

1 **NIRAVAM™**

CIV

2 (alprazolam orally disintegrating tablets)

3

4

5

6 **Rx Only**

7

8 **DESCRIPTION**

9 NIRAVAM™ (alprazolam orally disintegrating tablets) contains alprazolam which is a
10 triazolo analog of the 1,4 benzodiazepine class of central nervous system-active compounds.
11 NIRAVAM™ is an orally administered formulation of alprazolam which rapidly disintegrates
12 on the tongue and does not require water to aid dissolution or swallowing.

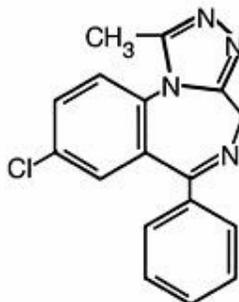
13

14 The chemical name of alprazolam is 8-Chloro-1-methyl-6-phenyl-4H-s-triazolo [4,3- α] [1,4]
15 benzodiazepine. The empirical formula is C₁₇H₁₃ClN₄ and the molecular weight is 308.76.

16

The structural formula is:

17



18

19 Alprazolam is a white crystalline powder, which is soluble in methanol or ethanol but which
20 has no appreciable solubility in water at physiological pH.

21

22 Each orally disintegrating tablet contains either 0.25, 0.5, 1 or 2 mg of alprazolam and the
23 following inactive ingredients: colloidal silicon dioxide, corn starch, crospovidone,
24 magnesium stearate, mannitol, methacrylic acid copolymer, microcrystalline cellulose, natural
25 and artificial orange flavor, sucralose and sucrose. In addition, the 0.25 mg and 0.5 mg
26 tablets contain yellow iron oxide.

27

28 **CLINICAL PHARMACOLOGY**

29 **Pharmacodynamics**

30 CNS agents of the 1,4 benzodiazepine class presumably exert their effects by binding at
31 stereo specific receptors at several sites within the central nervous system. Their exact
32 mechanism of action is unknown. Clinically, all benzodiazepines cause a dose-related central
33 nervous system depressant activity varying from mild impairment of task performance to
34 hypnosis.

35

36 **Pharmacokinetics**

37 Absorption

38 Following oral administration, alprazolam is readily absorbed. The peak plasma
39 concentration is reached about 1.5 to 2 hours after administration of NIRAVAM™ given with
40 or without water. When taken with water, mean T_{max} occurs about 15 minutes earlier than
41 when taken without water with no change in C_{max} or AUC. Plasma levels are proportional to
42 the dose given; over the dose range of 0.5 to 3.0 mg, peak levels of 8.0 to 37 ng/mL are
43 observed. The elimination half-life of alprazolam is approximately 12.5 hours (range 7.9 -
44 19.2 hours) after administration of NIRAVAM™ in healthy adults.

45

46 Food decreased the mean C_{max} by about 25% and increased the mean T_{max} by 2 hours from
47 2.2 hours to 4.4 hours after the ingestion of a high-fat meal. Food did not affect the extent of
48 absorption (AUC) or the elimination half-life.

49

50 Distribution

51 *In vitro*, alprazolam is bound (80 percent) to human serum protein. Serum albumin accounts
52 for the majority of the binding.

53

54 Metabolism/Elimination

55 Alprazolam is extensively metabolized in humans, primarily by cytochrome P450 3A4
56 (CYP3A4), to two major metabolites in the plasma: 4-hydroxyalprazolam and α -
57 hydroxyalprazolam. A benzophenone derived from alprazolam is also found in humans.
58 Their half-lives appear to be similar to that of alprazolam. The plasma concentrations of
59 4-hydroxyalprazolam and α -hydroxyalprazolam relative to unchanged alprazolam
60 concentration were always less than 4%. The reported relative potencies in benzodiazepine
61 receptor binding experiments and in animal models of induced seizure inhibition are 0.20 and
62 0.66, respectively, for 4-hydroxyalprazolam and α -hydroxyalprazolam. Such low
63 concentrations and the lesser potencies of 4-hydroxyalprazolam and α -hydroxyalprazolam
64 suggest that they are unlikely to contribute much to the pharmacological effects of
65 alprazolam. The benzophenone metabolite is essentially inactive.

66

67 Alprazolam and its metabolites are excreted primarily in the urine.

68

69 Special Populations

70 Changes in the absorption, distribution, metabolism and excretion of benzodiazepines have
71 been reported in a variety of disease states including alcoholism, impaired hepatic function
72 and impaired renal function. Changes have also been demonstrated in geriatric patients. A
73 mean half-life of alprazolam of 16.3 hours has been observed in healthy elderly subjects
74 (range: 9.0 - 26.9 hours, n=16) compared to 11.0 hours (range: 6.3 - 15.8 hours, n=16) in
75 healthy adult subjects. In patients with alcoholic liver disease the half-life of alprazolam
76 ranged between 5.8 and 65.3 hours (mean: 19.7 hours, n=17) as compared to between 6.3 and
77 26.9 hours (mean=11.4 hours, n=17) in healthy subjects. In an obese group of subjects the
78 half-life of alprazolam ranged between 9.9 and 40.4 hours (mean=21.8 hours, n=12) as
79 compared to between 6.3 and 15.8 hours (mean=10.6 hours, n=12) in healthy subjects.

80

81 Because of its similarity to other benzodiazepines, it is assumed that alprazolam undergoes
82 transplacental passage and that it is excreted in human milk.

83

84 Race — Maximal concentrations and half-life of alprazolam are approximately 15% and 25%
85 higher in Asians compared to Caucasians.

86

87 Pediatrics — The pharmacokinetics of alprazolam in pediatric patients have not been studied.

88

89 Gender — Gender has no effect on the pharmacokinetics of alprazolam.

90

91 Cigarette Smoking — Alprazolam concentrations may be reduced by up to 50% in smokers
92 compared to non-smokers.

93

94 Drug-Drug Interactions

95 Alprazolam is primarily eliminated by metabolism via cytochrome P450 3A (CYP3A). Most
96 of the interactions that have been documented with alprazolam are with drugs that inhibit or
97 induce CYP3A4.

98

99 Compounds that are potent inhibitors of CYP3A would be expected to increase plasma
100 alprazolam concentrations. Drug products that have been studied *in vivo*, along with their
101 effect on increasing alprazolam AUC, are as follows: ketoconazole, 3.98 fold; itraconazole,
102 2.70 fold; nefazodone, 1.98 fold; fluvoxamine, 1.96 fold; and erythromycin, 1.61 fold (see
103 CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS–Drug Interactions).

104

105 CYP3A inducers would be expected to decrease alprazolam concentrations and this has been
106 observed *in vivo*. The oral clearance of alprazolam (given in a 0.8 mg single dose) was
107 increased from 0.90 ± 0.21 mL/min/kg to 2.13 ± 0.54 mL/min/kg and the elimination $t_{1/2}$ was
108 shortened (from 17.1 ± 4.9 to 7.7 ± 1.7 h) following administration of 300 mg/day
109 carbamazepine for 10 days (see PRECAUTIONS–Drug Interactions). However, the
110 carbamazepine dose used in this study was fairly low compared to the recommended doses
111 (1000 - 1200 mg/day); the effect at usual carbamazepine doses is unknown.

112

113 The ability of alprazolam to induce or inhibit human hepatic enzyme systems has not been
114 determined. However, this is not a property of benzodiazepines in general. Further,
115 alprazolam did not affect the prothrombin or plasma warfarin levels in male volunteers
116 administered sodium warfarin orally.

117

118 **CLINICAL STUDIES**

119 **Anxiety Disorders**

120 Alprazolam was compared to placebo in double blind clinical studies (doses up to 4 mg/day)
121 in patients with a diagnosis of anxiety or anxiety with associated depressive symptomatology.
122 Alprazolam was significantly better than placebo at each of the evaluation periods of these
123 4-week studies as judged by the following psychometric instruments: Physician's Global
124 Impressions, Hamilton Anxiety Rating Scale, Target Symptoms, Patient's Global Impressions
125 and Self-Rating Symptom Scale.

126

127 **Panic Disorder**

128 Support for the effectiveness of alprazolam in the treatment of panic disorder came from three
129 short-term, placebo-controlled studies (up to 10 weeks) in patients with diagnoses closely
130 corresponding to DSM-III-R criteria for panic disorder.

131

132 The average dose of alprazolam was 5 - 6 mg/day in two of the studies, and the doses of
133 alprazolam were fixed at 2 and 6 mg/day in the third study. In all three studies, alprazolam
134 was superior to placebo on a variable defined as "the number of patients with zero panic
135 attacks" (range, 37 - 83% met this criterion), as well as on a global improvement score. In two
136 of the three studies, alprazolam was superior to placebo on a variable defined as "change from
137 baseline on the number of panic attacks per week" (range, 3.3 - 5.2), and also on a phobia
138 rating scale. A subgroup of patients who were improved on alprazolam during short-term
139 treatment in one of these trials was continued on an open basis up to 8 months, without
140 apparent loss of benefit.

141

142 **INDICATIONS AND USAGE**

143 **Anxiety Disorders**

144 NIRAVAM™ is indicated for the management of anxiety disorder (a condition corresponding
145 most closely to the APA Diagnostic and Statistical Manual [DSM-III-R] diagnosis of
146 generalized anxiety disorder) or the short-term relief of symptoms of anxiety. Anxiety or
147 tension associated with the stress of everyday life usually does not require treatment with an
148 anxiolytic.

149

150 Generalized anxiety disorder is characterized by unrealistic or excessive anxiety and worry
151 (apprehensive expectation) about two or more life circumstances, for a period of 6 months or
152 longer, during which the person has been bothered more days than not by these concerns. At
153 least 6 of the following 18 symptoms are often present in these patients: *Motor Tension*
154 (trembling, twitching, or feeling shaky; muscle tension, aches, or soreness; restlessness; easy
155 fatigability); *Autonomic Hyperactivity* (shortness of breath or smothering sensations;
156 palpitations or accelerated heart rate; sweating, or cold clammy hands; dry mouth; dizziness
157 or lightheadedness; nausea, diarrhea, or other abdominal distress; flushes or chills; frequent
158 urination; trouble swallowing or 'lump in throat'); *Vigilance and Scanning* (feeling keyed up
159 or on edge; exaggerated startle response; difficulty concentrating or 'mind going blank'
160 because of anxiety; trouble falling or staying asleep; irritability). These symptoms must not be
161 secondary to another psychiatric disorder or caused by some organic factor.
162

163 Anxiety associated with depression is responsive to alprazolam.
164

165 **Panic Disorder**

166 NIRAVAM™ is also indicated for the treatment of panic disorder, with or without
167 agoraphobia.
168

169 Studies supporting this claim were conducted in patients whose diagnoses corresponded
170 closely to the DSM-III-R/IV criteria for panic disorder (see CLINICAL STUDIES).
171

172 Panic disorder (DSM-IV) is characterized by recurrent unexpected panic attacks, ie, a discrete
173 period of intense fear or discomfort in which four (or more) of the following symptoms
174 develop abruptly and reach a peak within 10 minutes: (1) palpitations, pounding heart, or
175 accelerated heart rate; (2) sweating; (3) trembling or shaking; (4) sensations of shortness of
176 breath or smothering; (5) feeling of choking; (6) chest pain or discomfort; (7) nausea or
177 abdominal distress; (8) feeling dizzy, unsteady, lightheaded, or faint; (9) derealization
178 (feelings of unreality) or depersonalization (being detached from oneself); (10) fear of losing
179 control; (11) fear of dying; (12) paresthesias (numbness or tingling sensations); (13) chills or
180 hot flushes.
181

182 Demonstrations of the effectiveness of alprazolam by systematic clinical study are limited to
183 4 months duration for anxiety disorder and 4 to 10 weeks duration for panic disorder;
184 however, patients with panic disorder have been treated on an open basis for up to 8 months
185 without apparent loss of benefit. The physician should periodically reassess the usefulness of
186 the drug for the individual patient.
187

188 **CONTRAINDICATIONS**

189 NIRAVAM™ is contraindicated in patients with known sensitivity to this drug or other
190 benzodiazepines. NIRAVAM™ may be used in patients with open angle glaucoma who are
191 receiving appropriate therapy, but is contraindicated in patients with acute narrow angle
192 glaucoma.
193

194 NIRAVAM™ is contraindicated with ketoconazole and itraconazole, since these medications
195 significantly impair the oxidative metabolism mediated by cytochrome P450 3A (CYP3A)
196 (see CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS–Drug
197 Interactions).

198 **WARNINGS**

200 **Dependence and Withdrawal Reactions, Including Seizures**

201 Certain adverse clinical events, some life-threatening, are a direct consequence of physical
202 dependence to alprazolam. These include a spectrum of withdrawal symptoms; the most
203 important is seizure (see DRUG ABUSE AND DEPENDENCE). Even after relatively short-
204 term use at the doses recommended for the treatment of transient anxiety and anxiety disorder
205 (ie, 0.75 to 4.0 mg per day), there is some risk of dependence. Spontaneous reporting system
206 data suggest that the risk of dependence and its severity appear to be greater in patients
207 treated with doses greater than 4 mg/day and for long periods (more than 12 weeks).
208 However, in a controlled postmarketing discontinuation study of panic disorder patients, the
209 duration of treatment (3 months compared to 6 months) had no effect on the ability of patients
210 to taper to zero dose. In contrast, patients treated with doses of alprazolam greater than 4
211 mg/day had more difficulty tapering to zero dose than those treated with less than 4 mg/day.

212 The importance of dose and the risks of alprazolam as a treatment for panic disorder

213 Because the management of panic disorder often requires the use of average daily doses of
214 alprazolam above 4 mg, the risk of dependence among panic disorder patients may be higher
215 than that among those treated for less severe anxiety. Experience in randomized placebo-
216 controlled discontinuation studies of patients with panic disorder showed a high rate of
217 rebound and withdrawal symptoms in patients treated with alprazolam compared to placebo-
218 treated patients.

219
220
221 Relapse or return of illness was defined as a return of symptoms characteristic of panic
222 disorder (primarily panic attacks) to levels approximately equal to those seen at baseline
223 before active treatment was initiated. Rebound refers to a return of symptoms of panic
224 disorder to a level substantially greater in frequency, or more severe in intensity than seen at
225 baseline. Withdrawal symptoms were identified as those which were generally not
226 characteristic of panic disorder and which occurred for the first time more frequently during
227 discontinuation than at baseline.

228
229 In a controlled clinical trial in which 63 patients were randomized to alprazolam and where
230 withdrawal symptoms were specifically sought, the following were identified as symptoms of
231 withdrawal: heightened sensory perception, impaired concentration, dysosmia, clouded
232 sensorium, paresthesias, muscle cramps, muscle twitch, diarrhea, blurred vision, appetite
233 decrease, and weight loss. Other symptoms, such as anxiety and insomnia, were frequently
234 seen during discontinuation, but it could not be determined if they were due to return of
235 illness, rebound, or withdrawal.

236

237 In two controlled trials of 6 to 8 weeks duration where the ability of patients to discontinue
238 medication was measured, 71% - 93% of patients treated with alprazolam tapered completely
239 off therapy compared to 89% - 96% of placebo-treated patients. In a controlled postmarketing
240 discontinuation study of panic disorder patients, the duration of treatment (3 months
241 compared to 6 months) had no effect on the ability of patients to taper to zero dose.
242

243 Seizures attributable to alprazolam were seen after drug discontinuance or dose reduction in
244 8 of 1980 patients with panic disorder or in patients participating in clinical trials where doses
245 of alprazolam greater than 4 mg/day for over 3 months were permitted. Five of these cases
246 clearly occurred during abrupt dose reduction, or discontinuation from daily doses of 2 to
247 10 mg. Three cases occurred in situations where there was not a clear relationship to abrupt
248 dose reduction or discontinuation. In one instance, seizure occurred after discontinuation from
249 a single dose of 1 mg after tapering at a rate of 1 mg every 3 days from 6 mg daily. In two
250 other instances, the relationship to taper is indeterminate; in both of these cases the patients
251 had been receiving doses of 3 mg daily prior to seizure. The duration of use in the above 8
252 cases ranged from 4 to 22 weeks. There have been occasional voluntary reports of patients
253 developing seizures while apparently tapering gradually from alprazolam. The risk of seizure
254 seems to be greatest 24 - 72 hours after discontinuation (see DOSAGE AND
255 ADMINISTRATION for recommended tapering and discontinuation schedule).
256

257 **Status Epilepticus**

258 The medical event voluntary reporting system shows that withdrawal seizures have been
259 reported in association with the discontinuation of alprazolam. In most cases, only a single
260 seizure was reported; however, multiple seizures and status epilepticus were reported as well.
261

262 **Interdose Symptoms**

263 Early morning anxiety and emergence of anxiety symptoms between doses of alprazolam
264 have been reported in patients with panic disorder taking prescribed maintenance doses of
265 alprazolam. These symptoms may reflect the development of tolerance or a time interval
266 between doses which is longer than the duration of clinical action of the administered dose. In
267 either case, it is presumed that the prescribed dose is not sufficient to maintain plasma levels
268 above those needed to prevent relapse, rebound or withdrawal symptoms over the entire
269 course of the interdosing interval. In these situations, it is recommended that the same total
270 daily dose be given divided as more frequent administrations (see DOSAGE AND
271 ADMINISTRATION).
272

273 **Risk of Dose Reduction**

274 Withdrawal reactions may occur when dosage reduction occurs for any reason. This includes
275 purposeful tapering, but also inadvertent reduction of dose (eg, the patient forgets, the patient
276 is admitted to a hospital). Therefore, the dosage of NIRAVAM™ should be reduced or
277 discontinued gradually (see DOSAGE AND ADMINISTRATION).
278

279 **CNS Depression and Impaired Performance**

280 Because of its CNS depressant effects, patients receiving alprazolam should be cautioned
281 against engaging in hazardous occupations or activities requiring complete mental alertness
282 such as operating machinery or driving a motor vehicle. For the same reason, patients should
283 be cautioned about the simultaneous ingestion of alcohol and other CNS depressant drugs
284 during treatment with alprazolam.

285

286 **Risk of Fetal Harm**

287 Benzodiazepines can potentially cause fetal harm when administered to pregnant women. If
288 alprazolam is used during pregnancy, or if the patient becomes pregnant while taking this
289 drug, the patient should be apprised of the potential hazard to the fetus. Because of experience
290 with other members of the benzodiazepine class, alprazolam is assumed to be capable of
291 causing an increased risk of congenital abnormalities when administered to a pregnant woman
292 during the first trimester. Because use of these drugs is rarely a matter of urgency, their use
293 during the first trimester should almost always be avoided. The possibility that a woman of
294 childbearing potential may be pregnant at the time of institution of therapy should be
295 considered. Patients should be advised that if they become pregnant during therapy or intend
296 to become pregnant they should communicate with their physicians about the desirability of
297 discontinuing the drug.

298

299 **Alprazolam Interaction with Drugs that Inhibit Metabolism via Cytochrome P450 3A**

300 The initial step in alprazolam metabolism is hydroxylation catalyzed by cytochrome P450 3A
301 (CYP3A). Drugs that inhibit this metabolic pathway may have a profound effect on the
302 clearance of alprazolam. Consequently, alprazolam should be avoided in patients receiving
303 very potent inhibitors of CYP3A. With drugs inhibiting CYP3A to a lesser but still significant
304 degree, alprazolam should be used only with caution and consideration of appropriate dosage
305 reduction. For some drugs, an interaction with alprazolam has been quantified with clinical
306 data; for other drugs, interactions are predicted from *in vitro* data and/or experience with
307 similar drugs in the same pharmacologic class.

308

309 The following are examples of drugs known to inhibit the metabolism of alprazolam and/or
310 related benzodiazepines, presumably through inhibition of CYP3A.

311

312 Potent CYP3A Inhibitors

313 Azole antifungal agents— Ketoconazole and itraconazole are potent CYP3A inhibitors and
314 have been shown *in vivo* to increase plasma alprazolam concentrations 3.98 fold and
315 2.70 fold, respectively. The coadministration of alprazolam with these agents is not
316 recommended. Other azole-type antifungal agents should also be considered potent CYP3A
317 inhibitors and the coadministration of alprazolam with them is not recommended (see
318 CONTRAINDICATIONS).

319

320 Drugs demonstrated to be CYP3A inhibitors on the basis of clinical studies involving
321 alprazolam (caution and consideration of appropriate alprazolam dose reduction are
322 recommended during coadministration with the following drugs)
323

324 Nefazodone — Coadministration of nefazodone increased alprazolam concentration two-fold.
325

326 Fluvoxamine — Coadministration of fluvoxamine approximately doubled the maximum
327 plasma concentration of alprazolam, decreased clearance by 49%, increased half-life by 71%,
328 and decreased measured psychomotor performance.
329

330 Cimetidine — Coadministration of cimetidine increased the maximum plasma concentration
331 of alprazolam by 86%, decreased clearance by 42%, and increased half-life by 16%.
332

333 Other drugs possibly affecting alprazolam metabolism

334 Other drugs possibly affecting alprazolam metabolism by inhibition of CYP3A are discussed
335 in the PRECAUTIONS section (see PRECAUTIONS–Drug Interactions).
336

337 **PRECAUTIONS**

338 **General**

339 Suicide

340 As with other psychotropic medications, the usual precautions with respect to administration
341 of the drug and size of the prescription are indicated for severely depressed patients or those
342 in whom there is reason to expect concealed suicidal ideation or plans. Panic disorder has
343 been associated with primary and secondary major depressive disorders and increased reports
344 of suicide among untreated patients.
345

346 Mania

347 Episodes of hypomania and mania have been reported in association with the use of
348 alprazolam in patients with depression.
349

350 Uricosuric Effect

351 Alprazolam has a weak uricosuric effect. Although other medications with weak uricosuric
352 effect have been reported to cause acute renal failure, there have been no reported instances of
353 acute renal failure attributable to therapy with alprazolam.
354

355 Use in Patients with Concomitant Illness

356 It is recommended that the dosage be limited to the smallest effective dose to preclude the
357 development of ataxia or oversedation which may be a particular problem in elderly or
358 debilitated patients. (See DOSAGE AND ADMINISTRATION.) The usual precautions in
359 treating patients with impaired renal, hepatic or pulmonary function should be observed.
360 There have been rare reports of death in patients with severe pulmonary disease shortly after
361 the initiation of treatment with alprazolam. A decreased systemic alprazolam elimination rate
362 (eg, increased plasma half-life) has been observed in both alcoholic liver disease patients and
363 obese patients receiving alprazolam (see CLINICAL PHARMACOLOGY).
364

365 **Information for Patients**

366 For all users of NIRAVAM™

367 To assure safe and effective use of benzodiazepines, all patients prescribed NIRAVAM™
368 should be provided with the following guidance.

369

370 1. Do not remove NIRAVAM™ tablets from the bottle until just prior to dosing. With dry
371 hands, open the bottle, remove the tablet, and immediately place on the tongue to dissolve
372 and be swallowed with the saliva. The tablet may also be taken with water.

373

374 2. Discard any cotton that was included in the bottle and reseal the bottle tightly to prevent
375 introducing moisture that might cause the tablets to disintegrate.

376

377 3. If only one-half of a scored tablet is used for dosing, the unused portion of the tablet
378 should be discarded immediately because it may not remain stable.

379

380 4. Store away from moisture.

381

382 5. Inform your physician about any alcohol consumption and medicine you are taking now,
383 including medication you may buy without a prescription. Alcohol should generally not
384 be used during treatment with benzodiazepines.

385

386 6. Not recommended for use in pregnancy. Therefore, inform your physician if you are
387 pregnant, if you are planning to have a child, or if you become pregnant while you are
388 taking this medication.

389

390 7. Inform your physician if you are nursing.

391

392 8. Until you experience how this medication affects you, do not drive a car or operate
393 potentially dangerous machinery, etc.

394

395 9. Do not increase the dose even if you think the medication "does not work anymore"
396 without consulting your physician. Benzodiazepines, even when used as recommended,
397 may produce emotional and/or physical dependence.

398

399 10. Do not stop taking this medication abruptly or decrease the dose without consulting your
400 physician, since withdrawal symptoms can occur.

401

402 Additional advice for panic disorder patients

403 The use of alprazolam at doses greater than 4 mg/day, often necessary to treat panic disorder,
404 is accompanied by risks that you need to carefully consider. When used at doses greater than
405 4 mg/day, which may or may not be required for your treatment, alprazolam has the potential
406 to cause severe emotional and physical dependence in some patients and these patients may
407 find it exceedingly difficult to terminate treatment. In two controlled trials of 6 to 8 weeks
408 duration where the ability of patients to discontinue medication was measured, 7 to 29% of
409 patients treated with alprazolam did not completely taper off therapy. In a controlled
410 postmarketing discontinuation study of panic disorder patients, the patients treated with doses

411 of alprazolam greater than 4 mg/day had more difficulty tapering to zero dose than patients
412 treated with less than 4 mg/day. In all cases, it is important that your physician help you
413 discontinue this medication in a careful and safe manner to avoid overly extended use of
414 alprazolam.

415
416 In addition, the extended use at doses greater than 4 mg/day appears to increase the incidence
417 and severity of withdrawal reactions when alprazolam is discontinued. These are generally
418 minor but seizure can occur, especially if you reduce the dose too rapidly or discontinue the
419 medication abruptly. Seizure can be life-threatening.

420

421 **Laboratory Tests**

422 Laboratory tests are not ordinarily required in otherwise healthy patients. However, when
423 treatment is protracted, periodic blood counts, urinalysis, and blood chemistry analyses are
424 advisable in keeping with good medical practice.

425

426 **Drug Interactions**

427 Use with Other CNS Depressants

428 If NIRAVAM™ is to be combined with other psychotropic agents or anticonvulsant drugs,
429 careful consideration should be given to the pharmacology of the agents to be employed,
430 particularly with compounds which might potentiate the action of benzodiazepines. The
431 benzodiazepines, including alprazolam, produce additive CNS depressant effects when co-
432 administered with other psychotropic medications, anticonvulsants, antihistaminics, ethanol
433 and other drugs which themselves produce CNS depression.

434

435 Drugs Effecting Salivary Flow and Stomach pH

436 Because NIRAVAM™ disintegrates in the presence of saliva and the formulation requires an
437 acidic environment to dissolve, concomitant drugs or diseases that cause dry mouth or raise
438 stomach pH might slow disintegration or dissolution, resulting in slowed or decreased
439 absorption.

440

441 Use with Imipramine and Desipramine

442 The steady state plasma concentrations of imipramine and desipramine have been reported to
443 be increased an average of 31% and 20%, respectively, by the concomitant administration of
444 alprazolam in doses up to 4 mg/day. The clinical significance of these changes is unknown.

445

446 Drugs that inhibit alprazolam metabolism via cytochrome P450 3A

447 The initial step in alprazolam metabolism is hydroxylation catalyzed by cytochrome P450 3A
448 (CYP3A). Drugs which inhibit this metabolic pathway may have a profound effect on the
449 clearance of alprazolam (see CONTRAINDICATIONS and WARNINGS for additional drugs
450 of this type).

451

452 Drugs demonstrated to be CYP3A inhibitors of possible clinical significance on the basis of
453 clinical studies involving alprazolam (caution is recommended during coadministration with
454 alprazolam)

455

456 Fluoxetine — Coadministration of fluoxetine with alprazolam increased the maximum plasma
457 concentration of alprazolam by 46%, decreased clearance by 21%, increased half-life by 17%,
458 and decreased measured psychomotor performance.

459
460 Propoxyphene — Coadministration of propoxyphene decreased the maximum plasma
461 concentration of alprazolam by 6%, decreased clearance by 38%, and increased half-life by
462 58%.

463
464 Oral Contraceptives — Coadministration of oral contraceptives increased the maximum
465 plasma concentration of alprazolam by 18%, decreased clearance by 22%, and increased half-
466 life by 29%.

467
468 Drugs and other substances demonstrated to be CYP3A inhibitors on the basis of clinical
469 studies involving benzodiazepines metabolized similarly to alprazolam or on the basis of *in*
470 *vitro* studies with alprazolam or other benzodiazepines (caution is recommended during
471 coadministration with alprazolam)

472 Available data from clinical studies of benzodiazepines other than alprazolam suggest a
473 possible drug interaction with alprazolam for the following: diltiazem, isoniazid, macrolide
474 antibiotics such as erythromycin and clarithromycin, and grapefruit juice. Data from *in vitro*
475 studies of alprazolam suggest a possible drug interaction with alprazolam for the following:
476 sertraline and paroxetine. However, data from an *in vivo* drug interaction study involving a
477 single dose of alprazolam 1 mg and steady state doses of sertraline (50 to 150 mg/day) did not
478 reveal any clinically significant changes in the pharmacokinetics of alprazolam. Data from *in*
479 *vitro* studies of benzodiazepines other than alprazolam suggest a possible drug interaction for
480 the following: ergotamine, cyclosporine, amiodarone, nicardipine, and nifedipine. Caution is
481 recommended during the coadministration of any of these with alprazolam (see
482 WARNINGS).

483
484 Drugs demonstrated to be inducers of CYP3A

485 Carbamazepine can increase alprazolam metabolism and therefore can decrease plasma levels
486 of alprazolam.

487
488

489 **Drug/Laboratory Test Interactions**

490 Although interactions between benzodiazepines and commonly employed clinical laboratory
491 tests have occasionally been reported, there is no consistent pattern for a specific drug or
492 specific test.

493
494

495 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

496 No evidence of carcinogenic potential was observed during 2-year bioassay studies of
497 alprazolam in rats at doses up to 30 mg/kg/day (150 times the maximum recommended daily
498 human dose of 10 mg/day) and in mice at doses up to 10 mg/kg/day (50 times the maximum
499 recommended daily human dose).

500 Alprazolam was not mutagenic in the rat micronucleus test at doses up to 100 mg/kg, which is
501 500 times the maximum recommended daily human dose of 10 mg/day. Alprazolam also was
502 not mutagenic *in vitro* in the DNA Damage/Alkaline Elution Assay or the Ames Assay.

503

504 Alprazolam produced no impairment of fertility in rats at doses up to 5 mg/kg/day, which is
505 25 times the maximum recommended daily human dose of 10 mg/day.

506

507 **Pregnancy**

508 Teratogenic Effects: Pregnancy Category D: (See WARNINGS section).

509 Nonteratogenic Effects: It should be considered that the child born of a mother who is
510 receiving benzodiazepines may be at some risk for withdrawal symptoms from the drug
511 during the postnatal period. Also, neonatal flaccidity and respiratory problems have been
512 reported in children born of mothers who have been receiving benzodiazepines.

513

514 **Labor and Delivery**

515 NIRAVAM™ has no established use in labor or delivery.

516

517 **Nursing Mothers**

518 Benzodiazepines are known to be excreted in human milk. It should be assumed that
519 alprazolam is as well. Chronic administration of diazepam to nursing mothers has been
520 reported to cause their infants to become lethargic and to lose weight. As a general rule,
521 nursing should not be undertaken by mothers who must use NIRAVAM™.

522

523 **Pediatric Use**

524 Safety and effectiveness of NIRAVAM™ in individuals below 18 years of age have not been
525 established.

526

527 **Geriatric Use**

528 The elderly may be more sensitive to the effects of benzodiazepines. They exhibit higher
529 plasma alprazolam concentrations due to reduced clearance of the drug as compared with a
530 younger population receiving the same doses. The smallest effective dose of NIRAVAM™
531 should be used in the elderly to preclude the development of ataxia and oversedation (see
532 CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

533

534 **ADVERSE REACTIONS**

535 Side effects to alprazolam, if they occur, are generally observed at the beginning of therapy
536 and usually disappear upon continued medication. In the usual patient, the most frequent side
537 effects are likely to be an extension of the pharmacological activity of alprazolam, eg,
538 drowsiness or lightheadedness.

539

540 The data cited in the two tables below are estimates of untoward clinical event incidence
541 among patients who participated under the following clinical conditions: relatively short
542 duration (ie, four weeks) placebo-controlled clinical studies with dosages up to 4 mg/day of
543 alprazolam (for the management of anxiety disorders or for the short-term relief of the
544 symptoms of anxiety) and short-term (up to ten weeks) placebo-controlled clinical studies

545 with dosages up to 10 mg/day of alprazolam in patients with panic disorder, with or without
 546 agoraphobia.

547
 548 These data cannot be used to predict precisely the incidence of untoward events in the course
 549 of usual medical practice where patient characteristics, and other factors often differ from
 550 those in clinical trials. These figures cannot be compared with those obtained from other
 551 clinical studies involving related drug products and placebo as each group of drug trials are
 552 conducted under a different set of conditions.

553
 554 Comparison of the cited figures, however, can provide the prescriber with some basis for
 555 estimating the relative contributions of drug and non-drug factors to the untoward event
 556 incidence in the population studied. Even this use must be approached cautiously, as a drug
 557 may relieve a symptom in one patient but induce it in others. (For example, an anxiolytic drug
 558 may relieve dry mouth [a symptom of anxiety] in some subjects but induce it [an untoward
 559 event] in others.)

560
 561 Additionally, for anxiety disorders the cited figures can provide the prescriber with an
 562 indication as to the frequency with which physician intervention (eg, increased surveillance,
 563 decreased dosage or discontinuation of drug therapy) may be necessary because of the
 564 untoward clinical event.

565
 566 **Treatment-Emergent Adverse Events Reported in Placebo-Controlled Trials of Anxiety**
 567 **Disorders**

	ANXIETY DISORDERS		Incidence of Intervention Because of Symptom <u>ALPRAZOLAM</u>
	<u>ALPRAZOLAM</u>	<u>PLACEBO</u>	
Number of Patients	565	505	565
% of Patients Reporting:			
<u>Central Nervous System</u>			
Drowsiness	41.0	21.6	15.1
Lightheadedness	20.8	19.3	1.2
Depression	13.9	18.1	2.4
Headache	12.9	19.6	1.1
Confusion	9.9	10.0	0.9
Insomnia	8.9	18.4	1.3
Nervousness	4.1	10.3	1.1
Syncope	3.1	4.0	*
Dizziness	1.8	0.8	2.5
Akathisia	1.6	1.2	*
Tiredness/Sleepiness	*	*	1.8
<u>Gastrointestinal</u>			
Dry Mouth	14.7	13.3	0.7
Constipation	10.4	11.4	0.9
Diarrhea	10.1	10.3	1.2
Nausea/Vomiting	9.6	12.8	1.7
Increased Salivation	4.2	2.4	*
<u>Cardiovascular</u>			
Tachycardia/Palpitations	7.7	15.6	0.4
Hypotension	4.7	2.2	*
<u>Sensory</u>			

Blurred Vision	6.2	6.2	0.4
<u>Musculoskeletal</u>			
Rigidity	4.2	5.3	*
Tremor	4.0	8.8	0.4
<u>Cutaneous</u>			
Dermatitis/Allergy	3.8	3.1	0.6
<u>Other</u>			
Nasal Congestion	7.3	9.3	*
Weight Gain	2.7	2.7	*
Weight Loss	2.3	3.0	*

*None reported

†Events reported by 1% or more of alprazolam patients are included.

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In addition to the relatively common (ie, greater than 1%) untoward events enumerated in the table above, the following adverse events have been reported in association with the use of benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, transient amnesia or memory impairment, loss of coordination, fatigue, seizures, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

Treatment-Emergent Adverse Events Reported in Placebo-Controlled Trials of Panic Disorder

	PANIC DISORDER	
	Treatment-Emergent Symptom Incidence*	
	<u>ALPRAZOLAM</u>	<u>PLACEBO</u>
Number of Patients	1388	1231
% of Patients Reporting:		
<u>Central Nervous System</u>		
Drowsiness	76.8	42.7
Fatigue and Tiredness	48.6	42.3
Impaired Coordination	40.1	17.9
Irritability	33.1	30.1
Memory Impairment	33.1	22.1
Lightheadedness/Dizziness	29.8	36.9
Insomnia	29.4	41.8
Headache	29.2	35.6
Cognitive Disorder	28.8	20.5
Dysarthria	23.3	6.3
Anxiety	16.6	24.9
Abnormal Involuntary Movement	14.8	21.0
Decreased Libido	14.4	8.0
Depression	13.8	14.0
Confusional State	10.4	8.2
Muscular Twitching	7.9	11.8
Increased Libido	7.7	4.1
Change in Libido (Not Specified)	7.1	5.6
Weakness	7.1	8.4
Muscle Tone Disorders	6.3	7.5
Syncope	3.8	4.8
Akathisia	3.0	4.3
Agitation	2.9	2.6
Disinhibition	2.7	1.5
Paresthesia	2.4	3.2
Talkativeness	2.2	1.0
Vasomotor Disturbances	2.0	2.6
Derealization	1.9	1.2

Dream Abnormalities	1.8	1.5
Fear	1.4	1.0
Feeling Warm	1.3	0.5
<u>Gastrointestinal</u>		
Decreased Salivation	32.8	34.2
Constipation	26.2	15.4
Nausea/Vomiting	22.0	31.8
Diarrhea	20.6	22.8
Abdominal Distress	18.3	21.5
Increased Salivation	5.6	4.4
<u>Cardio-Respiratory</u>		
Nasal Congestion	17.4	16.5
Tachycardia	15.4	26.8
Chest Pain	10.6	18.1
Hyperventilation	9.7	14.5
Upper Respiratory Infection	4.3	3.7
<u>Sensory</u>		
Blurred Vision	21.0	21.4
Tinnitus	6.6	10.4
<u>Musculoskeletal</u>		
Muscular Cramps	2.4	2.4
Muscle Stiffness	2.2	3.3
<u>Cutaneous</u>		
Sweating	15.1	23.5
Rash	10.8	8.1
<u>Other</u>		
Increased Appetite	32.7	22.8
Decreased Appetite	27.8	24.1
Weight Gain	27.2	17.9
Weight Loss	22.6	16.5
Micturition Difficulties	12.2	8.6
Menstrual Disorders	10.4	8.7
Sexual Dysfunction	7.4	3.7
Edema	4.9	5.6
Incontinence	1.5	0.6
Infection	1.3	1.7

**Events reported by 1% or more of alprazolam patients are included.*

578

579 In addition to the relatively common (ie, greater than 1%) untoward events enumerated in the
580 table above, the following adverse events have been reported in association with the use of
581 alprazolam: seizures, hallucinations, depersonalization, taste alterations, diplopia, elevated
582 bilirubin, elevated hepatic enzymes, and jaundice.

583

584 Panic disorder has been associated with primary and secondary major depressive disorders
585 and increased reports of suicide among untreated patients (see PRECAUTIONS, General).

586

587 **Adverse Events Reported as Reasons for Discontinuation in Treatment of Panic** 588 **Disorder in Placebo-Controlled Trials**

589 In a larger database comprised of both controlled and uncontrolled studies in which
590 641 patients received alprazolam, discontinuation-emergent symptoms which occurred at a
591 rate of over 5% in patients treated with alprazolam and at a greater rate than the placebo-
592 treated group were as follows:

593

594

DISCONTINUATION-EMERGENT SYMPTOM INCIDENCE
**Percentage of 641 Alprazolam-Treated Panic Disorder
Patients Reporting Events**

<u>Body System/Event</u>			
Neurologic		Gastrointestinal	
Insomnia	29.5	Nausea/Vomiting	16.5
Lightheadedness	19.3	Diarrhea	13.6
Abnormal involuntary movement	17.3	Decreased salivation	10.6
Headache	17.0	Metabolic-Nutritional	
Muscular twitching	6.9	Weight loss	13.3
Impaired coordination	6.6	Decreased appetite	12.8
Muscle tone disorders	5.9	Dermatological	
Weakness	5.8	Sweating	14.4
Psychiatric		Cardiovascular	
Anxiety	19.2	Tachycardia	12.2
Fatigue and Tiredness	18.4	Special Senses	
Irritability	10.5	Blurred vision	10.0
Cognitive disorder	10.3		
Memory impairment	5.5		
Depression	5.1		
Confusional state	5.0		

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From the studies cited, it has not been determined whether these symptoms are clearly related to the dose and duration of therapy with alprazolam in patients with panic disorder. There have also been reports of withdrawal seizures upon rapid decrease or abrupt discontinuation of alprazolam (see WARNINGS).

To discontinue treatment in patients taking NIRAVAM™, the dosage should be reduced slowly in keeping with good medical practice. It is suggested that the daily dosage of NIRAVAM™ be decreased by no more than 0.5 mg every three days (see DOSAGE AND ADMINISTRATION). Some patients may benefit from an even slower dosage reduction. In a controlled postmarketing discontinuation study of panic disorder patients which compared this recommended taper schedule with a slower taper schedule, no difference was observed between the groups in the proportion of patients who tapered to zero dose; however, the slower schedule was associated with a reduction in symptoms associated with a withdrawal syndrome.

As with all benzodiazepines, paradoxical reactions such as stimulation, increased muscle spasticity, sleep disturbances, hallucinations and other adverse behavioral effects such as agitation, rage, irritability, and aggressive or hostile behavior have been reported rarely. In many of the spontaneous case reports of adverse behavioral effects, patients were receiving other CNS drugs concomitantly and/or were described as having underlying psychiatric conditions. Should any of the above events occur, alprazolam should be discontinued. Isolated published reports involving small numbers of patients have suggested that patients who have borderline personality disorder, a prior history of violent or aggressive behavior, or alcohol or substance abuse may be at risk for such events. Instances of irritability, hostility, and intrusive thoughts have been reported during discontinuation of alprazolam in patients with posttraumatic stress disorder.

624 **Post Introduction Reports:** Various adverse drug reactions have been reported in association
625 with the use of alprazolam since market introduction. The majority of these reactions were
626 reported through the medical event voluntary reporting system. Because of the spontaneous
627 nature of the reporting of medical events and the lack of controls, a causal relationship to the
628 use of alprazolam cannot be readily determined. Reported events include: liver enzyme
629 elevations, hepatitis, hepatic failure, Stevens-Johnson syndrome, hyperprolactinemia,
630 gynecomastia, and galactorrhea.

631

632 **DRUG ABUSE AND DEPENDENCE**

633 **Physical and Psychological Dependence**

634 Withdrawal symptoms similar in character to those noted with sedative/hypnotics and alcohol
635 have occurred following discontinuance of benzodiazepines, including alprazolam. The
636 symptoms can range from mild dysphoria and insomnia to a major syndrome that may include
637 abdominal and muscle cramps, vomiting, sweating, tremors and convulsions. Distinguishing
638 between withdrawal emergent signs and symptoms and the recurrence of illness is often
639 difficult in patients undergoing dose reduction. The long term strategy for treatment of these
640 phenomena will vary with their cause and the therapeutic goal. When necessary, immediate
641 management of withdrawal symptoms requires re-institution of treatment at doses of
642 alprazolam sufficient to suppress symptoms. There have been reports of failure of other
643 benzodiazepines to fully suppress these withdrawal symptoms. These failures have been
644 attributed to incomplete cross-tolerance but may also reflect the use of an inadequate dosing
645 regimen of the substituted benzodiazepine or the effects of concomitant medications.

646

647 While it is difficult to distinguish withdrawal and recurrence for certain patients, the time
648 course and the nature of the symptoms may be helpful. A withdrawal syndrome typically
649 includes the occurrence of new symptoms, tends to appear toward the end of taper or shortly
650 after discontinuation, and will decrease with time. In recurring panic disorder, symptoms
651 similar to those observed before treatment may recur either early or late, and they will persist.

652

653 While the severity and incidence of withdrawal phenomena appear to be related to dose and
654 duration of treatment, withdrawal symptoms, including seizures, have been reported after only
655 brief therapy with alprazolam at doses within the recommended range for the treatment of
656 anxiety (eg, 0.75 to 4 mg/day). Signs and symptoms of withdrawal are often more prominent
657 after rapid decrease of dosage or abrupt discontinuance. The risk of withdrawal seizures may
658 be increased at doses above 4 mg/day (see WARNINGS).

659

660 Patients, especially individuals with a history of seizures or epilepsy, should not be abruptly
661 discontinued from any CNS depressant agent, including alprazolam. It is recommended that
662 all patients on NIRAVAM™ who require a dosage reduction be gradually tapered under close
663 supervision (see WARNINGS and DOSAGE AND ADMINISTRATION).

664

665 Psychological dependence is a risk with all benzodiazepines, including NIRAVAM™. The
666 risk of psychological dependence may also be increased at doses greater than 4 mg/day and
667 with longer term use, and this risk is further increased in patients with a history of alcohol or
668 drug abuse. Some patients have experienced considerable difficulty in tapering and
669 discontinuing from alprazolam, especially those receiving higher doses for extended periods.
670 Addiction-prone individuals should be under careful surveillance when receiving
671 NIRAVAM™. As with all anxiolytics, repeat prescriptions should be limited to those who are
672 under medical supervision.

673

674 **Controlled Substance Class**

675 Alprazolam is a controlled substance under the Controlled Substance Act by the Drug
676 Enforcement Administration and NIRAVAM™ has been assigned to Schedule IV.

677

678 **OVERDOSAGE**

679 **Clinical Experience**

680 Manifestations of alprazolam overdose include somnolence, confusion, impaired
681 coordination, diminished reflexes and coma. Death has been reported in association with
682 overdoses of alprazolam by itself, as it has with other benzodiazepines. In addition, fatalities
683 have been reported in patients who have overdosed with a combination of a single
684 benzodiazepine, including alprazolam, and alcohol; alcohol levels seen in some of these
685 patients have been lower than those usually associated with alcohol-induced fatality.

686

687 The acute oral LD₅₀ in rats is 331 - 2171 mg/kg. Other experiments in animals have indicated
688 that cardiopulmonary collapse can occur following massive intravenous doses of alprazolam
689 (over 195 mg/kg; 975 times the maximum recommended daily human dose of 10 mg/day).

690 Animals could be resuscitated with positive mechanical ventilation and the intravenous
691 infusion of norepinephrine bitartrate.

692

693 Animal experiments have suggested that forced diuresis or hemodialysis are probably of little
694 value in treating overdose.

695

696 **General Treatment of Overdose**

697 Overdose reports with alprazolam are limited. As in all cases of drug overdose,
698 respiration, pulse rate, and blood pressure should be monitored. General supportive measures
699 should be employed, along with immediate gastric lavage. Intravenous fluids should be
700 administered and an adequate airway maintained. If hypotension occurs, it may be combated
701 by the use of vasopressors. Dialysis is of limited value. As with the management of
702 intentional overdosing with any drug, it should be borne in mind that multiple agents may
703 have been ingested.

704

705 Flumazenil, a specific benzodiazepine receptor antagonist, is indicated for the complete or
706 partial reversal of the sedative effects of benzodiazepines and may be used in situations when
707 an overdose with a benzodiazepine is known or suspected. Prior to the administration of
708 flumazenil, necessary measures should be instituted to secure airway, ventilation and
709 intravenous access. Flumazenil is intended as an adjunct to, not as a substitute for, proper
710 management of benzodiazepine overdose. Patients treated with flumazenil should be
711 monitored for re-sedation, respiratory depression, and other residual benzodiazepine effects
712 for an appropriate period after treatment. **The prescriber should be aware of a risk of**
713 **seizure in association with flumazenil treatment, particularly in long-term**
714 **benzodiazepine users and in cyclic antidepressant overdose.** The complete flumazenil
715 package insert including CONTRAINDICATIONS, WARNINGS and PRECAUTIONS
716 should be consulted prior to use.

717

718 **DOSAGE AND ADMINISTRATION**

719 Dosage should be individualized for maximum beneficial effect. While the usual daily
720 dosages given below will meet the needs of most patients, there will be some who require
721 doses greater than 4 mg/day. In such cases, dosage should be increased cautiously to avoid
722 adverse effects.

723

724 **Anxiety Disorders and Transient Symptoms of Anxiety**

725 Treatment for patients with anxiety should be initiated with a dose of 0.25 to 0.5 mg given
726 three times daily. The dose may be increased to achieve a maximum therapeutic effect, at
727 intervals of 3 to 4 days, to a maximum daily dose of 4 mg, given in divided doses. The lowest
728 possible effective dose should be employed and the need for continued treatment reassessed
729 frequently. The risk of dependence may increase with dose and duration of treatment.

730

731 In all patients, dosage should be reduced gradually when discontinuing therapy or when
732 decreasing the daily dosage. Although there are no systematically collected data to support a
733 specific discontinuation schedule, it is suggested that the daily dosage be decreased by no
734 more than 0.5 mg every 3 days. Some patients may require an even slower dosage reduction.

735

736 **Panic Disorder**

737 The successful treatment of many panic disorder patients has required the use of alprazolam at
738 doses greater than 4 mg daily. In controlled trials conducted to establish the efficacy of
739 alprazolam in panic disorder, doses in the range of 1 to 10 mg daily were used. The mean
740 dosage employed was approximately 5 to 6 mg daily. Among the approximately 1700 patients
741 participating in the panic disorder development program, about 300 received alprazolam in
742 dosages of greater than 7 mg/day, including approximately 100 patients who received
743 maximum dosages of greater than 9 mg/day. Occasional patients required as much as 10 mg a
744 day to achieve a successful response.

745

746 Dose Titration

747 Treatment may be initiated with a dose of 0.5 mg three times daily. Depending on the
748 response, the dose may be increased at intervals of 3 to 4 days in increments of no more than
749 1 mg per day. Slower titration to the dose levels greater than 4 mg/day may be advisable to
750 allow full expression of the pharmacodynamic effect of alprazolam. To lessen the possibility
751 of interdose symptoms, the times of administration should be distributed as evenly as possible
752 throughout the waking hours, that is, on a three or four times per day schedule.

753

754 Generally, therapy should be initiated at a low dose to minimize the risk of adverse responses
755 in patients especially sensitive to the drug. Dose should be advanced until an acceptable
756 therapeutic response (ie, a substantial reduction in or total elimination of panic attacks) is
757 achieved, intolerance occurs, or the maximum recommended dose is attained.

758

759 Dose Maintenance

760 For patients receiving doses greater than 4 mg/day, periodic reassessment and consideration
761 of dosage reduction is advised. In a controlled postmarketing dose-response study, patients
762 treated with doses of alprazolam greater than 4 mg/day for 3 months were able to taper to
763 50% of their total maintenance dose without apparent loss of clinical benefit. Because of the
764 danger of withdrawal, abrupt discontinuation of treatment should be avoided. (See
765 WARNINGS, PRECAUTIONS, DRUG ABUSE AND DEPENDENCE.)

766

767 The necessary duration of treatment for panic disorder patients responding to alprazolam is
768 unknown. After a period of extended freedom from attacks, a carefully supervised tapered
769 discontinuation may be attempted, but there is evidence that this may often be difficult to
770 accomplish without recurrence of symptoms and/or the manifestation of withdrawal
771 phenomena.

772

773 Dose Reduction

774 Because of the danger of withdrawal, abrupt discontinuation of treatment should be avoided
775 (see WARNINGS, PRECAUTIONS, DRUG ABUSE AND DEPENDENCE).

776

777 In all patients, dosage should be reduced gradually when discontinuing therapy or when
778 decreasing the daily dosage. Although there are no systematically collected data to support a
779 specific discontinuation schedule, it is suggested that the daily dosage be decreased by no
780 more than 0.5 mg every three days. Some patients may require an even slower dosage
781 reduction.

782

783 In any case, reduction of dose must be undertaken under close supervision and must be
784 gradual. If significant withdrawal symptoms develop, the previous dosing schedule should be
785 reinstated and, only after stabilization, should a less rapid schedule of discontinuation be
786 attempted. In a controlled postmarketing discontinuation study of panic disorder patients
787 which compared this recommended taper schedule with a slower taper schedule, no difference
788 was observed between the groups in the proportion of patients who tapered to zero dose;
789 however, the slower schedule was associated with a reduction in symptoms associated with a
790 withdrawal syndrome. It is suggested that the dose be reduced by no more than 0.5 mg every
791 3 days, with the understanding that some patients may benefit from an even more gradual
792 discontinuation. Some patients may prove resistant to all discontinuation regimens.
793

794 **Dosing in Special Populations**

795 In elderly patients, in patients with advanced liver disease or in patients with debilitating
796 disease, the usual starting dose is 0.25 mg, given two or three times daily. This may be
797 gradually increased if needed and tolerated. The elderly may be especially sensitive to the
798 effects of benzodiazepines. If side effects occur at the recommended starting dose, the dose
799 may be lowered.
800

801 **Instructions to be Given to Patients for Use/Handling NIRAVAM™ Tablets**

802 Just prior to administration, with dry hands, remove the tablet from the bottle. Immediately
803 place the NIRAVAM™ tablet on top of the tongue where it will disintegrate, and be
804 swallowed with saliva. Administration with liquid is not necessary.
805

806 If only one-half of a scored tablet is used for dosing, the unused portion of the tablet should
807 be discarded immediately because it may not remain stable.
808

809 Discard any cotton that was included in the bottle and reseal the bottle tightly to prevent
810 introducing moisture that might cause the tablets to disintegrate.
811

812 **HOW SUPPLIED**

813 NIRAVAM™ (alprazolam orally disintegrating tablets) 0.25 mg are yellow, round, orange-
814 flavored, scored and engraved “SP 321” on the unscored side and “0.25” on the scored side.
815 They are supplied as follows:
816

817 Bottles of 100 NDC 0091-3321-01
818

819 NIRAVAM™ (alprazolam orally disintegrating tablets) 0.5 mg are yellow, round, orange-
820 flavored, scored and engraved “SP 322” on the unscored side and “0.5” on the scored side.
821 They are supplied as follows:
822

823 Bottles of 100 NDC 0091-3322-01
824

825 NIRAVAM™ (alprazolam orally disintegrating tablets) 1 mg are white, round, orange-
826 flavored, scored and engraved “SP 323” on the unscored side and “1” on the scored side.
827 They are supplied as follows:
828

829 Bottles of 100 NDC 0091-3323-01

830

831 NIVARAM™ (alprazolam orally disintegrating tablets) 2 mg are white, round, orange-
832 flavored, scored and engraved “SP 324” on the unscored side and “2” on the scored side.
833 They are supplied as follows:

834

835 Bottles of 100 NDC 0091-3324-01

836

837 Store at 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° to 86°F)
838 [See USP Controlled Room Temperature]. Protect from moisture.

839

840 Dispense in a tight container as defined in the USP/NF.

841

842 ANIMAL STUDIES

843 When rats were treated with alprazolam at 3, 10, and 30 mg/kg/day (15 to 150 times the
844 maximum recommended human dose) orally for 2 years, a tendency for a dose related
845 increase in the number of cataracts was observed in females and a tendency for a dose related
846 increase in corneal vascularization was observed in males. These lesions did not appear until
847 after 11 months of treatment.

848

Manufactured for:

SCHWARZ

P H A R M A

849

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Milwaukee, WI 53201, USA

851

852

By: CIMA LABS INC.®

853

Eden Prairie, MN 55344, USA

854

855 NIVARAM™ uses CIMA® U.S. Patent Nos. 6,024,981 and 6,221,392.

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858 PC4714

859 Rev. 11/03

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