



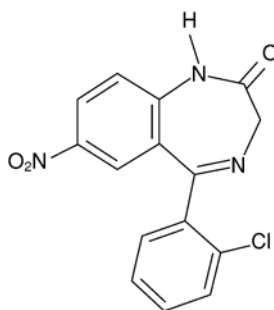
KLONOPIN® TABLETS (clonazepam)

Rx only

DESCRIPTION

Klonopin, a benzodiazepine, is available as scored tablets with a K-shaped perforation containing 0.5 mg of clonazepam and unscored tablets with a K-shaped perforation containing 1 mg or 2 mg of clonazepam. Each tablet also contains lactose, magnesium stearate, microcrystalline cellulose and corn starch, with the following colorants: 0.5 mg—FD&C Yellow No. 6 Lake; 1 mg—FD&C Blue No. 1 Lake and FD&C Blue No. 2 Lake.

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. Convulsions produced in rodents by pentylenetetrazol or, to a lesser extent, electrical stimulation are antagonized, as are convulsions produced by photic stimulation in susceptible baboons. A taming effect in aggressive primates, muscle weakness and hypnosis are also produced. In humans, clonazepam is capable of suppressing the spike and wave discharge in absence seizures (petit mal) and decreasing the frequency, amplitude, duration and spread of discharge in minor motor seizures.

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.

Clinical Trials: Panic Disorder: The effectiveness of Klonopin 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, Klonopin 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 Klonopin 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 Klonopin 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 Klonopin 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: Klonopin 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, Klonopin may be useful.

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

Panic Disorder: Klonopin is indicated for the treatment of panic disorder, with or without agoraphobia, as defined in DSM-IV. 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 Klonopin 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-IV) is characterized by recurrent unexpected panic attacks, ie, 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 Klonopin 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 Klonopin for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

Klonopin should not be used in patients with a history of sensitivity to benzodiazepines, nor in patients with clinical or biochemical evidence of significant liver disease. It may be used in patients with open angle glaucoma who are receiving appropriate therapy but is contraindicated in acute narrow angle glaucoma.

WARNINGS

Interference With Cognitive and Motor Performance: Since Klonopin 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 Klonopin therapy (see PRECAUTIONS: *Drug Interactions* and *Information for Patients*).

Suicidal Behavior and Ideation: Antiepileptic drugs (AEDs), including Klonopin, 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 (5-100 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 Klonopin 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.

Pregnancy Risks: Data from several sources raise concerns about the use of Klonopin during pregnancy.

Animal Findings: In three studies in which Klonopin was administered orally to pregnant rabbits at doses of 0.2, 1, 5 or 10 mg/kg/day (low dose approximately 0.2 times the maximum recommended human dose of 20 mg/day for seizure disorders and equivalent to the maximum dose of 4 mg/day for panic disorder, on a mg/m² basis) during the period of organogenesis, a similar pattern of malformations (cleft palate, open eyelid, fused sternebrae and limb defects) was observed in a low, non-dose-related incidence in exposed litters from all dosage groups. Reductions in maternal weight gain occurred at dosages of 5 mg/kg/day or greater and reduction in embryo-fetal growth occurred in one study at a dosage of 10 mg/kg/day. No adverse maternal or embryo-fetal effects were observed in mice and rats following administration during organogenesis of oral doses up to 15 mg/kg/day or 40 mg/kg/day, respectively (4 and 20 times the maximum recommended human dose of 20 mg/day for seizure disorders and 20 and 100 times the maximum dose of 4 mg/day for panic disorder, respectively, on a mg/m² basis).

General Concerns and Considerations About Anticonvulsants: Recent reports suggest an association between the use of anticonvulsant drugs by women with epilepsy and an elevated incidence of birth defects in children born to these women. Data are more extensive with respect to diphenylhydantoin and phenobarbital, but these are also the most commonly prescribed anticonvulsants; less systematic or anecdotal reports suggest a possible similar association with the use of all known anticonvulsant drugs.

In children of women treated with drugs for epilepsy, reports suggesting an elevated incidence of birth defects cannot be regarded as adequate to prove a definite cause and effect relationship. There are intrinsic methodologic problems in obtaining adequate data on drug teratogenicity in humans; the possibility also exists that other factors (eg, genetic factors or the epileptic condition itself) may be more important than drug therapy in leading to birth defects. The great majority of mothers on anticonvulsant medication deliver normal infants. It is important to note that anticonvulsant drugs should not be discontinued in patients in whom the drug is administered to prevent seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that the removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy; however, it cannot be said with any confidence that even mild seizures do not pose some hazards to the developing embryo or fetus.

General Concerns About Benzodiazepines: An increased risk of congenital malformations associated with the use of benzodiazepine drugs has been suggested in several studies.

There may also be non-teratogenic risks associated with the use of benzodiazepines during pregnancy. There have been reports of neonatal flaccidity, respiratory and feeding difficulties, and hypothermia in children born to mothers who have been receiving benzodiazepines late in pregnancy. In addition, children born to mothers receiving benzodiazepines late in pregnancy may be at some risk of experiencing withdrawal symptoms during the postnatal period.

Advice Regarding the Use of Klonopin in Women of Childbearing Potential: In general, the use of Klonopin in women of childbearing potential, and more specifically during known pregnancy, should be considered only when the clinical situation warrants the risk to the fetus.

The specific considerations addressed above regarding the use of anticonvulsants for epilepsy in women of childbearing potential should be weighed in treating or counseling these women.

Because of experience with other members of the benzodiazepine class, Klonopin is assumed to be capable of causing an increased risk of congenital abnormalities when administered to a pregnant woman during the first trimester. Because use of these drugs is rarely a matter of urgency in the treatment of panic disorder, their use during the first trimester should almost always be avoided. The possibility that a woman of childbearing potential may be pregnant at the time of institution of therapy should be considered. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Patients should also be advised that if they become pregnant during therapy or intend to become pregnant, they should communicate with their physician about the desirability of discontinuing the drug.

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, Klonopin 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 Klonopin may produce absence status.

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

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

Caution in Renally Impaired Patients: Metabolites of Klonopin 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: Klonopin may produce an increase in salivation. This should be considered before giving the drug to patients who have difficulty handling secretions. Because of this and the possibility of respiratory depression, Klonopin should be used with caution in patients with chronic respiratory diseases.

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

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 Klonopin therapy does not affect them adversely.

Suicidal Thinking and Behavior: Patients, their caregivers, and families should be counseled that AEDs, including Klonopin, 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 Klonopin (see WARNINGS: *Pregnancy Risks*). 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. To enroll, patients can call the toll free number 1-888-233-2334 (see PRECAUTIONS: *Pregnancy*).

Nursing: Patients should be advised not to breastfeed an infant if they are taking Klonopin.

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 Klonopin.

Drug Interactions: Effect of Clonazepam on the Pharmacokinetics of Other Drugs: Clonazepam does not appear to alter the pharmacokinetics of phenytoin, carbamazepine

or phenobarbital. 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 C_{max} of clonazepam was 20% lower when the orally disintegrating tablet was given with propantheline compared to when it was given alone.

Fluoxetine does not affect the pharmacokinetics of clonazepam. Cytochrome P-450 inducers, such as phenytoin, carbamazepine and phenobarbital, induce clonazepam metabolism, causing an approximately 30% 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, should be used cautiously in patients receiving clonazepam.

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: Carcinogenicity studies have not been conducted with clonazepam.

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

In a two-generation fertility study in which clonazepam was given orally to rats at 10 and 100 mg/kg/day (low dose approximately 5 times and 24 times the maximum recommended human dose of 20 mg/day for seizure disorder and 4 mg/day for panic disorder, respectively, on a mg/m^2 basis), there was a decrease in the number of pregnancies and in the number of offspring surviving until weaning.

Pregnancy: Teratogenic Effects: Pregnancy Category D (see WARNINGS: *Pregnancy Risks*).

To provide information regarding the effects of in utero exposure to Klonopin, physicians are advised to recommend that pregnant patients taking Klonopin 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 Klonopin 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 WARNINGS: *Pregnancy Risks*).

Nursing Mothers: Mothers receiving Klonopin should not breastfeed their infants.

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 Klonopin 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.

Geriatric Use: Clinical studies of Klonopin 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 Klonopin 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 Klonopin and observed closely.

ADVERSE REACTIONS

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

Seizure Disorders: The most frequently occurring side effects of Klonopin 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, are:

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, hallucinations, hysteria, increased libido, insomnia, psychosis (the behavior effects are more likely to occur in patients with a

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, aggressive reaction, apathy, attention lack, excitement, feeling mad, 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 (eg, convulsions, psychosis, hallucinations,

behavioral disorder, 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 (eg, 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.** 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.

DOSAGE AND ADMINISTRATION

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

Seizure Disorders: 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.

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

Pediatric Patients: Klonopin 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 Klonopin in seizure disorder patients 65 years of age and older. In general, elderly patients should be started on low doses of Klonopin 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 Klonopin 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 Klonopin in panic disorder patients under 18 years of age.

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

HOW SUPPLIED

Klonopin tablets are available as scored tablets with a K-shaped perforation—0.5 mg, orange (NDC 0004-0068-01); and unscored tablets with a K-shaped perforation—1 mg, blue (NDC 0004-0058-01); 2 mg, white (NDC 0004-0098-01)—bottles of 100.

Imprint on tablets:

0.5 mg — 1/2 KLONOPIN (front)
ROCHE (scored side)



1 mg — 1 KLONOPIN (front)
ROCHE (reverse side)



2 mg — 2 KLONOPIN (front)
ROCHE (reverse side)



Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F).

Distributed by:

Genentech USA, Inc.
A Member of the Roche Group
1 DNA Way
South San Francisco, CA 94080-4990

Revised: Month Year

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Medication Guide
KLONOPIN® (KLON-oh-pin)
(clonazepam)
Tablets



Read this Medication Guide before you start taking KLONOPIN and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or treatment.

KLONOPIN can cause serious side effects. Because stopping KLONOPIN suddenly can also cause serious problems, do not stop taking KLONOPIN without talking to your healthcare provider first.

What is the most important information I should know about KLONOPIN?

Do not stop taking KLONOPIN without first talking to your healthcare provider. Stopping KLONOPIN suddenly can cause serious problems.

KLONOPIN can cause serious side effects, including:

1. KLONOPIN can slow your thinking and motor skills

- Do not drive, operate heavy machinery, or do other dangerous activities until you know how KLONOPIN affects you.
- Do not drink alcohol or take other drugs that may make you sleepy or dizzy while taking KLONOPIN until you talk to your healthcare provider. When taken with alcohol or drugs that cause sleepiness or dizziness, KLONOPIN may make your sleepiness or dizziness worse.

2. Like other antiepileptic drugs, KLONOPIN may cause suicidal thoughts or actions in a very small number of people, about 1 in 500.

Call a healthcare provider right away if you have any of these symptoms, especially if they are new, worse, or worry you:

- thoughts about suicide or dying
- attempt to commit suicide
- new or worse depression
- new or worse anxiety
- feeling agitated or restless
- panic attacks
- trouble sleeping (insomnia)
- new or worse irritability
- acting aggressive, being angry, or violent
- acting on dangerous impulses
- an extreme increase in activity and talking (mania)
- other unusual changes in behavior or mood

How can I watch for early symptoms of suicidal thoughts and actions?

- Pay attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings.
- Keep all follow-up visits with your healthcare provider as scheduled.

Call your healthcare provider between visits as needed, especially if you are worried about symptoms.

Suicidal thoughts or actions can be caused by things other than medicines. If you have suicidal thoughts or actions, your healthcare provider may check for other causes.

Do not stop KLONOPIN without first talking to a healthcare provider.

Stopping KLONOPIN suddenly can cause serious problems. Stopping KLONOPIN suddenly can cause seizures that will not stop (status epilepticus).

3. KLONOPIN may harm your unborn or developing baby.

- If you take KLONOPIN during pregnancy, your baby is at risk for serious birth defects. These defects can happen as early as in the first month of pregnancy, even before you know you are pregnant. Birth defects may occur even in children born to women who are not taking any medicines and do not have other risk factors.
- Children born to mothers receiving benzodiazepine medications (including KLONOPIN) late in pregnancy may be at some risk of experiencing breathing problems, feeding problems, hypothermia, and withdrawal symptoms.
- Tell your healthcare provider right away if you become pregnant while taking KLONOPIN. You and your healthcare provider should decide if you will take KLONOPIN while you are pregnant.
- If you become pregnant while taking KLONOPIN, talk to your healthcare provider about registering with the North American Antiepileptic Drug Pregnancy Registry. You can register by calling 1-888-233-2334. The purpose of this registry is to collect information about the safety of antiepileptic drugs during pregnancy.
- KLONOPIN can pass into breast milk. Talk to your healthcare provider about the best way to feed your baby if you take KLONOPIN. You and your healthcare provider should decide if you will take KLONOPIN or breast feed. You should not do both.

4. KLONOPIN can cause abuse and dependence.

- Do not stop taking KLONOPIN all of a sudden. Stopping KLONOPIN suddenly can cause seizures that do not stop, hearing or seeing things that are not there (hallucinations), shaking, and stomach and muscle cramps.

- Talk to your doctor about slowly stopping KLONOPIN to avoid getting sick with withdrawal symptoms.
- Physical dependence is not the same as drug addiction. Your healthcare provider can tell you more about the differences between physical dependence and drug addiction.

KLONOPIN is a federally controlled substance (C-IV) because it can be abused or lead to dependence. Keep KLONOPIN in a safe place to prevent misuse and abuse. Selling or giving away KLONOPIN may harm others, and is against the law. Tell your doctor if you have ever abused or been dependent on alcohol, prescription medicines or street drugs.

What is KLONOPIN?

KLONOPIN is a prescription medicine used alone or with other medicines to treat:

- certain types of seizure disorders (epilepsy) in adults and children
- panic disorder with or without fear of open spaces (agoraphobia) in adults

It is not known if KLONOPIN is safe or effective in treating panic disorder in children younger than 18 years old.

Who should not take KLONOPIN?

Do not take KLONOPIN if you:

- are allergic to benzodiazepines
- have significant liver disease
- have an eye disease called acute narrow angle glaucoma

Ask your healthcare provider if you are not sure if you have any of the problems listed above.

What should I tell my healthcare provider before taking KLONOPIN?

Before you take KLONOPIN, tell your healthcare provider if you:

- have liver or kidney problems
- have lung problems (respiratory disease)
- have or have had depression, mood problems, or suicidal thoughts or behavior
- have any other medical conditions

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Taking KLONOPIN with certain other medicines can cause side effects or affect

how well they work. Do not start or stop other medicines without talking to your healthcare provider.

Know the medicines you take. Keep a list of them and show it to your healthcare provider and pharmacist when you get a new medicine.

How should I take KLONOPIN?

- Take KLONOPIN exactly as your healthcare provider tells you. KLONOPIN is available as a tablet.
- Do not stop taking KLONOPIN without first talking to your healthcare provider. Stopping KLONOPIN suddenly can cause serious problems.
- **KLONOPIN tablets** should be taken with water and swallowed whole.
- If you take too much KLONOPIN, call your healthcare provider or local Poison Control Center right away.

What should I avoid while taking KLONOPIN?

- KLONOPIN can slow your thinking and motor skills. Do not drive, operate heavy machinery, or do other dangerous activities until you know how KLONOPIN affects you.
- Do not drink alcohol or take other drugs that may make you sleepy or dizzy while taking KLONOPIN until you talk to your healthcare provider. When taken with alcohol or drugs that cause sleepiness or dizziness, KLONOPIN may make your sleepiness or dizziness worse.

What are the possible side effects of KLONOPIN?

See “What is the most important information I should know about KLONOPIN?”

KLONOPIN can also make your seizures happen more often or make them worse. Call your healthcare provider right away if your seizures get worse while taking KLONOPIN.

The most common side effects of KLONOPIN include:

- Drowsiness
- Problems with walking and coordination
- Dizziness
- Depression
- Fatigue
- Problems with memory

These are not all the possible side effects of KLONOPIN. For more information, ask your healthcare provider or pharmacist.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store KLONOPIN?

- Store KLONOPIN between 59°F to 86°F (15°C to 30°C)

Keep KLONOPIN and all medicines out of the reach of children.

General Information about KLONOPIN

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use KLONOPIN for a condition for which it was not prescribed. Do not give KLONOPIN to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about KLONOPIN. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about KLONOPIN that is written for health professionals.

For more information, go to www.gene.com/gene/products/information/klonopin or call 1-888-835-2555.

What are the ingredients in KLONOPIN?

Active ingredient: clonazepam

Inactive ingredients:

- Tablets:
 - 0.5 mg tablets contain lactose, magnesium stearate, microcrystalline cellulose, corn starch, FD&C Yellow No. 6 Lake
 - 1 mg tablets contain lactose, magnesium stearate, microcrystalline cellulose, corn starch, FD&C Blue No. 1 Lake and FD&C Blue No. 2 Lake
 - 2 mg tablets contain lactose, magnesium stearate, microcrystalline cellulose, corn starch

Issued: Month Year

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Distributed by:

Genentech USA, Inc.

A Member of the Roche Group

1 DNA Way

South San Francisco, CA 94080-4990

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For additional copies of this Medication Guide, please call 1-877-436-3683 or visit

www.gene.com/gene/products/information/klonopin.



1
2 **KLONOPIN[®] TABLETS**
3 **(clonazepam)**

4 **KLONOPIN[®] WAFERS**
5 **(clonazepam orally disintegrating tablets)**

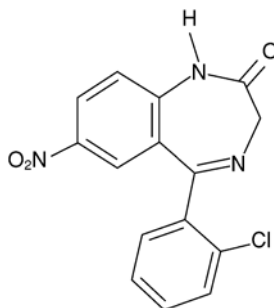
6 **Rx only**

7 **DESCRIPTION**

8 Klonopin, a benzodiazepine, is available as scored tablets with a K-shaped perforation
9 containing 0.5 mg of clonazepam and unscored tablets with a K-shaped perforation
10 containing 1 mg or 2 mg of clonazepam. Each tablet also contains lactose, magnesium
11 stearate, microcrystalline cellulose and corn starch, with the following colorants: 0.5
12 mg—FD&C Yellow No. 6 Lake; 1 mg—FD&C Blue No. 1 Lake and FD&C Blue No. 2
13 Lake.

14 Klonopin is also available as an orally disintegrating tablet containing 0.125 mg, 0.25
15 mg, 0.5 mg, 1 mg or 2 mg clonazepam. Each orally disintegrating tablet also contains
16 gelatin, mannitol, methylparaben sodium, propylparaben sodium and xanthan gum.

17 Chemically, clonazepam is 5-(2-chlorophenyl)-1,3-dihydro-7-nitro-2H-1,4-
18 benzodiazepin-2-one. It is a light yellow crystalline powder. It has a molecular weight of
19 315.72 and the following structural formula:



20
21 **CLINICAL PHARMACOLOGY**

22 **Pharmacodynamics:** The precise mechanism by which clonazepam exerts its antiseizure
23 and antipanic effects is unknown, although it is believed to be related to its ability to
24 enhance the activity of gamma aminobutyric acid (GABA), the major inhibitory
25 neurotransmitter in the central nervous system. Convulsions produced in rodents by
26 pentylenetetrazol or, to a lesser extent, electrical stimulation are antagonized, as are
27 convulsions produced by photic stimulation in susceptible baboons. A taming effect in
28 aggressive primates, muscle weakness and hypnosis are also produced. In humans,
29 clonazepam is capable of suppressing the spike and wave discharge in absence seizures
30 (petit mal) and decreasing the frequency, amplitude, duration and spread of discharge in
31 minor motor seizures.

32 ***Pharmacokinetics:*** Clonazepam is rapidly and completely absorbed after oral
33 administration. The absolute bioavailability of clonazepam is about 90%. Maximum
34 plasma concentrations of clonazepam are reached within 1 to 4 hours after oral
35 administration. Clonazepam is approximately 85% bound to plasma proteins.
36 Clonazepam is highly metabolized, with less than 2% unchanged clonazepam being
37 excreted in the urine. Biotransformation occurs mainly by reduction of the 7-nitro group
38 to the 4-amino derivative. This derivative can be acetylated, hydroxylated and
39 glucuronidated. Cytochrome P-450 including CYP3A, may play an important role in
40 clonazepam reduction and oxidation. The elimination half-life of clonazepam is typically
41 30 to 40 hours. Clonazepam pharmacokinetics are dose-independent throughout the
42 dosing range. There is no evidence that clonazepam induces its own metabolism or that
43 of other drugs in humans.

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

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

57 Study 1 was a 9-week, fixed-dose study involving Klonopin doses of 0.5, 1, 2, 3 or 4
58 mg/day or placebo. This study was conducted in four phases: a 1-week placebo lead-in, a
59 3-week upward titration, a 6-week fixed dose and a 7-week discontinuance phase. A
60 significant difference from placebo was observed consistently only for the 1 mg/day
61 group. The difference between the 1 mg dose group and placebo in reduction from
62 baseline in the number of full panic attacks was approximately 1 panic attack per week.
63 At endpoint, 74% of patients receiving clonazepam 1 mg/day were free of full panic
64 attacks, compared to 56% of placebo-treated patients.

65 Study 2 was a 6-week, flexible-dose study involving Klonopin in a dose range of 0.5 to 4
66 mg/day or placebo. This study was conducted in three phases: a 1-week placebo lead-in, a
67 6-week optimal-dose and a 6-week discontinuance phase. The mean clonazepam dose
68 during the optimal dosing period was 2.3 mg/day. The difference between Klonopin and
69 placebo in reduction from baseline in the number of full panic attacks was approximately
70 1 panic attack per week. At endpoint, 62% of patients receiving clonazepam were free of
71 full panic attacks, compared to 37% of placebo-treated patients.

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

74 **INDICATIONS AND USAGE**

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

79 In some studies, up to 30% of patients have shown a loss of anticonvulsant activity, often
80 within 3 months of administration. In some cases, dosage adjustment may reestablish
81 efficacy.

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

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

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

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

103 **CONTRAINDICATIONS**

104 Klonopin should not be used in patients with a history of sensitivity to benzodiazepines,
105 nor in patients with clinical or biochemical evidence of significant liver disease. It may
106 be used in patients with open angle glaucoma who are receiving appropriate therapy but
107 is contraindicated in acute narrow angle glaucoma.

108 **WARNINGS**

109 **Interference With Cognitive and Motor Performance:** Since Klonopin produces CNS
110 depression, patients receiving this drug should be cautioned against engaging in
111 hazardous occupations requiring mental alertness, such as operating machinery or driving
112 a motor vehicle. They should also be warned about the concomitant use of alcohol or

113 other CNS-depressant drugs during Klonopin therapy (see PRECAUTIONS: *Drug*
114 *Interactions and Information for Patients*).

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

120 Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy)
121 of 11 different AEDs showed that patients randomized to one of the AEDs had
122 approximately twice the risk (adjusted Relative Risk 1.8, 95% CI:1.2, 2.7) of suicidal
123 thinking or behavior compared to patients randomized to placebo. In these trials, which
124 had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal
125 behavior or ideation among 27,863 AED-treated patients was 0.43% compared to 0.24%
126 among 16,029 placebo-treated patients, representing an increase of approximately one
127 case of suicidal thinking or behavior for every 530 patients treated. There were four
128 suicides in drug-treated patients in the trials and none in placebo-treated patients, but the
129 number is too small to allow any conclusion about drug effect on suicide.

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

134 The risk of suicidal thoughts or behavior was generally consistent among drugs in the
135 data analyzed. The finding of increased risk with AEDs of varying mechanisms of action
136 and across a range of indications suggests that the risk applies to all AEDs used for any
137 indication. The risk did not vary substantially by age (5-100 years) in the clinical trials
138 analyzed.

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

140 **Table 1 Risk by Indication for Antiepileptic Drugs in the Pooled**
141 **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

142
143 The relative risk for suicidal thoughts or behavior was higher in clinical trials for epilepsy
144 than in clinical trials for psychiatric or other conditions, but the absolute risk differences
145 were similar for the epilepsy and psychiatric indications.

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

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

158 ***Pregnancy Risks:*** Data from several sources raise concerns about the use of Klonopin
159 during pregnancy.

160 *Animal Findings:* In three studies in which Klonopin was administered orally to pregnant
161 rabbits at doses of 0.2, 1, 5 or 10 mg/kg/day (low dose approximately 0.2 times the
162 maximum recommended human dose of 20 mg/day for seizure disorders and equivalent
163 to the maximum dose of 4 mg/day for panic disorder, on a mg/m² basis) during the period
164 of organogenesis, a similar pattern of malformations (cleft palate, open eyelid, fused
165 sternebrae and limb defects) was observed in a low, non-dose-related incidence in
166 exposed litters from all dosage groups. Reductions in maternal weight gain occurred at
167 dosages of 5 mg/kg/day or greater and reduction in embryo-fetal growth occurred in one
168 study at a dosage of 10 mg/kg/day. No adverse maternal or embryo-fetal effects were
169 observed in mice and rats following administration during organogenesis of oral doses up
170 to 15 mg/kg/day or 40 mg/kg/day, respectively (4 and 20 times the maximum
171 recommended human dose of 20 mg/day for seizure disorders and 20 and 100 times the
172 maximum dose of 4 mg/day for panic disorder, respectively, on a mg/m² basis).

173 *General Concerns and Considerations About Anticonvulsants:* Recent reports suggest an
174 association between the use of anticonvulsant drugs by women with epilepsy and an
175 elevated incidence of birth defects in children born to these women. Data are more
176 extensive with respect to diphenylhydantoin and phenobarbital, but these are also the
177 most commonly prescribed anticonvulsants; less systematic or anecdotal reports suggest a
178 possible similar association with the use of all known anticonvulsant drugs.

179 In children of women treated with drugs for epilepsy, reports suggesting an elevated
180 incidence of birth defects cannot be regarded as adequate to prove a definite cause and
181 effect relationship. There are intrinsic methodologic problems in obtaining adequate data
182 on drug teratogenicity in humans; the possibility also exists that other factors (eg, genetic
183 factors or the epileptic condition itself) may be more important than drug therapy in
184 leading to birth defects. The great majority of mothers on anticonvulsant medication
185 deliver normal infants. It is important to note that anticonvulsant drugs should not be
186 discontinued in patients in whom the drug is administered to prevent seizures because of
187 the strong possibility of precipitating status epilepticus with attendant hypoxia and threat

188 to life. In individual cases where the severity and frequency of the seizure disorder are
189 such that the removal of medication does not pose a serious threat to the patient,
190 discontinuation of the drug may be considered prior to and during pregnancy; however, it
191 cannot be said with any confidence that even mild seizures do not pose some hazards to
192 the developing embryo or fetus.

193 General Concerns About Benzodiazepines: An increased risk of congenital
194 malformations associated with the use of benzodiazepine drugs has been suggested in
195 several studies.

196 There may also be non-teratogenic risks associated with the use of benzodiazepines
197 during pregnancy. There have been reports of neonatal flaccidity, respiratory and feeding
198 difficulties, and hypothermia in children born to mothers who have been receiving
199 benzodiazepines late in pregnancy. In addition, children born to mothers receiving
200 benzodiazepines late in pregnancy may be at some risk of experiencing withdrawal
201 symptoms during the postnatal period.

202 Advice Regarding the Use of Klonopin in Women of Childbearing Potential: In general,
203 the use of Klonopin in women of childbearing potential, and more specifically during
204 known pregnancy, should be considered only when the clinical situation warrants the risk
205 to the fetus.

206 The specific considerations addressed above regarding the use of anticonvulsants for
207 epilepsy in women of childbearing potential should be weighed in treating or counseling
208 these women.

209 Because of experience with other members of the benzodiazepine class, Klonopin is
210 assumed to be capable of causing an increased risk of congenital abnormalities when
211 administered to a pregnant woman during the first trimester. Because use of these drugs
212 is rarely a matter of urgency in the treatment of panic disorder, their use during the first
213 trimester should almost always be avoided. The possibility that a woman of childbearing
214 potential may be pregnant at the time of institution of therapy should be considered. If
215 this drug is used during pregnancy, or if the patient becomes pregnant while taking this
216 drug, the patient should be apprised of the potential hazard to the fetus. Patients should
217 also be advised that if they become pregnant during therapy or intend to become
218 pregnant, they should communicate with their physician about the desirability of
219 discontinuing the drug.

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

222 **PRECAUTIONS**

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

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

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

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

238 Hypersalivation: Klonopin may produce an increase in salivation. This should be
239 considered before giving the drug to patients who have difficulty handling secretions.
240 Because of this and the possibility of respiratory depression, Klonopin should be used
241 with caution in patients with chronic respiratory diseases.

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

246 Dose Changes: To assure the safe and effective use of benzodiazepines, patients should
247 be informed that, since benzodiazepines may produce psychological and physical
248 dependence, it is advisable that they consult with their physician before either increasing
249 the dose or abruptly discontinuing this drug.

250 Interference With Cognitive and Motor Performance: Because benzodiazepines have the
251 potential to impair judgment, thinking or motor skills, patients should be cautioned about
252 operating hazardous machinery, including automobiles, until they are reasonably certain
253 that Klonopin therapy does not affect them adversely.

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

260 Pregnancy: Patients should be advised to notify their physician if they become pregnant
261 or intend to become pregnant during therapy with Klonopin (see WARNINGS:
262 *Pregnancy Risks*). Patients should be encouraged to enroll in the North American
263 Antiepileptic Drug (NAAED) Pregnancy Registry if they become pregnant. This registry
264 is collecting information about the safety of antiepileptic drugs during pregnancy. To
265 enroll, patients can call the toll free number 1-888-233-2334 (see PRECAUTIONS:
266 *Pregnancy*).

267 Nursing: Patients should be advised not to breastfeed an infant if they are taking
268 Klonopin.

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

272 Alcohol: Patients should be advised to avoid alcohol while taking Klonopin.

273 **Drug Interactions: Effect of Clonazepam on the Pharmacokinetics of Other Drugs:**
274 Clonazepam does not appear to alter the pharmacokinetics of phenytoin, carbamazepine
275 or phenobarbital. The effect of clonazepam on the metabolism of other drugs has not
276 been investigated.

277 **Effect of Other Drugs on the Pharmacokinetics of Clonazepam:** Literature reports suggest
278 that ranitidine, an agent that decreases stomach acidity, does not greatly alter clonazepam
279 pharmacokinetics.

280 In a study in which the 2 mg clonazepam orally disintegrating tablet was administered
281 with and without propantheline (an anticholinergic agent with multiple effects on the GI
282 tract) to healthy volunteers, the AUC of clonazepam was 10% lower and the C_{max} of
283 clonazepam was 20% lower when the orally disintegrating tablet was given with
284 propantheline compared to when it was given alone.

285 Fluoxetine does not affect the pharmacokinetics of clonazepam. Cytochrome P-450
286 inducers, such as phenytoin, carbamazepine and phenobarbital, induce clonazepam
287 metabolism, causing an approximately 30% decrease in plasma clonazepam levels.
288 Although clinical studies have not been performed, based on the involvement of the
289 cytochrome P-450 3A family in clonazepam metabolism, inhibitors of this enzyme
290 system, notably oral antifungal agents, should be used cautiously in patients receiving
291 clonazepam.

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

297 **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Carcinogenicity studies have not
298 been conducted with clonazepam.

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

301 In a two-generation fertility study in which clonazepam was given orally to rats at 10 and
302 100 mg/kg/day (low dose approximately 5 times and 24 times the maximum
303 recommended human dose of 20 mg/day for seizure disorder and 4 mg/day for panic
304 disorder, respectively, on a mg/m² basis), there was a decrease in the number of
305 pregnancies and in the number of offspring surviving until weaning.

306 ***Pregnancy: Teratogenic Effects:*** Pregnancy Category D (see WARNINGS: *Pregnancy*
307 *Risks*).

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

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

318 ***Nursing Mothers:*** Mothers receiving Klonopin should not breastfeed their infants.

319 ***Pediatric Use:*** Because of the possibility that adverse effects on physical or mental
320 development could become apparent only after many years, a benefit-risk consideration
321 of the long-term use of Klonopin is important in pediatric patients being treated for
322 seizure disorder (see INDICATIONS AND USAGE and DOSAGE AND
323 ADMINISTRATION).

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

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

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

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

341 **ADVERSE REACTIONS**

342 The adverse experiences for Klonopin are provided separately for patients with seizure
343 disorders and with panic disorder.

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

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

352 *Psychiatric:* Confusion, depression, amnesia, hallucinations, hysteria, increased libido,
353 insomnia, psychosis (the behavior effects are more likely to occur in patients with a
354 history of psychiatric disturbances). The following paradoxical reactions have been
355 observed: excitability, irritability, aggressive behavior, agitation, nervousness, hostility,
356 anxiety, sleep disturbances, nightmares and vivid dreams

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

359 *Cardiovascular:* Palpitations

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

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

363 *Genitourinary:* Dysuria, enuresis, nocturia, urinary retention

364 *Musculoskeletal:* Muscle weakness, pains

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

367 *Hematopoietic:* Anemia, leukopenia, thrombocytopenia, eosinophilia

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

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

378 The stated frequencies of adverse events represent the proportion of individuals who
379 experienced, at least once, a treatment-emergent adverse event of the type listed. An

380 event was considered treatment-emergent if it occurred for the first time or worsened
381 while receiving therapy following baseline evaluation.

382

383

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

385 ***Adverse Events Associated With Discontinuation of Treatment:***

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

390 **Table 2 Most Common Adverse Events ($\geq 1\%$) Associated with**
391 **Discontinuation of Treatment**

Adverse Event	Klonopin (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%

392 ***Adverse Events Occurring at an Incidence of 1% or More Among Klonopin-Treated***
393 ***Patients:***

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

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

407 **Table 3 Treatment-Emergent Adverse Event Incidence in 6- to 9-**
408 **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 Klonopin 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

Clonazepam Maximum Daily Dose						
Adverse Event by Body System	<1mg n=96 %	1-<2mg n=129 %	2-<3mg n=113 %	≥3mg n=235 %	All Klonopin Groups N=574 %	Placebo N=294 %
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

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

411 † Indicates that the p-value for the dose-trend test (Cochran-Mantel-Haenszel) for
412 adverse event incidence was ≤0.10.

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

415 Commonly Observed Adverse Events:

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

Adverse Event (Genentech Preferred Term)	Clonazepam (N=574)	Placebo (N=294)
Somnolence	37%	10%
Depression	7%	1%
Coordination Abnormal	6%	0%
Ataxia	5%	0%

418 * Treatment-emergent events for which the incidence in the clonazepam patients was
419 $\geq 5\%$ and at least twice that in the placebo patients.

420 Treatment-Emergent Depressive Symptoms:

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

430 Other Adverse Events Observed During the Premarketing Evaluation of Klonopin in
431 Panic Disorder:

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

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

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

446 *Cardiovascular Disorders:* chest pain, hypotension postural

- 447 *Central and Peripheral Nervous System Disorders:* migraine, paresthesia, drunkenness,
448 feeling of enuresis, paresis, tremor, burning skin, falling, head fullness, hoarseness,
449 hyperactivity, hypoesthesia, tongue thick, twitching
- 450 *Gastrointestinal System Disorders:* abdominal discomfort, gastrointestinal inflammation,
451 stomach upset, toothache, flatulence, pyrosis, saliva increased, tooth disorder, bowel
452 movements frequent, pain pelvic, dyspepsia, hemorrhoids
- 453 *Hearing and Vestibular Disorders:* vertigo, otitis, earache, motion sickness
- 454 *Heart Rate and Rhythm Disorders:* palpitation
- 455 *Metabolic and Nutritional Disorders:* thirst, gout
- 456 *Musculoskeletal System Disorders:* back pain, fracture traumatic, sprains and strains, pain
457 leg, pain nape, cramps muscle, cramps leg, pain ankle, pain shoulder, tendinitis,
458 arthralgia, hypertonia, lumbago, pain feet, pain jaw, pain knee, swelling knee
- 459 *Platelet, Bleeding and Clotting Disorders:* bleeding dermal
- 460 *Psychiatric Disorders:* insomnia, organic disinhibition, anxiety, depersonalization,
461 dreaming excessive, libido loss, appetite increased, libido increased, reactions decreased,
462 aggressive reaction, apathy, attention lack, excitement, feeling mad, hunger abnormal,
463 illusion, nightmares, sleep disorder, suicide ideation, yawning
- 464 *Reproductive Disorders, Female:* breast pain, menstrual irregularity
- 465 *Reproductive Disorders, Male:* ejaculation decreased
- 466 *Resistance Mechanism Disorders:* infection mycotic, infection viral, infection
467 streptococcal, herpes simplex infection, infectious mononucleosis, moniliasis
- 468 *Respiratory System Disorders:* sneezing excessive, asthmatic attack, dyspnea, nosebleed,
469 pneumonia, pleurisy
- 470 *Skin and Appendages Disorders:* acne flare, alopecia, xeroderma, dermatitis contact,
471 flushing, pruritus, pustular reaction, skin burns, skin disorder
- 472 *Special Senses Other, Disorders:* taste loss
- 473 *Urinary System Disorders:* dysuria, cystitis, polyuria, urinary incontinence, bladder
474 dysfunction, urinary retention, urinary tract bleeding, urine discoloration
- 475 *Vascular (Extracardiac) Disorders:* thrombophlebitis leg
- 476 *Vision Disorders:* eye irritation, visual disturbance, diplopia, eye twitching, styes, visual
477 field defect, xerophthalmia
- 478 **DRUG ABUSE AND DEPENDENCE**
- 479 *Controlled Substance Class:* Clonazepam is a Schedule IV controlled substance.

480 ***Physical and Psychological Dependence:*** Withdrawal symptoms, similar in character to
481 those noted with barbiturates and alcohol (eg, convulsions, psychosis, hallucinations,
482 behavioral disorder, tremor, abdominal and muscle cramps) have occurred following
483 abrupt discontinuance of clonazepam. The more severe withdrawal symptoms have
484 usually been limited to those patients who received excessive doses over an extended
485 period of time. Generally milder withdrawal symptoms (eg, dysphoria and insomnia)
486 have been reported following abrupt discontinuance of benzodiazepines taken
487 continuously at therapeutic levels for several months. Consequently, after extended
488 therapy, abrupt discontinuation should generally be avoided and a gradual dosage
489 tapering schedule followed (see DOSAGE AND ADMINISTRATION). Addiction-prone
490 individuals (such as drug addicts or alcoholics) should be under careful surveillance when
491 receiving clonazepam or other psychotropic agents because of the predisposition of such
492 patients to habituation and dependence.

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

501 **OVERDOSAGE**

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

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

508 Flumazenil, a specific benzodiazepine-receptor antagonist, is indicated for the complete
509 or partial reversal of the sedative effects of benzodiazepines and may be used in
510 situations when an overdose with a benzodiazepine is known or suspected. Prior to the
511 administration of flumazenil, necessary measures should be instituted to secure airway,
512 ventilation and intravenous access. Flumazenil is intended as an adjunct to, not as a
513 substitute for, proper management of benzodiazepine overdose. Patients treated with
514 flumazenil should be monitored for re sedation, respiratory depression and other residual
515 benzodiazepine effects for an appropriate period after treatment. **The prescriber should
516 be aware of a risk of seizure in association with flumazenil treatment, particularly in
517 long-term benzodiazepine users and in cyclic antidepressant overdose.** The complete
518 flumazenil package insert, including CONTRAINDICATIONS, WARNINGS and
519 PRECAUTIONS, should be consulted prior to use.

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

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

524 **DOSAGE AND ADMINISTRATION**

525 Clonazepam is available as a tablet or an orally disintegrating tablet (wafer). The tablets
526 should be administered with water by swallowing the tablet whole. The orally
527 disintegrating tablet should be administered as follows: After opening the pouch, peel
528 back the foil on the blister. Do not push tablet through foil. Immediately upon opening
529 the blister, using dry hands, remove the tablet and place it in the mouth. Tablet
530 disintegration occurs rapidly in saliva so it can be easily swallowed with or without
531 water.

532

533 ***Seizure Disorders: Adults:*** The initial dose for adults with seizure disorders should not
534 exceed 1.5 mg/day divided into three doses. Dosage may be increased in increments of
535 0.5 to 1 mg every 3 days until seizures are adequately controlled or until side effects
536 preclude any further increase. Maintenance dosage must be individualized for each
537 patient depending upon response. Maximum recommended daily dose is 20 mg.

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

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

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

552 ***Panic Disorder: Adults:*** The initial dose for adults with panic disorder is 0.25 mg bid. An
553 increase to the target dose for most patients of 1 mg/day may be made after 3 days. The
554 recommended dose of 1 mg/day is based on the results from a fixed dose study in which
555 the optimal effect was seen at 1 mg/day. Higher doses of 2, 3 and 4 mg/day in that study
556 were less effective than the 1 mg/day dose and were associated with more adverse
557 effects. Nevertheless, it is possible that some individual patients may benefit from doses
558 of up to a maximum dose of 4 mg/day, and in those instances, the dose may be increased
559 in increments of 0.125 to 0.25 mg bid every 3 days until panic disorder is controlled or

560 until side effects make further increases undesired. To reduce the inconvenience of
561 somnolence, administration of one dose at bedtime may be desirable.

562 Treatment should be discontinued gradually, with a decrease of 0.125 mg bid every
563 3 days, until the drug is completely withdrawn.

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

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

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

573 **HOW SUPPLIED**

574 Klonopin tablets are available as scored tablets with a K-shaped perforation—0.5 mg,
575 orange (NDC 0004-0068-01); and unscored tablets with a K-shaped perforation—1 mg,
576 blue (NDC 0004-0058-01); 2 mg, white (NDC 0004-0098-01)—bottles of 100.

577 Imprint on tablets:

578 0.5 mg — 1/2 KLONOPIN (front)
579 ROCHE (scored side)



580 1 mg — 1 KLONOPIN (front)
581 ROCHE (reverse side)



582 2 mg — 2 KLONOPIN (front)
583 ROCHE (reverse side)



584 Klonopin Wafers (clonazepam orally disintegrating tablets) are white, round and
585 debossed with the tablet strength expressed as a fraction or whole number (1/8, 1/4, 1/2,
586 1, or 2). The tablets are available in blister packages of 60 (10 pouches/carton) as
587 follows:

588 0.125 mg debossed 1/8, (NDC 0004-0279-22)

589 0.25 mg debossed 1/4, (NDC 0004-0280-22)

590 0.5 mg debossed 1/2, (NDC 0004-0281-22)

591 1 mg debossed 1, (NDC 0004-0282-22)

592 2 mg debossed 2, (NDC 0004-0283-22)

593 Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F).

594

Distributed by:

Genentech USA, Inc.

A Member of the Roche Group

1 DNA Way

South San Francisco, CA 94080-4990

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597 Revised: Month Year

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1 **Medication Guide**

2 **KLONOPIN® (KLON-oh-pin)**

3 **(clonazepam)**

4 **Tablets and Wafers**



6 Read this Medication Guide before you start taking KLONOPIN and each time
7 you get a refill. There may be new information. This information does not take the
8 place of talking to your healthcare provider about your medical condition or
9 treatment.

10 KLONOPIN can cause serious side effects. Because stopping KLONOPIN
11 suddenly can also cause serious problems, do not stop taking KLONOPIN without
12 talking to your healthcare provider first.

13 **What is the most important information I should know about KLONOPIN?**

14 **Do not stop taking KLONOPIN without first talking to your healthcare**
15 **provider.** Stopping KLONOPIN suddenly can cause serious problems.

16 **KLONOPIN can cause serious side effects, including:**

17 **1. KLONOPIN can slow your thinking and motor skills**

- 18 • Do not drive, operate heavy machinery, or do other dangerous activities
19 until you know how KLONOPIN affects you.
- 20 • Do not drink alcohol or take other drugs that may make you sleepy or
21 dizzy while taking KLONOPIN until you talk to your healthcare
22 provider. When taken with alcohol or drugs that cause sleepiness or
23 dizziness, KLONOPIN may make your sleepiness or dizziness worse.

24 **2. Like other antiepileptic drugs, KLONOPIN may cause suicidal thoughts**
25 **or actions in a very small number of people, about 1 in 500.**

26 **Call a healthcare provider right away if you have any of these**
27 **symptoms, especially if they are new, worse, or worry you:**

- 28 ■ thoughts about suicide or dying
29 ■ attempt to commit suicide
30 ■ new or worse depression
31 ■ new or worse anxiety
32 ■ feeling agitated or restless
33 ■ panic attacks
34 ■ trouble sleeping (insomnia)
35 ■ new or worse irritability
36 ■ acting aggressive, being angry, or violent
37 ■ acting on dangerous impulses
38 ■ an extreme increase in activity and talking (mania)

- 39 ▪ other unusual changes in behavior or mood

40 **How can I watch for early symptoms of suicidal thoughts and actions?**

- 41 • Pay attention to any changes, especially sudden changes, in mood,
42 behaviors, thoughts, or feelings.

- 43 • Keep all follow-up visits with your healthcare provider as scheduled.

44 Call your healthcare provider between visits as needed, especially if you are
45 worried about symptoms.

46
47 Suicidal thoughts or actions can be caused by things other than medicines. If
48 you have suicidal thoughts or actions, your healthcare provider may check
49 for other causes.

50 **Do not stop KLONOPIN without first talking to a healthcare provider.**

51 Stopping KLONOPIN suddenly can cause serious problems. Stopping
52 KLONOPIN suddenly can cause seizures that will not stop (status
53 epilepticus).

54 **3. KLONOPIN may harm your unborn or developing baby.**

- 55 • If you take KLONOPIN during pregnancy, your baby is at risk for serious
56 birth defects. These defects can happen as early as in the first month of
57 pregnancy, even before you know you are pregnant. Birth defects may
58 occur even in children born to women who are not taking any medicines
59 and do not have other risk factors.

- 60 • Children born to mothers receiving benzodiazepine medications (including
61 KLONOPIN) late in pregnancy may be at some risk of experiencing
62 breathing problems, feeding problems, hypothermia, and withdrawal
63 symptoms.

- 64 • Tell your healthcare provider right away if you become pregnant while
65 taking KLONOPIN. You and your healthcare provider should decide if
66 you will take KLONOPIN while you are pregnant.

- 67 • If you become pregnant while taking KLONOPIN, talk to your healthcare
68 provider about registering with the North American Antiepileptic Drug
69 Pregnancy Registry. You can register by calling 1-888-233-2334. The
70 purpose of this registry is to collect information about the safety of
71 antiepileptic drugs during pregnancy.

- 72 • KLONOPIN can pass into breast milk. Talk to your healthcare provider
73 about the best way to feed your baby if you take KLONOPIN. You and
74 your healthcare provider should decide if you will take KLONOPIN or
75 breast feed. You should not do both.

76 **4. KLONOPIN can cause abuse and dependence.**

- 77 • Do not stop taking KLONOPIN all of a sudden. Stopping KLONOPIN
78 suddenly can cause seizures that do not stop, hearing or seeing things that
79 are not there (hallucinations), shaking, and stomach and muscle cramps.
- 80 ○ Talk to your doctor about slowly stopping KLONOPIN to avoid
81 getting sick with withdrawal symptoms.
- 82 ○ Physical dependence is not the same as drug addiction. Your
83 healthcare provider can tell you more about the differences
84 between physical dependence and drug addiction.

85 **KLONOPIN is a federally controlled substance (C-IV) because it can be**
86 **abused or lead to dependence. Keep KLONOPIN in a safe place to prevent**
87 **misuse and abuse. Selling or giving away KLONOPIN may harm others, and**
88 **is against the law. Tell your doctor if you have ever abused or been**
89 **dependent on alcohol, prescription medicines or street drugs.**

90 **What is KLONOPIN?**

91 KLONOPIN is a prescription medicine used alone or with other medicines to
92 treat:

- 93 • certain types of seizure disorders (epilepsy) in adults and children
94 • panic disorder with or without fear of open spaces (agoraphobia) in adults

95 It is not known if KLONOPIN is safe or effective in treating panic disorder in
96 children younger than 18 years old.

97 **Who should not take KLONOPIN?**

98 Do not take KLONOPIN if you:

- 99 • are allergic to benzodiazepines
100 • have significant liver disease
101 • have an eye disease called acute narrow angle glaucoma

102 **Ask your healthcare provider if you are not sure if you have any of the**
103 **problems listed above.**

104 **What should I tell my healthcare provider before taking KLONOPIN?**

105 Before you take KLONOPIN, tell your healthcare provider if you:

- 106 • have liver or kidney problems
107 • have lung problems (respiratory disease)
108 • have or have had depression, mood problems, or suicidal thoughts or
109 behavior
110 • have any other medical conditions
111

112 **Tell your healthcare provider about all the medicines you take**, including
113 prescription and non-prescription medicines, vitamins, and herbal supplements.
114 Taking KLONOPIN with certain other medicines can cause side effects or affect
115 how well they work. Do not start or stop other medicines without talking to your
116 healthcare provider.

117 Know the medicines you take. Keep a list of them and show it to your healthcare
118 provider and pharmacist when you get a new medicine.

119 **How should I take KLONOPIN?**

- 120 • Take KLONOPIN exactly as your healthcare provider tells you.
121 KLONOPIN is available as a tablet or as an orally disintegrating tablet
122 (wafer).
- 123 • Do not stop taking KLONOPIN without first talking to your healthcare
124 provider. Stopping KLONOPIN suddenly can cause serious problems.
- 125 • **KLONOPIN tablets** should be taken with water and swallowed whole.
- 126 • **KLONOPIN wafers** can be taken with or without water.
 - 127 ○ Do not open the pouch until you are ready to take KLONOPIN.
 - 128 ○ After opening the pouch, peel back the foil on the blister pack.
 - 129 ○ Do not push the wafer through the foil.
 - 130 ○ After opening the blister pack, with dry hands, take the wafer and
131 place it in your mouth.
 - 132 ○ The wafer will melt quickly.
- 133 • If you take too much KLONOPIN, call your healthcare provider or local
134 Poison Control Center right away.

135 **What should I avoid while taking KLONOPIN?**

- 136 • KLONOPIN can slow your thinking and motor skills. Do not drive,
137 operate heavy machinery, or do other dangerous activities until you know
138 how KLONOPIN affects you.
- 139 • Do not drink alcohol or take other drugs that may make you sleepy or
140 dizzy while taking KLONOPIN until you talk to your healthcare
141 provider. When taken with alcohol or drugs that cause sleepiness or
142 dizziness, KLONOPIN may make your sleepiness or dizziness worse.

143 **What are the possible side effects of KLONOPIN?**

144 **See “What is the most important information I should know about**
145 **KLONOPIN?”**

146 KLONOPIN can also make your seizures happen more often or make them worse.
147 Call your healthcare provider right away if your seizures get worse while taking
148 KLONOPIN.

149 The most common side effects of KLONOPIN include:

- 150 • Drowsiness
- 151 • Problems with walking and coordination
- 152 • Dizziness
- 153 • Depression
- 154 • Fatigue
- 155 • Problems with memory

156 These are not all the possible side effects of KLONOPIN. For more information,
157 ask your healthcare provider or pharmacist.

158 Tell your healthcare provider if you have any side effect that bothers you or that
159 does not go away.

160 Call your doctor for medical advice about side effects. You may report side
161 effects to FDA at 1-800-FDA-1088.

162 **How should I store KLONOPIN?**

- 163 • Store KLONOPIN between 59°F to 86°F (15°C to 30°C)

164 **Keep KLONOPIN and all medicines out of the reach of children.**

165 **General Information about KLONOPIN**

166 Medicines are sometimes prescribed for purposes other than those listed in a
167 Medication Guide. Do not use KLONOPIN for a condition for which it was not
168 prescribed. Do not give KLONOPIN to other people, even if they have the same
169 symptoms that you have. It may harm them.

170 This Medication Guide summarizes the most important information about
171 KLONOPIN. If you would like more information, talk with your healthcare
172 provider. You can ask your pharmacist or healthcare provider for information
173 about KLONOPIN that is written for health professionals.

174 For more information, go to www.gene.com/gene/products/information/klonopin
175 or call 1-888-835-2555.

176 **What are the ingredients in KLONOPIN?**

177 Active ingredient: clonazepam

178 Inactive ingredients:

- 179 • Tablets:
 - 180 ○ 0.5 mg tablets contain lactose, magnesium stearate,
181 microcrystalline cellulose, corn starch, FD&C Yellow No. 6 Lake
 - 182 ○ 1 mg tablets contain lactose, magnesium stearate, microcrystalline
183 cellulose, corn starch, FD&C Blue No. 1 Lake and FD&C Blue
184 No. 2 Lake
 - 185 ○ 2 mg tablets contain lactose, magnesium stearate, microcrystalline
186 cellulose, corn starch

187 • Wafers: gelatin, mannitol, methylparaben sodium, propylparaben sodium
188 and xanthan gum
189

190 Issued: Month Year

191 This Medication Guide has been approved by the U.S. Food and Drug
192 Administration.

193

Distributed by:

Genentech USA, Inc.

A Member of the Roche Group

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194 South San Francisco, CA 94080-4990

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197 www.gene.com/gene/products/information/klonopin.