

ALPRAZOLAM- alprazolam tablet

PD-Rx Pharmaceuticals, Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ALPRAZOLAM TABLETS safely and effectively. See full prescribing information for ALPRAZOLAM TABLETS.

ALPRAZOLAM tablets, for oral use, CIV

Initial U.S. Approval: 1981

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

See full prescribing information for complete boxed warning.

- **Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing for use in 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. (5.1, 7.1)**
- **The use of benzodiazepines, including alprazolam tablets, exposes users to risks of abuse, misuse, and addiction, which can lead to overdose or death. Before prescribing alprazolam tablets and throughout treatment, assess each patient's risk for abuse, misuse, and addiction. (5.2)**
- **Abrupt discontinuation or rapid dosage reduction of alprazolam 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 tablets or reduce the dosage. (2.2, 5.3)**

-----RECENT MAJOR CHANGES-----

Boxed Warning	2/2021
Dosage and Administration (2.3)	2/2021
Warnings and Precautions (5.2, 5.3)	2/2021

-----INDICATIONS AND USAGE-----

Alprazolam Tablets are a benzodiazepine indicated for the:

- Acute treatment of generalized anxiety disorder in adults. (1)
- Treatment of panic disorder with or without agoraphobia in adults. (1)

-----DOSAGE AND ADMINISTRATION-----

- Generalized Anxiety Disorder:(2.1)
 - Recommended starting oral dosage is 0.25 mg to 0.5 mg three times daily.
 - Dosage may be increased, at intervals of every 3 to 4 days, to a maximum recommended daily dose of 4 mg, given in divided doses.
 - Use the lowest possible effective dose and frequently assess the need for continued treatment.
- Panic Disorder:Recommended starting oral dosage is 0.5 mg three times daily. The dosage may be increased at intervals of every 3 to 4 days in increments of no more than 1 mg per day. (2.2)
- When tapering, decrease dosage by no more than 0.5 mg every 3 days. Some patients may require an even slower dosage reduction. (2.3, 5.2)
- See the Full Prescribing Information for the recommended dosage in geriatric patients, patients with hepatic impairment, and with use with ritonavir. (2.4, 2.5, 2.6)

-----DOSAGE FORMS AND STRENGTHS-----

Tablets: 0.25 mg, 0.5 mg, 1 mg, and 2 mg (3)

-----CONTRAINDICATIONS-----

- Known hypersensitivity to alprazolam or other benzodiazepines. (4)
- Concomitant use with strong cytochrome P450 3A (CYP3A) inhibitors, except ritonavir. (4, 5.5, 7.1)

-----**WARNINGS AND PRECAUTIONS**-----

- Effects on Driving and Operating Machinery: Patients receiving alprazolam tablets should be cautioned against operating machinery or driving a motor vehicle, as well as avoiding concomitant use of alcohol and other central nervous system (CNS) depressant drugs. (5.4)
- Neonatal Sedation and Withdrawal Syndrome (NOWS): Use of alprazolam tablets during pregnancy can result in neonatal sedation and neonatal withdrawal syndrome. (5.5, 8.1)
- Patients with Depression: Exercise caution in patients with signs or symptoms of depression. Prescribe the least number of tablets feasible to avoid intentional overdosage. (5.7)

-----**ADVERSE REACTIONS**-----

The most common adverse reactions reported in clinical trials for generalized anxiety disorder and panic disorder (incidence $\geq 5\%$ and at least twice that of placebo) include: impaired coordination, hypotension, dysarthria, and increased libido. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Breckenridge Pharmaceutical, Inc. at 1-800-367-3395 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

-----**DRUG INTERACTIONS**-----

- Use with Opioids: Increase the risk of respiratory depression. (7.1)
- Use with Other CNS Depressants: Produces additive CNS depressant effects. (7.1)
- Use with Digoxin: Increase the risk of digoxin toxicity. (7.1)
- Use with CYP3A Inhibitors (except ritonavir): Increase the risk of adverse reactions of alprazolam. (4, 5.6, 7.1)
- Use with CYP3A Inducers: Increase the risk of reduced efficacy of alprazolam. (7.1)

-----**USE IN SPECIFIC POPULATIONS**-----

Lactation:Breastfeeding not recommended. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 4/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

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

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

- 2.1 Dosage in Generalized Anxiety Disorder
- 2.2 Dosage in Panic Disorder
- 2.3 Discontinuation or Dosage Reduction of Alprazolam Tablets
- 2.4 Dosage Recommendations in Geriatric Patients
- 2.5 Dosage Recommendations in Patients with Hepatic Impairment
- 2.6 Dosage Modifications for Drug Interactions

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Risks from Concomitant Use with Opioids
- 5.2 Abuse, Misuse, and Addiction
- 5.3 Dependence and Withdrawal Reactions
- 5.4 Effects on Driving and Operating Machinery
- 5.5 Neonatal Sedation and Withdrawal Syndrome
- 5.6 Interaction with Drugs that Inhibit Metabolism via Cytochrome P450 3A
- 5.7 Patients with Depression
- 5.8 Mania

5.9 Risk in Patients with Impaired Respiratory Function

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

6.2 Postmarketing Experience

7 DRUG INTERACTIONS

7.1 Drugs Having Clinically Important Interactions with Alprazolam Tablets

7.2 Drug/Laboratory Test Interactions

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Lactation

8.4 Pediatric Use

8.5 Geriatric Use

8.6 Hepatic Impairment

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

10 OVERDOSAGE

10.1 Clinical Experience

10.2 Management of Overdose

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

14.1 Generalized Anxiety Disorder

14.2 Panic Disorder

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

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 (5.1)*, *Drug Interactions (7.1)*] .**

The use of benzodiazepines, including alprazolam 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 tablets and throughout treatment, assess each patient's risk for abuse, misuse, and addiction [see *Warnings and Precautions (5.2)*] .

The continued use of benzodiazepines, including alprazolam 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 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 tablets or reduce the dosage [see *Dosage and Administration (2.2)*, *Warnings and Precautions (5.3)*] .

1 INDICATIONS AND USAGE

Alprazolam tablets are indicated for the:

- acute treatment of generalized anxiety disorder (GAD) in adults.
- treatment of panic disorder (PD), with or without agoraphobia in adults.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage in Generalized Anxiety Disorder

The recommended starting oral dosage of alprazolam tablets for the acute treatment of patients with GAD is 0.25 mg to 0.5 mg administered three times daily. Depending upon the response, the dosage may be adjusted at intervals of every 3 to 4 days. The maximum recommended dosage is 4 mg daily (in divided doses).

Use the lowest possible effective dose and frequently assess the need for continued treatment [see *Warnings and Precautions (5.2)*] .

2.2 Dosage in Panic Disorder

The recommended starting oral dosage of alprazolam tablets for the treatment of PD is 0.5 mg three times daily. Depending on the response, the dosage may be increased at intervals of every 3 to 4 days in increments of no more than 1 mg per day.

Controlled trials of alprazolam tablets in the treatment of panic disorder included dosages in the range of 1 mg to 10 mg daily. The mean dosage was approximately 5 mg to 6 mg daily. Occasional patients required as much as 10 mg per day.

For patients receiving doses greater than 4 mg per day, periodic reassessment and consideration of dosage reduction is advised. In a controlled postmarketing dose-response study, patients treated with doses of alprazolam tablets greater than 4 mg per day for 3 months were able to taper to 50% of their total maintenance dose without apparent loss of clinical benefit.

The necessary duration of treatment for PD in patients responding to alprazolam tablets is unknown. After a period of extended freedom from panic 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 [see *Dosage and Administration (2.3)*].

2.3 Discontinuation or Dosage Reduction of Alprazolam Tablets

To reduce the risk of withdrawal reactions, use a gradual taper to discontinue alprazolam 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 and Precautions (5.3), Drug Abuse and Dependence (9.3)*].

Reduce the dosage by no more than 0.5 mg every 3 days. Some patients may benefit from an even more gradual discontinuation. Some patients may prove resistant to all discontinuation regimens.

In a controlled postmarketing discontinuation study of panic disorder patients which compared the 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.

2.4 Dosage Recommendations in Geriatric Patients

In geriatric patients, the recommended starting oral dosage of alprazolam tablets is 0.25 mg, given 2 or 3 times daily. This may be gradually increased if needed and tolerated. Geriatric patients may be especially sensitive to the effects of benzodiazepines. If adverse reactions occur at the recommended starting dosage, the dosage may be reduced [see *Use in Specific Populations (8.5), Clinical Pharmacology (12.3)*].

2.5 Dosage Recommendations in Patients with Hepatic Impairment

In patients with hepatic impairment, the recommended starting oral dosage of alprazolam tablets is 0.25 mg, given 2 or 3 times daily. This may be gradually increased if needed and tolerated. If adverse reactions occur at the recommended starting dose, the dosage may be reduced [see *Use in Specific Populations (8.6), Clinical Pharmacology (12.3)*].

2.6 Dosage Modifications for Drug Interactions

Alprazolam tablets should be reduced to half of the recommended dosage when a patient is started on ritonavir and alprazolam together, or when ritonavir is administered to a patient treated with alprazolam. Increase the alprazolam tablets dosage to the target dose after 10 to 14 days of dosing ritonavir and alprazolam together. It is not necessary to reduce alprazolam tablets dose in patients who have been taking ritonavir for more than 10 to 14 days.

Alprazolam tablets are contraindicated with concomitant use of all strong CYP3A inhibitors, except ritonavir [see *Contraindications (4), Warnings and Precautions (5.5)*].

3 DOSAGE FORMS AND STRENGTHS

Alprazolam Tablets, USP are available as:

- 0.25 mg: White to off white, oval, biconvex tablets with break line on one side and debossed "B704" on the other side.
- 0.5 mg: Light orange to orange, oval, biconvex tablets with break line on one side and debossed "B705" on the other side.
- 1 mg: Light blue to blue, oval, biconvex tablets with break line on one side and debossed "B706" on the other side.
- 2 mg: Light blue to blue, rectangle tablets with three break lines on one side and two notches in between two break lines, debossed "B707" on the other side.

4 CONTRAINDICATIONS

Alprazolam tablets are contraindicated in patients:

- with known hypersensitivity to alprazolam or other benzodiazepines. Angioedema has been reported [see *Adverse Reactions (6.2)*].
- taking strong cytochrome P450 3A (CYP3A) inhibitors (e.g., ketoconazole, itraconazole), except ritonavir [see *Dosage and Administration (2.6), Warnings and Precautions (5.5), Drug Interactions (7.1)*].

5 WARNINGS AND PRECAUTIONS

5.1 Risks from Concomitant Use with Opioids

Concomitant use of benzodiazepines, including alprazolam 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 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 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 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 tablets is 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 *Drug Interactions (7.1)*].

5.2 Abuse, Misuse, and Addiction

The use of benzodiazepines, including alprazolam 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 (9.2)*].

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

5.3 Dependence and Withdrawal Reactions

To reduce the risk of withdrawal reactions, use a gradual taper to discontinue alprazolam tablets or reduce the dosage (a patient-specific plan should be used to taper the dose) [see *Dosage and Administration (2.3)*].

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 tablets, may lead to clinically significant physical dependence. Abrupt discontinuation or rapid dosage reduction of alprazolam 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 (9.3)*].

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 (9.3)*].

Certain adverse clinical events, some life-threatening, are a direct consequence of physical dependence to alprazolam tablets. These include a spectrum of withdrawal symptoms; the most important is seizure [see *Drug Abuse and Dependence (9.3)*]. Even after relatively short-term use at doses of ≤ 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.

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.

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.

5.4 Effects on Driving and Operating Machinery

Because of its CNS depressant effects, patients receiving alprazolam 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 concomitant use of alcohol and other CNS depressant drugs during treatment with alprazolam tablets [*see Drug Interactions (7.1)*].

5.5 Neonatal Sedation and Withdrawal Syndrome

Use of alprazolam tablets during later stages of pregnancy can result in sedation (respiratory depression, lethargy, hypotonia) and withdrawal symptoms (hyperreflexia, irritability, restlessness, tremors, inconsolable crying, and feeding difficulties) in the neonate. Observe newborns for signs of sedation and neonatal withdrawal syndrome and manage accordingly [*see Use in Specific Populations (8.1)*].

5.6 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.

Strong CYP3A Inhibitors

Alprazolam tablets are contraindicated in patients receiving strong inhibitors of CYP3A (such as azole antifungal agents), except ritonavir [*see Contraindications (4)*].

Ketoconazole and itraconazole have been shown in vivo to increase plasma alprazolam concentrations 3.98 fold and 2.70 fold, respectively.

Dosage adjustment is necessary when alprazolam tablets and ritonavir are initiated concomitantly or when ritonavir is added to a stable dosage of alprazolam tablets [see *Dosage and Administration (2.6)*, *Drug Interactions (7.1)*].

Drugs demonstrated to be CYP3A inhibitors on the basis of clinical studies involving alprazolam: nefazodone, fluvoxamine, and cimetidine [see *Drug Interaction (7.1)*, *Clinical Pharmacology (12.3)*]. Use caution and consider dose reduction of alprazolam tablets, as appropriate, during co-administration with these drugs.

5.7 Patients with Depression

Benzodiazepines may worsen depression. Panic disorder has been associated with primary and secondary major depressive disorders and increased reports of suicide among untreated patients. Consequently, appropriate precautions (e.g., limiting the total prescription size and increased monitoring for suicidal ideation) should be considered in patients with depression.

5.8 Mania

Episodes of hypomania and mania have been reported in association with the use of alprazolam tablets in patients with depression [see *Adverse Reactions (6.2)*].

5.9 Risk in Patients with Impaired Respiratory Function

There have been reports of death in patients with severe pulmonary disease shortly after the initiation of treatment with alprazolam tablets. Closely monitor patients with impaired respiratory function. If signs and symptoms of respiratory depression, hypoventilation, or apnea occur, discontinue alprazolam tablets.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Risks from Concomitant Use with Opioids [see *Warnings and Precautions (5.1)*]
- Abuse, Misuse, and Addiction [see *Warnings and Precautions (5.2)*]
- Dependence and Withdrawal Reactions [see *Warnings and Precautions (5.3)*]
- Effects on Driving and Operating Machinery [see *Warnings and Precautions (5.4)*]
- Neonatal Sedation and Withdrawal Syndrome [see *Warnings and Precautions (5.5)*]
- Patients with Depression [see *Warnings and Precautions (5.7)*]
- Risks in Patients with Impaired Respiratory Function [see *Warnings and Precautions (5.9)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data in the two tables below are estimates of adverse reaction incidence among adult patients who participated in:

- 4-week placebo-controlled clinical studies with alprazolam tablets dosages up to 4 mg per day for the acute treatment of generalized anxiety disorder (Table 1)
- Short-term (up to 10 weeks) placebo-controlled clinical studies with alprazolam tablets dosages up to 10 mg per day for panic disorder, with or without agoraphobia (Table 2).

Table 1: Adverse Reactions Occurring in $\geq 1\%$ in Alprazolam Tablets-treated Patients and Greater than Placebo-treated Patients in Placebo-Controlled Trials for Generalized Anxiety

	Alprazolam tablets n=565	Placebo n=505
Nervous system disorders		
Drowsiness	41%	22%
Light-headedness	21%	19%
Dizziness	2%	1%
Akathisia	2%	1%
Gastrointestinal disorders		
Dry mouth	15%	13%
Increased salivation	4%	2%
Cardiovascular disorders		
Hypotension	5%	2%
Skin and subcutaneous tissue disorders		
Dermatitis/allergy	4%	3%

In addition to the adverse reactions (i.e., greater than 1%) enumerated in the table above for patients with generalized anxiety disorder, the following adverse reactions 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.

Table 2: Adverse Reactions Occurring in $\geq 1\%$ in Alprazolam Tablets-treated Patients and Greater than Placebo-treated Patients in Placebo-Controlled Trials (Up to 10 Weeks) for Panic Disorder

	Alprazolam Tablets n=1388	Placebo n=1231
Drowsiness	77%	43%
Fatigue and Tiredness	49%	42%
Impaired Coordination	40%	18%
Irritability	33%	30%

Memory Impairment	33%	22%
Cognitive Disorder	29%	21%
Decreased Libido	14%	8%
Dysarthria	23%	6%
Confusional state	10%	8%
Increased libido	8%	4%
Change in libido (not specified)	7%	6%
Disinhibition	3%	2%
Talkativeness	2%	1%
Derealization	2%	1%
Gastrointestinal disorders		
Constipation	26%	15%
Increased salivation	6%	4%
Skin and subcutaneous tissue disorders		
Rash	11%	8%
Other		
Increased appetite	33%	23%
Decreased appetite	28%	24%
Weight gain	27%	18%
Weight loss	23%	17%
Micturition difficulties	12%	9%
Menstrual disorders	11%	9%
Sexual dysfunction	7%	4%
Incontinence	2%	1%

In addition to the reactions (i.e., greater than 1%) enumerated in the table above for patients with panic disorder, the following adverse reactions have been reported in association with the use of alprazolam tablets: seizures, hallucinations, depersonalization, taste alterations, diplopia, elevated bilirubin, elevated hepatic enzymes, and jaundice.

Adverse Reactions Reported as Reasons for Discontinuation in Treatment of Panic Disorder in Placebo-Controlled Trials

In a larger database comprised of both controlled and uncontrolled studies in which 641 patients received alprazolam tablets, discontinuation-emergent symptoms which occurred at a rate of over 5% in patients treated with alprazolam tablets and at a greater rate than the placebo-treated group are shown in Table 3.

Table 3: Discontinuation-Emergent Symptom Incidence Reported in $\geq 5\%$ of Alprazolam Tablets-treated Patients and $>$ Placebo-treated Patients

	Alprazolam tablets-treated Patients n=641
Nervous system disorders	

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

n=number of patients.

There have also been reports of withdrawal seizures upon rapid decrease or abrupt discontinuation of alprazolam tablets [see *Warning and Precautions (5.2) and Drug Abuse and Dependence (9.3)*]. 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 post-traumatic stress disorder.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of alprazolam tablets. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

*Endocrine disorders:*Hyperprolactinemia

*General disorders and administration site conditions:*Edema peripheral

*Hepatobiliary disorders:*Hepatitis, hepatic failure

*Investigations:*Liver enzyme elevations

*Psychiatric disorders:*Hypomania, mania

*Reproductive system and breast disorders:*Gynecomastia, galactorrhea

*Skin and subcutaneous tissue disorders:*Photosensitivity reaction, angioedema, Stevens-Johnson syndrome

7 DRUG INTERACTIONS

7.1 Drugs Having Clinically Important Interactions with Alprazolam Tablets

Table 4 includes clinically significant drug interactions with alprazolam tablets [see *Clinical Pharmacology (12.3)*].

Table 4: Clinically Significant Drug Interactions with Alprazolam Tablets

Opioids	
Clinical implication	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 gamma-aminobutyric acid (GABA _A) sites and opioids interact primarily at mu receptors. When benzodiazepines and opioids are combined, the potential for benzodiazepines to significantly worsen opioid-related respiratory depression exists.
Prevention or management	Limit dosage and duration of concomitant use of alprazolam tablets and opioids, and monitor patients closely for respiratory depression and sedation [see <i>Warnings and Precautions (5.1)</i>].
Examples	Morphine, buprenorphine, hydromorphone, oxycodone, fentanyl, methadone, alfentanil, butorpenol, codeine, dihydrocodeine, meperidine, pentazocine, remifentanil, sufentanil, tapentadol, tramadol.
CNS Depressants	
Clinical implication	The benzodiazepines, including alprazolam, produce additive CNS depressant effects when coadministered with other CNS depressants.
Prevention or	Limit dosage and duration of alprazolam tablets during concomitant

management	use with CNS depressants [see <i>Warnings and Precautions (5.3)</i>] .
Examples	Psychotropic medications, anticonvulsants, antihistaminics, ethanol, and other drugs which themselves produce CNS depression.
Strong Inhibitors of CYP3A (except ritonavir)	
Clinical implication	Concomitant use of alprazolam tablets with strong CYP3A inhibitors has a profound effect on the clearance of alprazolam, resulting in increased concentrations of alprazolam and increased risk of adverse reactions [see <i>Clinical Pharmacology (12.3)</i>] .
Prevention or management	Concomitant use of alprazolam tablets with a strong CYP3A4 inhibitor (except ritonavir) is contraindicated [see <i>Contraindications (4), Warnings and Precautions (5.5)</i>] .
Examples	Ketoconazole, itraconazole, clarithromycin
Moderate or Weak Inhibitors of CYP3A	
Clinical implication	Concomitant use of alprazolam tablets with CYP3A inhibitors may increase the concentrations of alprazolam tablets, resulting in increased risk of adverse reactions of alprazolam [see <i>Clinical Pharmacology (12.3)</i>] .
Prevention or management	Avoid use and consider appropriate dose reduction when alprazolam tablets is coadministered with a moderate or weak CYP3A inhibitor [see <i>Warnings and Precautions (5.5)</i>] .
Examples	Nefazodone, fluvoxamine, cimetidine, erythromycin
CYP3A Inducers	
Clinical implication	Concomitant use of CYP3A inducers can increase alprazolam metabolism and therefore can decrease plasma levels of alprazolam [see <i>Clinical Pharmacology (12.3)</i>] .
Prevention or management	Caution is recommended during coadministration with alprazolam tablets.
Examples	Carbamazepine, phenytoin
Ritonavir	
Clinical implication	Interactions involving ritonavir and alprazolam are complex and time dependent. Short term administration of ritonavir increased alprazolam exposure due to CYP3A4 inhibition. Following long term treatment of ritonavir (>10 to 14 days), CYP3A4 induction offsets this inhibition. Alprazolam exposure was not meaningfully affected in the presence of ritonavir.
Prevention or management	Reduce alprazolam tablets dosage when ritonavir and alprazolam are initiated concomitantly, or when ritonavir is added to a regimen where alprazolam is stabilized. Increase alprazolam tablets dosage to the target dosage after 10 to 14 days of dosing ritonavir and alprazolam tablets concomitantly. No dosage adjustment of alprazolam tablets is necessary in patients receiving ritonavir for more than 10 to 14 days [see <i>Dosage and Administration (2.6)</i>] . Concomitant use of alprazolam tablets with a strong CYP3A inhibitor, except ritonavir, is contraindicated [see <i>Contraindications (4), Warnings and Precautions (5.5)</i>] .
Digoxin	
	Increased digoxin concentrations have been reported when

Clinical implication	alprazolam was given, especially in geriatric patients(>65 years of age).
Prevention or management	In patients on digoxin therapy, measure serum digoxin concentrations before initiating alprazolam tablets. Continue monitoring digoxin serum concentration and toxicity frequently. Reduce the digoxin dose if necessary.

7.2 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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to alprazolam tablets during pregnancy. Healthcare providers are encouraged to register patients by calling the National Pregnancy Registry for Other Psychiatric Medications at 1-866-961-2388 or visiting online at <https://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/othermedications/>.

Risk Summary

Neonates born to mothers using benzodiazepines during the later stages of pregnancy have been reported to experience symptoms of sedation and neonatal withdrawal [see *Warnings and Precautions (5.4), Clinical Considerations*]. Overall available data from published observational studies of pregnant women exposed to alprazolam have not established a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes (see *Data*).

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated risk of major birth defects and of miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Fetal/Neonatal adverse reactions

Benzodiazepines cross the placenta and may produce respiratory depression and sedation in neonates. Monitor neonates exposed to benzodiazepines during pregnancy and labor for signs of sedation, respiratory depression, withdrawal, and feeding problems and manage accordingly [see *Warnings and Precautions (5.4)*].

Data

Human Data

Published data from observational studies on the use of benzodiazepines during pregnancy do not report a clear association with benzodiazepines and major birth defects. Although early studies reported an increased risk of congenital malformations with diazepam and chlordiazepoxide, there was no consistent pattern noted. In addition, the majority of recent case-control and cohort studies of benzodiazepine use during pregnancy, which were adjusted for confounding exposures to alcohol, tobacco, and other medications, have not confirmed these findings. At this time, there is no clear evidence that alprazolam exposure in early pregnancy can cause major birth defects. Neonates exposed to benzodiazepines during the late third trimester of pregnancy or during labor have been reported to exhibit sedation and neonatal withdrawal symptoms.

8.2 Lactation

Risk Summary

Limited data from published literature reports the presence of alprazolam in human breast milk. There are reports of sedation and withdrawal symptoms in breastfed neonates and infants exposed to alprazolam. The effects of alprazolam on lactation are unknown.

Because of the potential for serious adverse reactions, including sedation and withdrawal symptoms in breastfed neonates and infants, advise patients that breastfeeding is not recommended during treatment with alprazolam tablets.

8.4 Pediatric Use

Safety and effectiveness of alprazolam tablets have not been established in pediatric patients.

8.5 Geriatric Use

Alprazolam-treated geriatric patients had higher plasma concentrations of alprazolam (due to reduced clearance) compared to younger adult patients receiving the same doses. Therefore, dosage reduction of alprazolam tablets is recommended in geriatric patients [*see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)*].

8.6 Hepatic Impairment

Patients with alcoholic liver disease exhibit a longer elimination half-life (19.7 hours), compared to healthy subjects (11.4 hours). This may be caused by decreased clearance of alprazolam in patients with alcoholic liver disease. Dosage reduction of alprazolam tablets is recommended in patients with hepatic impairment [*see Dosage and Administration (2.4), Clinical Pharmacology (12.3)*].

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Alprazolam tablets contain alprazolam, which is a Schedule IV controlled substance.

9.2 Abuse

Alprazolam 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 and Precautions (5.2)*].

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).

9.3 Dependence

Alprazolam 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 and Precautions (5.3)*].

To reduce the risk of withdrawal reactions, use a gradual taper to discontinue alprazolam tablets or reduce the dosage [*see Dosage and Administration (2.3), Warnings and Precautions (5.3)*].

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 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 tablets may develop; however, little tolerance develops to the amnestic reactions and other cognitive impairments caused by benzodiazepines.

10 OVERDOSAGE

10.1 Clinical Experience

Manifestations of alprazolam overdose 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.

10.2 Management of Overdose

In case of an overdose, consult a Certified Poison Control Center at 1-800-222-1222 for latest recommendations.

As in all cases of drug overdose, 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. As with the management of intentional overdosing with any drug, it should be borne in mind that multiple agents may have been ingested.

Flumazenil may be useful 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

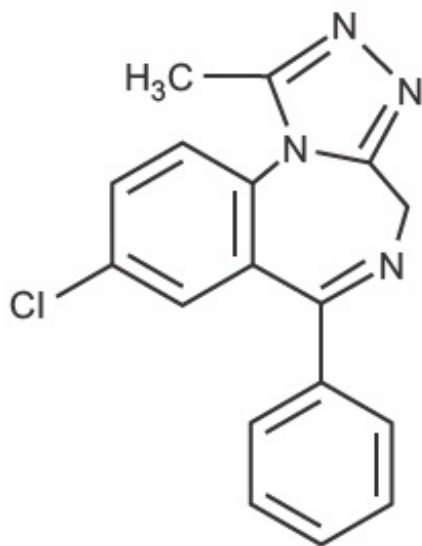
depression, and other residual benzodiazepine effects for an appropriate period after treatment. The prescriber should be aware of a risk of seizure in association with flumazenil treatment, particularly in long-term benzodiazepine users and in cyclic antidepressant overdose. The complete flumazenil package insert should be consulted prior to use.

11 DESCRIPTION

Alprazolam 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-4H-s-triazolo [4,3- α] [1,4] benzodiazepine.

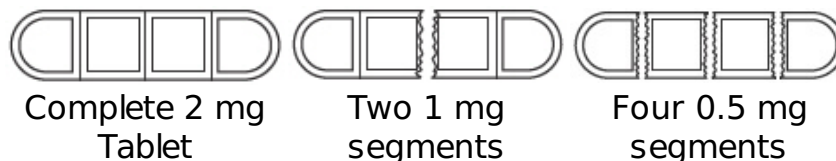
The structural formula is:



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

Each Alprazolam tablet, USP, for oral administration, contains 0.25 mg, 0.5 mg, 1 mg, or 2 mg of alprazolam.

Alprazolam Tablets, USP, 2 mg, are multi-scored and may be divided as shown below:



Inactive ingredients: Lactose monohydrate, microcrystalline cellulose, sodium starch glycolate, hydroxyl propyl cellulose, sodium lauryl sulfate and magnesium stearate. In addition, the 0.5 mg tablet contains FD&C Yellow 6 lake and the 1 mg and 2 mg tablets contain FD&C Blue 2 lake.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Alprazolam is a 1,4 benzodiazepine. Alprazolam exerts its effect for the acute treatment of generalized anxiety disorder and panic disorder through binding to the benzodiazepine site of gamma-aminobutyric acid-A (GABA_A) receptors in the brain and enhances GABA-mediated synaptic inhibition.

12.3 Pharmacokinetics

Plasma levels of alprazolam increase proportionally to the dose over the range of 0.5 to 3.0 mg.

Absorption

Following oral administration, peak plasma concentration of alprazolam (C_{max}) occurs in 1 to 2 hours post dose.

Distribution

Alprazolam is 80% bound to human serum protein, and albumin accounts for the majority of the binding.

Elimination

The mean plasma elimination half-life ($T_{1/2}$) of alprazolam is approximately 11.2 hours (range: 6.3 to 26.9 hours) in healthy adults.

Metabolism

Alprazolam is extensively metabolized in humans, primarily by cytochrome P450 3A4 (CYP3A4), to 2 major active metabolites in the plasma: 4-hydroxyalprazolam and α -hydroxyalprazolam. The plasma circulation levels of the two active metabolites are less than 4% of the parent. The reported relative potencies in benzodiazepine receptor binding experiments and in animal models of induced seizure inhibition are 0.20 and 0.66, respectively, for 4-hydroxyalprazolam and α -hydroxyalprazolam. The low concentrations and low potencies of 4-hydroxyalprazolam and α -hydroxyalprazolam indicate that they unlikely contribute much to the effects of alprazolam. A benzophenone derived from alprazolam is also found in humans. Their half-lives appear to be similar to that of alprazolam.

Excretion

Alprazolam and its metabolites are excreted primarily in the urine.

Specific Populations

Geriatric Patients

The mean $T_{1/2}$ of alprazolam was 16.3 hours (range: 9.0 to 26.9 hours) in healthy elderly subjects compared to 11.0 hours (range: 6.3 to 15.8 hours, n=16) in healthy younger adult subjects.

Obese Patients

The mean $T_{1/2}$ of alprazolam was 21.8 hours (range: 9.9 to 40.4 hours) in a group of obese subjects.

Patients with Hepatic Impairment

The mean $T_{1/2}$ of alprazolam was 19.7 hours (range: 5.8 to 65.3 hours) in patients with alcoholic liver disease.

Racial or Ethnic Groups

Maximal concentrations and $T_{1/2}$ of alprazolam are approximately 15% and 25% higher in Asians compared to Caucasians.

Smoking

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

Drug Interaction Studies

In Vivo Studies

Most of the interactions that have been documented with alprazolam are with drugs that modulate CYP3A4 activity.

Compounds that are inhibitors or inducers of CYP3A would be expected to increase or decrease plasma alprazolam concentrations, respectively. Drug products that have been studied in vivo, along with their effect on increasing alprazolam AUC, are as follows: ketoconazole, 3.98 fold; itraconazole, 2.66 fold; nefazodone, 1.98 fold; fluvoxamine, 1.96 fold; and erythromycin, 1.61 fold [see *Contraindications (4), Warnings and Precautions (5.5), Drug Interactions (7.2)*]. Other studied drugs include:

Cimetidine: Coadministration of cimetidine increased the maximum plasma concentration of alprazolam by 82%, decreased clearance by 42%, and increased $T_{1/2}$ by 16%.

Fluoxetine: Coadministration of fluoxetine with alprazolam increased the maximum plasma concentration of alprazolam by 46%, decreased clearance by 21%, increased $T_{1/2}$ by 17%, and decreased measured psychomotor performance.

Oral Contraceptives: Coadministration of oral contraceptives increased the maximum plasma concentration of alprazolam by 18%, decreased clearance by 22%, and increased $T_{1/2}$ by 29%.

Carbamazepine: The oral clearance of alprazolam (given in a 0.8 mg single dose) was increased from 0.90 ± 0.21 mL/min/kg to 2.13 ± 0.54 mL/min/kg and the elimination $T_{1/2}$ was shortened (from 17.1 ± 4.9 to 7.7 ± 1.7 hour) following administration of 300 mg per day carbamazepine for 10 days [see *Drug Interactions (7.2)*]. However, the carbamazepine dose used in this study was fairly low compared to the recommended doses (1000-1200 mg per day); the effect at usual carbamazepine doses is unknown.

Ritonavir: Interactions involving HIV protease inhibitors (e.g., ritonavir) and alprazolam are complex and time dependent. Short-term low doses of ritonavir (4 doses of 200 mg) increased mean AUC of alprazolam by about 2.5-fold, and did not significantly affect C_{max} of alprazolam. The elimination $T_{1/2}$ was prolonged (30 hours versus 13 hours). However, upon extended exposure to ritonavir (500 mg, twice daily for 10 days), CYP3A induction offset this inhibition. Alprazolam AUC and C_{max} was reduced by 12% and 16%, respectively, in the presence of ritonavir. The elimination $T_{1/2}$ of alprazolam was not significantly changed [see *Warnings and Precautions (5.5)*].

Sertraline: A single dose of alprazolam 1 mg and steady state dose of sertraline (50 mg to 150 mg per day) did not reveal any clinically significant changes in the pharmacokinetics of alprazolam.

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 per day.

Warfarin:Alprazolam did not affect the prothrombin or plasma warfarin levels in male volunteers administered sodium warfarin orally.

In Vitro Studies

Data from in vitro studies of alprazolam suggest a possible drug interaction of alprazolam with paroxetine. The ability of alprazolam to induce human hepatic enzyme systems has not yet been determined.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

No evidence of carcinogenic potential was observed in rats or mice administered alprazolam for 2-years at doses up to 30 and 10 mg/kg/day respectively. These doses are 29 times and 4.8 times the maximum recommended human dose of 10 mg/day based on mg/m^2 body surface area, respectively.

Mutagenesis

Alprazolam was negative in the in vitro Ames bacterial reverse mutation assay and DNA Damage/Alkaline Elution Assay and in vivo rat micronucleus genetic toxicology assays.

Impairment of Fertility

Alprazolam produced no impairment of fertility in rats at doses up to 5 mg/kg per day, which is approximately 5 times the maximum recommended human dose of 10 mg per day based on mg/m^2 body surface area.

13.2 Animal Toxicology and/or Pharmacology

When rats were treated with alprazolam at oral doses of 3 mg, 10 mg, and 30 mg/kg/day (3 to 29 times the maximum recommended human dose based on mg/m^2 body surface area) 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.

14 CLINICAL STUDIES

14.1 Generalized Anxiety Disorder

Alprazolam tablets were compared to placebo in double-blind clinical studies (doses up to 4 mg per day) in patients with a diagnosis of anxiety or anxiety with associated depressive symptomatology. Alprazolam tablets were significantly better than placebo at each of the evaluation periods of these 4-week studies as judged by the following

psychometric instruments: Physician's Global Impressions, Hamilton Anxiety Rating Scale, Target Symptoms, Patient's Global Impressions, and Self-Rating Symptom Scale.

14.2 Panic Disorder

The effectiveness of alprazolam tablets in the treatment of panic disorder was studied in 3 short-term, placebo-controlled studies (up to 10 weeks) in patients with diagnoses closely corresponding to DSM-III-R criteria for panic disorder.

The average dose of alprazolam tablets was 5 mg to 6 mg per day in 2 of the studies, and the doses of alprazolam tablets were fixed at 2 mg and 6 mg per day in the third study. In all 3 studies, alprazolam tablets were superior to placebo on a variable defined as "the number of patients with zero panic attacks" (range, 37% to 83% met this criterion), as well as on a global improvement score. In 2 of the 3 studies, alprazolam tablets were superior to placebo on a variable defined as "change from baseline on the number of panic attacks per week" (range, 3.3 to 5.2), and also on a phobia rating scale. A subgroup of patients who improved on alprazolam tablets during short-term treatment in 1 of these trials was continued on an open basis up to 8 months, without apparent loss of benefit.

16 HOW SUPPLIED/STORAGE AND HANDLING

Alprazolam Tablets, USP, 0.5 mg are available as follows:

Light orange to orange, oval, biconvex tablets with break line on one side and debossed "B705" on the other side.

NDC 72789-024-06 Bottles of 6

NDC 72789-024-30 Bottles of 30

NDC 72789-024-60 Bottles of 60

NDC 72789-024-90 Bottles of 90

Store at controlled room temperature 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].

Protect from light. Dispense in tight (USP), light-resistant, child-resistant containers.

17 PATIENT COUNSELING INFORMATION

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 tablets are used with opioids and not to use such drugs concomitantly unless supervised by a healthcare provider. Advise patients not to drive or operate heavy machinery until the effects of concomitant use with the opioid have been determined [see *Warnings and Precautions (5.1)*, *Drug Interactions (7.1)*].

Abuse, Misuse, and Addiction

Inform patients that the use of alprazolam 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 and Precautions (5.2)*, *Drug Abuse and Dependence (9.2)*] .

Withdrawal Reactions

Inform patients that the continued use of alprazolam tablets may lead to clinically significant physical dependence and that abrupt discontinuation or rapid dosage reduction of alprazolam 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 tablets may require a slow taper [see *Warnings and Precautions (5.3)*, *Drug Abuse and Dependence (9.3)*] .

Effects on Driving and Operating Machinery

Advise patients not to drive a motor vehicle or operate heavy machinery while taking alprazolam tablets due to its CNS depressant effects. Also advise patients to avoid use of alcohol or other CNS depressants while taking alprazolam tablets [see *Warnings and Precautions (5.3)*] .

Patients with Depression

Advise patients, their families, and caregivers to look for signs of suicidality or worsening depression, and to inform the patient's healthcare provider immediately [see *Warnings and Precautions (5.6)*] .

Concomitant Medications

Advise patients to inform their healthcare provider of all medicines they take, including prescription and nonprescription medications, vitamins and herbal supplements [see *Drug Interactions (7)*] .

Pregnancy

Benzodiazepines cross the placenta and may produce respiratory depression and sedation in neonates. Advise mothers using alprazolam tablets to monitor neonates for signs of sedation, respiratory depression, withdrawal symptoms, and feeding problems. Instruct patients to inform their healthcare provider if they are pregnant or intend to become pregnant during treatment with alprazolam tablets [see *Warnings and Precautions (5.4)*] . Advise patients that there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to alprazolam tablets during pregnancy [see *Use in Specific Populations (8.1)*] .

Lactation

Advise women not to breastfeed during treatment with alprazolam tablets [see *Use in Specific Populations (8.2)*] .

Manufactured By:

Centaur Pharmaceuticals Pvt. Ltd.

Pune - 411057, INDIA.

Distributed by:
Breckenridge Pharmaceutical, Inc.
Berlin, CT 06037

211262

MEDICATION GUIDE
Alprazolam (al pra' zoe lam)
Tablets, USP, C-IV

What is the most important information I should know about alprazolam tablets?

- **Alprazolam 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 tablets with opioids affects you.

- **Risk of abuse, misuse, and addiction.** There is a risk of abuse, misuse, and addiction with benzodiazepines, including alprazolam 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 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 tablets as prescribed by your healthcare provider.**
 - **Take alprazolam tablets exactly as your healthcare provider prescribed.**
 - Do not share your alprazolam tablets with other people.
 - Keep alprazolam tablets in a safe place and away from children.
- **Physical dependence and withdrawal reactions.** Alprazolam tablets can cause physical dependence and withdrawal reactions.
 - **Do not suddenly stop taking alprazolam tablets.** Stopping alprazolam 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 these 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 tablets than prescribed or take alprazolam tablets for longer than prescribed.

What are alprazolam tablets?

- Alprazolam tablets are a prescription medicine used:
 - to treat anxiety disorders
 - for the short-term relief of the symptoms of anxiety
 - to treat panic disorder with or without a fear of places and situations that might cause panic, helplessness, or embarrassment (agoraphobia)
- **Alprazolam tablets are a federal controlled substance (C-IV) because they contain alprazolam that can be abused or lead to dependence.** Keep alprazolam tablets in a safe place to prevent misuse and abuse. Selling or giving away alprazolam 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 tablets are safe and effective in children.
- Elderly patients are especially susceptible to dose related adverse effects when taking alprazolam tablets.
- It is not known if alprazolam tablets are safe and effective when used to treat anxiety disorder for longer than 4 months.
- It is not known if alprazolam tablets are safe and effective when used to treat panic disorder for longer than 10 weeks.

Do not take alprazolam tablets if:

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

Before you take alprazolam 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 tablets may harm your unborn baby. You and your healthcare provider should decide if you should take alprazolam 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 tablets. You should not breastfeed while taking alprazolam tablets.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Taking alprazolam tablets with certain other medicines can cause side effects or affect how well alprazolam tablets or the other medicines work. Do not start or stop other medicines without talking to your healthcare provider.

How should I take alprazolam tablets?

- See "What is the most important information I should know about alprazolam tablets?"
- Take alprazolam tablets exactly as your healthcare provider tells you to take them. Your healthcare provider will tell you how much alprazolam tablets to take and when to take them.
- If you take too much alprazolam tablets, call your healthcare provider or go to the nearest hospital emergency room right away.

What are the possible side effects of alprazolam tablets?

Alprazolam tablets may cause serious side effects, including:

- See "What is the most important information I should know about alprazolam tablets?"
- **Seizures.** Stopping alprazolam tablets can cause seizures and seizures that will not stop (status epilepticus).
- **Mania.** Alprazolam tablets may cause an increase in activity and talking (hypomania and mania) in people who have depression.
 - **Alprazolam 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 tablets affect you.
 - **Do not drink alcohol or take other drugs that may make you sleepy or dizzy while taking alprazolam tablets without first talking to your healthcare provider.** When taken with alcohol or drugs that cause sleepiness or dizziness, alprazolam tablets may make your sleepiness or dizziness much worse.

The most common side effects of alprazolam tablets include:

- problems with coordination
- hypotension
- trouble saying words clearly (dysarthria)
- changes in sex drive (libido)

These are not all the possible side effects of alprazolam 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 tablets?

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

General information about the safe and effective use of alprazolam tablets.

- Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide.
- Do not use alprazolam tablets for a condition for which it was not prescribed.
- Do not give alprazolam 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 tablets that is written for health professionals.

What are the ingredients in alprazolam tablets?

Active ingredient:alprazolam

Inactive ingredients:Lactose monohydrate, microcrystalline cellulose, sodium starch glycolate, hydroxyl propyl cellulose, sodium lauryl sulfate and magnesium stearate. In addition, the 0.5 mg tablet contains FD&C Yellow 6 lake and the 1 mg and 2 mg tablets contain FD&C Blue 2 lake.

For more information, go to www.bpirx.com or call Breckenridge Pharmaceutical, Inc. 1-800-367-3395.

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

Manufactured By:

Centaur Pharmaceuticals Pvt. Ltd.

Pune - 411057, INDIA.

Distributed by:

Breckenridge Pharmaceutical, Inc.

Berlin, CT 06037

Revised: 04/2021

PRINCIPAL DISPLAY PANEL - 0.5 mg Tablet Bottle Label

CIV

Alprazolam
Tablets, USP

0.5 mg

PHARMACIST: Dispense the
accompanying Medication Guide
to each patient.

Rx Only

AVOID ALCOHOL WHILE TAKING THIS PRODUCT. MAY CAUSE DROWSINESS. USE CAUTION WHILE PERFORMING TASKS REQUIRING MENTAL ALERTNESS. CAUTION: FEDERAL LAW PROHIBITS THE TRANSFER OF THIS DRUG TO ANY PERSON OTHER THAN TO WHOM IT WAS PRESCRIBED.

R only WARNING: KEEP THIS OUT OF THE REACH OF CHILDREN
DOSAGE and STORAGE: SEE PACKAGE INSERT

72789-024-90	72789-024-90	72789-024-90
ALPRAZolam	ALPRAZolam	ALPRAZolam
USP	USP	USP
0.5 MG	0.5 MG	0.5 MG
90 TABLETS	90 TABLETS	90 TABLETS
ReOrder # 110880	ReOrder # 110880	ReOrder # 110880
LOT C22A22	LOT C22A22	LOT C22A22
EXP 01/2023	EXP 01/2023	EXP 01/2023

CALL YOUR DOCTOR FOR MEDICAL ADVICE ABOUT SIDE EFFECTS. YOU MAY REPORT SIDE EFFECTS TO THE FDA AT 1-800-FDA-1088

TAKE ___ TABLET(S) ___ TIMES A DAY.
TOME ___ TABLETA(S) ___ VECES AL DIA.

Each TABLET Contains: ALPRAZOLAM
USP 0.5 MG

NDC: 72789-024-90



ALPRAZolam
USP

0.5 MG

90 TABLETS



GTIN: 00372789024905
SNO: C22A22000001
EXP: 01/2023
LOT: C22A22

51991070501
CENTAUR PHARM PVT LTD
PUNE, MAHARASHTRA
411057, INDIA

ORANGE
ORGANOLEPTIC MARKINGS:
B 705
OVAL/BRKLINE

ALPRAZOLAM

alprazolam tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:72789-024(NDC:51991-705)
Route of Administration	ORAL	DEA Schedule	CIV

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
ALPRAZOLAM (UNII: YU55MQ3IZY) (ALPRAZOLAM - UNII:YU55MQ3IZY)	ALPRAZOLAM	0.5 mg

Inactive Ingredients

Ingredient Name	Strength
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
SODIUM STARCH GLYCOLATE TYPE A CORN (UNII: AG9B65PV6B)	
HYDROXYPROPYL CELLULOSE (1600000 WAMW) (UNII: RFW2ET671P)	
SODIUM LAURYL SULFATE (UNII: 368GB5141J)	
MAGNESIUM STEARATE (UNII: 70097M6130)	
FD&C YELLOW NO. 6 (UNII: H77VEI93A8)	

Product Characteristics

Color	orange (light orange to orange)	Score	2 pieces
Shape	OVAL	Size	9mm

Flavor		Imprint Code	B705	
Contains				
Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:72789-024-06	6 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	02/19/2020	10/31/2025
2	NDC:72789-024-30	30 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	02/24/2020	10/31/2025
3	NDC:72789-024-60	60 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	03/10/2020	10/31/2025
4	NDC:72789-024-90	90 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	10/31/2019	10/31/2025
Marketing Information				
Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date	
ANDA	ANDA207507	07/09/2018	10/31/2025	

Labeler - PD-Rx Pharmaceuticals, Inc. (156893695)

Registrant - PD-Rx Pharmaceuticals, Inc. (156893695)

Establishment

Name	Address	ID/FEI	Business Operations
PD-Rx Pharmaceuticals, Inc.		156893695	repack(72789-024)

Revised: 8/2023

PD-Rx Pharmaceuticals, Inc.