

# CLOZYPAM TABLETS

## Composition

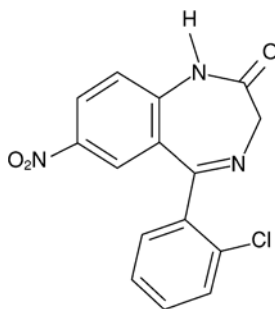
CLOZYPAM 0.25 MD tablet.

Clonazepam 0.25 mg mouth dissolving Tablet

## DESCRIPTION

Clozypam, a benzodiazepine, is available as scored Mouth Dissolving tablets with containing 0.25 mg of clonazepam.

Chemically, clonazepam is 5-(2-chlorophenyl)-1,3-dihydro-7-nitro-2H-1,4-benzodiazepin-2-one. It is a light yellow crystalline powder. It has a molecular weight of 315.72 and the following structural formula:



## CLINICAL PHARMACOLOGY

**Pharmacodynamics:** The precise mechanism by which clonazepam exerts its antiseizure and antipanic effects is unknown, although it is believed to be related to its ability to enhance the activity of gamma aminobutyric acid (GABA), the major inhibitory neurotransmitter in the central nervous system.

**Pharmacokinetics:** Clonazepam is rapidly and completely absorbed after oral administration. The absolute bioavailability of clonazepam is about 90%. Maximum plasma concentrations of clonazepam are reached within 1 to 4 hours after oral administration.. Clonazepam is approximately 85% bound to plasma proteins. Clonazepam is highly metabolized, with less than 2% unchanged clonazepam being excreted in the urine. Biotransformation occurs mainly by reduction of the 7-nitro group to the 4-amino derivative. This derivative can be acetylated, hydroxylated and glucuronidated. Cytochrome P-450 including CYP3A, may play an important role in clonazepam reduction and oxidation. The elimination half-life of clonazepam is typically 30 to 40 hours. Clonazepam pharmacokinetics are dose-independent throughout the dosing range. There is no evidence that clonazepam induces its own metabolism or that of other drugs in humans.

**Pharmacokinetics in Demographic Subpopulations and in Disease States:** Controlled studies examining the influence of gender and age on clonazepam pharmacokinetics have not been conducted, nor have the effects of renal or liver disease on clonazepam pharmacokinetics been studied. Because clonazepam undergoes hepatic metabolism, it is possible that liver disease will impair clonazepam elimination. Thus, caution should be exercised when administering clonazepam to these patients (see CONTRAINDICATIONS).

In children, clearance values of  $0.42 \pm 0.32$  mL/min/kg (ages 2 – 18 years) and  $0.88 \pm 0.4$  mL/min/kg (ages 7 – 12 years) were reported; these values decreased with increasing body weight. Ketogenic diet in children does not affect clonazepam concentrations.

#### **Clinical Trials:**

**Panic Disorder:** The effectiveness of Clozypam (Clonazepam) in the treatment of panic disorder was demonstrated in two double-blind, placebo-controlled studies of adult outpatients who had a primary diagnosis of panic disorder (DSM-III-R) with or without agoraphobia. In these studies, Clozypam was shown to be significantly more effective than placebo in treating panic disorder on change from baseline in panic attack frequency, the Clinician's Global Impression Severity of Illness Score and the Clinician's Global Impression Improvement Score.

**Study 1** was a 9-week, fixed-dose study involving Clonazepam doses of 0.5, 1, 2, 3 or 4 mg/day or placebo. This study was conducted in four phases: a 1-week placebo lead-in, a 3-week upward titration, a 6-week fixed dose, and a 7-week discontinuance phase. A significant difference from placebo was observed consistently only for the 1 mg/day group. The difference between the 1 mg dose group and placebo in reduction from baseline in the number of full panic attacks was approximately 1 panic attack per week. At endpoint, 74% of patients receiving clonazepam 1 mg/day were free of full panic attacks, compared to 56% of placebo-treated patients.

**Study 2** was a 6-week, flexible-dose study involving Clozypam in a dose range of 0.5 to 4 mg/day or placebo. This study was conducted in three phases: a 1-week placebo lead-in, a 6-week optimal-dose, and a 6-week discontinuance phase. The mean clonazepam

dose during the optimal dosing period was 2.3 mg/day. The difference between Clozypam

and placebo in reduction from baseline in the number of full panic attacks was approximately 1 panic attack per week. At endpoint, 62% of patients receiving clonazepam were free of full panic attacks, compared to 37% of placebo-treated patients.

Subgroup analyses did not indicate that there were any differences in treatment outcomes as a function of race or gender.

## **INDICATIONS AND USAGE**

**Seizure Disorders:** Clozypam is useful alone or as an adjunct in the treatment of the Lennox-Gastaut syndrome (petit mal variant), akinetic, and myoclonic seizures. In patients with absence seizures (petit mal) who have failed to respond to succinimides, Clozypam may be useful.

Some loss of effect may occur during the course of clonazepam treatment (see PRECAUTIONS: *Loss of Effect*).

**Panic Disorder:** Clozypam is indicated for the treatment of panic disorder, with or without agoraphobia, as defined in DSM-V. Panic disorder is characterized by the occurrence of unexpected panic attacks and associated concern about having additional attacks, worry about the implications or consequences of the attacks, and/or a significant change in behavior related to the attacks.

The efficacy of Clozypam was established in two 6- to 9-week trials in panic disorder patients whose diagnoses corresponded to the DSM-III-R category of panic disorder (see CLINICAL PHARMACOLOGY: *Clinical Trials*).

Panic disorder (DSM-V) is characterized by recurrent unexpected panic attacks, i.e., a discrete period of intense fear or discomfort in which four (or more) of the following symptoms develop abruptly and reach a peak within 10 minutes: (1) palpitations, pounding heart or accelerated heart rate; (2) sweating; (3) trembling or shaking; (4) sensations of shortness of breath or smothering; (5) feeling of choking; (6) chest pain or discomfort; (7) nausea or abdominal distress; (8) feeling dizzy, unsteady, lightheaded or faint; (9) derealization (feelings of unreality) or depersonalization (being detached from oneself); (10) fear of losing control; (11) fear of dying; (12) paresthesias (numbness or tingling sensations); (13) chills or hot flushes.

The effectiveness of Clozypam in long-term use, that is, for more than 9 weeks, has not been systematically studied in controlled clinical trials. The physician who elects to use Clozypam for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

## **CONTRAINDICATIONS**

Clozypam is contraindicated in patients with the following conditions:

- History of sensitivity to benzodiazepines
- Clinical or biochemical evidence of significant liver disease
- Acute narrow angle glaucoma (it may be used in patients with open angle glaucoma who are receiving appropriate therapy).

## **WARNINGS**

**Risks from Concomitant Use with Opioids:** Concomitant use of benzodiazepines, including Clozypam, and opioids may result in profound sedation, respiratory depression, coma, and death. Because of these risks, reserve concomitant prescribing of benzodiazepines and opioids for use in patients for whom alternative treatment options are inadequate.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioids alone. If a decision is made to prescribe Clozypam concomitantly with opioids, prescribe the lowest effective dosages and minimum durations of concomitant use, and follow patients closely for signs and symptoms of respiratory depression and sedation. Advise both patients and caregivers about the risks of respiratory depression and sedation when Clozypam is used with opioids (see PRECAUTIONS: *Information for Patients* and PRECAUTIONS: *Drug Interactions*).

**Interference with Cognitive and Motor Performance:** Since Clozypam produces CNS depression, patients receiving this drug should be cautioned against engaging in hazardous occupations requiring mental alertness, such as operating machinery or driving a motor vehicle. They should also be warned about the concomitant use of alcohol or other CNS-depressant drugs during Clozypam therapy (see PRECAUTIONS: *Drug Interactions* and PRECAUTIONS: *Information for Patients*).

**Suicidal Behavior and Ideation:** Antiepileptic drugs (AEDs), including Clozypam, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs showed that patients randomized to one of the AEDs had approximately twice the risk of suicidal thinking or behavior compared to patients randomized to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behavior or ideation among 27,863 AED-treated patients was 0.43% compared to 0.24% among 16,029 placebo-treated patients, representing an increase of approximately one case of suicidal thinking or behavior for every 530 patients treated. There were four suicides in drug-treated patients in the trials and none in placebo-treated patients, but the number is too small to allow any conclusion about drug effect on suicide.

The increased risk of suicidal thoughts or behavior with AEDs was observed as early as one week after starting drug treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behavior beyond 24 weeks could not be assessed.

The risk of suicidal thoughts or behavior was generally consistent among drugs in the data analyzed. The finding of increased risk with AEDs of varying mechanisms of action

and across a range of indications suggests that the risk applies to all AEDs used for any

indication. The risk did not vary substantially by age (5–100 years) in the clinical trials analyzed.

Table 1 shows absolute and relative risk by indication for all evaluated AEDs.

**Table 1 Risk by Indication for Antiepileptic Drugs in the Pooled Analysis**

<b>Indication</b>	<b>Placebo Patients with Events Per 1000 Patients</b>	<b>Drug Patients with Events Per 1000 Patients</b>	<b>Relative Risk: Incidence of Events in Drug Patients/Incidence in Placebo Patients</b>	<b>Risk Difference: Additional Drug Patients with Events per 1000 Patients</b>
Epilepsy	1.0	3.4	3.5	2.4
Psychiatric	5.7	8.5	1.5	2.9
Other	1.0	1.8	1.9	0.9
Total	2.4	4.3	1.8	1.9

The relative risk for suicidal thoughts or behavior was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications.

Anyone considering prescribing Clozapine or any other AED must balance the risk of suicidal thoughts or behavior with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and with an increased risk of suicidal thoughts and behavior. Should suicidal thoughts and behavior emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated?

Patients, their caregivers, and families should be informed that AEDs increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of the signs and symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers.

**Withdrawal Symptoms:** Withdrawal symptoms of the barbiturate type have occurred after the discontinuation of benzodiazepines (see DRUG ABUSE AND DEPENDENCE).

**PRECAUTIONS**

**General:**

**Worsening of Seizures:** When used in patients in whom several different types of seizure disorders coexist, Clozapam may increase the incidence or precipitate the onset of generalized tonic-clonic seizures (grand mal). This may require the addition of appropriate anticonvulsants or an increase in their dosages. The concomitant use of valproic acid and Clozapam may produce absence status.



**Loss of Effect:** In some studies, up to 30% of patients who initially responded have shown a loss of anticonvulsant activity, often within 3 months of administration. In some cases, dosage adjustment may reestablish efficacy.

**Laboratory Testing During Long-Term Therapy:** Periodic blood counts and liver function tests are advisable during long-term therapy with Clozypam.

**Psychiatric and Paradoxical Reactions:** Paradoxical reactions, such as agitation, irritability, aggression, anxiety, anger, nightmares, hallucinations, and psychoses are known to occur when using benzodiazepines (see ADVERSE REACTIONS: *Psychiatric*). Should this occur, the use of the drug should be discontinued gradually (see PRECAUTIONS: *Risks of Abrupt Withdrawal* and DRUG ABUSE AND DEPENDENCE: *Physical and Psychological Dependence*). Paradoxical reactions are more likely to occur in children and in the elderly.

**Risks of Abrupt Withdrawal:** The abrupt withdrawal of Clozypam, particularly in those patients on long-term, high-dose therapy, may precipitate status epilepticus. Therefore, when discontinuing Clozypam, gradual withdrawal is essential. While Clozypam is being gradually withdrawn, the simultaneous substitution of another anticonvulsant may be indicated.

**Caution in Renally Impaired Patients:** Metabolites of Clozypam are excreted by the kidneys; to avoid their excess accumulation, caution should be exercised in the administration of the drug to patients with impaired renal function.

**Hyper-salivation:** Clozypam may produce an increase in salivation. This should be considered before giving the drug to patients who have difficulty handling secretions.

**Respiratory Depression:** Clozypam may cause respiratory depression and should be used with caution in patients with compromised respiratory function (e.g., chronic obstructive pulmonary disease, sleep apnea).

**Porphyria:** Clozypam may have a porphyrogenic effect and should be used with care in patients with porphyria.

### **Information for Patients:**

A Clozypam Medication Guide must be given to the patient each time Clozypam is dispensed, as required by law. Patients should be instructed to take Clozypam only as prescribed. Physicians are advised to discuss the following issues with patients for whom they prescribe Clozypam:

**Risks from Concomitant Use with Opioids:** Inform patients and caregivers that potentially fatal additive effects may occur if Clozypam is used with opioids and not to use such drugs concomitantly unless supervised by a health care provider (see WARNINGS: *Risks from Concomitant Use with Opioids* and PRECAUTIONS: *Drug Interactions*).

**Dose Changes:** To assure the safe and effective use of benzodiazepines, patients should be informed that, since benzodiazepines may produce psychological and

physical

dependence, it is advisable that they consult with their physician before either increasing the dose or abruptly discontinuing this drug.

**Interference With Cognitive and Motor Performance:** Because benzodiazepines 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 Clozypam therapy does not affect them adversely.

**Suicidal Thinking and Behavior:** Patients, their caregivers, and families should be counseled that AEDs, including Clozypam, may increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers.

*Pregnancy:* Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy with Clozypam (see PRECAUTIONS: *Pregnancy*). Patients should be encouraged to enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry if they become pregnant. This registry is collecting information about the safety of antiepileptic drugs during pregnancy.(see PRECAUTIONS: *Pregnancy*).

**Nursing:** Patients should be advised to notify their physician if they are breastfeeding or intend to breastfeed during therapy.

**Concomitant Medication:** Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for interactions.

**Alcohol:** Patients should be advised to avoid alcohol while taking Clozypam.

#### **Drug Interactions:**

**Effect of Concomitant Use of Benzodiazepines and Opioids:** The concomitant use of benzodiazepines and opioids increases the risk of respiratory depression because of actions at different receptor sites in the CNS that control respiration. Benzodiazepines interact at GABA<sub>A</sub> sites, and opioids interact primarily at mu receptors. When benzodiazepines and opioids are combined, the potential for benzodiazepines to significantly worsen opioid-related respiratory depression exists. Limit dosage and duration of concomitant use of benzodiazepines and opioids, and follow patients closely for respiratory depression and sedation.

**Effect of Clonazepam on the Pharmacokinetics of Other Drugs:** Clonazepam does not appear to alter the pharmacokinetics of carbamazepine or phenobarbital. Clonazepam has the potential to influence concentrations of phenytoin. Monitoring of phenytoin concentration is recommended when clonazepam is co-administrated with phenytoin. The effect of clonazepam on the metabolism of other drugs has not been investigated.

Literature reports suggest that ranitidine, an agent that decreases stomach acidity, does not greatly alter clonazepam pharmacokinetics.

In a study in which **Effect of Other Drugs on the Pharmacokinetics of Clonazepam:** the 2 mg clonazepam orally disintegrating tablet was administered with and without propantheline (an anticholinergic agent with multiple effects on the GI tract) to healthy volunteers, the AUC of clonazepam was 10% lower and the  $C_{max}$  of clonazepam was 20% lower when the orally disintegrating tablet was given with propantheline compared to when it was given alone.

The selective serotonin reuptake inhibitors sertraline (weak CYP3A4 inducer) and fluoxetine (CYP2D6 inhibitor), and the anti-epileptic drug felbamate (CYP2C19 inhibitor and CYP3A4 inducer) do not affect the pharmacokinetics of clonazepam. Cytochrome P-450 inducers, such as phenytoin, carbamazepine, lamotrigine, and phenobarbital induce clonazepam metabolism, causing an approximately 38% decrease in plasma clonazepam levels. Although clinical studies have not been performed, based on the involvement of the cytochrome P-450 3A family in clonazepam metabolism, inhibitors of this enzyme system, notably oral antifungal agents (e.g., fluconazole), should be used cautiously in patients receiving clonazepam because they may impair the metabolism of clonazepam leading to exaggerated concentrations and effects.

**Pharmacodynamic Interactions:** The CNS-depressant action of the benzodiazepine class of drugs may be potentiated by alcohol, narcotics, barbiturates, nonbarbiturate hypnotics, antianxiety agents, the phenothiazines, thioxanthene and butyrophenone classes of antipsychotic agents, monoamine oxidase inhibitors and the tricyclic antidepressants, and by other anticonvulsant drugs.

### **Carcinogenesis, Mutagenesis, Impairment of Fertility:**

#### Carcinogenesis

Carcinogenicity studies have not been conducted with clonazepam.

#### Mutagenesis

The data currently available are not sufficient to determine the genotoxic potential of clonazepam.

#### Impairment of Fertility

In a two-generation fertility study in which clonazepam was given orally to rats at 10 and 100 mg/kg/day, there was a decrease in the number of pregnancies and in the number of offspring surviving until weaning. The lowest dose tested is approximately 5 and 24 times the maximum recommended human dose (MRHD) of 20 mg/day for seizure disorders and 4 mg/day for panic disorder, respectively, on a body surface area ( $\text{mg}/\text{m}^2$ ) basis.

**Pregnancy:** There are no adequate and well-controlled studies of Clozepam in pregnant women. Available human data on the risk of teratogenicity are inconclusive. There is insufficient evidence in humans to assess the effect of benzodiazepine exposure during

pregnancy on neurodevelopment. Administration of benzodiazepines immediately prior to or during childbirth can result in a syndrome of hypothermia, hypotonia, respiratory depression, and difficulty feeding. In addition, infants born to mothers who have taken benzodiazepines during the later stages of pregnancy can develop dependence, and subsequently withdrawal, during the postnatal period.

In three studies in which clonazepam was administered orally to pregnant rabbits at doses of 0.2, 1, 5, or 10 mg/kg/day during the period of organogenesis, a similar pattern of malformations (cleft palate, open eyelid, fused sternebrae and limb defects) was observed at all doses, in a low, non-dose-related incidence. The lowest dose tested is less than the maximum recommended human dose (MRHD) of 20 mg/day for seizure disorders and similar to the MRHD of 4 mg/day for panic disorder, on a mg/m<sup>2</sup> basis. Reductions in maternal weight gain occurred at doses of 5 mg/kg/day or greater and reduction in embryofetal growth occurred in one study at a dose of 10 mg/kg/day.

No adverse maternal or embryofetal effects were observed in mice or rats following oral administration of clonazepam during organogenesis of doses up to 15 or 40 mg/kg/day, respectively (4 and 20 times the MRHD of 20 mg/day for seizure disorders and 20 and 100 times the MRHD of 4 mg/day for panic disorder, respectively, on a mg/m<sup>2</sup> basis).

Data for other benzodiazepines suggest the possibility of adverse developmental effects (long-term effects on neurobehavioral and immunological function) in animals following prenatal exposure to benzodiazepines.

To provide information regarding the effects of in utero exposure to Clozypam, physicians are advised to recommend that pregnant patients taking Clozypam enroll in the NAAED Pregnancy Registry. This can be done by calling the toll free number 1-888-233-2334, and must be done by patients themselves. Information on this registry can also be found at the website <http://www.aedpregnancyregistry.org/>.

**Labor and Delivery:** The effect of Clozypam on labor and delivery in humans has not been specifically studied; however, perinatal complications have been reported in children born to mothers who have been receiving benzodiazepines late in pregnancy, including findings suggestive of either excess benzodiazepine exposure or of withdrawal phenomena (see PRECAUTIONS: *Pregnancy*).

**Nursing Mothers:** The effects of Clozypam on the breastfed infant and on milk production are unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Clozypam and any potential adverse effects on the breastfed infant from Clozypam or from the underlying maternal condition.

**Pediatric Use:** Because of the possibility that adverse effects on physical or mental development could become apparent only after many years, a benefit-risk consideration of the long-term use of Clozypam is important in pediatric patients being treated for seizure disorder.

Safety and effectiveness in pediatric patients with panic disorder below the age of 18 have not been established.

**Geriatric Use:** Clinical studies of Clozypam did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Because clonazepam undergoes hepatic metabolism, it is possible that liver disease will impair clonazepam elimination. Metabolites of Clozypam are excreted by the kidneys; to avoid their excess accumulation, caution should be exercised in the administration of the drug to patients with impaired renal function. Because elderly patients are more likely to have decreased hepatic and/or renal function, care should be taken in dose selection, and it may be useful to assess hepatic and/or renal function at the time of dose selection.

Sedating drugs may cause confusion and over-sedation in the elderly; elderly patients generally should be started on low doses of Clozypam and observed closely.

## **ADVERSE REACTIONS**

The adverse experiences for Clozypam are provided separately for patients with seizure disorders and with panic disorder.

**Seizure Disorders:** The most frequently occurring side effects of Clozypam are referable to CNS depression. Experience in treatment of seizures has shown that drowsiness has occurred in approximately 50% of patients and ataxia in approximately 30%. In some cases, these may diminish with time; behavior problems have been noted in approximately 25% of patients. Others, listed by system, including those identified during postapproval use of Clozypam are:

Cardiovascular: Palpitations

Dermatologic: Hair loss, hirsutism, skin rash, ankle and facial edema

Gastrointestinal: Anorexia, coated tongue, constipation, diarrhea, dry mouth, encopresis, gastritis, increased appetite, nausea, sore gums

Genitourinary: Dysuria, enuresis, nocturia, urinary retention

Hematopoietic: Anemia, leukopenia, thrombocytopenia, eosinophilia

Hepatic: Hepatomegaly, transient elevations of serum transaminases and alkaline phosphatase

Musculoskeletal: Muscle weakness, pains

Miscellaneous: Dehydration, general deterioration, fever, lymphadenopathy, weight loss or gain

Neurologic: Abnormal eye movements, aphonia, choreiform movements, coma, diplopia, dysarthria, dysdiadochokinesis, “glassy-eyed” appearance, headache, hemiparesis, hypotonia, nystagmus, respiratory depression, slurred speech, tremor, vertigo

Psychiatric: Confusion, depression, amnesia, hysteria, increased libido, insomnia, psychosis (the behavior effects are more likely to occur in patients with a history of psychiatric disturbances).

The following paradoxical reactions have been observed: irritability, aggression, agitation, nervousness, hostility, anxiety, sleep disturbances, nightmares, abnormal dreams, hallucinations.

Respiratory: Chest congestion, rhinorrhea, shortness of breath, hypersecretion in upper respiratory passages

**Panic Disorder**: Adverse events during exposure to Clozapam were obtained by spontaneous report and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. In the tables and tabulations that follow, CIGY dictionary terminology has been used to classify reported adverse events, except in certain cases in which redundant terms were collapsed into more meaningful terms, as noted below.

The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation.

**Adverse Findings Observed in Short-Term, Placebo-Controlled Trials:**

Adverse Events Associated with Discontinuation of Treatment:

Overall, the incidence of discontinuation due to adverse events was 17% in Clozapam compared to 9% for placebo in the combined data of two 6- to 9-week trials. The most common events (□1%) associated with discontinuation and a dropout rate twice or greater for Clozapam than that of placebo included the following:

**Table 2 Most Common Adverse Events (□1%) Associated with Discontinuation of Treatment**

Adverse Event	Clozapam (N=574)	Placebo (N=294)
Somnolence	7%	1%
Depression	4%	1%
Dizziness	1%	<1%
Nervousness	1%	0%
Ataxia	1%	0%

Intellectual Ability Reduced	1%	0%
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Adverse Events Occurring at an Incidence of 1% or More among Clozypam-Treated Patients:

Table 3 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred during acute therapy of panic disorder from a pool of two 6- to 9-week trials. Events reported in 1% or more of patients treated with Clozypam (doses ranging from 0.5 to 4 mg/day) and for which the incidence was greater than that in placebo-treated patients are included.

The prescriber should be aware that the figures in Table 3 cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence in the population studied.

**Table 3 Treatment-Emergent Adverse Event Incidence in 6- to 9-Week Placebo-Controlled Clinical Trials\***

Clonazepam Maximum Daily Dose						
Adverse Event by Body System	□ 1mg n=96 %	1- □ 2mg n=129 %	2- □ 3mg n=113 %	□ 3mg n=235 %	All Clozypa m Groups N=574 %	Placeb o N=294 %
<b>Central &amp; Peripheral Nervous System</b>						
Somnolence†	26	35	50	36	37	10
Dizziness	5	5	12	8	8	4
Coordination Abnormal†	1	2	7	9	6	0
Ataxia†	2	1	8	8	5	0
Dysarthria†	0	0	4	3	2	0
<b>Psychiatric</b>						
Depression	7	6	8	8	7	1
Memory Disturbance	2	5	2	5	4	2
Nervousness	1	4	3	4	3	2
Intellectual Ability Reduced	0	2	4	3	2	0
Emotional Lability	0	1	2	2	1	1
Libido Decreased	0	1	3	1	1	0
Confusion	0	2	2	1	1	0

<b>Respiratory System</b>						
Upper Respiratory Tract Infection†	10	10	7	6	8	4
Sinusitis	4	2	8	4	4	3
Rhinitis	3	2	4	2	2	1
Coughing	2	2	4	0	2	0

Clonazepam Maximum Daily Dose						
Adverse Event by Body System	□1mg n=96 %	1- □2mg n=129 %	2- □3mg n=113 %	□3mg n=235 %	All Clozypa m Groups N=574 %	Placeb o N=294 %
Pharyngitis	1	1	3	2	2	1
Bronchitis	1	0	2	2	1	1
<b>Gastrointestinal System</b>						
Constipation†	0	1	5	3	2	2
Appetite	1	1	0	3	1	1
Decreased Abdominal Pain†	2	2	2	0	1	1
<b>Body as a Whole</b>						
Fatigue	9	6	7	7	7	4
Allergic Reaction	3	1	4	2	2	1
<b>Musculoskeletal</b>						
Myalgia	2	1	4	0	1	1
<b>Resistance Mechanism Disorders</b>						
Influenza	3	2	5	5	4	3
<b>Urinary System</b>						
Micturition Frequency	1	2	2	1	1	0
Urinary Tract Infection†	0	0	2	2	1	0
<b>Vision Disorders</b>						
Blurred Vision	1	2	3	0	1	1
<b>Reproductive Disorders‡</b>						
Female						
Dysmenorrhe	0	6	5	2	3	2
a Colpitis	4	0	2	1	1	1
Male						
Ejaculation Delayed	0	0	2	2	1	0
Impotence	3	0	2	1	1	0

\* Events reported by at least 1% of patients treated with Clozypam and for which the incidence was greater than that for placebo.

† Indicates that the p-value for the dose-trend test (Cochran-Mantel-Haenszel) for adverse event incidence was  $\leq 0.10$ .

‡ Denominators for events in gender-specific systems are: n=240 (clonazepam), 102 (placebo) for male, and 334 (clonazepam), 192 (placebo) for female.

Commonly Observed Adverse Events:

**Table 4 Incidence of Most Commonly Observed Adverse Events\* in Acute Therapy in Pool of 6- to 9-Week Trials**

<b>Adverse Event</b>	<b>Clonazepam (N=574)</b>	<b>Placebo (N=294)</b>
Somnolence	37%	10%

Depression	7%	1%
Coordination Abnormal	6%	0%
Ataxia	5%	0%

\* Treatment-emergent events for which the incidence in the clonazepam patients was  $\geq$ 5% and at least twice that in the placebo patients.

Treatment-Emergent Depressive Symptoms:

In the pool of two short-term placebo-controlled trials, adverse events classified under the preferred term “depression” were reported in 7% of Clozypam-treated patients compared to 1% of placebo-treated patients, without any clear pattern of dose relatedness. In these same trials, adverse events classified under the preferred term “depression” were reported as leading to discontinuation in 4% of Clozypam-treated patients compared to 1% of placebo-treated patients. While these findings are noteworthy, Hamilton Depression Rating Scale (HAM-D) data collected in these trials revealed a larger decline in HAM-D scores in the clonazepam group than the placebo group suggesting that clonazepam- treated patients were not experiencing a worsening or emergence of clinical depression.

Other Adverse Events Observed During the Premarketing Evaluation of Clozypam in Panic Disorder:

Following is a list of modified CIGY terms that reflect treatment-emergent adverse events reported by patients treated with Clozypam at multiple doses during clinical trials. All reported events are included except those already listed in Table 3 or elsewhere in labeling, those events for which a drug cause was remote, those event terms which were so general as to be uninformative, and events reported only once and which did not have a substantial probability of being acutely life-threatening. It is important to emphasize that, although the events occurred during treatment with Clozypam, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency. These adverse events were reported infrequently, which is defined as occurring in 1/100 to 1/1000 patients.

Body as a Whole: weight increase, accident, weight decrease, wound, edema, fever, shivering, abrasions, ankle edema, edema foot, edema periorbital, injury, malaise, pain, cellulitis, inflammation localized

Cardiovascular Disorders: chest pain, hypotension postural

Central and Peripheral Nervous System Disorders: migraine, paresthesia, drunkenness, feeling of enuresis, paresis, tremor, burning skin, falling, head fullness, hoarseness, hyperactivity, hypoesthesia, tongue thick, twitching

Gastrointestinal System Disorders: abdominal discomfort, gastrointestinal inflammation, stomach upset, toothache, flatulence, pyrosis, saliva increased, tooth disorder, bowel movements frequent, pain pelvic, dyspepsia, hemorrhoids

Hearing and Vestibular Disorders: vertigo, otitis, earache, motion sickness

Heart Rate and Rhythm Disorders: palpitation

Metabolic and Nutritional Disorders: thirst, gout

Musculoskeletal System Disorders: back pain, fracture traumatic, sprains and strains, pain leg, pain nape, cramps muscle, cramps leg, pain ankle, pain shoulder, tendinitis, arthralgia, hypertonia, lumbago, pain feet, pain jaw, pain knee, swelling knee

Platelet, Bleeding and Clotting Disorders: bleeding dermal

Psychiatric Disorders: insomnia, organic disinhibition, anxiety, depersonalization, dreaming excessive, libido loss, appetite increased, libido increased, reactions decreased, aggression, apathy, disturbance in attention, excitement, anger, hunger abnormal, illusion, nightmares, sleep disorder, suicide ideation, yawning

Reproductive Disorders, Female: breast pain, menstrual irregularity

Reproductive Disorders, Male: ejaculation decreased

Resistance Mechanism Disorders: infection mycotic, infection viral, infection streptococcal, herpes simplex infection, infectious mononucleosis, moniliasis

Respiratory System Disorders: sneezing excessive, asthmatic attack, dyspnea, nosebleed, pneumonia, pleurisy

Skin and Appendages Disorders: acne flare, alopecia, xeroderma, dermatitis contact, flushing, pruritus, pustular reaction, skin burns, skin disorder

Special Senses Other, Disorders: taste loss

Urinary System Disorders: dysuria, cystitis, polyuria, urinary incontinence, bladder dysfunction, urinary retention, urinary tract bleeding, urine discoloration

Vascular (Extracardiac) Disorders: thrombophlebitis leg

Vision Disorders: eye irritation, visual disturbance, diplopia, eye twitching, styes, visual field defect, xerophthalmia

## **DRUG ABUSE AND DEPENDENCE**

**Controlled Substance Class:** Clonazepam is a Schedule IV controlled substance.

**Physical and Psychological Dependence:** Withdrawal symptoms, similar in character to those noted with barbiturates and alcohol (e.g., convulsions, psychosis, hallucinations, behavioral disorder, mood changes, tremor, abdominal and muscle cramps) have occurred following abrupt discontinuance of clonazepam. The more severe withdrawal symptoms have usually been limited to those patients who received excessive doses over an extended period of time. Generally milder withdrawal symptoms (e.g., dysphoria and insomnia) have been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months. Consequently, after extended therapy, abrupt discontinuation should generally be avoided and a gradual dosage tapering schedule followed (see DOSAGE AND ADMINISTRATION). Addiction-prone

individuals (such as drug addicts or alcoholics) should be under careful surveillance when receiving clonazepam or other psychotropic agents because of the predisposition of such patients to habituation and dependence.

Following the short-term treatment of patients with panic disorder in Studies 1 and 2 (see CLINICAL PHARMACOLOGY: *Clinical Trials*), patients were gradually withdrawn during a 7-week downward-titration (discontinuance) period. Overall, the discontinuance period was associated with good tolerability and a very modest clinical deterioration, without evidence of a significant rebound phenomenon. However, there are not sufficient data from adequate and well-controlled long-term clonazepam studies in patients with panic disorder to accurately estimate the risks of withdrawal symptoms and dependence that may be associated with such use.

## **OVERDOSAGE**

**Human Experience:** Symptoms of clonazepam overdose, like those produced by other CNS depressants, include somnolence, confusion, coma, and diminished reflexes.

**Overdose Management:** Treatment includes monitoring of respiration, pulse and blood pressure, general supportive measures and immediate gastric lavage. Intravenous fluids should be administered and an adequate airway maintained. Hypotension may be combated by the use of levarterenol or metaraminol. Dialysis is of no known value.

Flumazenil, a specific benzodiazepine-receptor antagonist, is indicated for the complete or partial reversal of the sedative effects of benzodiazepines and may be used in situations when an overdose with a benzodiazepine is known or suspected. Prior to the administration of flumazenil, necessary measures should be instituted to secure airway, ventilation and intravenous access. Flumazenil is intended as an adjunct to, not as a substitute for, proper management of benzodiazepine overdose. Patients treated with flumazenil should be monitored for re sedation, respiratory depression and other residual benzodiazepine effects for an appropriate period after treatment. **The prescriber should be aware of a risk of seizure in association with flumazenil treatment, particularly in long-term benzodiazepine users and in cyclic antidepressant overdose.**

**Clozypam is not indicated in patients with epilepsy who have been treated with benzodiazepines. Antagonism of the benzodiazepine effect in such patients may provoke seizures.**

Serious sequelae are rare unless other drugs or alcohol have been taken concomitantly.

## **DOSAGE AND ADMINISTRATION**

Clonazepam is available as a tablet. The tablets should be administered with water by swallowing the tablet whole.

### **Seizure Disorders:**

The use of multiple anticonvulsants may result in an increase of CNS depressant adverse effects. This should be considered before adding Clozypam to an existing anticonvulsant regimen.

Adults: The initial dose for adults with seizure disorders should not exceed 1.5 mg/day divided into three doses. Dosage may be increased in increments of 0.5 to 1 mg every 3 days until seizures are adequately controlled or until side effects preclude any further increase. Maintenance dosage must be individualized for each patient depending upon response. Maximum recommended daily dose is 20 mg.

Pediatric Patients: Clozypam is administered orally. In order to minimize drowsiness, the initial dose for infants and children (up to 10 years of age or 30 kg of body weight) should be between 0.01 and 0.03 mg/kg/day but not to exceed 0.05 mg/kg/day given in two or three divided doses. Dosage should be increased by no more than 0.25 to 0.5 mg every third day until a daily maintenance dose of 0.1 to 0.2 mg/kg of body weight has been reached, unless seizures are controlled or side effects preclude further increase. Whenever possible, the daily dose should be divided into three equal doses. If doses are not equally divided, the largest dose should be given before retiring.

Geriatric Patients: There is no clinical trial experience with Clozypam in seizure disorder patients 65 years of age and older. In general, elderly patients should be started on low doses of Clozypam and observed closely (see PRECAUTIONS: *Geriatric Use*).

#### **Panic Disorder:**

Adults: The initial dose for adults with panic disorder is 0.25 mg bid. An increase to the target dose for most patients of 1 mg/day may be made after 3 days. The recommended dose of 1 mg/day is based on the results from a fixed dose study in which the optimal effect was seen at 1 mg/day. Higher doses of 2, 3 and 4 mg/day in that study were less effective than the 1 mg/day dose and were associated with more adverse effects. Nevertheless, it is possible that some individual patients may benefit from doses of up to a maximum dose of 4 mg/day, and in those instances, the dose may be increased in increments of 0.125 to 0.25 mg bid every 3 days until panic disorder is controlled or until side effects make further increases undesired. To reduce the inconvenience of somnolence, administration of one dose at bedtime may be desirable.

Treatment should be discontinued gradually, with a decrease of 0.125 mg bid every 3 days, until the drug is completely withdrawn.

There is no body of evidence available to answer the question of how long the patient treated with clonazepam should remain on it. Therefore, the physician who elects to use Clozypam for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient.

Pediatric Patients: There is no clinical trial experience with Clozypam in panic disorder patients under 18 years of age.



Geriatric Patients: There is no clinical trial experience with Clozypam in panic disorder patients 65 years of age and older. In general, elderly patients should be started on low doses of Clozypam and observed closely (see PRECAUTIONS: *Geriatric Use*).

#### **WARNING: RISKS FROM CONCOMITANT USE WITH OPIOIDS**

**Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death (see WARNINGS and PRECAUTIONS).**

- **Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.**
- **Limit dosages and durations to the minimum required.**
- **Follow patients for signs and symptoms of respiratory depression and sedation.**

#### **HOW SUPPLIED**

Clozypam tablets are available in mouth dissolving Tablet in 10 tablet in a strip and 10 strips comes in a box.

CLOZYPAM 0.25 MD tablet.