experiencing (1) a significant suicide attempt, including a com-risk of suicide, (2) hospitalization due to imminent suicide risk, including increased level of surveillance for suicidality for patients already hospitalized; or (3) worsening of suicidal symptoms, and after a high fat meal. When FazaClo® was administered after a high fat meal, the Cmax of both clozapine and its active metabolite, desmethylclozapine, were decreased by approximately 20%, compared to administration under fasting conditions, while the AUC values were unchanged. This decrease in Cmax is not clinically significant. Therefore, Clozapine orally disintegrating tablets can be taken without regard to meals.
CLOZAPINE ODT (Orally Disintegrating Tablets) for oral use

16 HOW SUPPLIED/STORAGE AND HANDLING
16.1 How Supplied
12.5 mg
1/4-inch diameter round yellow tablet debossed with “A05” on one side.
Bottles of 100:
100 tablets in an HDPE bottle with child-resistant cap............NDC No. 0093-3011-01
25 mg
5/16-inch diameter round yellow tablet debossed with “A06” on one side.
Bottles of 100:
100 tablets in an HDPE bottle with child-resistant cap...........NDC No. 0093-3012-01
Cartons of 48 for Institutional Use Only:
8 cards, 6 non child-resistant blisters per card.....................NDC No. 0093-3012-84
100 mg
1/2-inch diameter round yellow tablet debossed with “A08” on one side.
Bottles of 100:
100 tablets in an HDPE bottle with child-resistant cap............NDC No. 0093-3010-01
Cartons of 48 for Institutional Use Only:
8 cards, 6 non child-resistant blisters per card.....................NDC No. 0093-3010-84
150 mg
9/16-inch diameter round, yellow tablet debossed with “A09” on one side.
Bottles of 100:
100 tablets in an HDPE bottle with child-resistant cap............NDC No. 0093-3086-01
Cartons of 48 for Institutional Use Only:
8 cards, 6 non child-resistant blisters per card.....................NDC No. 0093-3086-84
200 mg
5/8-inch diameter round, yellow tablet debossed with “A10” on one side.
Bottles of 100:
100 tablets in an HDPE bottle with child-resistant cap............NDC No. 0093-3087-01
Cartons of 48 for Institutional Use Only:
8 cards, 6 non child-resistant blisters per card.....................NDC No. 0093-3087-84

16.2 Storage and Handling
Store Clozapine ODT at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). (See USP Controlled Room Temperature.) Protect from moisture. KEEP OUT OF REACH OF CHILDREN.

Clozapine ODT must remain in the original package until used by the patient.
Drug dispensing should not ordinarily exceed a weekly supply. If a patient is eligible for ANC testing every 2 weeks, then a 2-week supply of Clozapine ODT can be dispensed. If a patient is eligible for ANC testing every 4 weeks, then a 4-week supply of Clozapine ODT can be dispensed. Dispensing should be contingent upon the ANC testing results.

17 PATIENT COUNSELING INFORMATION
Discuss the following issues with patients and caregivers:
• Severe Neutropenia:
  - Instruct patients (and caregivers) beginning treatment with Clozapine ODT about the risk of developing severe neutropenia and infection.
  - Instruct patients to immediately report to their physician any symptom or sign of infection (e.g., flu-like illness; fever; lethargy; general weakness or malaise; mucus membrane ulceration; skin, pharyngeal, vaginal, urinary, or pulmonary infection; or extreme weakness or lethargy) occurring at any time during Clozapine ODT therapy, to aid in evaluation for neutropenia and to institute prompt and appropriate management. [see Warnings and Precautions (5.1), (5.11), and (5.13)].
  - Inform patients and caregivers Clozapine ODT is available only through a restricted program called the Clozapine REMS Program designed to ensure the required blood monitoring, in order to reduce the risk of developing severe neutropenia. Advise patients and caregivers of the importance of having blood tests performed as follows:
    - Weekly blood tests are required for the first 6 months.
    - An ANC is required every 2 weeks for the next 6 months if an acceptable ANC is maintained during the first 6 months of continuous therapy.
    - An ANC is required once every 4 weeks thereafter if an acceptable ANC is maintained during the second 6 months of continuous therapy.

• Orthostatic Hypotension, Bradycardia, and Syncope:
Inform patients and caregivers about the risk of orthostatic hypotension and syncope, especially during the period of initial dose titration. Instruct them to strictly follow the clinician’s instructions for dosage and administration. Advise patients to consult their clinician immediately if they feel faint, lose consciousness, or have signs or symptoms suggestive of orthostatic hypotension, Syncope.

• Falls:
Inform patients of the risk of falls, which may lead to fractures or other injuries [see Warnings and Precautions (5.6)].

• Seizures:
Inform patients and caregivers about the significant risk of seizure during Clozapine ODT treatment. Caution them about driving and any other potentially hazardous activity while taking Clozapine ODT [see Warnings and Precautions (5.4)].

• QT Interval Prolongation:
Advise patients to consult their clinician immediately if they feel faint, lose consciousness, or have signs or symptoms suggestive of atrial arrhythmia. Instruct patients not to take Clozapine ODT with other drugs that cause QT interval prolongation. Instruct patients to inform their clinicians that they are taking Clozapine ODT before any new drug [see Warnings and Precautions (5.9)].

• Metabolic Changes (hyperglycemia and diabetes mellitus, dyslipidemia, weight gain):
Advise patients and caregivers about the risk of metabolic changes and the need for specific monitoring. The risks include hyperglycemia and diabetes mellitus, dyslipidemia, weight gain, and cardiovascular reactions. Educate patients and caregivers about the symptoms of hyperglycemia (high blood sugar) and diabetes mellitus (e.g., polydipsia, polyuria, polyphagia, and weakness). Monitor all patients for these symptoms. Patients who are diagnosed with diabetes or have risk factors for diabetes (obesity, family history of diabetes) should have their fasting blood glucose monitored before beginning treatment and periodically during treatment. Patients who develop symptoms of hyperglycemia should have assessments of fasting glucose. Clinical monitoring of weight is recommended [see Warnings and Precautions (5.10)].

• Patients with Phenylketonuria:
Inform patients and caregivers that Clozapine ODT contains phenylalanine (a component of aspartame) [see Warnings and Precautions (5.18)].

• Interference with Cognitive and Motor Performance:
Because Clozapine ODT may have the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that Clozapine ODT therapy does not affect them adversely [see Warnings and Precautions (5.16)].

• Hepatotoxicity:
Inform patients to immediately report to their physician any symptom or sign of potential liver injury (e.g., fatigue, malaise, anorexia, nausea, jaundice, bilirubinemia, coagulopathy, and hepatic encephalopathy). [see Warnings and Precautions (5.13)].

• Missed Doses and Re-Initiating Treatment:
Inform patients and caregivers that if the patient misses taking Clozapine ODT for more than 2 days, he or she should not restart his or her medication at the same dosage but should contact their physician for dosing instructions [see Dosing and Administration (2.5) and Warnings and Precautions (4.4)].

• Pregnancy:
Advise patients and caregivers to notify the clinician if the patient becomes pregnant or intends to become pregnant during therapy [see Use in Specific Populations (8.1)].

• Nursing:
Advise patients and caregivers that the patient should not breast feed an infant if she is taking Clozapine ODT [see Use in Specific Populations (8.3)].

• Concomitant Medication:
Advise patients to inform their health care provider if they are taking, or plan to take, any prescription or over-the-counter drugs; there is a potential for significant drug-drug interactions [see Dosage and Administration (2.3), Drug Interactions (7.1), and Table 1].

• Administration:
Patients should be advised that Clozapine ODT should remain in the original package until immediately before use [see Dosage and Administration (2.2)].
CLOZAPINE ORALLY DISINTEGRATING TABLETS

1 INDIcATIONS AND USAGE

Cardiomyopathy; Increased Mortality in Elderly Patients with Dementia-Related Psychosis

5 WARNINGS AND PRECAUTIONS

• Eosinophilia: Assess for organ involvement (e.g., myocarditis, pancreatitis, hepatitis, colitis, nephritis). Discontinue if these occur. (5.8)
• QT Interval Prolongation: Can be fatal. Consider additional risk factors for prolonged QT interval (disorders and drugs). (5.9)
• Metabolic Changes: Atypical antipsychotic drugs have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes include:
  o Hyperglycemia and Diabetes Mellitus: Monitor for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Monitor glucose regularly in patients with diabetes or at risk for diabetes. (5.10)
  o Dyslipidemia: Undesirable alterations in lipids have occurred in patients treated with atypical antipsychotics. (5.10)
  o Weight Gain: Significant weight gain has occurred. Monitor weight gain. (5.10)
• Neuroleptic Malignant Syndrome (NMS): Immediately discontinue and monitor closely. Assess for co-morbidity conditions. (5.11)
• Hepatotoxicity: Can be fatal. Monitor for hepatotoxicity. Discontinue if hepatomegaly or transaminase elevations combined with other symptoms occur (5.12).
• Fever: Evaluate for infection and for neutropenia, NMS. (5.13)
• Pulmonary Embolism (PE): Consider PE if respiratory distress, chest pain, or deep-vein thrombosis occur. (5.14)
• Anticholinergic Toxicity: Use cautiously in presence of specific conditions (e.g., narrow angle glaucoma, use of anticholinergic drugs). (5.15)
• Intolerance with Cognitive and Motor Performance: Advise caution when operating machinery, including automobiles. (5.16)

2 DOSAGE AND ADMINISTRATION

Discontinue if symptoms suggest these cardiac reactions. (5.6)

3 DOSAGE FORMS AND STRENGTHS

Orally disintegrating tablets: 12.5 mg, 25 mg and 100 mg (3)

CONTRAINDICATIONS

Known serious hypersensitivity to clozapine or any other component of clozapine orally disintegrating tablets (4.1)

FULL PRESCRIBING INFORMATION: CONTENTS*

9 USE IN SPECIFIC POPULATIONS

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5.7 Increased Mortality in Elderly Patients with Dementia-Related Psychosis
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7 DRUG INTERACTIONS

5.7 Most common adverse reactions (≥15%): CNS reactions (sedation, dizziness/ vertigo, headache, and tremor); cardiovascular reactions (tachycardia, hypotension, and syncope); autonomic nervous system reactions (hypersalivation, sweating, dry mouth, and visual disturbances); gastrointestinal reactions (constipation and nausea); and fever. (6.1)

8 USE IN SPECIFIC POPULATIONS

5.7 To report SUSPECTED ADVERSE REACTIONS, contact Teva Pharmaceuticals USA, Inc. at 1-888-836-2872 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

4 CONTRAINDICATIONS

5.8 Warnings and Precautions, Falls (5.4), Hepatotoxicity (5.12) 02/2017

INDICATIONS AND USAGE

- Severe Neutropenia: Clozapine can cause severe neutropenia, which can lead to serious and fatal infections. Patients initiating and continuing treatment with clozapine must have a baseline blood absolute neutrophil count (ANC) measured before treatment initiation and regular ANC monitoring during treatment. (3.1)
- Clozapine is available only through a restricted program called the Clozapine REMS. (5.2)
- Orthostatic Hypotension, Bradycardia, and Syncope: Risk is dose-related. Starting dose is 12.5 mg. Titrate gradually and use divided doses. Use with caution in patients with history of severe or risk factors for seizure. (2.2, 5.5)
- Myocarditis and Cardiomyopathy: Can be fatal. Discontinue and obtain cardiac evaluation if findings suggest these cardiac reactions. (5.6)
- Increased Mortality in Elderly Patients with Dementia-Related Psychosis: Clozapine is not approved for this condition. (5.7)

ADVERSE REACTIONS

Most common adverse reactions (≥15%): CNS reactions (sedation, dizziness/ vertigo, headache, and tremor); cardiovascular reactions (tachycardia, hypotension, and syncope); autonomic nervous system reactions (hypersalivation, sweating, dry mouth, and visual disturbances); gastrointestinal reactions (constipation and nausea); and fever. (6.1)

5 WARNINGS AND PRECAUTIONS

5.9 QT Interval Prolongation
5.10 Eosinophilia
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6 ADVERSE REACTIONS

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10 OVERDOSAGE
10.1 Overdose Experience
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11 DESCRIPTION
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FULL PRESCRIBING INFORMATION

WARNING: SEVERE NEUTROPENIA; ORTHOSTATIC HYPOTENSION, BRADYCARDIA, AND SYNCOPE; SEIZURE; MYOCARDITIS AND CARDIOMYOPATHY; INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

Severe Neutropenia
Clozapine treatment has caused severe neutropenia, defined as an absolute neutrophil count (ANC) less than 500/μL. Severe neutropenia can lead to serious infection and death. Prior to initiating treatment with clozapine, a baseline ANC must be at least 1500/μL for the general population, and must be at least 1000/μL for patients with documented Benign Ethnic Neutropenia (BEN). During treatment, patients must have regular ANC monitoring. Advise patients to immediately report symptoms consistent with severe neutropenia or infection (e.g., fever, weakness, lethargy, or sore throat) [see Dosage and Administration (2.1), and Warnings and Precautions (5.1)]. Because of the risk of severe neutropenia, clozapine is available only through a restricted program under a Risk Evaluation Mitigation Strategy (REMS) called the Clozapine REMS Program [see Warnings and Precautions (5.2)].

Orthostatic Hypotension, Bradycardia, Syncope
Orthostatic hypotension, bradycardia, syncope, and cardiac arrest have occurred with clozapine treatment. The risk is highest during the initial titration period, particularly with rapid dose escalation. These reactions can occur with the first dose, with doses as low as 12.5 mg per day. Initial treatment at 12.5 mg once or twice daily; titrate slowly, and use divided dosages. Use clozapine cautiously in patients with cardiovascular or cerebrovascular disease or conditions predisposing to hypotension (e.g., dehydration, use of antihypertensive medications) [see Dosage and Administration (2.3, and 2.6), and Warnings and Precautions (5.3)].

Seizures
Seizures have occurred with clozapine treatment. The risk is dose-related. Initiate treatment at 12.5 mg, titrate gradually, and use divided dosing. Use caution when administering clozapine to patients with a history of seizures or other predisposing risk factors for seizure (CNS pathology, medications that lower the seizure threshold, alcohol abuse). Caution patients about engaging in any activity where sudden loss of consciousness could cause serious risk to themselves or others [see Dosage and Administration (2.3), Warnings and Precautions (5.5)].

Myocarditis and Cardiomyopathy
Fatal myocarditis and cardiomyopathy have occurred with clozapine treatment. Discontinue clozapine and obtain a cardiac evaluation upon suspicion of these reactions. Generally, patients with clozapine-related myocarditis or cardiomyopathy should not be rechallenged with clozapine. Consider the possibility of myocarditis or cardiomyopathy if chest pain, tachycardia, palpitations, dyspnea, fever, flu-like symptoms, hypotension, or ECG changes occur [see Warnings and Precautions (5.6)].

Increased Mortality in Elderly Patients with Dementia-Related Psychosis
Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Clozapine is not approved for use in patients with dementia-related psychosis [see Warnings and Precautions (5.7)].

1 INDICATIONS AND USAGE
1.1 Treatment-Resistant Schizophrenia
Clozapine orally disintegrating tablets are indicated for the treatment of severely ill patients with schizophrenia who fail to respond adequately to standard antipsychotic treatment. Because of the risks of severe neutropenia and of seizure associated with their use, clozapine orally disintegrating tablets should be used only in patients who have failed to respond adequately to standard antipsychotic treatment [see Warnings and Precautions (5.1, 5.5)].

The effectiveness of clozapine orally disintegrating tablets in treatment-resistant schizophrenia was demonstrated in a 6-week, randomized, double-blind, active-controlled study comparing clozapine orally disintegrating tablets and chlorpromazine in patients who had failed other antipsychotics [see Clinical Studies (14.1)].

1.2 Reduction in the Risk of Recurrent Suicidal Behavior in Schizophrenia or Schizoaffective Disorder
Clozapine orally disintegrating tablets are indicated for reducing the risk of recurrent suicidal behavior in patients with schizophrenia or schizoaffective disorder who are judged to be at chronic risk for re-experiencing suicidal behavior, based on history and recent clinical state. Suicidal behavior refers to actions by a patient that put him/herself at risk for death. The effectiveness of clozapine orally disintegrating tablets in reducing the risk of recurrent suicidal behavior was demonstrated over a two-year treatment period in the InterSePT trial [see Clinical Studies (14.2)].

2 DOSAGE AND ADMINISTRATION
2.1 Required Laboratory Testing Prior to Initiation and During Therapy
Prior to initiating treatment with clozapine orally disintegrating tablets, a baseline ANC must be obtained. The baseline ANC must be at least 1500/μL for the general population, and at least 1000/μL for patients with documented Benign Ethnic Neutropenia (BEN). To continue treatment, the ANC must be monitored regularly [see Warnings and Precautions (5.1)].

2.2 Important Administration Instructions
Clozapine orally disintegrating tablets should be immediately placed in the mouth after removing the tablet from the blister pack or bottle. The tablet disintegrates rapidly after placement in the mouth. The tablets can be allowed to disintegrate, or they may be chewed. They may be swallowed with salvia. No water is necessary for administration.

The orally disintegrating tablets in a blister pack should be left in the unopened blister until the time of use. Just prior to use, peel the foil from the blister and gently remove the oral disintegrating tablet. Do not push the tablets through the foil, because this could damage the tablet.

2.3 Dosing Information
The starting dose is 12.5 mg once daily or twice daily. The total daily dose can be increased in increments of 25 mg to 50 mg per day, if well-tolerated, to achieve a target dose of 500 mg to 450 mg per day (administered in divided doses) by the end of 2 weeks. Subsequently, the dose can be increased once weekly or twice weekly, in increments of up to 100 mg. The maximum dose is 900 mg per day. To minimize the risk of orthostatic hypotension, bradycardia, and syncope, it is necessary to use this low starting dose, gradual titration schedule, and divided dosages [see Warnings and Precautions (5.3)].

Clozapine orally disintegrating tablets can be taken with or without food [see Pharmacokinetics (12.3)].

2.4 Maintenance Treatment
Generally, patients responding to clozapine orally disintegrating tablets should continue maintenance treatment on their effective dose beyond the acute episode.

2.5 Discontinuation of Treatment
Method of treatment discontinuation will vary depending on the patient’s last ANC:
• See Tables 2 or 3 for appropriate ANC monitoring based on the level of neutropenia if abrupt treatment discontinuation is necessary because of moderate to severe neutropenia.
• Reduce the dose gradually over a period of 1 to 2 weeks if termination of clozapine therapy is planned and there is no evidence of moderate to severe neutropenia.
• For abrupt clozapine discontinuation for a reason unrelated to neutropenia, continuation of the existing ANC monitoring is recommended for general population patients until their ANC is ≥1500/μL and for BEN patients until their ANC is ≥1000/μL or above their baseline.
• Additional ANC monitoring is required for any patient reporting onset of fever (temperature of 38.5°C or 101.3°F, or greater) during the 2 weeks after discontinuation [see Warnings and Precautions (5.1)].
• Monitor all patients carefully for the recurrence of psychotic symptoms and symptoms related to cholinergic rebound such as profuse sweating, headache, nausea, vomiting, and diarrhea.

2.6 Re-initiation of Treatment
When restarting clozapine orally disintegrating tablets in patients who have discontinued clozapine orally disintegrating tablets (i.e., 2 days or more since the last dose), re-initiate with 12.5 mg once daily or twice daily. This is necessary to minimize the risk of hypotension, bradycardia, and syncope [see Warnings and Precautions (5.3)]. If that dose is well-tolerated, the dose may be increased to the previously therapeutic dose more quickly than recommended for initial treatment.

2.7 Dose Adjustment with Concomitant Use of CYP1A2, CYP2D6, CYP3A4 Inhibitors or CYP1A2, CYP3A4 Inducers
Dose adjustments may be necessary in patients with concomitant use of:
• CYP1A2 inhibitors (e.g., fluvoxamine, ciprofloxacin, or enoxacin); or CYP1A2 inducers (e.g., tobacco, carbamazepine, St. John’s wort, or rifampin); or CYP3A4 inhibitors (e.g., phenytoin, barbiturates, carbamazepine, quinidine, diltiazem, terbinafine, or sertraline); CYP3A4 inducers (e.g., phenytoin, carbamazepine, St. John’s wort, or rifampin) [see Drug Interactions (7)].
Table 1: Dose Adjustment in Patients Taking Concomitant Medications

<table>
<thead>
<tr>
<th>Co-medications</th>
<th>Scenarios</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initiating clozapine orally disintegrating tablets while taking a co-medication</td>
<td></td>
</tr>
<tr>
<td>Adding a co-medication while taking clozapine orally disintegrating tablets</td>
<td>Increase clozapine orally disintegrating tablets dose based on clinical response.</td>
</tr>
<tr>
<td>Discontinuing a co-medication while continuing clozapine orally disintegrating tablets</td>
<td></td>
</tr>
</tbody>
</table>

Strong CYP1A2 Inhibitors
- Use one third of the clozapine orally disintegrating tablets dose.
- Increase clozapine orally disintegrating tablets dose based on clinical response.
- Monitor for adverse reactions. Consider reducing the clozapine orally disintegrating tablets dose if necessary.
- Obtain at least two baseline ANC levels before initiating treatment. Patients in the general population with an ANC equal to or greater than (>1500/μL) are considered within normal range (Table 2).

Moderate or Weak CYP1A2 Inhibitors
- Monitor for adverse reactions. Consider reducing the clozapine orally disintegrating tablets dose if necessary.
- Reduce clozapine orally disintegrating tablets dose based on clinical response.

CYP2D6 or CYP3A4 Inhibitors
- Monitor for decreased effectiveness.
- Consider increasing the clozapine orally disintegrating tablets dose if necessary.
- Consider reducing the clozapine orally disintegrating tablets dose if necessary.

Strong CYP3A4 Inducers
- Concomitant use is not recommended. However, if the inducer is necessary, it may be necessary to increase the clozapine orally disintegrating tablets dose.
- Monitor for decreased effectiveness.
- Monitor for adverse reactions. Consider reducing the clozapine orally disintegrating tablets dose if necessary.

Moderate or weak CYP1A2 or CYP3A4 Inducers
- Monitor for decreased effectiveness.
- Consider increasing the clozapine orally disintegrating tablets dose if necessary.

2.8 Renal or Hepatic Impairment or CYP2D6 Poor Metabolizers
It may be necessary to reduce the clozapine orally disintegrating tablets dose in patients with significant renal or hepatic impairment, or in CYP2D6 poor metabolizers (see Use in Specific Populations (8.8, 8.9)).

3 DOSAGE FORMS AND STRENGTHS
Clozapine Orally Disintegrating Tablets are available as 12.5 mg, 25 mg and 100 mg, round, yellow, orally disintegrating tablets.

4 CONTRAINDICATIONS
4.1 Hypersensitivity
Clozapine orally disintegrating tablets are contraindicated in patients with a history of serious hypersensitivity to clozapine (e.g., photosensitivity, vasculitis, erythema multiforme, or Stevens-Johnson Syndrome) or any other component of clozapine orally disintegrating tablets (see Adverse Reactions (6.2)).

5 WARNINGS AND PRECAUTIONS
5.1 Severe Neutropenia
Background
Clozapine can cause neutropenia (a low absolute neutrophil count (ANC)), defined as a reduction below pre-treatment normal levels of blood neutrophils. The ANC is usually available as a component of the complete blood count (CBC), including differential, and is more relevant to drug-induced neutropenia than is the white blood cell (WBC) count. The ANC may also be calculated using the following formula: ANC equals the total WBC count multiplied by the total percentage of neutrophils obtained from the differential (neutrophil “segs” plus neutrophil “bands”). Other granulocytes (basophils and eosinophils) contribute minimally to neutropenia and their measurement is not necessary (see Adverse Reactions (6.2)).

Neutropenia may be mild, moderate, or severe (see Tables 2 and 3). To improve and standardize understanding, “severe neutropenia” replaces the previous terms severe leukopenia, severe granulocytopenia, or agranulocytosis.

Severe neutropenia, ANC less than (<) 500/μL, occurs in a small percentage of patients taking clozapine and is associated with an increase in the risk of serious and potentially fatal infections. Risk of neutropenia appears greatest during the first 18 weeks on treatment and then declines. The mechanism by which clozapine causes neutropenia is unknown and is not dose-dependent.

Two separate management algorithms are provided below, the first for patients in the general population, and the second for patients identified to have baseline neutropenia. (see Table 2)

Obtain a CBC, including the ANC value, prior to initiating treatment with clozapine to ensure the presence of a normal baseline neutrophil count (equal to or greater than 1500/μL) and to permit later comparisons. Patients in the general population with an ANC equal to or greater than (>1500/μL) are considered within normal range (Table 2) and are eligible to initiate treatment. Weekly ANC monitoring is required for all patients during the first 6 months of treatment. If a patient’s ANC remains equal to or greater than 1500/μL for the first 6 months of treatment, monitoring frequency may be reduced to every 2 weeks for the next 6 months. If the ANC remains equal to or greater than 1500/μL for the second 6 months of continuous therapy, ANC monitoring frequency may be reduced to once every 4 weeks thereafter.

Table 2: Clozapine Treatment Recommendations Based on Absolute Neutrophil Count (ANC) Monitoring for the General Patient Population

<table>
<thead>
<tr>
<th>ANC Level</th>
<th>Clozapine Treatment Recommendations</th>
<th>ANC Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal range (&lt;1500/μL)</td>
<td>• Initiate treatment</td>
<td>• Weekly from initiation to 6 months</td>
</tr>
<tr>
<td>Moderate Neutropenia (500 to 999/μL)</td>
<td>• Recommend hematology consultation</td>
<td>• Three times weekly until ANC ≥1500/μL</td>
</tr>
<tr>
<td>Severe Neutropenia (less than 500/μL)</td>
<td>• Recommend hematology consultation</td>
<td>• Daily until ANC ≥1500/μL</td>
</tr>
</tbody>
</table>

1. Confirm all initial reports of ANC less than 1500/μL with a repeat ANC measurement within 24 hours.
2. If clinically appropriate.

Clozapine Treatment and Monitoring in Patients with Benign Ethnic Neutropenia (see Table 3)

Benign ethnic neutropenia (BEN) is a condition observed in certain ethnic groups whose average ANC values are lower than “standard” laboratory ranges for neutrophils. It is most commonly observed in individuals of African descent (approximate prevalence of 25 to 50%), some Middle Eastern ethnic groups, and in other non-Caucasian ethnic groups with darker skin. BEN is more common in men. Patients with BEN have normal hematopoietic stem-cell number and myeloid maturation, are healthy, and do not suffer from repeated or severe infections. They are not at increased risk for developing clozapine-induced neutropenia. Additional evaluation may be needed to determine if baseline neutropenia is due to BEN. Consider hematology consultation before initiating or during clozapine treatment as necessary.

Patients with BEN require a different ANC algorithm for clozapine management due to their lower baseline ANC levels. Table 3 provides guidelines for managing clozapine treatment and ANC monitoring in patients with BEN.

Table 3: Patients with Benign Ethnic Neutropenia (BEN): Clozapine Treatment Recommendations Based on Absolute Neutrophil Count (ANC) Monitoring

<table>
<thead>
<tr>
<th>ANC Level</th>
<th>Treatment Recommendations</th>
<th>ANC Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal BEN Range (Established ANC baseline &lt;1000/μL)</td>
<td>• Obtain at least two baseline ANC levels before initiating treatment</td>
<td>• Weekly from initiation to 6 months</td>
</tr>
<tr>
<td></td>
<td>• If treatment interrupted:</td>
<td>• Every 2 weeks from 6 to 12 months</td>
</tr>
<tr>
<td></td>
<td>- &lt;30 days, continue monitoring as before</td>
<td>• Monthly after 12 months</td>
</tr>
<tr>
<td></td>
<td>- ≥30 days, monitor as if new patient</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Discontinuation of treatment for reasons other than neutropenia</td>
<td>• See Section 2.4</td>
</tr>
</tbody>
</table>
### ANC Monitoring

<table>
<thead>
<tr>
<th>ANC Level</th>
<th>Treatment Recommendations</th>
<th>ANC Monitoring</th>
</tr>
</thead>
</table>
| **BEN Neutropenia 500 to 999/μL** | • Recommend hematology consultation and continue treatment                                 | • Three times weekly until ANC =1000/μL or > patient’s known baseline  
• Once ANC >1000/μL or at patient’s known baseline, check ANC weekly for 4 weeks, then return to patient’s last “Normal BEN Range” ANC monitoring interval.¹ |
| **BEN Severe Neutropenia less than 500/μL** | • Recommend hematology consultation  
• Interrupt treatment for suspected clozapine-induced neutropenia  
• Do not rechallenge unless prescriber determines benefits outweigh risks | • Daily until ANC =500/μL, then  
• Three times weekly until ANC >patient’s baseline  
• If patient rechallenged, resume treatment as a new patient under “Normal Range” monitoring once ANC ≥1000/μL or at patient’s baseline |

¹ Confirm all initial reports of ANC less than 1500/μL with a repeat ANC measurement within 24 hours

²_clinically appropriate

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**5.4 Falls**

Falls may cause somnolence, postural hypotension, and motor and sensory instability, which may lead to falls and, consequently, fractures or other injuries. For patients with diseases, conditions, or medications that could exacerbate these effects, complete fall risk assessments when initiating antipsychotic treatment and recurrently for patients on long-term antipsychotic treatment.

**5.5 Seizures**

Seizures have 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 1274 patients exposed to clozapine during its clinical trial prior to domestic marketing (i.e., a crude rate of 3.5%). The risk of seizure is dose-related. Initiate treatment with a low dose (12.5 mg), titrate slowly, and use divided dosing. Use caution when administering clozapine to patients with a history of seizures or other conditions such as malaise, malnutrition, renal disease, or use of medications that lower the seizure threshold, or alcohol abuse. Because of the substantial risk of seizure associated with clozapine use, caution patients about engaging in any activity where sudden loss of consciousness could cause serious risk to themselves or others (e.g., driving an automobile, operating complex machinery, swimming, climbing).

**5.6 Myocarditis and Cardiomyopathy**

Myocarditis and cardiomyopathy have occurred with the use of clozapine. These reactions can be fatal. Discontinue clozapine and obtain a cardiac evaluation upon suspicion of myocarditis or cardiomyopathy. Generally, patients with a history of chronic myocarditis or cardiomyopathy should not be rechallenged with clozapine. However, if the benefit of clozapine treatment is judged to outweigh the potential risks of recurrent myocarditis or cardiomyopathy, the clinician may consider rechallenge with clozapine in consultation with a cardiologist, after a complete cardiac evaluation, and under close monitoring.

**5.7 Increased Mortality in Elderly Patients with Dementia-Related Psychosis**

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death 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. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotics may increase mortality in this population. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. Clozapine is not approved for the treatment of patients with dementia-related psychosis (see boxed Warning).

**5.8 Eosinophilia**

Eosinophilia, defined as a blood eosinophil count of greater than 700/μL, has occurred with clozapine treatment. In clinical trials, approximately 1% of patients developed eosinophilia. Clozapine-related eosinophilia usually occurs during the first month of treatment. In some patients, it has been associated with myocarditis, pancreatitis, hepatitis, colitis, and nephritis. Such organ involvement could be consistent with a drug reaction with eosinophilia and systemic symptoms syndrome (DRESS), also known as drug induced hypersensitivity syndrome (DIHS). If eosinophilia develops during clozapine treatment, evaluate promptly for signs and symptoms of systemic involvement, such as rash or other signs of collagen vascular disease, parasitic infections, and specific neoplasms, or other organ-specific disease associated with eosinophilia. If clozapine-related systemic disease is suspected, discontinue clozapine immediately.

If a cause of eosinophilia unrelated to clozapine is identified (e.g., asthma, allergies, collagen vascular disease, parasitic infections, and specific neoplasms), treat the underlying cause and continue clozapine treatment if appropriate.

Clozapine-related eosinophilia has also occurred in the absence of organ involvement and can resolve without intervention. There are reports of occult serious disease after discontinuation of clozapine, without recurrence of eosinophilia. In the absence of organ effects, complete fall risk assessments when initiating antipsychotic treatment and recurrently for patients on long-term antipsychotic treatment.

**5.3 Orthostatic Hypotension, Bradycardia, and Syncope**

Orthostatic hypotension, bradycardia, and syncope have occurred with clozapine treatment. The risk is highest during the initial titration period, particularly with rapid dose-escalation. These reactions can occur with the first dose, at doses as low as 12.5 mg. These reactions can be fatal. The syndrome is consistent with neurally mediated reflex bradycardia (NMRB). Treatment must begin at a maximum dose of 12.5 mg once daily or twice daily. The total daily dose can be increased in increments of 25 mg to 50 mg per day, if well-tolerated, to a target dose of 300 mg to 450 mg per day (administered in divided doses) by the end of 2 weeks. Subsequently, the dose can be increased weekly or twice weekly, in increments of up to 100 mg. The maximum dose is 900 mg per day.

Use cautious titration and a divided dosage schedule to minimize the risk of serious cardiovascular reactions [see Dosage and Administration (2.3)]. Consider reducing the dose if hypotension occurs. When restarting patients who have had even a brief interval off clozapine (i.e., 2 days or more since the last dose), reinitiate treatment at 12.5 mg once daily or twice daily [see Dosage and Administration (2.6)]. Use clozapine cautiously in patients with cardiovascular disease (history of myocardial infarction or ischemia, heart failure, or conduction abnormalities), cerebrovascular disease, and conditions which would predispose patients to hypotension (e.g., concomitant use of antihypertensives, dehydration and hypovolemia).

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**Further information is available at www.clozapinerems.com or 1-844-267-8678.**
involved, continue clozapine under careful monitoring. If the total eosinophil count continues to increase over several weeks in the absence of systemic disease, the decision to interrupt clozapine therapy and rechallenge after the eosinophil count decreases should be based on the overall clinical assessment, in consultation with an internist or hematologist.

5.9 QT Interval Prolongation

QT prolongation, Torsades de Pointes and other life-threatening ventricular arrhythmias, cardiac arrest, and sudden death have occurred with clozapine treatment. When prescribing clozapine, consider the presence of additional risk factors for QT prolongation and serious cardiovascular conditions. Conditions that increase these risks include the following: history of QT prolongation, long QT syndrome, family history of sudden cardiac death, significant cardiac arrhythmia, recent myocardial infarction, uncompensated heart failure, treatment with other medications that cause QT prolongation, treatment with medications that inhibit potassium channels or prolong the QT interval, or treatments that increase the QT interval. Use caution when administering concomitant medications that prolong the QT interval or inhibit the metabolism of clozapine orally disintegrating tablets. Drugs that cause QT prolongation include: specific antipsychotics (e.g., ziprasidone, iloperidone, chlorpromazine, thioridazine, mesoridazine, droperidol, pimozide), specific antiarrhythmics (e.g., erythromycin, ketoconazole, moxifloxacin, clarithromycin, fluconazole), and selective serotonin reuptake inhibitors (e.g., amiodarone, sotalol, and others). Obtain a baseline and periodic follow-up lipid evaluations in patients using clozapine, is recommended.

In a pooled data analysis of 10 studies in adult subjects with schizophrenia, clozapine treatment was associated with increases in serum total cholesterol. No data were collected on LDL and HDL cholesterol. The mean increase in total cholesterol was 13 mg/dL in the clozapine group and 15 mg/dL in the chlorpromazine group. In a pooled data analysis of 2 studies in adult subjects with schizophrenia, clozapine treatment was associated with increases in fasting serum triglyceride. The mean increase in fasting triglyceride was 71 mg/dL (54%) in the clozapine group and 39 mg/dL (35%) in the chlorpromazine group (Table 5). In addition, clozapine treatment was associated with categorical increases in serum total cholesterol and triglyceride, as illustrated in Table 6. The proportion of patients with categorical increases in total cholesterol or fasting triglyceride increased with the duration of exposure. The median duration of clozapine and chlorpromazine exposure was 45 days and 38 days, respectively. The clozapine dose range was 100 mg to 900 mg daily; the maximum chlorpromazine dose was 1800 mg daily.

Table 4: Categorical Changes in Fasting Glucose Level in Studies in Adult Subjects with Schizophrenia

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>Category Change (at least one) from Baseline</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine</td>
<td>N=198</td>
<td>53 (27)</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>N=135</td>
<td>10 (14)</td>
</tr>
<tr>
<td>Borderline (100 to 125 mg/dL) to High (≥126 mg/dL)</td>
<td>N=57</td>
<td>42 (24)</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>N=43</td>
<td>12 (28)</td>
</tr>
</tbody>
</table>

Dyslipidemia

Unsatisfactory alterations in lipids have occurred in patients treated with atypical antipsychotics, including clozapine. Clinical monitoring, including baseline and periodic follow-up lipid evaluations in patients using clozapine, is recommended. In a pooled data analysis of 8 studies in adult subjects with schizophrenia, clozapine treatment was associated with increases in total carbohydrate. No data were collected on LDL and HDL cholesterol. The mean increase in total cholesterol was 13 mg/dL in the clozapine group and 15 mg/dL in the chlorpromazine group. In a pooled data analysis of 2 studies in adult subjects with schizophrenia, clozapine treatment was associated with increases in fasting serum triglyceride. The mean increase in fasting triglyceride was 71 mg/dL (54%) in the clozapine group and 39 mg/dL (35%) in the chlorpromazine group.

Table 5: Mean Changes in Total Cholesterol and Triglyceride Concentration in Studies in Adult Subjects with Schizophrenia

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>Baseline Total Cholesterol Concentration (mg/dL)</th>
<th>Change from Baseline mg/dL (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine (N=334)</td>
<td>184</td>
<td>+13 (7)</td>
</tr>
<tr>
<td>Chlorpromazine (N=165)</td>
<td>182</td>
<td>+15 (8)</td>
</tr>
<tr>
<td>Borderline (200 to 239 mg/dL) to High (≥240 mg/dL)</td>
<td>N=130</td>
<td>+71 (54)</td>
</tr>
<tr>
<td>Chlorpromazine (N=7)</td>
<td>110</td>
<td>+39 (35)</td>
</tr>
</tbody>
</table>

Table 6: Categorical Changes in Lipid Concentrations in Studies in Adult Subjects with Schizophrenia

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>Category Change (at least one) from Baseline</th>
<th>Treatment Arm</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Cholesterol (random or fasting)</td>
<td>Increase by &gt;40 mg/dL</td>
<td>Clozapine 334</td>
<td>111 (33)</td>
</tr>
<tr>
<td></td>
<td>Normal (&lt;200 mg/dL) to High (≥240 mg/dL)</td>
<td>Clozapine 222</td>
<td>18 (8)</td>
</tr>
<tr>
<td></td>
<td>Borderline (200 to 239 mg/dL) to High (≥240 mg/dL)</td>
<td>Clozapine 132</td>
<td>3 (2)</td>
</tr>
<tr>
<td></td>
<td>Increase by &lt;50 mg/dL</td>
<td>Clozapine 79</td>
<td>30 (38)</td>
</tr>
<tr>
<td></td>
<td>Normal (&lt;150 mg/dL) to High (≥200 mg/dL)</td>
<td>Chlorpromazine 34</td>
<td>14 (41)</td>
</tr>
<tr>
<td></td>
<td>Borderline (&gt;150 mg/dL and &lt;200 mg/dL) to High (≥200 mg/dL)</td>
<td>Chlorpromazine 1</td>
<td>1 (100)</td>
</tr>
<tr>
<td>Triglycerides (fasting)</td>
<td>Normal (&lt;150 mg/dL) to High (≥200 mg/dL)</td>
<td>Clozapine 4</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td>Borderline (&gt;150 mg/dL and &lt;200 mg/dL) to High (≥200 mg/dL)</td>
<td>Chlorpromazine 6</td>
<td>2 (33)</td>
</tr>
<tr>
<td></td>
<td>Increase by &gt;50 mg/dL</td>
<td>Clozapine 1</td>
<td>1 (100)</td>
</tr>
</tbody>
</table>

Weight Gain

Weight gain has occurred with the use of antipsychotics, including clozapine. Monitor weight during treatment with clozapine. Table 7 summarizes the data on weight gain by the duration of exposure pooled from 11 studies with clozapine and comparative antipsychotics. The median duration of exposure was 60, 72, and 42 days, in the clozapine, olanzapine, and chlorpromazine group, respectively.
Table 8 summarizes pooled data from 11 studies in adult subjects with schizophrenia demonstrating weight gain ≥7% of body weight relative to baseline. The median duration of exposure was 609, 728, and 42 days, in the clozapine, olanzapine, and chlorpromazine group, respectively.

Table 8: Proportion of Adult Subjects in Schizophrenia Studies with Weight Gain ≥7% Relative to Baseline Body Weight

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Exposure Duration</th>
<th>Clozapine (N=669)</th>
<th>Olanzapine (N=442)</th>
<th>Chlorpromazine (N=155)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight change from baseline</td>
<td></td>
<td>n</td>
<td>Mean</td>
<td>n</td>
</tr>
<tr>
<td>2 weeks (Day 11 to 17)</td>
<td></td>
<td>6</td>
<td>+0.9</td>
<td>3</td>
</tr>
<tr>
<td>4 weeks (Day 21 to 35)</td>
<td></td>
<td>23</td>
<td>+0.7</td>
<td>8</td>
</tr>
<tr>
<td>8 weeks (Day 49 to 63)</td>
<td></td>
<td>12</td>
<td>+1.9</td>
<td>13</td>
</tr>
<tr>
<td>12 weeks (Day 70 to 98)</td>
<td></td>
<td>17</td>
<td>+2.8</td>
<td>5</td>
</tr>
<tr>
<td>24 weeks (Day 154 to 182)</td>
<td></td>
<td>42</td>
<td>-0.6</td>
<td>12</td>
</tr>
<tr>
<td>48 weeks (Day 322 to 350)</td>
<td></td>
<td>3</td>
<td>+3.7</td>
<td>3</td>
</tr>
</tbody>
</table>

Table 6.16 Interference with Cognitive and Motor Performance
Clozapine can cause sedation and impairment of cognitive and motor performance. Caution patients about operating hazardous machinery, including automobiles, until they are reasonably certain that clozapine does not affect them adversely. These reactions may be dose-related. Consider reducing the dose if they occur.

5.17 Tardive Dyskinesia
Tardive dyskinesia (TD) has occurred in patients treated with antipsychotic drugs, including clozapine. The syndrome consists of potentially irreversible, involuntary, dyskinetic movements. The risk of TD and the likelihood that it will become irreversible are believed to increase with greater durations of treatment and higher total cumulative doses. However, the syndrome can develop after relatively brief treatment periods at low doses. Prescribe clozapine in a manner that is most likely to minimize the risk of developing TD. Use the lowest effective dose and the shortest duration necessary to control symptoms. Periodically assess the need for continued treatment. Consider discontinuing treatment if TD occurs. However, some patients may require treatment with clozapine despite the presence of TD. There is no known treatment for TD. However, the syndrome may remit partially or completely if treatment is discontinued. Antipsychotic treatment, itself, may suppress (or partially suppress) the signs and symptoms, and it has the potential to mask the underlying process. The effect of symptom suppression on the long-term course of TD is unknown.

5.18 Patients with Phenylketonuria
Phenylketonuric patients should be informed that clozapine orally disintegrating tablets contain phenylalanine (a component of aspartame). Each 12.5 mg, orally disintegrating tablet contains 1.4 mg phenylalanine. Each 25 mg, orally disintegrating tablet contains 2.8 mg phenylalanine. Each 100 mg, orally disintegrating tablet contains 11.2 mg phenylalanine.

5.19 Cerebrovascular Adverse Reactions
In controlled trials, elderly patients with dementia-related psychosis treated with some atypical antipsychotics had an increased risk (compared to placebo) of cerebrovascular adverse reactions (e.g., stroke, transient ischemic attack), including fatalities. The mechanism for this increased risk is not known. An increased risk cannot be excluded for clozapine or other antipsychotics or other patient populations. Clozapine should be used cautiously with patients with risk factors for cerebrovascular adverse reactions.

6. ADVERSE REACTIONS
The following adverse reactions are discussed in more detail in other sections of the labeling:

• Severe Neutropenia [see Warnings and Precautions (5.1)].
• Orthostatic Hypotension, Bradycardia, and Syncope [see Warnings and Precautions (5.3)].
• Falls [see Warnings and Precautions (5.4)].
• Seizures [see Warnings and Precautions (5.5)].
• Myocarditis and Cardiomyopathy [see Warnings and Precautions (5.6)].
• Increased Mortality in Elderly Patients with Dementia-Related Psychosis [see Warnings and Precautions (5.7)].
• Eosinophilia [see Warnings and Precautions (5.8)].
• QT Interval Prolongation [see Warnings and Precautions (5.9)].
• Metabolic Changes (Hyperglycemia and Diabetes Mellitus, Dyslipidemia, and Weight Gain) [see Warnings and Precautions (5.10)].
• Neuroleptic Malignant Syndrome [see Warnings and Precautions (5.11)].
• Hepatotoxicity [see Warnings and Precautions (5.12)].
• Fever [see Warnings and Precautions (5.13)].
• Pulmonary Embolism [see Warnings and Precautions (5.14)].
• Anticholinergic Toxicity [see Warnings and Precautions (5.15)].
• Interference with Cognitive and Motor Performance [see Warnings and Precautions (5.16)].
• Tardive Dyskinesia [see Warnings and Precautions (5.17)].
• Patients with Phenylketonuria [see Warnings and Precautions (5.18)].
• Cerebrovascular Adverse Reactions [see Warnings and Precautions (5.19)].
• Recurrence of Psychosis and Cholinergic Rebound after Abrupt Discontinuation of Clozapine [see Warnings and Precautions (5.20)].

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice. The most commonly reported adverse reactions (≥5%) across clozapine clinical trials were: CNS reactions, including sedation, dizziness/vertigo, headache, and tremor; cardiovascular reactions, including tachycardia, hypotension, and syncope; autonomic nervous system reactions, including hypersalivation, sweating, dry mouth, and visual disturbances; gastrointestinal reactions, including constipation and nausea; and fever. Table 9 summarizes the most commonly reported adverse reactions (≥5%) in clozapine-treated patients (compared to chlorpromazine-treated patients) in the pivotal, 6-week, controlled trial treatment-resistant schizophrenia.
### Table 9: Common Adverse Reactions (≥5%) in the 6-Week, Randomized, Chlorpromazine-Controlled Trial in Treatment-Resistant Schizophrenia

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Clozapine (N=126) (%)</th>
<th>Chlorpromazine (N=142) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sedation</td>
<td>21</td>
<td>13</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>17</td>
<td>11</td>
</tr>
<tr>
<td>Constipation</td>
<td>16</td>
<td>12</td>
</tr>
<tr>
<td>Dizziness</td>
<td>14</td>
<td>16</td>
</tr>
<tr>
<td>Hypotension</td>
<td>13</td>
<td>38</td>
</tr>
<tr>
<td>Fever (hyperthermia)</td>
<td>13</td>
<td>4</td>
</tr>
<tr>
<td>Hypersalivation</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>Headache</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Nausea/Vomiting</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>5</td>
<td>20</td>
</tr>
</tbody>
</table>

Table 10 summarizes the adverse reactions reported in clozapine-treated patients at a frequency of 2% or greater across all clozapine studies (excluding the 2 year InterSePT™ Study). These rates are not adjusted for duration of exposure.

### Table 10: Adverse Reactions (≥2%) Reported in Clozapine-treated Patients (N=842) Across all Clozapine Studies (excluding the 2 year InterSePT™ Study)

<table>
<thead>
<tr>
<th>Body System</th>
<th>Clozapine N=842 Percentage of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central Nervous System</td>
<td>Drowsiness/Sedation 39</td>
</tr>
<tr>
<td></td>
<td>Dizziness/Vertigo 19</td>
</tr>
<tr>
<td></td>
<td>Headache 7</td>
</tr>
<tr>
<td></td>
<td>Tremor 6</td>
</tr>
<tr>
<td></td>
<td>Syncope 6</td>
</tr>
<tr>
<td></td>
<td>Disturbed Sleep/Nightmares 4</td>
</tr>
<tr>
<td></td>
<td>Restlessness 4</td>
</tr>
<tr>
<td></td>
<td>Hypokinesia/Akinesia 4</td>
</tr>
<tr>
<td></td>
<td>Agitation 4</td>
</tr>
<tr>
<td></td>
<td>Seizures (convulsions) 3</td>
</tr>
<tr>
<td></td>
<td>Rigidity 3</td>
</tr>
<tr>
<td></td>
<td>Akathisia 3</td>
</tr>
<tr>
<td></td>
<td>Confusion 3</td>
</tr>
<tr>
<td></td>
<td>Fatigue 2</td>
</tr>
<tr>
<td></td>
<td>Insomnia 2</td>
</tr>
<tr>
<td>Cardiovascular System</td>
<td>Tachycardia 25</td>
</tr>
<tr>
<td></td>
<td>Hypotension 9</td>
</tr>
<tr>
<td></td>
<td>Hypertension 4</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Constipation 14</td>
</tr>
<tr>
<td></td>
<td>Nausea 5</td>
</tr>
<tr>
<td></td>
<td>Abdominal Discomfort/Heartburn 4</td>
</tr>
<tr>
<td></td>
<td>Nausea/Vomiting 3</td>
</tr>
<tr>
<td></td>
<td>Vomiting 3</td>
</tr>
<tr>
<td></td>
<td>Diarrhea 2</td>
</tr>
<tr>
<td>Urogenital</td>
<td>Urinary abnormalities 2</td>
</tr>
<tr>
<td>Autonomic Nervous System</td>
<td>Salivation 31</td>
</tr>
<tr>
<td></td>
<td>Sweating 6</td>
</tr>
<tr>
<td></td>
<td>Dry mouth 6</td>
</tr>
<tr>
<td></td>
<td>Urinary disturbances 5</td>
</tr>
<tr>
<td>Skin</td>
<td>Rash 2</td>
</tr>
<tr>
<td>Hemic/Lymphatic</td>
<td>Leukopenia/Decreased WBC/Neutropenia 3</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Fever 5</td>
</tr>
<tr>
<td></td>
<td>Weight Gain 4</td>
</tr>
</tbody>
</table>

1 Rate based on population of approximately 1700 exposed during premarket clinical evaluation of clozapine.

Table 11 summarizes the most commonly reported adverse reactions (≥10% of the clozapine or olanzapine group) in the InterSePT™ Study. This was an adequate evaluation of clozapine.

### Table 11: Incidence of Adverse Reactions in Patients Treated with Clozapine or Olanzapine in the InterSePT™ Study (≥10% in the clozapine or olanzapine group)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Clozapine N=479 % Reporting</th>
<th>Olanzapine N=477 % Reporting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salivary hypersecretion</td>
<td>48%</td>
<td>6%</td>
</tr>
<tr>
<td>Somnolence</td>
<td>46%</td>
<td>25%</td>
</tr>
<tr>
<td>Weight increased</td>
<td>31%</td>
<td>56%</td>
</tr>
<tr>
<td>Dizziness (excluding vertigo)</td>
<td>27%</td>
<td>12%</td>
</tr>
<tr>
<td>Constipation</td>
<td>25%</td>
<td>10%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>20%</td>
<td>33%</td>
</tr>
<tr>
<td>Nausea</td>
<td>17%</td>
<td>10%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>17%</td>
<td>9%</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>14%</td>
<td>8%</td>
</tr>
</tbody>
</table>

Dystonia

Class effect: Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and at higher doses of first generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups.

### 6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of clozapine. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

#### Central Nervous System

Dizziness, ataxia, akathisia, myoclonus, paresthesia, possible cataplexy, status epilepticus, obsessive compulsive symptoms, and post-discontinuation cholinergic rebound adverse reactions.

#### Cardiovascular System

Atrial or ventricular fibrillation, ventricular tachycardia, QT interval prolongation, Torsades de Pointes, myocardial infarction, cardiac arrest, and periorbital edema.

#### Endocrine System

Pseudopheochromocytoma.

#### Gastrointestinal System

Acute pancreatitis, dysphagia, salivary gland swelling.

#### Hepatobiliary System

Cholestasis, hepatitis, jaundice, hepatotoxicity, hepatic steatosis, hepatic necrosis, hepatic fibrosis, hepatic cirrhosis, liver injury (hepatic, cholestatic, and mixed), and liver failure.

#### Immune System Disorders

Angioedema, leukocytoclastic vasculitis.

#### Urogenital System

Acute interstitial nephritis, nocturnal enuresis, priapism, and renal failure.

#### Skin and Subcutaneous Tissue Disorders

Hypersensitivity reactions, photosensitivity, vasculitis, erythema multiforme, skin pigmentation disorder, and Stevens-Johnson Syndrome.

#### Musculoskeletal System and Connective Tissue Disorders

Myasthenic syndrome, rhabdomyolysis, and systemic lupus erythematosus.

#### Respiratory System

Aspiration, pleural effusion, pneumonia, lower respiratory tract infection.

#### Hemic and Lymphatic System

Mild, moderate, or severe leukopenia, agranulocytosis, granulocytopenia, WBC decreased, deep-vein thrombosis, elevated hemoglobin/hematocrit, erythrocyte sedimentation rate (ESR) increased, sepsis, thrombocytopenia, and thrombocytopenia.

#### Vision Disorders

Narrow-angle glaucoma.

#### Miscellaneous

Creatine phosphokinase elevation, hyperuricemia, hyponatremia, and weight loss.

### 7. Drug Interactions

#### 7.1 Potential for Other Drugs to Affect Clozapine

Clozapine is a substrate for many cytochrome P450 isozymes, in particular CYP1A2, CYP3A4, and CYP2D6. Use caution when administering clozapine orally disintegrating tablets concomitantly with drugs that are inducers or inhibitors of these enzymes.

#### CYP1A2 Inhibitors

Concomitant use of clozapine orally disintegrating tablets and CYP1A2 inhibitors can increase plasma levels of clozapine, potentially resulting in adverse reactions. Reduce the clozapine orally disintegrating tablets dose to one-third of the original dose when clozapine orally disintegrating tablets are coadministered with strong CYP1A2 inhibitors (e.g., fluvoxamine, ciprofloxacin, or enoxacin). The clozapine orally disintegrating tablets dose should be increased to the original dose when coadministration of strong CYP1A2 inhibitors is discontinued [see Dosage and Administration (2.7), Clinical Pharmacology (12.3)].

Moderate or weak CYP1A2 inhibitors include oral contraceptives and caffeine. Monitor patients closely when clozapine orally disintegrating tablets are coadministered with these inhibitors. Consider reducing the clozapine orally disintegrating tablets dosage if necessary [see Dosage and Administration (2.7)].
8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

Risk Summary
There are no adequate or well-controlled studies of clozapine in pregnant women. Reproductive studies have been performed in rats and rabbits at doses up to 0.4 and 0.9 times, respectively, the maximum recommended human dose (MRHD) of 900 mg/day on a mg/m² body surface area basis. The studies revealed no evidence of impaired fertility or harm to the fetus due to clozapine. Because animal reproduction studies are not always predictive of human response, clozapine orally disintegrating tablets should be used during pregnancy only if clearly needed.

Clinical Considerations

Consider the risk of exacerbation of psychosis when discontinuing or changing treatment with antipsychotic medications during pregnancy and postpartum. Consider early screening for patients treated with antipsychotics or other medications [see Warnings and Precautions (5.10)]. Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. Monitor neonates for symptoms of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding difficulties. The severity of these complications can vary from self-limited symptoms to some neonates requiring intensive care unit support and prolonged hospitalization.

Animal Data

In embryofetal developmental studies, clozapine had no effects on maternal parameters, litter sizes, or fetal parameters when administered orally to pregnant rats and rabbits during the period of organogenesis at doses up to 0.4 and 0.9 times, respectively, the MRHD of 900 mg/day on a mg/m² body surface area basis. In peri/postnatal developmental studies, pregnant female rats were administered clozapine over the last third of pregnancy and until day 21 postpartum. Observations were made on fetuses at birth and during the postnatal period; the offspring were allowed to reach sexual maturity and mated. Clozapine caused a decrease in maternal body weight but had no effects on litter size or body weights of either F1 or F2 generations at doses up to 0.4 times the MRHD of 900 mg/day on a mg/m² body surface area basis.

8.2 Nursing Mothers

Clozapine is present in human milk. Because of the potential for serious adverse reactions in nursing infants from clozapine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

There have been sufficient numbers of geriatric patients in clinical studies utilizing clozapine to determine whether those over 65 years of age differ from younger subjects in their response to clozapine.

Orthostatic hypotension and tachycardia can occur with clozapine treatment [see Boxed Warning and Warnings and Precautions (5.3)]. Elderly patients, particularly those with compromised cardiovascular functioning, may be more susceptible to these effects.

Elderly patients may be particularly susceptible to the anticholinergic effects of clozapine, such as urinary retention and constipation [see Warnings and Precautions (5.15)]. Carefully select clozapine doses in elderly patients, taking into consideration their greater sensitivity of decreased hepatic, renal, or cardiac function, as well as other concomitant disease and other drug therapy. Clinical experience suggests that the prevalence of tardive dyskinesia appears to be highest among the elderly; especially elderly women [see Warnings and Precautions (5.17)].

8.6 Patients with Renal or Hepatic Impairment

Dose reduction may be necessary in patients with significant impairment of renal or hepatic function. Clozapine concentrations may be increased in these patients, because clozapine is almost completely metabolized and then excreted [see Dosage and Administration (2.8), Clinical Pharmacology (12.3)].

8.7 CYP2D6 Poor Metabolizers

Dose reduction may be necessary in patients who are CYP2D6 poor metabolizers. Clozapine concentrations may be increased in these patients, because clozapine is almost completely metabolized and then excreted [see Dosage and Administration (2.8), Clinical Pharmacology (12.3)].

8.8 Hospice Patients

For hospice patients (i.e., terminally ill patients with an estimated life expectancy of 6 months or less), the prescriber may reduce the ANC monitoring frequency to once every 6 months, after a discussion with the patient and his/her caregiver. Individual treatment decisions should weigh the importance of monitoring ANC in the context of the need to control psychiatric symptoms and the patient's terminal illness.
12.2 Pharmacodynamics
Clozapine demonstrated binding affinity to the following receptors: histamine H₁ (Kᵣ = 1.1 nM), adrenergic α₂ (Kᵣ = 1.6 nM), serotonin 5-HT₄ (Kᵣ = 4.6 nM), serotonin 5-HT₁₃ (Kᵣ = 5.4 nM), muscarinic M₁ (Kᵣ = 6.2 nM), serotonin 5-HT₂ (Kᵣ = 6.3 nM), serotonin 5-HT₂C (Kᵣ = 9.4 nM), dopamine D₁ (Kᵣ = 24 nM), adrenergic α₂ (Kᵣ = 90 nM), serotonin 5-HT₃ (Kᵣ = 95 nM), serotonin 5-HT₆ (Kᵣ = 120 nM), dopamine D₂ (Kᵣ = 160 nM), dopamine D₃ (Kᵣ = 270 nm), dopamine D₄ (Kᵣ = 454 nm), and dopamine D₅ (Kᵣ = 555 nm).

Clozapine causes little or no prolactin elevation. Clinical electroencephalogram (EEG) studies demonstrated 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 have reported 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 immediately after falling asleep.

12.3 Pharmacokinetics
Absorption
In man, clozapine tablets (25 mg and 100 mg) are equally bioavailable relative to a clozapine solution. Clozapine orally disintegrating tablets are bioequivalent to Clozaril® (clozapine) tablets, a registered trademark of Novartis Pharmaceuticals Corporation. Following a dosing of 100 mg b.i.d., the average steady-state peak plasma concentration (Cmax,ss) for clozapine was 135 ng/mL, the average peak plasma concentration (Cmax,ss) for norclozapine was 35 ng/mL, and the average minimum plasma concentrations at steady-state were 168 ng/mL (range: 45 to 574 ng/mL), after 100 mg b.i.d. dosing. A comparative bioequivalence/bioavailability study was conducted in 32 patients (with schizophrenia or schizoaffective disorder) comparing clozapine orally disintegrating 200 mg tablets to 2 x clozapine orally disintegrating 100 mg tablets (the approved reference product) under fasted conditions. The study also evaluated the effect of food and chewing on the pharmacokinetics of the 200 mg tablet. Under fasted conditions, the mean AUCₚ,ₚₚ of clozapine for the 200 mg tablets were equivalent to those of the 2 x 100 mg tablets. The mean Cmax,ss of clozapine for oral disintegrating tablets was 85% that for 2 x 100 mg clozapine orally disintegrating tablets. This decrease in Cmax,ss for clozapine orally disintegrating 200 mg tablets is not clinically significant.

For clozapine orally disintegrating 200 mg tablets, food significantly increased the Cmax,ss of clozapine, but however, this increase is not clinically significant. The mean AUCₚ,ₚₚ and Cmax,ss of clozapine under fed conditions were equivalent to those under fasted conditions. Food delayed clozapine absorption by 1.5 hours, from a grating tablets under non-chewed conditions, while the AUCss and Cmin,ss values were similar between the chewed and non-chewed conditions.

In a food-effect study, a single dose of clozapine orally disintegrating tablets 12.5 mg was administered to healthy volunteers under fasting conditions and after a high-fat meal. When clozapine orally disintegrating tablets were administered after a high-fat meal, the Cmax,ss of both clozapine and its active metabolite, desmethylclozapine, were decreased by approximately 20%, compared to administration under fasting conditions, while the AUC,ss values were unchanged. This decrease in Cmax,ss is not clinically significant. Therefore, clozapine orally disintegrating tablets can be taken without regard to meals.

Distribution
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 Drug Interactions (7)).

Metabolism and Excretion
Clozapine is almost completely metabolized prior to excretion, and only trace amounts of unchanged drug are detected in the urine and feces. Clozapine is a substrate for many cytochrome P450 isozymes, in particular CYP1A2, CYP2D6, and CYP3A4. 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 36 hours (range: 29 to 47 hours), compared to a mean elimination half-life of 12 hours (range: 4 to 66 hours), after achieving steady state with 100 mg twice daily dosing. A comparison of single-dose and multiple-dose administration of clozapine demonstrated 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, approximately 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 twice daily.

Drug-Drug Interaction Studies
Fluvoxamine
A pharmacokinetic study was conducted in 16 schizophrenic patients who received clozapine under steady-state conditions. After coadministration of fluvoxamine for 14 days, mean trough concentrations of clozapine and its metabolites, N-desmethylclozapine and clozapine N-oxide, were elevated above three-fold compared to baseline state concentrations.

CYP2D6 Poor Metabolizers
A subset (3% to 10%) of the population has reduced activity of CYP2D6 (CYP2D6 poor metabolizers). These individuals may develop higher than expected plasma concentrations of clozapine when given usual doses.

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis
No carcinogenic potential was demonstrated in long-term studies in mice and rats at doses up to 0.3 times and 0.4 times, respectively, the maximum recommended human dose (MRHD) of 900 mg/day on a mg/m² body surface area basis.

Mutagenesis
Clozapine was not genotoxic when tested in the following gene mutation and chromosomal aberration tests: the bacterial Ames test, the in vitro mammalian V79 Chinese hamster cells, the in vitro unscheduled DNA synthesis in rat hepatocytes or the in vivo micronucleus assay in mice.

Impairment of Fertility
Clozapine had no effect on any parameters of fertility, pregnancy, fetal weight or postnatal development when administered orally to male rats 70 days before mating and to female rats for 14 days before mating at doses up to 0.4 times the MRHD of 900 mg/day on a mg/m² body surface area basis.

14 CLINICAL STUDIES
14.1 Treatment-Resistant Schizophrenia
The efficacy of clozapine in treatment-resistant schizophrenia was established in a multicenter, randomized, double-blind, active-controlled (chlorpromazine) study in patients with a DSM-III diagnosis of schizophrenia who had inadequate responses to at least two antipsychotic medications (from at least 2 different chemical classes) during the preceding 5 years. The antipsychotic trials must have been judged adequate; the antipsychotic dosages must have been equivalent to or greater than 1000 mg per day of chlorpromazine for a period of at least 6 weeks, each without significant reduction of symptoms. There must have been no period of good functioning within the preceding 5 years. Patients must have had a baseline score of at least 45 on the investigator-rated Brief Psychiatric Rating Scale (BPRS). On the 18-item BPRS, 1 indicates the absence of symptoms, and 7 indicates severe symptoms; the maximum potential total BPRS score is 126. At baseline, the mean BPRS score was 61. In addition, patients must have had a score of at least 4 on at least two of the four items related to specific symptoms: thought disorder, hallucinatory behavior, and unusual thought content. Patients must have had a Clinical Global Impressions – Severity Scale score of at least 4 (moderately ill).

In the prospective, lead-in phase of the trial, all patients (N=305) initially received single-blind treatment with haloperidol (the mean dose was 61 mg per day) for 6 weeks. More than 80% of patients completed the 6 week trial. Patients with an inadequate response to haloperidol (n=268) were randomized to double-blind treatment with clozapine (N=126) or chlorpromazine (N=142). The maximum daily clozapine dose was 900 mg; the mean daily dose was 660 mg. The maximum daily chlorpromazine dose was 1800 mg; the mean daily dose was >1200 mg.

The primary endpoint was treatment response, predefined as a decrease in BPRS score of at least 20% and either (1) a CGI-S score of ≤3 (mildly ill), or (2) a BPRS score of ≤35, at the end of 6 weeks of treatment. Approximately 88% of patients from the clozapine and chlorpromazine groups completed the 6-week trial. At the end of six weeks, 30% of the clozapine group responded to treatment, and 4% of the chlorpromazine group responded to treatment. The difference was statistically significant (p <0.001). The mean change in total BPRS score was -16 and -5 in the clozapine and chlorpromazine group, respectively; the mean change in the 4 key BPRS items scores was -5 and -2 in the clozapine and chlorpromazine group, respectively; and the mean change in CGI-S score was -1.2 and -0.4, in the chlorpromazine and clozapine group, respectively. These changes in the clozapine group were statistically significantly greater than in the chlorpromazine group (p <0.001 in each analysis).

14.2 Recurrent Suicidal Behavior in Schizophrenia or Schizoaffective Disorder
The effectiveness of clozapine in reducing the risk of recurrent suicidal behavior was assessed in the Internationalrita International Trial (InterSePT, a trademark of Novartis Pharmaceuticals Corporation). This was a prospective, randomized, open-label, active-controlled, multicenter, international, parallel-group comparison of clozapine (Clozaril®) versus olanzapine (Zyprexa®), a registered trademark of Eli Lilly and Company in 968 patients with schizophrenia or schizoaffective disorder (DSM-IV) who were judged to be at risk for recurrent suicidal behavior. Only about one-fourth of these patients (27%) were considered resistant to standard antipsychotic drug treatment. To enter the trial, patients must have met one of the following criteria:

- They had attempted suicide within the three years prior to their baseline evaluation.
- They had been hospitalized to prevent a suicide attempt within the three years prior to their baseline evaluation.
CLOzapine ORALLY DISINTEGRATING TABLETS

• They demonstrated moderate-to-severe suicidal ideation with a depressive component within one week prior to their baseline evaluation.
• They demonstrated moderate-to-severe suicidal ideation accompanied by command hallucinations to do self-harm within one week prior to their baseline evaluation.

Dosing regimens for each treatment group were determined by individual investigators and were individualized by patient. Dosing was flexible, with a dose range of 200 to 900 mg/day for clozapine and 5 to 20 mg/day for olanzapine. For the 956 patients who received clozapine or olanzapine in this study, there was extensive use of concomitant psychotropic: 84% with antipsychotics, 65% with antidepressants, 53% with antipsychotics, and 28% with mood stabilizers. There was significantly greater use of concomitant psychotropic medications among the patients in the olanzapine group. The primary efficacy measure was time to (1) a significant suicide attempt, including a completed suicide; (2) hospitalization due to imminent suicide risk, including increased level of surveillance for suicidality for patients already hospitalized; or (3) worsening of suicidality severity as demonstrated by “much worsening” or “very much worsening” from baseline in the Clinical Global Impression of Severity of Suicidality as assessed by the Blinded Psychiatrist (CGI-S-S-SP) scale. A determination of whether or not a reported event met criterion 1 or 2 above was made by the Suicide Monitoring Board (SMB), a group of experts blinded to patient data.

A total of 980 patients were randomized to the study and 956 received study medication. Sixty-two percent of the patients were diagnosed with schizophrenia, and the remainder (38%) were diagnosed with schizoaffective disorder. Only about one-fourth of the total patient population (27%) was identified as “treatment-resistant” at baseline. There were more males than females in the study (61% of all patients were male). The mean age of patients entering the study was 57 years of age (range 18 to 69). Most patients were Caucasian (71%), 15% were Black, 1% were Asian, and 13% were classified as being of “other” races.

Patients treated with clozapine had a statistically significant longer delay in the time to recurrent suicidal behavior in comparison with olanzapine. This result should be interpreted only as evidence of the effectiveness of clozapine in delaying time to recurrent suicidal behavior and not a determination of the superior efficacy of clozapine over olanzapine.

The probability of experiencing (1) a significant suicide attempt, including a completed suicide, or (2) hospitalization because of imminent suicide risk, including increased level of surveillance for suicidality for patients already hospitalized, was lower for clozapine patients than for olanzapine patients at Week 104: clozapine 24% versus olanzapine 32%; 95% CI of the difference: 2%, 14% (Figure 1).

Figure 1: Cumulative Probability of a Significant Suicide Attempt or Hospitalization to Prevent Suicide in Patients with Schizophrenia or Schizoaffective Disorder at High Risk of Suicidality

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

12.5 mg
Yellow, round, flat-faced, beveled-edge, unscored tablet. Debossed with I3 on one side and plain on the other side. Available in bottles of 100 (NDC 0093-5417-01). and cartons of 48 tablets for Institutional Use Only (8x6 blister cards) (NDC 0093-5417-84).

25 mg
Yellow, round, flat-faced, beveled-edge, unscored tablet. Debossed with I7 on one side and plain on the other side. Available in bottles of 100 (NDC 0093-5417-01) and cartons of 48 tablets for Institutional Use Only (8x6 blister cards) (NDC 0093-5417-84).

100 mg
Yellow, round, flat-faced, beveled-edge, unscored tablet. Debossed with I2 on one side and plain on the other side. Available in bottles of 100 (NDC 0093-5417-01) and cartons of 48 tablets for Institutional Use Only (8x6 blister cards) (NDC 0093-5417-84).

16.2 Storage and Handling

Store Clozapine Orally Disintegrating Tablets at 20° to 25°C (68° to 77°F). (See USP Controlled Room Temperature.) Protect from moisture. Keep in a sealed blister until time of use. This unit-dose package is non child-resistant.

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

Clozapine Orally Disintegrating Tablets must remain in the original package until used by the patient.

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).
Concomitant Medication: Advise patients to inform their healthcare provider if they are taking, or plan to take, any prescription or over-the-counter drugs; there is a potential for significant drug-drug interactions [see Dosage and Administration (2.6), Drug Interactions (7.1), and Table 1].

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