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## KLONOPIN TABLETS

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(clonazepam)

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## KLONOPIN WAFERS

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(clonazepam orally disintegrating tablets)

6

**Rx only**

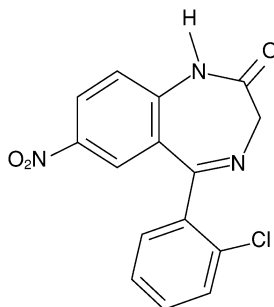
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### DESCRIPTION

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:



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### 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/m<sup>2</sup> 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/m<sup>2</sup> 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:** Patients should be instructed to take Klonopin only as  
243 prescribed. Physicians are advised to discuss the following issues with patients for whom  
244 they prescribe Klonopin:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

300 In a two-generation fertility study in which clonazepam was given orally to rats at 10 and  
301 100 mg/kg/day (low dose approximately 5 times and 24 times the maximum  
302 recommended human dose of 20 mg/day for seizure disorder and 4 mg/day for panic  
303 disorder, respectively, on a mg/m<sup>2</sup> basis), there was a decrease in the number of  
304 pregnancies and in the number of offspring surviving until weaning.

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

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

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

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

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

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

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

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

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

## 340 **ADVERSE REACTIONS**

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

343 **Seizure Disorders:** The most frequently occurring side effects of Klonopin are referable  
344 to CNS depression. Experience in treatment of seizures has shown that drowsiness has  
345 occurred in approximately 50% of patients and ataxia in approximately 30%. In some

346 cases, these may diminish with time; behavior problems have been noted in  
347 approximately 25% of patients. Others, listed by system, are:

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

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

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

358 *Cardiovascular:* Palpitations

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

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

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

363 *Musculoskeletal:* Muscle weakness, pains

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

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

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

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

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

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

382 Adverse Events Associated With Discontinuation of Treatment:

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

387 **Table 2 Most Common Adverse Events ( $\geq 1\%$ ) Associated with**  
 388 **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%

389 Adverse Events Occurring at an Incidence of 1% or More Among Klonopin-Treated  
 390 Patients:

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

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

404 **Table 3 Treatment-Emergent Adverse Event Incidence in 6- to 9-**  
 405 **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 %	$\geq 3$ mg 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

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

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

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

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

412 Commonly Observed Adverse Events:

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

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

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

417 Treatment-Emergent Depressive Symptoms:

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

427 Other Adverse Events Observed During the Premarketing Evaluation of Klonopin in  
428 Panic Disorder:

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

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

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

443 *Cardiovascular Disorders:* chest pain, hypotension postural

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

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

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

#### 498 **OVERDOSAGE**

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

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

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

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

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

521 **DOSAGE AND ADMINISTRATION**

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

529 ***Seizure Disorders: Adults:*** The initial dose for adults with seizure disorders should not  
530 exceed 1.5 mg/day divided into three doses. Dosage may be increased in increments of  
531 0.5 to 1 mg every 3 days until seizures are adequately controlled or until side effects  
532 preclude any further increase. Maintenance dosage must be individualized for each  
533 patient depending upon response. Maximum recommended daily dose is 20 mg.

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

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

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

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

558 Treatment should be discontinued gradually, with a decrease of 0.125 mg bid every  
559 3 days, until the drug is completely withdrawn.

560 There is no body of evidence available to answer the question of how long the patient  
561 treated with clonazepam should remain on it. Therefore, the physician who elects to use

562 Klonopin for extended periods should periodically reevaluate the long-term usefulness of  
563 the drug for the individual patient.

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

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

## 569 HOW SUPPLIED

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

573 Imprint on tablets:

574 0.5 mg — 1/2 KLONOPIN (front)  
575 ROCHE (scored side)



576 1 mg — 1 KLONOPIN (front)  
577 ROCHE (reverse side)



578 2 mg — 2 KLONOPIN (front)  
579 ROCHE (reverse side)



580 Klonopin Wafers (clonazepam orally disintegrating tablets) are white, round and  
581 debossed with the tablet strength expressed as a fraction or whole number (1/8, 1/4, 1/2,  
582 1, or 2). The tablets are available in blister packages of 60 (10 pouches/carton) as  
583 follows:

584 0.125 mg debossed 1/8, (NDC 0004-0279-22)

585 0.25 mg debossed 1/4, (NDC 0004-0280-22)

586 0.5 mg debossed 1/2, (NDC 0004-0281-22)

587 1 mg debossed 1, (NDC 0004-0282-22)

588 2 mg debossed 2, (NDC 0004-0283-22)

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

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