SUMMARY OF PRODUCT CHARACTERISTICS
CLONEX®

1. NAME OF THE MEDICINAL PRODUCT
Clonex® 0.5 mg
Clonex® 2 mg
Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Clonex 0.5 mg - each tablet contains clonazepam 0.5 mg
Excipient with known effect:
75 mg of lactose monohydrate and 0.188 mg of color FD&C Yellow No. 6.

Clonex 2 mg - each tablet contains clonazepam 2 mg
Excipient with known effect:
120 mg of lactose monohydrate.

For the full list of excipients, see "DESCRIPTION"

3. THERAPEUTIC INDICATIONS
- Typical or atypical petit mal, Lennox - Gastaut syndrome (petit mal variant), generalized primary or secondary tonic-clonic seizures including grand mal and focal seizures.
- Panic disorder.

WARNING: RISKS FROM CONCOMITANT USE WITH OPIOIDS; ABUSE, MISUSE, AND ADDICTION; and DEPENDENCE AND WITHDRAWAL REACTIONS

- **Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death . Reserve concomitant prescribing of these drugs for 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 (see WARNING and PRECAUTIONS).**
- **The use of benzodiazepines , including clonazepam tablets, exposes users to risks of abuse, misuse , and addiction, which can lead to overdose or death. Abuse and misuse of benzodiazepines commonly involve concomitant use of other medications, alcohol, and/or illicit substances, which is associated with an increased frequency of serious adverse outcomes. Before prescribing clonazepam tablets and throughout treatment, assess each patient's risk for abuse, misuse, and addiction (see WARNINGS).**
- **The continued use of benzodiazepines, including clonazepam tablets, may lead to clinically significant physical dependence. The risks of dependence and withdrawal increase with longer treatment duration and higher daily dose. Abrupt discontinuation or rapid dosage reduction of clonazepam**

tablets after continued use may precipitate acute withdrawal reactions, which can be life-threatening. To reduce the risk of withdrawal reactions, use a gradual taper to discontinue clonazepam tablets or reduce the dosage (see DOSAGE AND ADMINISTRATION and WARNINGs).

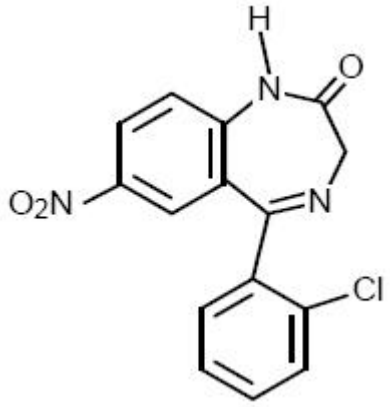
4. DESCRIPTION

Each tablet, for oral administration, contains 0.5 mg or 2 mg clonazepam , a benzodiazepine.

Each tablet of Clonex 0.5 mg also contains starch, lactose monohydrate, talc, magnesium stearate, color FD&C yellow No. 6 and color D&C yellow No. 10.

Each tablet of Clonex 2 mg also contains lactose monohydrate, starch, talc and magnesium stearate.

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



$C_{15}H_{10}ClN_3O_3$ M.W. 315.72

5. CLINICAL PHARMACOLOGY

5.1 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.

5.2 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 ± 0.32 mL/min/kg (ages 2 to 18 years) and 0.88 ± 0.4 mL/min/kg (ages 7 to 12 years) were reported; these values decreased with increasing body weight. Ketogenic diet in children does not affect clonazepam concentrations.

5.3 Clinical Trials

Panic Disorder

The effectiveness of 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-IIIR) with or without agoraphobia. In these studies, clonazepam 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 clonazepam 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 clonazepam 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.

6. CONTRAINDICATIONS

Clonazepam is contraindicated in patients with the following conditions:

- Hypersensitivity to the active substance or to any of the excipients listed in DESCRIPTION
- 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).

7. WARNINGS

Risks from Concomitant Use with Opioids

Concomitant use of benzodiazepines, including clonazepam, 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 clonazepam 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 clonazepam is used with opioids (see ***PRECAUTIONS, Information for Patients*** and ***PRECAUTIONS, Drug Interactions***).

Abuse, Misuse, and Addiction

The use of benzodiazepines, including clonazepam tablets, exposes users to the risks of abuse, misuse, and addiction, which can lead to overdose or death. Abuse and misuse of benzodiazepines often (but not always) involve the use of doses greater than the maximum recommended dosage and commonly involve concomitant use of other medications, alcohol, and/or illicit substances, which is associated with an increased frequency of serious adverse outcomes, including respiratory depression, overdose, or death (see **DRUG ABUSE AND DEPENDENCE: Abuse**).

Before prescribing clonazepam tablets and throughout treatment, assess each patient's risk for abuse, misuse, and addiction (e.g., using a standardized screening tool). Use of clonazepam tablets, particularly in patients at elevated risk, necessitates

counseling about the risks and proper use of clonazepam tablets along with monitoring for signs and symptoms of abuse, misuse, and addiction. Prescribe the lowest effective dosage; avoid or minimize concomitant use of CNS depressants and other substances associated with abuse, misuse, and addiction (e.g., opioid analgesics, stimulants); and advise patients on the proper disposal of unused drug. If a substance use disorder is suspected, evaluate the patient and institute (or refer them for) early treatment, as appropriate.

Dependence and Withdrawal Reactions

To reduce the risk of withdrawal reactions, use a gradual taper to discontinue clonazepam tablets or reduce the dosage (a patient-specific plan should be used to taper the dose) (see **DOSAGE AND ADMINISTRATION**: **Discontinuation or Dosage Reduction of clonazepam tablets**).

Patients at an increased risk of withdrawal adverse reactions after benzodiazepine discontinuation or rapid dosage reduction include those who take higher dosages, and those who have had longer durations of use.

Acute Withdrawal Reactions

The continued use of benzodiazepines, including clonazepam tablets, may lead to clinically significant physical dependence. Abrupt discontinuation or rapid dosage reduction of clonazepam tablets after continued use, or administration of flumazenil (a benzodiazepine antagonist) may precipitate acute withdrawal reactions, which can be life-threatening (e.g., seizures) (see **DRUG ABUSE AND DEPENDENCE: Dependence**).

Protracted Withdrawal Syndrome

In some cases, benzodiazepine users have developed a protracted withdrawal syndrome with withdrawal symptoms lasting weeks to more than 12 months (see **DRUG ABUSE AND DEPENDENCE: Dependence**).

Interference with Cognitive and Motor Performance

Since clonazepam 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 clonazepam therapy (see **PRECAUTIONS: Drug Interactions** and ***PRECAUTIONS: Information for Patients***).

Suicidal Behavior and Ideation

Antiepileptic drugs (AEDs), including clonazepam, 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 (adjusted Relative Risk 1.8, 95% CI:1.2, 2.7) 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 to 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

Indication	Placebo Patients with Events Per 1000 Patients	Drug Patients with Events Per 1000 Patients	Relative Risk: Incidence of Events in Drug Patients/Incidence in Placebo Patients	Risk Difference: Additional Drug Patients with Events per 1000 Patients
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 clonazepam 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 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.

8. PRECAUTIONS

General

Worsening of Seizures

When used in patients in whom several different types of seizure disorders coexist, clonazepam 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 clonazepam 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 clonazepam.

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 WARNINGS: Dependence and Withdrawal Reactions and *DRUG ABUSE AND DEPENDENCE: Dependence*). Paradoxical reactions are more likely to occur in children and in the elderly.

Caution in Renally Impaired Patients

Metabolites of clonazepam 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.

Hypersalivation

Clonazepam may produce an increase in salivation. This should be considered before giving the drug to patients who have difficulty handling secretions.

Respiratory Depression

Clonazepam 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

Clonazepam may have a porphyrogenic effect and should be used with care in patients with porphyria.

Inactive ingredients

Clonex 0.5 mg and Clonex 2 mg contain lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Clonex 0.5 mg and contains color FD&C yellow No. 6 (E 110) which may cause allergic reactions.

Information for Patients

Patients should be instructed to take clonazepam only as prescribed. Physicians are advised to discuss the following issues with patients for whom they prescribe clonazepam:

Risks from Concomitant Use with Opioids

Inform patients and caregivers that potentially fatal additive effects may occur if clonazepam 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***).

Abuse, Misuse, and Addiction
Inform patients that the use of clonazepam tablets, even at recommended dosages, exposes users to risks of abuse, misuse, and addiction, which can lead to overdose and death, especially when used in combination with other medications (e.g., opioid analgesics), alcohol, and/or illicit substances. Inform patients about the signs and symptoms of benzodiazepine abuse, misuse, and addiction; to seek medical help if they develop these signs and/or symptoms; and on the proper disposal of unused drug (see **WARNINGS:** ***Abuse, Misuse, and Addiction*** and **DRUG ABUSE AND DEPENDENCE**).

Withdrawal Reactions
Inform patients that the continued use of clonazepam tablets may lead to clinically significant physical dependence and that abrupt discontinuation or rapid dosage reduction of clonazepam tablets may precipitate acute withdrawal reactions, which can be life-threatening. Inform patients that in some cases, patients taking benzodiazepines have developed a protracted withdrawal syndrome with withdrawal symptoms lasting weeks to more than 12 months. Instruct patients that discontinuation or dosage reduction of clonazepam tablets may require a slow taper (see **WARNINGS:** ***Dependence and Withdrawal Reactions*** and **DRUG ABUSE AND DEPENDENCE**).

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 clonazepam therapy does not affect them adversely.

Suicidal Thinking and Behavior

Patients, their caregivers, and families should be counseled that AEDs, including clonazepam, 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 clonazepam (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 clonazepam.

9. *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 $GABA_A$ 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 coadministrated with phenytoin. The effect of clonazepam on the metabolism of other drugs has not been investigated.

Effect of Other Drugs on the Pharmacokinetics of Clonazepam

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

In a study in which 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 Cmax 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 (mg/m2) basis.

10. *Pregnancy*

There are no adequate and well-controlled studies of clonazepam 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^2 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^2 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.

11. *Labor and Delivery*

The effect of clonazepam 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***).

12. *Nursing Mothers*

The effects of clonazepam 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 clonazepam and any potential adverse effects on the breastfed infant from clonazepam or from the underlying maternal condition.

13. *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 clonazepam is important in pediatric patients being treated for seizure disorder (see **INDICATIONS AND USAGE** and **DOSAGE AND ADMINISTRATION**).

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

14. *Geriatric Use*

Clinical studies of clonazepam 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 clonazepam 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 clonazepam and observed closely.

15. ADVERSE REACTIONS

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

15.1 Seizure Disorders

The most frequently occurring side effects of clonazepam 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 clonazepam 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 and hallucinations.

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

15.2 Panic Disorder

Adverse events during exposure to clonazepam 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.

15.3 Adverse Findings Observed in Short-Term, Placebo-Controlled Trials

15.3.1 Adverse Events Associated with Discontinuation of Treatment

Overall, the incidence of discontinuation due to adverse events was 17% in clonazepam 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 clonazepam than that of placebo included the following:

Table 2: Most Common Adverse Events (≥ 1%) Associated With Discontinuation of Treatment

Adverse Event	**Clonazepam (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%

15.3.2 Adverse Events Occurring at an Incidence of 1% or More among Clonazepam-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 clonazepam (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	**< 1 mg n = 96 %**	**1 to < 2 mg n = 129 %**	**2 to < 3 mg n = 113 %**	**≥ 3 mg n = 235 %**	**All Clonazepam Groups N = 574 %**	**Placebo N = 294 %**
Central & Peripheral Nervous System						
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
Psychiatric						
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
Respiratory System						
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
Pharyngitis	1	1	3	2	2	1
Bronchitis	1	0	2	2	1	1
Gastrointestinal System						
Constipation†	0	1	5	3	2	2
Appetite Decreased	1	1	0	3	1	1
Abdominal Pain†	2	2	2	0	1	1
Body as a Whole						
Fatigue	9	6	7	7	7	4
Allergic Reaction	3	1	4	2	2	1
Musculoskeletal						
Myalgia	2	1	4	0	1	1
Resistance Mechanism Disorders						
Influenza	3	2	5	5	4	3
Urinary System						
Micturition Frequency	1	2	2	1	1	0
Urinary Tract Infection†	0	0	2	2	1	0
Vision Disorders						
Blurred Vision	1	2	3	0	1	1
Reproductive Disorders‡						
Female						
Dysmenorrhea	0	6	5	2	3	2
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 clonazepam 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 ≤ 0.10.

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

15.3.3 Commonly Observed Adverse Events

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

Adverse Event	Clonazepam (N = 574)	Placebo (N = 294)
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 ≥ 5% and at least twice that in the placebo patients.

15.3.4 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 clonazepam-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 clonazepam-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.

15.3.5 Other Adverse Events Observed During the Premarketing Evaluation of Clonazepam in Panic Disorder

Following is a list of modified CIGY terms that reflect treatment-emergent adverse events reported by patients treated with clonazepam 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 clonazepam, 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

16. Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/

17. DRUG ABUSE AND DEPENDENCE

17.1 Controlled Substance

Clonazepam is a Schedule IV controlled substance.

17.2 Abuse:

Clonazepam tablets is a benzodiazepine and a CNS depressant with a potential for abuse and addiction. Abuse is the intentional, non-therapeutic use of a drug, even once, for its desirable psychological or physiological effects. Misuse is the intentional use, for therapeutic purposes, of a drug by an individual in a way other than prescribed by a health care provider or for whom it was not prescribed. Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that may include a strong desire to take the drug, difficulties in controlling drug use (e.g., continuing drug use despite harmful consequences, giving a higher priority to drug use than other activities and obligations), and possible tolerance or physical dependence. Even taking benzodiazepines as prescribed may put patients at risk for abuse and misuse of their medication. Abuse and misuse of benzodiazepines may lead to addiction.

Abuse and misuse of benzodiazepines often (but not always) involve the use of doses greater than the maximum recommended dosage and commonly involve concomitant use of other medications, alcohol, and/or illicit substances, which is associated with an increased frequency of serious adverse outcomes, including respiratory depression, overdose, or death. Benzodiazepines are often sought by individuals who abuse drugs and other substances, and by individuals with addictive disorders (see **WARNINGS: *Abuse, Misuse, and Addiction***).

The following adverse reactions have occurred with benzodiazepine abuse and/or misuse: abdominal pain, amnesia, anorexia, anxiety, aggression, ataxia, blurred vision, confusion, depression, disinhibition, disorientation, dizziness, euphoria, impaired concentration and memory, indigestion, irritability, muscle pain, slurred speech, tremors, and vertigo.

The following severe adverse reactions have occurred with benzodiazepine abuse and/or misuse: delirium, paranoia, suicidal ideation and behavior, seizures, coma, breathing difficulty, and death. Death is more often associated with polysubstance use (especially benzodiazepines with other CNS depressants such as opioids and alcohol).

17.3 Dependence

Physical Dependence

Clonazepam tablets may produce physical dependence from continued therapy. Physical dependence is a state that develops as a result of physiological adaptation in response to repeated drug use, manifested by withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug. Abrupt discontinuation or rapid dosage reduction of benzodiazepines or administration of flumazenil, a benzodiazepine antagonist, may precipitate acute withdrawal reactions, including seizures, which can be life-threatening. Patients at an increased risk of withdrawal adverse reactions after benzodiazepine discontinuation or rapid dosage reduction include those who take higher dosages (i.e., higher and/or more frequent doses) and those who have had longer durations of use (see **WARNINGS: *Dependence and Withdrawal Reactions***).

To reduce the risk of withdrawal reactions, use a gradual taper to discontinue

clonazepam tablets or reduce the dosage (see **DOSAGE AND ADMINISTRATION:** ***Discontinuation or Dosage Reduction of clonazepam tablets*** and **WARNINGS:** ***Dependence and Withdrawal Reactions***).

Acute Withdrawal Signs and Symptoms

Acute withdrawal signs and symptoms associated with benzodiazepines have included abnormal involuntary movements, anxiety, blurred vision, depersonalization, depression, derealization, dizziness, fatigue, gastrointestinal adverse reactions (e.g., nausea, vomiting, diarrhea, weight loss, decreased appetite), headache, hyperacusis, hypertension, irritability, insomnia, memory impairment, muscle pain and stiffness, panic attacks, photophobia, restlessness, tachycardia, and tremor. More severe acute withdrawal signs and symptoms, including life-threatening reactions, have included catatonia, convulsions, delirium tremens, depression, hallucinations, mania, psychosis, seizures, and suicidality.

Protracted Withdrawal Syndrome

Protracted withdrawal syndrome associated with benzodiazepines is characterized by anxiety, cognitive impairment, depression, insomnia, formication, motor symptoms (e.g., weakness, tremor, muscle twitches), paresthesia, and tinnitus that persists beyond 4 to 6 weeks after initial benzodiazepine withdrawal. Protracted withdrawal symptoms may last weeks to more than 12 months. As a result, there may be difficulty in differentiating withdrawal symptoms from potential re-emergence or continuation of symptoms for which the benzodiazepine was being used.

Tolerance

Tolerance to clonazepam tablets may develop from continued therapy. Tolerance is a physiological state characterized by a reduced response to a drug after repeated administration (i.e., a higher dose of a drug is required to produce the same effect that was once obtained at a lower dose). Tolerance to the therapeutic effect of clonazepam tablets may develop; however, little tolerance develops to the amnestic reactions and other cognitive impairments caused by benzodiazepines.

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.

18. OVERDOSAGE

18.1 Human Experience

Symptoms of clonazepam overdosage, like those produced by other CNS depressants, include somnolence, confusion, coma, and diminished reflexes.

18.2 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 resedation, 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.** The complete flumazenil package insert, including **CONTRAINDICATIONS**, **WARNINGS** and **PRECAUTIONS**, should be consulted prior to use.

Flumazenil 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.

19. DOSAGE AND ADMINISTRATION

Clonazepam tablets should be administered with water.

Clonex 0.5 mg can be divided into equal halves

Clonex 2 mg can be divided into 4 equal quarters.

19.1 Typical or atypical petit mal, Lennox-Gastaut syndrome (petit mal variant), generalized primary or secondary tonic-clonic seizures including grand mal and focal seizures.

The use of multiple anticonvulsant therapy may result in an increase of depressant adverse effects. This should be considered before including Clonex in an existing anti-convulsant regimen.

Infants and Children
In order to minimize drowsiness, the initial dosage for infants and children (up to 10 years of age or 30 kg body weight) should be 0.01-0.03 mg/kg/ body weight/day given in 2-3 divided doses. Dosage should be increased by no more than 0.25-0.5 mg every 3 days, until a daily maintenance dosage of 0.1-0.2 mg/kg body weight has been reached, unless seizures are controlled or side effects preclude further increase. Whenever possible, the daily dosage should be divided into 3 equal doses. If doses are not equally divided, the largest dose should be given before retiring.

Adults
The initial adult dosage should not exceed 1.5 mg/day, divided into 3 doses. Dosage may be increased by increments of 0.5-1 mg every 3 days, until seizures are adequately controlled or until side effects preclude any further increase. The maintenance dosage must be individualized for each patient, depending on response. The maximum recommended daily dosage is 20 mg.

19.2 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. 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 0.25 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 0.25 mg daily every 3 days, until the drug is completely withdrawn.

Pediatric Patients:
There is no clinical trial experience with clonazepam in panic disorder patients under 18 years of age (see Warnings).

Use in Geriatrics:
There is no clinical trial experience with clonazepam in panic disorder patients 65 years of age and older. In general, elderly patients should be started on low doses of clonazepam and observed closely.

There is no body of evidence available to answer the question of how long the patient treated with clonazepam should remain on it. The effectiveness of clonazepam in long-term use, that is, for more than 9 weeks, has not been systematically studied in controlled clinical trials. Therefore, the physician who elects to use Clonex for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient.

20. HOW SUPPLIED

Clonex 0.5 mg are light orange, round flat beveled tablet, bisected on one side, plain on the other. The tablet can be divided into equal halves

Clonex 2 mg are white, round flat beveled tablet, quadrisected on one side, engraved "TEVA" on the other. The tablet can be divided into 4 equal quarters.

Each package contains 30 or 100 tablets.

Not all pack sizes may be marketed.

21. STORAGE

Store in dry place, below 25°C.

Shelf life- The expiry date of the product is indicated on the packaging materials.

22. LICENCE HOLDER AND MANUFACTURER

Teva Israel Ltd.
124 Dvora HaNevi'a St., Tel Aviv 6944020 Israel

23. REGISTRATION NUMBERS

Clonex 0.5 mg: 027.85.22043

Clonex 2 mg: 035.99.22044

this leaflet was revised in April 2022 according to MOHs guidelines.