

**ALPRAZOLAM - alprazolam tablet, extended release**  
**Aurobindo Pharma Limited**

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**Alprazolam Extended-Release Tablets USP CIV**  
**Rx only**

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

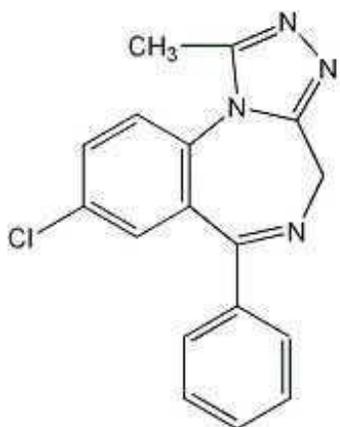
- **Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing of these drugs for patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients for signs and symptoms of respiratory depression and sedation (see WARNINGS and PRECAUTIONS).**
- **The use of benzodiazepines, including alprazolam extended-release tablets, exposes users to risks of abuse, misuse, and addiction, which can lead to overdose or death. Abuse and misuse of benzodiazepines commonly involve concomitant use of other medications, alcohol, and/or illicit substances, which is associated with an increased frequency of serious adverse outcomes. Before prescribing alprazolam extended-release tablets and throughout treatment, assess each patient's risk for abuse, misuse, and addiction (see WARNINGS).**
- **The continued use of benzodiazepines, including alprazolam extended-release tablets, may lead to clinically significant physical dependence. The risks of dependence and withdrawal increase with longer treatment duration and, higher daily dose. Abrupt discontinuation or rapid dosage reduction of alprazolam extended-release tablets after continued use may precipitate acute withdrawal reactions, which can be life-threatening. To reduce the risk of withdrawal reactions, use a gradual taper to discontinue alprazolam extended-release tablets or reduce the dosage (see DOSAGE AND ADMINISTRATION and WARNINGS).**

**DESCRIPTION**

Alprazolam extended-release tablets USP contain alprazolam which is a triazolo analog of the 1,4 benzodiazepine class of central nervous system-active compounds.

The chemical name of alprazolam is 8-chloro-1-methyl-6-phenyl-4*H*-s-triazolo [4,3- $\alpha$ ] [1,4] benzodiazepine. The molecular formula is C<sub>17</sub>H<sub>13</sub>ClN<sub>4</sub> which corresponds to a molecular weight of 308.76.

The structural formula is represented below:



Alprazolam USP is a white to off-white, crystalline powder, which is soluble in methanol or ethanol but which has no appreciable solubility in water at physiological pH.

Each alprazolam extended-release tablet USP, for oral administration, contains 0.5 mg, 1 mg, 2 mg, or 3 mg of alprazolam. The inactive ingredients are colloidal silicon dioxide, hypromellose, lactose monohydrate, and magnesium stearate. In addition, the 1 mg and 3 mg tablets contain D&C Yellow No. 10 aluminum lake and the 2 mg and 3 mg tablets contain FD&C Blue No. 2 lake.

Meets USP Dissolution Test 4.

## **CLINICAL PHARMACOLOGY**

### **Pharmacodynamics**

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

### **Pharmacokinetics**

#### ***Absorption***

Following oral administration of alprazolam (immediate-release) tablets, alprazolam is readily absorbed. Peak concentrations in the plasma occur in one to two hours following administration. Plasma levels are proportional to the dose given; over the dose range of 0.5 to 3 mg, peak levels of 8 to 37 ng/mL were observed. Using a specific assay methodology, the mean plasma elimination half-life of alprazolam has been found to be about 11.2 hours (range: 6.3 to 26.9 hours) in healthy adults.

The mean absolute bioavailability of alprazolam from alprazolam extended-release tablets is approximately 90%, and the relative bioavailability compared to alprazolam tablets is 100%. The bioavailability and pharmacokinetics of alprazolam following administration of alprazolam extended-release tablets are similar to that for alprazolam tablets, with the exception of a slower rate of absorption. The slower absorption rate results in a relatively constant concentration that is maintained between 5 and 11 hours after the dosing. The pharmacokinetics of alprazolam and two of its major active metabolites (4-hydroxyalprazolam and  $\alpha$ -hydroxyalprazolam) are linear, and concentrations are proportional up to the recommended maximum daily dose of 10 mg given once daily. Multiple dose studies indicate that the metabolism and elimination of alprazolam are similar for the immediate-release and the extended-release products.

Food has a significant influence on the bioavailability of alprazolam extended-release tablets. A high-fat meal given up to 2 hours before dosing with alprazolam extended-release tablets increased the mean  $C_{\max}$  by about 25%. The effect of this meal on  $T_{\max}$  depended on the timing of the meal, with a reduction in  $T_{\max}$  by about 1/3 for subjects eating immediately before dosing and an increase in  $T_{\max}$  by about 1/3 for subjects eating 1 hour or more after dosing. The extent of exposure (AUC) and elimination half-life ( $t_{1/2}$ ) were not affected by eating.

There were significant differences in absorption rate for the alprazolam extended-release tablet, depending on the time of day administered, with the  $C_{\max}$  increased by 30% and the  $T_{\max}$  decreased by an hour following dosing at night, compared to morning dosing.

### ***Distribution***

The apparent volume of distribution of alprazolam is similar for alprazolam extended-release tablets and alprazolam tablets. *In vitro*, alprazolam is bound (80%) to human serum protein. Serum albumin accounts for the majority of the binding.

### ***Metabolism***

Alprazolam is extensively metabolized in humans, primarily by cytochrome P450 3A4 (CYP3A4), to two major metabolites in the plasma: 4-hydroxyalprazolam and  $\alpha$ -hydroxyalprazolam. A benzophenone derived from alprazolam is also found in humans. Their half-lives appear to be similar to that of alprazolam. The pharmacokinetic parameters at steady-state for the two hydroxylated metabolites of alprazolam (4-hydroxyalprazolam and  $\alpha$ -hydroxyalprazolam) were similar for alprazolam and alprazolam extended-release tablets, indicating that the metabolism of alprazolam is not affected by absorption rate. The plasma concentrations of 4-hydroxyalprazolam and  $\alpha$ -hydroxyalprazolam relative to unchanged alprazolam concentration after both alprazolam extended-release tablets and alprazolam tablets were always less than 10% and 4%, respectively. The reported relative potencies in benzodiazepine receptor binding experiments and in animal models of induced seizure inhibition are 0.2 and 0.66, respectively, for 4-hydroxyalprazolam and  $\alpha$ -hydroxyalprazolam. Such low concentrations and the lesser potencies of 4-hydroxyalprazolam and  $\alpha$ -hydroxyalprazolam suggest that they are unlikely to contribute much to the pharmacological effects of alprazolam. The benzophenone metabolite is essentially inactive.

## **Elimination**

Alprazolam and its metabolites are excreted primarily in the urine. The mean plasma elimination half-life of alprazolam following administration of alprazolam extended-release tablet ranges from 10.7 to 15.8 hours in healthy adults.

## **Special Populations**

While pharmacokinetic studies have not been performed in special populations with alprazolam extended-release tablets, the factors (such as age, gender, hepatic or renal impairment) that would affect the pharmacokinetics of alprazolam after the administration of alprazolam tablets would not be expected to be different with the administration of alprazolam extended-release tablets.

Changes in the absorption, distribution, metabolism, and excretion of benzodiazepines have been reported in a variety of disease states including alcoholism, impaired hepatic function, and impaired renal function. Changes have also been demonstrated in geriatric patients. A mean half-life of alprazolam of 16.3 hours has been observed in healthy elderly subjects (range: 9 to 26.9 hours, n=16) compared to 11 hours (range: 6.3 to 15.8 hours, n=16) in healthy adult subjects. In patients with alcoholic liver disease the half-life of alprazolam ranged between 5.8 and 65.3 hours (mean: 19.7 hours, n=17) as compared to between 6.3 and 26.9 hours (mean=11.4 hours, n=17) in healthy subjects. In an obese group of subjects the half-life of alprazolam ranged between 9.9 and 40.4 hours (mean=21.8 hours, n=12) as compared to between 6.3 and 15.8 hours (mean=10.6 hours, n=12) in healthy subjects.

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

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

Pediatrics — The pharmacokinetics of alprazolam after administration of the alprazolam extended-release tablet in pediatric patients have not been studied.

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

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

## **Drug-Drug Interactions**

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

Compounds that are potent inhibitors of CYP3A would be expected to increase plasma alprazolam concentrations. Drug products that have been studied *in vivo*, along with their effect on increasing alprazolam AUC, are as follows: ketoconazole, 3.98 fold;

itraconazole, 2.7 fold; nefazodone, 1.98 fold; fluvoxamine, 1.96 fold; and erythromycin, 1.61 fold (see **CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS - Drug Interactions**).

CYP3A inducers would be expected to decrease alprazolam concentrations and this has been observed *in vivo*. The oral clearance of alprazolam (given in a 0.8 mg single dose) was increased from  $0.9 \pm 0.21$  mL/min/kg to  $2.13 \pm 0.54$  mL/min/kg and the elimination  $t_{1/2}$  was shortened (from  $17.1 \pm 4.9$  to  $7.7 \pm 1.7$  h) following administration of 300 mg/day carbamazepine for 10 days (see **PRECAUTIONS-Drug Interactions**). However, the carbamazepine dose used in this study was fairly low compared to the recommended doses (1000 to 1200 mg/day); the effect at usual carbamazepine doses is unknown.

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

### **CLINICAL EFFICACY TRIALS**

The efficacy of alprazolam extended-release tablets in the treatment of panic disorder was established in two 6-week, placebo-controlled studies of alprazolam extended-release tablets in patients with panic disorder.

In two 6-week, flexible-dose, placebo-controlled studies in patients meeting DSM-III criteria for panic disorder, patients were treated with alprazolam extended-release tablets in a dose range of 1 to 10 mg/day, on a once-a-day basis. The effectiveness of alprazolam extended-release tablets was assessed on the basis of changes in various measures of panic attack frequency, on various measures of the Clinical Global Impression, and on the Overall Phobia Scale. In all, there were seven primary efficacy measures in these studies, and alprazolam extended-release tablets was superior to placebo on all seven outcomes in both studies. The mean dose of alprazolam extended-release tablets at the last treatment visit was 4.2 mg/day in the first study and 4.6 mg/day in the second.

In addition, there were two 8-week, fixed-dose, placebo-controlled studies of alprazolam extended-release tablets in patients with panic disorder, involving fixed alprazolam extended-release tablets doses of 4 and 6 mg/day, on a once-a-day basis, that did not show a benefit for either dose of alprazolam extended-release tablets.

The longer-term efficacy of alprazolam extended-release tablets in panic disorder has not been systematically evaluated.

Analyses of the relationship between treatment outcome and gender did not suggest any differential responsiveness on the basis of gender.

### **INDICATIONS AND USAGE**

Alprazolam extended-release tablets are indicated for the treatment of panic disorder, with or without agoraphobia.

This claim is supported on the basis of two positive studies with alprazolam extended-release tablets conducted in patients whose diagnoses corresponded closely to the DSM-III-R/IV criteria for panic disorder (see **CLINICAL EFFICACY TRIALS**).

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

The longer-term efficacy of alprazolam extended-release tablets has not been systematically evaluated. Thus, the physician who elects to use this drug for periods longer than 8 weeks should periodically reassess the usefulness of the drug for the individual patient.

## **CONTRAINDICATIONS**

Alprazolam extended-release tablets are contraindicated in patients with known sensitivity to this drug or other benzodiazepines.

Alprazolam extended-release tablets are contraindicated with ketoconazole and itraconazole, since these medications significantly impair the oxidative metabolism mediated by cytochrome P450 3A (CYP3A) (see **CLINICAL PHARMACOLOGY, WARNINGS** and **PRECAUTIONS - Drug Interactions**).

## **WARNINGS**

### **Risks from Concomitant Use with Opioids**

Concomitant use of benzodiazepines, including alprazolam extended-release tablets, and opioids may result in profound sedation, respiratory depression, coma, and death. Because of these risks, reserve concomitant prescribing of these drugs in patients for whom alternative treatment options are inadequate.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioids alone. If a decision is made to prescribe alprazolam extended-release tablets concomitantly with opioids, prescribe the lowest effective dosages and minimum durations of concomitant use, and follow patients closely for signs and symptoms of

respiratory depression and sedation. In patients already receiving an opioid analgesic, prescribe a lower initial dose of alprazolam extended-release tablets than indicated in the absence of an opioid and titrate based on clinical response. If an opioid is initiated in a patient already taking alprazolam extended-release tablets, prescribe a lower initial dose of the opioid and titrate based upon clinical response.

Advise both patients and caregivers about the risks of respiratory depression and sedation when alprazolam extended-release tablets are used with opioids. Advise patients not to drive or operate heavy machinery until the effects of concomitant use with the opioid have been determined (see **PRECAUTIONS - Drug Interactions**).

### **Abuse, Misuse, and Addiction**

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

Before prescribing alprazolam extended-release tablets and throughout treatment, assess each patient's risk for abuse, misuse, and addiction (e.g., using a standardized screening tool). Use of alprazolam extended-release tablets, particularly in patients at elevated risk, necessitates counseling about the risks and proper use of alprazolam extended-release tablets along with monitoring for signs and symptoms of abuse, misuse, and addiction. Prescribe the lowest effective dosage; avoid or minimize concomitant use of CNS depressants and other substances associated with abuse, misuse, and addiction (e.g., opioid analgesics, stimulants); and advise patients on the proper disposal of unused drug. If a substance use disorder is suspected, evaluate the patient and institute (or refer them for) early treatment, as appropriate.

### **Dependence and Withdrawal Reactions**

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

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

#### **Acute Withdrawal Reactions**

The continued use of benzodiazepines, including alprazolam extended-release tablets, may lead to clinically significant physical dependence. Abrupt discontinuation or rapid dosage reduction of alprazolam extended-release tablets after continued use, or

administration of flumazenil (a benzodiazepine antagonist) may precipitate acute withdrawal reactions, which can be life-threatening (e.g., seizures) (see **DRUG ABUSE AND DEPENDENCE - Dependence**).

### Protracted Withdrawal Syndrome

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

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

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

The rate of relapse, rebound, and withdrawal in patients with panic disorder who received alprazolam extended-release tablets has not been systematically studied. Experience in randomized placebo-controlled discontinuation studies of patients with panic disorder who received alprazolam tablets showed a high rate of rebound and withdrawal symptoms compared to placebo treated patients.

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

In two controlled trials of 6 to 8 weeks duration where the ability of patients to discontinue medication was measured, 71% to 93% of patients treated with alprazolam tablets tapered completely off therapy compared to 89% to 96% of placebo treated patients. In a controlled postmarketing discontinuation study of panic disorder patients treated with alprazolam tablets, the duration of treatment (3 months compared to 6

months) had no effect on the ability of patients to taper to zero dose.

Seizures were reported for three patients in panic disorder clinical trials with alprazolam extended-release tablets. In two cases, the patients had completed 6 weeks of treatment with alprazolam extended-release tablets 6 mg/day before experiencing a single seizure. In one case, the patient abruptly discontinued alprazolam extended-release tablets, and in both cases, alcohol intake was implicated. The third case involved multiple seizures after the patient completed treatment with alprazolam extended-release tablets 4 mg/day and missed taking the medication on the first day of taper. All three patients recovered without sequelae.

Seizures have also been observed in association with dose reduction or discontinuation of alprazolam tablets, the immediate release form of alprazolam. Seizures attributable to alprazolam were seen after drug discontinuance or dose reduction in 8 of 1980 patients with panic disorder or in patients participating in clinical trials where doses of alprazolam greater than 4 mg/day for over 3 months were permitted. Five of these cases clearly occurred during abrupt dose reduction, or discontinuation from daily doses of 2 to 10 mg. Three cases occurred in situations where there was not a clear relationship to abrupt dose reduction or discontinuation. In one instance, seizure occurred after discontinuation from a single dose of 1 mg after tapering at a rate of 1 mg every three days from 6 mg daily. In two other instances, the relationship to taper is indeterminate; in both of these cases the patients had been receiving doses of 3 mg daily prior to seizure. The duration of use in the above 8 cases ranged from 4 to 22 weeks. There have been occasional voluntary reports of patients developing seizures while apparently tapering gradually from alprazolam. The risk of seizure seems to be greatest 24 to 72 hours after discontinuation (see **DOSAGE AND ADMINISTRATION - Discontinuation or Dosage Reduction of Alprazolam Extended-Release Tablets**).

### **Status Epilepticus**

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

### **Interdose Symptoms**

Early morning anxiety and emergence of anxiety symptoms between doses of alprazolam tablets have been reported in patients with panic disorder taking prescribed maintenance doses. These symptoms may reflect the development of tolerance or a time interval between doses which is longer than the duration of clinical action of the administered dose. In either case, it is presumed that the prescribed dose is not sufficient to maintain plasma levels above those needed to prevent relapse, rebound, or withdrawal symptoms over the entire course of the interdosing interval.

### **CNS Depression and Impaired Performance**

Because of its CNS depressant effects, patients receiving alprazolam extended-release tablets should be cautioned against engaging in hazardous occupations or activities requiring complete mental alertness such as operating machinery or driving a motor

vehicle. For the same reason, patients should be cautioned about the simultaneous ingestion of alcohol and other CNS depressant drugs during treatment with alprazolam extended-release tablets.

### **Risk of Fetal Harm**

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

### **Alprazolam Interaction With Drugs That Inhibit Metabolism Via Cytochrome P450 3A**

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

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

#### ***Potent CYP3A Inhibitors***

Azole antifungal agents — Ketoconazole and itraconazole are potent CYP3A inhibitors and have been shown *in vivo* to increase plasma alprazolam concentrations 3.98 fold and 2.7 fold, respectively. The coadministration of alprazolam with these agents is not recommended. Other azole-type antifungal agents should also be considered potent CYP3A inhibitors and the coadministration of alprazolam with them is not recommended (see **CONTRAINDICATIONS**).

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

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

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

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

### ***Other Drugs Possibly Affecting Alprazolam Metabolism***

Other drugs possibly affecting alprazolam metabolism by inhibition of CYP3A are discussed in the **PRECAUTIONS** section (see **PRECAUTIONS - Drug Interactions**).

## **PRECAUTIONS**

### **General**

#### ***Suicide***

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

#### ***Mania***

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

#### ***Uricosuric Effect***

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

#### ***Use in Patients with Concomitant Illness***

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

### **Information for Patients**

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

### Risks from Concomitant Use with Opioids

Advise both patients and caregivers about the risks of potentially fatal respiratory depression and sedation when alprazolam extended-release tablets are used with opioids and not to use such drugs concomitantly unless supervised by a health care provider. Advise patients not to drive or operate heavy machinery until the effects of concomitant use with the opioid have been determined (see **PRECAUTIONS** – Drug Interactions).

### Abuse, Misuse, and Addiction

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

### Withdrawal Reactions

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

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

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

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

## **Laboratory Tests**

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

## **Drug Interactions**

### ***Use with Opioids***

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

### ***Use with Other CNS Depressants***

If alprazolam extended-release tablets are to be combined with other psychotropic agents or anticonvulsant drugs, careful consideration should be given to the pharmacology of the agents to be employed, particularly with compounds which might potentiate the action of benzodiazepines. The benzodiazepines, including alprazolam, produce additive CNS depressant effects when coadministered with other psychotropic medications, anticonvulsants, antihistaminics, ethanol and other drugs which themselves produce CNS depression.

### ***Use with Imipramine and Desipramine***

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

### ***Drugs that inhibit alprazolam metabolism via cytochrome P450 3A***

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

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

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

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

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

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

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

***Drugs demonstrated to be inducers of CYP3A***

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

**Drug/Laboratory Test Interactions**

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

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

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

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

## **Pregnancy**

### ***Teratogenic Effects***

(see **WARNINGS** section).

### ***Nonteratogenic Effects***

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

## **Labor and Delivery**

Alprazolam has no established use in labor or delivery.

## **Nursing Mothers**

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

## **Pediatric Use**

Safety and effectiveness of alprazolam in individuals below 18 years of age have not been established.

## **Geriatric Use**

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

## **ADVERSE REACTIONS**

The information included in the subsection on Adverse Events Observed in Short-Term, Placebo-Controlled Trials with alprazolam extended-release tablets is based on pooled data of five 6- and 8-week placebo-controlled clinical studies in panic disorder.

Adverse event reports were elicited either by general inquiry or by checklist, and were recorded by clinical investigators using terminology of their own choosing. The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment emergent if it occurred for the first time or worsened during therapy following baseline evaluation. In the tables and tabulations that follow, standard MedDRA terminology (version 4.0) was used to classify reported adverse events.

### **Adverse Events Observed in Short-Term, Placebo-Controlled Trials of Alprazolam Extended-Release Tablets**

#### ***Adverse Events Reported as Reasons for Discontinuation of Treatment in Placebo-Controlled Trials***

Approximately 17% of the 531 patients who received alprazolam extended-release tablets in placebo-controlled clinical trials for panic disorder had at least one adverse event that led to discontinuation compared to 8% of 349 placebo-treated patients. The most common events leading to discontinuation and considered to be drug-related (i.e., leading to discontinuation in at least 1% of the patients treated with alprazolam extended-release tablets at a rate at least twice that of placebo) are shown in the following table.

#### **Common Adverse Events Leading to Discontinuation of Treatment in Placebo-Controlled Trials**

<b>System Organ Class/ Adverse Event</b>	<b>Percentage of Patients Discontinuing Due to Adverse Events</b>	
	<b>Alprazolam Extended-Release Tablets (n=531)</b>	<b>Placebo (n=349)</b>
<b>Nervous system disorders</b>	7.5	0.6
Sedation	3.2	0.3
Somnolence	2.1	0
Dysarthria	1.9	0.3
Coordination abnormal	1.5	0.3
Memory impairment		
<b>General disorders/administration site conditions</b>		
Fatigue	1.7	0.6
<b>Psychiatric disorders</b>		
Depression	2.5	1.2

**Adverse Events Occurring at an Incidence of 1% or More Among Patients Treated with Alprazolam Extended-Release Tablets**

The prescriber should be aware that adverse event incidence cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with event incidence obtained from other clinical investigations involving different treatments, uses, and investigators. The cited values, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the adverse event incidence rate in the population studied.

The following table shows the incidence of treatment-emergent adverse events that occurred during 6- to 8-week placebo-controlled trials in 1% or more of patients treated with alprazolam extended-release tablets where the incidence in patients treated with alprazolam extended-release tablets was greater than the incidence in placebo-treated patients. The most commonly observed adverse events in panic disorder patients treated with alprazolam extended-release tablets (incidence of 5% or greater and at least twice the incidence in placebo patients) were: sedation, somnolence, memory impairment, dysarthria, coordination abnormal, ataxia, libido decreased (see table).

**Treatment-Emergent Adverse Events: Incidence in Short-Term, Placebo-Controlled Clinical Trials with Alprazolam Extended-Release Tablets**

System Organ Class/Adverse Event	Percentage of Patients Reporting Adverse Event	
	Alprazolam Extended-Release Tablets (n=531)	Placebo (n=349)
<b>Nervous system disorders</b>		
Sedation		
Somnolence	45.2	22.6
Memory impairment	23	6
Dysarthria	15.4	6.9
Coordination abnormal	10.9	2.6
Mental impairment	9.4	0.9
Ataxia	7.2	5.7
Disturbance in attention	7.2	3.2
Balance impaired	3.2	0.6
Paresthesia	3.2	0.6
Dyskinesia	2.4	1.7
Hypoesthesia	1.7	1.4
Hypersomnia	1.3	0.3
	1.3	0
<b>General disorders/administration site conditions</b>		

Fatigue	13.9	9.2
Lethargy	1.7	0.6
<b>Infections and infestations</b>		
Influenza		
Upper respiratory tract infections	2.4	2.3
	1.9	1.7
<b>Psychiatric disorders</b>		
Depression		
Libido decreased	12.1	9.2
Disorientation	6	2.3
Confusion	1.5	0
Depressed mood	1.5	0.9
Anxiety	1.3	0.3
	1.1	0.6
<b>Metabolism and nutrition disorders</b>		
Appetite decreased	7.3	7.2
Appetite increased	7	6
Anorexia	1.5	0
<b>Gastrointestinal disorders</b>		
Dry mouth		
Constipation	10.2	9.7
Nausea	8.1	4.3
Pharyngolaryngeal pain	6	3.2
	3.2	2.6
<b>Investigations</b>		
Weight increased		
Weight decreased	5.1	4.3
	4.3	3.7
<b>Injury, poisoning, and procedural complications</b>		
Road traffic accident	1.5	0
<b>Reproductive system and breast disorders</b>		
Dysmenorrhea	3.6	2.9
Sexual dysfunction	2.4	1.1
Premenstrual syndrome	1.7	0.6
<b>Musculoskeletal and connective tissue disorders</b>		
Arthralgia	2.4	0.6
Myalgia	1.5	1.1
Pain in limb	1.1	0.3
<b>Vascular disorders</b>		
Hot flushes		
	1.5	1.4
<b>Respiratory, thoracic, and mediastinal disorders</b>		
Dyspnea	1.5	0.3
Rhinitis allergic	1.1	0.6
<b>Skin and subcutaneous tissue</b>		

<b>disorders</b> Pruritus	1.1	0.9
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### **Other Adverse Events Observed During the Premarketing Evaluation of Alprazolam Extended-Release Tablets**

Following is a list of MedDRA terms that reflect treatment-emergent adverse events reported by 531 patients with panic disorder treated with alprazolam extended-release tablets. All potentially important reported events are included except those already listed in the above table or elsewhere in labeling, those events for which a drug cause was remote, those event terms that were so general as to be uninformative, and those events that occurred at rates similar to background rates in the general population. It is important to emphasize that, although the events reported occurred during treatment with alprazolam extended-release tablets, they were not necessarily caused by the drug. Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on 1 or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in less than 1/100 patients but at least 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

**Cardiac disorders:** *Frequent:* palpitation; *Infrequent:* sinus tachycardia

**Ear and Labyrinth disorders:** *Frequent:* Vertigo; *Infrequent:* tinnitus, ear pain

**Eye disorders:** *Frequent:* blurred vision; *Infrequent:* mydriasis, photophobia

**Gastrointestinal disorders:** *Frequent:* diarrhea, vomiting, dyspepsia, abdominal pain; *Infrequent:* dysphagia, salivary hypersecretion

**General disorders and administration site conditions:** *Frequent:* malaise, weakness, chest pains; *Infrequent:* fall, pyrexia, thirst, feeling hot and cold, edema, feeling jittery, sluggishness, asthenia, feeling drunk, chest tightness, increased energy, feeling of relaxation, hangover, loss of control of legs, rigors

**Musculoskeletal and connective tissue disorders:** *Frequent:* back pain, muscle cramps, muscle twitching

**Nervous system disorders:** *Frequent:* headache, dizziness, tremor; *Infrequent:* amnesia, clumsiness, syncope, hypotonia, seizures, depressed level of consciousness, sleep apnea syndrome, sleep talking, stupor

**Psychiatric system disorders:** *Frequent:* irritability, insomnia, nervousness, derealization, libido increased, restlessness, agitation, depersonalization, nightmare; *Infrequent:* abnormal dreams, apathy, aggression, anger, bradyphrenia, euphoric mood, logorrhea, mood swings, dysphonia, hallucination, homicidal ideation, mania, hypomania, impulse control, psychomotor retardation, suicidal ideation

**Renal and urinary disorders:** *Frequent:* difficulty in micturition; *Infrequent:* urinary

frequency, urinary incontinence

**Respiratory, thoracic, and mediastinal disorders:** *Frequent:* nasal congestion, hyperventilation; *Infrequent:* choking sensation, epistaxis, rhinorrhea

**Skin and subcutaneous tissue disorders:** *Frequent:* sweating increased; *Infrequent:* clamminess, rash, urticaria

**Vascular disorders:** *Infrequent:* hypotension

The categories of adverse events reported in the clinical development program for alprazolam tablets in the treatment of panic disorder differ somewhat from those reported for alprazolam extended-release tablets because the clinical trials with alprazolam tablets and alprazolam extended-release tablets used different standard medical nomenclature for reporting the adverse events. Nevertheless, the types of adverse events reported in the clinical trials with alprazolam tablets were generally the same as those reported in the clinical trials with alprazolam extended-release tablets.

**Discontinuation-Emergent Adverse Events Occurring at an Incidence of 5% or More Among Patients Treated with Alprazolam Extended-Release Tablets**

The following table shows the incidence of discontinuation-emergent adverse events that occurred during short-term, placebo-controlled trials in 5% or more of patients treated with alprazolam extended-release tablets where the incidence in patients treated with alprazolam extended-release tablets was two times greater than the incidence in placebo-treated patients.

**Discontinuation-Emergent Symptoms: Incidence in Short-Term, Placebo-Controlled Trials with Alprazolam Extended-Release Tablets**

System Organ Class/ Adverse Event	Percentage of Patients Reporting Adverse Event	
	Alprazolam Extended- Release Tablets (n=422)	Placebo (n=261)
<b>Nervous system disorders</b>		
Tremor	28.2	10.7
Headache	26.5	12.6
Hypoesthesia	7.8	2.3
Paraesthesia	7.1	2.7
<b>Psychiatric disorders</b>		
Insomnia	24.2	9.6
Nervousness	21.8	8.8
Depression	10.9	5
Derealization	8	3.8
Anxiety	7.8	2.7

Depersonalization	5.7	1.9
<b>Gastrointestinal disorders</b>		
Diarrhea	12.1	3.1
<b>Respiratory, thoracic and mediastinal disorders</b>		
Hyperventilation	8.5	2.7
<b>Metabolism and nutrition disorders</b>		
Appetite decreased	9.5	3.8
<b>Musculoskeletal and connective tissue disorders</b>		
Muscle twitching	7.4	2.7
<b>Vascular disorders</b>		
Hot flushes	5.9	2.7

There have also been reports of withdrawal seizures upon rapid decrease or abrupt discontinuation of alprazolam (see **WARNINGS**).

To discontinue treatment in patients taking alprazolam extended-release tablets, the dosage should be reduced slowly in keeping with good medical practice. It is suggested that the daily dosage of alprazolam extended-release tablets 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.

## **Post Introduction Reports**

Various adverse drug reactions have been reported in association with the use of alprazolam tablets since market introduction. The majority of these reactions were reported through the medical event voluntary reporting system. Because of the spontaneous nature of the reporting of medical events and the lack of controls, a causal relationship to the use of alprazolam tablets cannot be readily determined. Reported events include: gastrointestinal disorder, hypomania, mania, liver enzyme elevations, hepatitis, hepatic failure, Stevens-Johnson syndrome, angioedema, peripheral edema, hyperprolactinemia, gynecomastia, and galactorrhea (**see PRECAUTIONS**).

## **DRUG ABUSE AND DEPENDENCE**

### **Controlled Substance**

Alprazolam extended-release tablets contain alprazolam, a Schedule IV controlled substance.

### **Abuse**

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

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

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

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

## Dependence

### Physical Dependence

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

To reduce the risk of withdrawal reactions, use a gradual taper to discontinue alprazolam extended-release tablets or reduce the dosage (see **DOSAGE AND ADMINISTRATION - Discontinuation or Dosage Reduction of Alprazolam Extended-Release Tablets** and **WARNINGS - Dependence and Withdrawal Reactions**).

### *Acute Withdrawal Signs and Symptoms*

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

### *Protracted Withdrawal Syndrome*

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

### Tolerance

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

## **OVERDOSAGE**

### **Clinical Experience**

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

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

### **General Treatment of Overdose**

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

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

## **DOSAGE AND ADMINISTRATION**

Alprazolam extended-release tablets may be administered once daily, preferably in the morning. The tablets should be taken intact; they should not be chewed, crushed, or broken.

The suggested total daily dose ranges between 3 to 6 mg/day. Dosage should be individualized for maximum beneficial effect. While the suggested total daily dosages given will meet the needs of most patients, there will be some patients who require doses greater than 6 mg/day. In such cases, dosage should be increased cautiously to avoid adverse effects.

### **Dosing in Special Populations**

In elderly patients, in patients with advanced liver disease, or in patients with debilitating disease, the usual starting dose of alprazolam extended-release tablets is 0.5 mg once daily. This may be gradually increased if needed and tolerated (see **Dose Titration**). The elderly may be especially sensitive to the effects of benzodiazepines.

### **Dose Titration**

Treatment with alprazolam extended-release tablets may be initiated with a dose of 0.5 mg to 1 mg once daily. Depending on the response, the dose may be increased at intervals of 3 to 4 days in increments of no more than 1 mg/day. Slower titration to the dose levels may be advisable to allow full expression of the pharmacodynamic effect of alprazolam extended-release tablets.

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

### **Dose Maintenance**

In controlled trials conducted to establish the efficacy of alprazolam extended-release tablets in panic disorder, doses in the range of 1 to 10 mg/day were used. Most patients showed efficacy in the dose range of 3 to 6 mg/day. Occasional patients required as much as 10 mg/day to achieve a successful response.

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

### **Discontinuation or Dosage Reduction of Alprazolam Extended-Release Tablets**

To reduce the risk of withdrawal reactions, use a gradual taper to discontinue alprazolam extended-release tablets or reduce the dosage. If a patient develops withdrawal reactions, consider pausing the taper or increasing the dosage to the

previous tapered dosage level. Subsequently decrease the dosage more slowly (see **WARNINGS - Dependence and Withdrawal Reactions and DRUG ABUSE AND DEPENDENCE - Dependence**).

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.

Reduce the dosage by no more than 0.5 mg every three days. Some patients may benefit from an even more gradual discontinuation. Some patients may prove resistant to all discontinuation regimens.

### **Switch from Alprazolam (Immediate-Release) Tablets to Alprazolam Extended-Release Tablets**

Patients who are currently being treated with divided doses of alprazolam (immediate-release) tablets, for example 3 to 4 times a day, may be switched to alprazolam extended-release tablets at the same total daily dose taken once daily. If the therapeutic response after switching is inadequate, the dosage may be titrated as outlined above.

### **HOW SUPPLIED**

**Alprazolam Extended-Release Tablets USP, 0.5 mg** are white to off-white, round, biconvex tablets with beveled edge debossed with 'X' on one side and '70' on the other side.

Bottles of 60	NDC 65862-454-60
Bottles of 1,000	NDC 65862-454-99
Bottles of 7,000	NDC 65862-454-71

**Alprazolam Extended-Release Tablets USP, 1 mg** are yellow colored, round, biconvex tablets with beveled edge debossed with 'X' on one side and '73' on the other side. The tablets may be mottled.

Bottles of 60	NDC 65862-455-60
Bottles of 1,000	NDC 65862-455-99
Bottles of 7,000	NDC 65862-455-71

**Alprazolam Extended-Release Tablets USP, 2 mg** are blue colored, round, biconvex tablets with beveled edge debossed with 'X' on one side and '74' on the other side. The tablets may be mottled.

Bottles of 60	NDC 65862-456-60
Bottles of 1,000	NDC 65862-456-99
Bottles of 7,000	NDC 65862-456-71

**Alprazolam Extended-Release Tablets USP, 3 mg** are green colored, round, biconvex tablets with beveled edge debossed with 'X' on one side and '75' on the other side. The tablets may be mottled.

Bottles of 60	NDC 65862-457-60
Bottles of 1,000	NDC 65862-457-99
Bottles of 7,000	NDC 65862-457-71

**Store at** 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

## ANIMAL STUDIES

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

**Dispense with Medication Guide available at:**  
**[www.aurobindousa.com/medication-guides](http://www.aurobindousa.com/medication-guides)**.

<b>MEDICATION GUIDE</b> <b>Alprazolam Extended-Release Tablets USP C-IV</b> <b>(al pra' zoe lam)</b>
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**What is the most important information I should know about alprazolam extended-release tablets?**

- **Alprazolam extended-release tablets are a benzodiazepine medicine. Taking benzodiazepines with opioid medicines, alcohol, or other central nervous system (CNS) depressants (including street drugs) can cause severe drowsiness, breathing problems (respiratory depression), coma and death.** Get emergency help right away if any of the following happens:
  - shallow or slowed breathing
  - breathing stops (which may lead to the heart stopping)
  - excessive sleepiness (sedation)

Do not drive or operate heavy machinery until you know how taking alprazolam extended-release tablets with opioids affects you.

- **Risk of abuse, misuse, and addiction.** There is a risk of abuse, misuse, and addiction with benzodiazepines including alprazolam extended-release tablets which can lead to overdose and serious side effects including coma and death.

- **Serious side effects including coma and death have happened in people who have abused or misused benzodiazepines, including alprazolam extended-release tablets.** These serious side effects may also include delirium, paranoia, suicidal thoughts or actions, seizures, and difficulty breathing. **Call your healthcare provider or go to the nearest hospital emergency room right away if you get any of these serious side effects.**
- **You can develop an addiction even if you take alprazolam extended-release tablets as prescribed by your healthcare provider.**
- **Take alprazolam extended-release tablets exactly as your healthcare provider prescribed.**
- Do not share your alprazolam extended-release tablets with other people.
- Keep alprazolam extended-release tablets in a safe place and away from children.
- **Physical dependence and withdrawal reactions.** Alprazolam extended-release tablets can cause physical dependence and withdrawal reactions.
  - **Do not suddenly stop taking alprazolam extended-release tablets.** Stopping alprazolam extended-release tablets suddenly can cause serious and life-threatening side effects, including, unusual movements, responses, or expressions, seizures, sudden and severe mental or nervous system changes, depression, seeing or hearing things that others do not see or hear, an extreme increase in activity or talking, losing touch with reality, and suicidal thoughts or actions. **Call your healthcare provider or go to the nearest hospital emergency room right away if you get any of the following symptoms.**
  - **Some people who suddenly stop benzodiazepines, have symptoms that can last for several weeks to more than 12 months,** including, anxiety, trouble remembering, learning, or concentrating, depression, problems sleeping, feeling like insects are crawling under your skin, weakness, shaking, muscle twitching, burning or prickling feeling in your hands, arms, legs or feet, and ringing in your ears.
  - Physical dependence is not the same as drug addiction. Your healthcare provider can tell you more about the differences between physical dependence and drug addiction.
  - Do not take more alprazolam extended-release tablets than prescribed or take alprazolam extended-release tablets for longer than prescribed.

### **What are alprazolam extended-release tablets?**

- Alprazolam extended-release tablets are a prescription medicine used to treat panic disorder, with or without a fear of places and situations that might cause panic, helplessness, or embarrassment (agoraphobia)
- **Alprazolam extended-release tablets are a federal controlled substance (C-IV) because it contains alprazolam that can be abused or lead to dependence.** Keep alprazolam extended-release tablets in a safe place to prevent misuse and abuse. Selling or giving away alprazolam extended-release tablets may harm others and is against the law. Tell your healthcare provider if you have abused or been dependent on alcohol, prescription medicines or street drugs.
- It is not known if alprazolam extended-release tablets are safe and effective in

children.

- Elderly patients are especially susceptible to dose related adverse effects when taking alprazolam extended-release tablets.
- It is not known if alprazolam extended-release tablets are safe and effective in the treatment of panic disorder for use longer than 8 weeks.

**Do not take alprazolam extended-release tablets if:**

- you are allergic to alprazolam, other benzodiazepines, or any of the ingredients in alprazolam extended-release tablets. See the end of this Medication Guide for a complete list of ingredients in alprazolam extended-release tablets.
- you are taking antifungal medicines including ketoconazole and itraconazole

**Before you take alprazolam extended-release tablets, tell your healthcare provider about all of your medical conditions, including if you:**

- have or have had depression, mood problems, or suicidal thoughts or behavior
- have liver or kidney problems
- have lung disease or breathing problems
- are pregnant or plan to become pregnant. Alprazolam extended-release tablets may harm your unborn baby. You and your healthcare provider should decide if you should take alprazolam extended-release tablets while you are pregnant.
- are breastfeeding or plan to breastfeed. Alprazolam passes into your breast milk and may harm your baby. Talk to your healthcare provider about the best way to feed your baby if you take alprazolam extended-release tablets. You should not breastfeed while taking alprazolam extended-release tablets.

**Tell your healthcare provider about all the medicines you take**, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Taking alprazolam extended-release tablets with certain other medicines can cause side effects or affect how well alprazolam extended-release tablets or the other medicines work. Do not start or stop other medicines without talking to your healthcare provider.

**How should I take alprazolam extended-release tablets?**

- **See “What is the most important information I should know about alprazolam extended-release tablets?”**
- Take alprazolam extended-release tablets exactly as your healthcare provider tells you to take it. Your healthcare provider will tell you how much alprazolam extended-release tablets to take and when to take it.
- If you take too much alprazolam, call your healthcare provider or go to the nearest hospital emergency room right away.
- Swallow alprazolam extended-release tablets whole. Do not crush, chew or break alprazolam extended-release tablets

**What are the possible side effects of alprazolam extended-release tablets?**

**Alprazolam extended-release tablets may cause serious side effects,**

**including:**

- **See “What is the most important information I should know about alprazolam extended-release tablets?”**
- **Seizures.** Stopping alprazolam extended-release tablets can cause seizures and seizures that will not stop (status epilepticus).
- **Mania.** Alprazolam extended-release tablets may cause an increase in activity and talking (hypomania and mania) in people who have depression.
- **Alprazolam extended-release tablets can make you sleepy or dizzy and can slow your thinking and motor skills.**
  - Do not drive, operate heavy machinery, or do other dangerous activities until you know how alprazolam extended-release tablets affects you.
  - **Do not drink alcohol or take other drugs that may make you sleepy or dizzy while taking alprazolam extended-release tablets without first talking to your healthcare provider.** When taken with alcohol or drugs that cause sleepiness or dizziness, alprazolam extended-release tablets may make your sleepiness or dizziness much worse.

**The most common side effects of alprazolam extended-release tablets include:**

- sedation
- trouble saying words clearly
- problems with coordination
- tiredness
- drowsiness
- depression
- memory problems

These are not all the possible side effects of alprazolam extended-release tablets. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

**How should I store alprazolam extended-release tablets?**

- Store alprazolam extended-release tablets at room temperature between 68°F to 77°F (20°C to 25°C)
- **Keep alprazolam extended-release tablets and all medicines out of the reach of children.**

- **General information about the safe and effective use of alprazolam extended-release tablets.**
- Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide.
- Do not use alprazolam extended-release tablets for a condition for which it was not prescribed.
- Do not give alprazolam extended-release tablets to other people, even if they have the same symptoms that you have. It may harm them.
- You can ask your pharmacist or healthcare provider for information about alprazolam extended-release tablets that is written for health professionals.

**What are the ingredients in alprazolam extended-release tablets?**

**Active ingredient:** alprazolam

**Inactive ingredients:** colloidal silicon dioxide, hypromellose, lactose monohydrate, and magnesium stearate. In addition, the 1 mg and 3 mg tablet contains D&C Yellow No. 10 aluminum lake and the 2 mg and 3 mg tablets contain FD&C Blue No. 2 lake.

For more information, call Aurobindo Pharma USA, Inc. at 1-866-850-2876

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

**Dispense with Medication Guide available at:  
[www.aurobindousa.com/medication-guides](http://www.aurobindousa.com/medication-guides).**

Distributed by:

**Aurobindo Pharma USA, Inc.**  
279 Princeton-Hightstown Road  
East Windsor, NJ 08520

Manufactured by:

**Aurobindo Pharma Limited**  
Hyderabad-500 038, India

Revised: 03/2021

**PACKAGE LABEL-PRINCIPAL DISPLAY PANEL - 0.5 mg (60 Tablet Bottle)**

NDC 65862-454-60

**Rx only**

**Alprazolam CIV**

**Extended-Release**

**Tablets USP**

**0.5 mg**

**PHARMACIST: Dispense the Medication**

**Guide provided separately to each patient.**

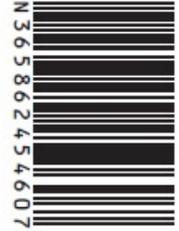
**AUROBINDO**

**60 Tablets**

NDC 65862-454-60

Each extended-release tablet contains: Alprazolam USP 0.5 mg.

Distributed by:  
**Aurobindo Pharma USA, Inc.**  
279 Princeton-Hightstown Road  
East Windsor, NJ 08520



Rx only

**Alprazolam**   
**Extended-Release  
Tablets USP**

**0.5 mg**

**PHARMACIST: Dispense the Medication  
Guide provided separately to each patient.**

 AUROBINDO

**60 Tablets**

**USUAL DOSAGE:** See accompanying  
prescribing information.

**Store at 20° to 25°C (68° to 77°F);  
excursions permitted to 15° to 30°C  
(59° to 86°F) [see USP Controlled  
Room Temperature].**

Dispense in tight, light resistant  
containers (USP).

Made in India

Code: TS/DRUGS/19/1993

P1421780



\*Over printing Zone

Coding Area  
(45 x 15 mm)

Dotted lines not to be printed

**PACKAGE LABEL-PRINCIPAL DISPLAY PANEL - 1 mg (60 Tablet Bottle)**

NDC 65862-455-60

**Rx only**

**Alprazolam CIV  
Extended-Release  
Tablets USP**

**1 mg**

**PHARMACIST: Dispense the Medication  
Guide provided separately to each patient.**

**AUROBINDO**

**60 Tablets**

NDC 65862-455-60

Each extended-release tablet contains: Alprazolam USP 1 mg.

Distributed by:  
**Aurobindo Pharma USA, Inc.**  
279 Princeton-Hightstown Road  
East Windsor, NJ 08520



Rx only

# Alprazolam <sup>Ⓒ</sup> Extended-Release Tablets USP

**1 mg**

**PHARMACIST: Dispense the Medication  
Guide provided separately to each patient.**



**60 Tablets**

**USUAL DOSAGE:** See accompanying  
prescribing information.

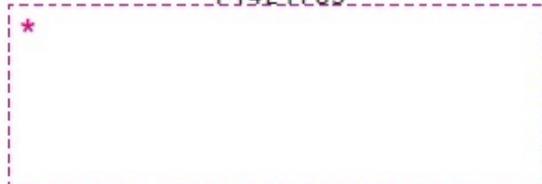
**Store at 20° to 25°C (68° to 77°F);**  
excursions permitted to 15° to 30°C  
(59° to 86°F) [see USP Controlled  
Room Temperature].

Dispense in tight, light resistant  
containers (USP).

Made in India

Code: TS/DRUGS/19/1993

P1421783



\*Over printing Zone

Coding Area  
(45 x 15 mm)  
Dotted lines not to be printed

## PACKAGE LABEL-PRINCIPAL DISPLAY PANEL - 2 mg (60 Tablet Bottle)

NDC 65862-456-60

**Rx only**

# Alprazolam CIV Extended-Release Tablets USP

**2 mg**

**PHARMACIST: Dispense the Medication  
Guide provided separately to each patient.**

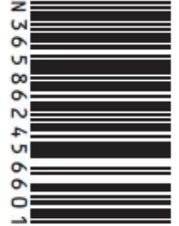
**AUROBINDO**

**60 Tablets**

NDC 65862-456-60

Each extended-release tablet contains: Alprazolam USP 2 mg.

Distributed by:  
**Aurobindo Pharma USA, Inc.**  
279 Princeton-Hightstown Road  
East Windsor, NJ 08520



Rx only

**Alprazolam**   
**Extended-Release  
Tablets USP**

**2 mg**

**PHARMACIST: Dispense the Medication  
Guide provided separately to each patient.**



**60 Tablets**

**USUAL DOSAGE:** See accompanying  
prescribing information.

**Store at 20° to 25°C (68° to 77°F);  
excursions permitted to 15° to 30°C  
(59° to 86°F) [see USP Controlled  
Room Temperature].**

Dispense in tight, light resistant  
containers (USP).

Made in India

Code: TS/DRUGS/19/1993

P1421786



\*Over printing Zone

Coding Area  
(45 x 15 mm)

Dotted lines not to be printed

### PACKAGE LABEL-PRINCIPAL DISPLAY PANEL - 3 mg (60 Tablet Bottle)

NDC 65862-457-60

**Rx only**

**Alprazolam CIV  
Extended-Release  
Tablets USP**

**3 mg**

**PHARMACIST: Dispense the Medication  
Guide provided separately to each patient.**

**AUROBINDO**

**60 Tablets**

NDC 65862-457-60

Each extended-release tablet contains: Alprazolam USP 3 mg.

Distributed by:  
**Aurobindo Pharma USA, Inc.**  
279 Princeton-Hightstown Road  
East Windsor, NJ 08520

Rx only

**Alprazolam**   
**Extended-Release  
Tablets USP****3 mg**PHARMACIST: Dispense the Medication  
Guide provided separately to each patient. AUROBINDO**60 Tablets****USUAL DOSAGE:** See accompanying  
prescribing information.**Store at 20° to 25°C (68° to 77°F);**  
excursions permitted to 15° to 30°C  
(59° to 86°F) [see USP Controlled  
Room Temperature].Dispense in tight, light resistant  
containers (USP).

Made in India

Code: TS/DRUGS/19/1993

P1421789



\*Over printing Zone

Coding Area  
(45 x 15 mm)

Dotted lines not to be printed

**ALPRAZOLAM**

alprazolam tablet, extended release

**Product Information**

<b>Product Type</b>	HUMAN PRESCRIPTION DRUG	<b>Item Code (Source)</b>	NDC:65862-454
<b>Route of Administration</b>	ORAL	<b>DEA Schedule</b>	CIV

**Active Ingredient/Active Moiety**

Ingredient Name	Basis of Strength	Strength
<b>ALPRAZOLAM</b> (UNII: YU55MQ3IZY) (ALPRAZOLAM - UNII: YU55MQ3IZY)	ALPRAZOLAM	0.5 mg

**Inactive Ingredients**

Ingredient Name	Strength
<b>SILICON DIOXIDE</b> (UNII: ETJ7Z6XBU4)	
<b>HYPROMELLOSE 2208 (4000 MPA.S)</b> (UNII: 39J80LT57T)	
<b>HYPROMELLOSE 2208 (100 MPA.S)</b> (UNII: B1QE5P712K)	
<b>LACTOSE MONOHYDRATE</b> (UNII: EWQ57Q8I5X)	
<b>MAGNESIUM STEARATE</b> (UNII: 70097M6130)	

**Product Characteristics**

<b>Color</b>	WHITE (White to Off-white)	<b>Score</b>	no score
<b>Shape</b>	ROUND (Biconvex)	<b>Size</b>	9mm
<b>Flavor</b>		<b>Imprint Code</b>	X;70
<b>Contains</b>			

## Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:65862-454-60	60 in 1 BOTTLE; Type 0: Not a Combination Product	06/07/2011	
2	NDC:65862-454-99	1000 in 1 BOTTLE; Type 0: Not a Combination Product	06/07/2011	
3	NDC:65862-454-71	7000 in 1 BOTTLE; Type 0: Not a Combination Product	06/07/2011	

## Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA090871	06/07/2011	

## ALPRAZOLAM

alprazolam tablet, extended release

### Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:65862-455
Route of Administration	ORAL	DEA Schedule	CIV

### Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
ALPRAZOLAM (UNII: YU55MQ3IZY) (ALPRAZOLAM - UNII:YU55MQ3IZY)	ALPRAZOLAM	1 mg

### Inactive Ingredients

Ingredient Name	Strength
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
HYPROMELLOSE 2208 (4000 MPA.S) (UNII: 39J80LT57T)	
HYPROMELLOSE 2208 (100 MPA.S) (UNII: B1QE5P712K)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
D&C YELLOW NO. 10 (UNII: 35SW5USQ3G)	

### Product Characteristics

Color	YELLOW	Score	no score
Shape	ROUND (Biconvex)	Size	9mm
Flavor		Imprint Code	X;73
Contains			

## Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:65862-455-60	60 in 1 BOTTLE; Type 0: Not a Combination Product	06/07/2011	
2	NDC:65862-455-99	1000 in 1 BOTTLE; Type 0: Not a Combination Product	06/07/2011	
3	NDC:65862-455-71	7000 in 1 BOTTLE; Type 0: Not a Combination Product	06/07/2011	

## Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA090871	06/07/2011	

## ALPRAZOLAM

alprazolam tablet, extended release

### Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:65862-456
Route of Administration	ORAL	DEA Schedule	CIV

### Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
ALPRAZOLAM (UNII: YU55MQ3IZY) (ALPRAZOLAM - UNII:YU55MQ3IZY)	ALPRAZOLAM	2 mg

### Inactive Ingredients

Ingredient Name	Strength
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
HYPROMELLOSE 2208 (4000 MPA.S) (UNII: 39J80LT57T)	
HYPROMELLOSE 2208 (100 MPA.S) (UNII: B1QE5P712K)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
FD&C BLUE NO. 2 (UNII: L06K8R7DQK)	

### Product Characteristics

Color	BLUE	Score	no score
Shape	ROUND (Biconvex)	Size	9mm
Flavor		Imprint Code	X;74
Contains			

## Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:65862-456-60	60 in 1 BOTTLE; Type 0: Not a Combination Product	06/07/2011	
2	NDC:65862-456-99	1000 in 1 BOTTLE; Type 0: Not a Combination Product	06/07/2011	
3	NDC:65862-456-71	7000 in 1 BOTTLE; Type 0: Not a Combination Product	06/07/2011	

## Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA090871	06/07/2011	

## ALPRAZOLAM

alprazolam tablet, extended release

### Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:65862-457
Route of Administration	ORAL	DEA Schedule	CIV

### Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
ALPRAZOLAM (UNII: YU55MQ3IZY) (ALPRAZOLAM - UNII: YU55MQ3IZY)	ALPRAZOLAM	3 mg

### Inactive Ingredients

Ingredient Name	Strength
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
HYPROMELLOSE 2208 (4000 MPA.S) (UNII: 39J80LT57T)	
HYPROMELLOSE 2208 (100 MPA.S) (UNII: B1QE5P712K)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
D&C YELLOW NO. 10 (UNII: 35SW5USQ3G)	
FD&C BLUE NO. 2 (UNII: L06K8R7DQK)	

### Product Characteristics

Color	GREEN	Score	no score
Shape	ROUND (Biconvex)	Size	9mm
Flavor		Imprint Code	X;75
Contains			

## Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:65862-457-60	60 in 1 BOTTLE; Type 0: Not a Combination Product	06/07/2011	
2	NDC:65862-457-99	1000 in 1 BOTTLE; Type 0: Not a Combination Product	06/07/2011	
3	NDC:65862-457-71	7000 in 1 BOTTLE; Type 0: Not a Combination Product	06/07/2011	

## Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA090871	06/07/2011	

**Labeler** - Aurobindo Pharma Limited (650082092)

## Establishment

Name	Address	ID/FEI	Business Operations
Aurobindo Pharma Limited		918917642	ANALYSIS(65862-454, 65862-455, 65862-456, 65862-457) , MANUFACTURE(65862-454, 65862-455, 65862-456, 65862-457)

Revised: 3/2021

Aurobindo Pharma Limited