ALPRAZOLAM- alprazolam tablet
Actavis Pharma, 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, exposes users to risks of abuse, misuse, and addiction, which can lead to overdose or death. Before prescribing alprazolam and throughout treatment, assess each patient's risk for abuse, misuse, and addiction. (5.2)**
- **Abrupt discontinuation or rapid dosage reduction of alprazolam 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 or reduce the dosage. (2.2, 5.3)**

RECENT MAJOR CHANGES

Warnings and Precautions (5.8) 1/2023

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 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)
- Patients with Depression: Exercise caution in patients with signs or symptoms of depression. Prescribe the least number of tablets feasible to avoid intentional overdosage. (5.6)
- Neonatal Sedation and Withdrawal Syndrome: Alprazolam use during pregnancy can result in neonatal sedation and/or neonatal withdrawal. (5.8, 8.1)

ADVERSE REACTIONS

The most common adverse reactions reported in clinical trials for generalized anxiety disorder and panic disorder (incidence ≥5% and at least twice that of placebo) include: impaired coordination, hypotension, dysarthria, and increased libido. (6.1)
To report SUSPECTED ADVERSE REACTIONS, contact Teva at 1-888-838-2872 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, 5.5, 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: 1/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

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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, 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 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, 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 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 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)]*.

Reduced 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 tablets together, or when ritonavir administered to a patient treated with alprazolam tablets. Increase the alprazolam tablets dosage to the target dose after 10 to 14 days of dosing ritonavir and alprazolam tablets 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 is 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 follows:

• 0.25 mg: white, round tablet imprinted with ℞ on one side and 027 and bisect on the other side

• 0.5 mg: peach, round tablet imprinted with ℞ on one side and 029 and bisect on the other side

• 1 mg: blue, round tablet imprinted with ℞ on one side and 031 and bisect on the other side

• 2 mg: yellow, rectangle shaped, flat faced, beveled edge tablet imprinted with ℞ and 039 on one side and multi-scored on both sides

4 CONTRAINDICATIONS

Alprazolam is 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, 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 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 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, 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 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, 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 and throughout treatment, assess each patient's risk for abuse, misuse, and addiction (e.g., using a standardized screening tool). Use of alprazolam, particularly in patients at elevated risk, necessitates counseling about the risks and proper use of alprazolam 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 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, may lead to clinically significant physical dependence. Abrupt discontinuation or rapid dosage reduction of alprazolam 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. 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, 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 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 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 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 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 *[see Drug Interactions (7.1)]*.

5.5 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 is 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 and ritonavir are initiated concomitantly or when ritonavir is added to a stable dosage of alprazolam *[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, as appropriate, during co-administration with these drugs.

5.6 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.

5.7 Mania

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

5.8 Neonatal Sedation and Withdrawal Syndrome

Use of alprazolam late in pregnancy can result in sedation (respiratory depression, lethargy, hypotonia) and/or withdrawal symptoms (hyperreflexia, irritability, restlessness, tremors, inconsolable crying, and feeding difficulties) in the neonate *[see Use in Specific Populations (8.1)]*. Monitor neonates exposed to alprazolam during pregnancy or labor for signs of sedation and monitor neonates exposed to alprazolam during pregnancy for signs of withdrawal; manage these neonates accordingly.

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. Closely monitor patients with impaired respiratory function. If signs and symptoms of respiratory depression, hypoventilation, or apnea occur, discontinue alprazolam.

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)]*
- Patients with Depression *[see Warnings and Precautions (5.6)]*
- Neonatal Sedation and Withdrawal Syndrome *[see Warnings and Precautions (5.8)]*
- 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 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 dosages up to 10 mg per day for panic disorder, with or without agoraphobia (Table 2).

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

	Alprazolam 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 ≥1% in Alprazolam-treated Patients and Greater than Placebo-treated Patients in Placebo-Controlled Trials (Up to 10 Weeks) for Panic Disorder

	Alprazolam 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 Increased salivation	 26% 6%	 15% 4%
Skin and subcutaneous tissue disorders Rash	11%	8%
Other Increased appetite Decreased appetite Weight gain Weight loss Micturition difficulties Menstrual disorders Sexual dysfunction Incontinence	 33% 28% 27% 23% 12% 11% 7% 2%	 23% 24% 18% 17% 9% 9% 4% 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: 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 discontinuation-emergent symptoms which occurred at a rate of over 5% in patients treated with alprazolam and at a greater rate than the placebo-treated group are shown in Table 3.

Table 3: Discontinuation-Emergent Symptom Incidence Reported in ≥5% of Alprazolam-treated Patients and > Placebo-treated Patients

	Alprazolam-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 *[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 posttraumatic stress disorder.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of alprazolam. 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

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

Table 4: Clinically Significant Drug Interactions with Alprazolam

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 and opioids, and monitor patients closely for respiratory depression and sedation *[see Warnings and Precautions (5.1)]*.
Examples	Morphine, buprenorphine, hydromorphone, oxymorphone, 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 management	Limit dosage and duration of alprazolam during concomitant use with CNS depressants *[see Warnings and Precautions (5.3)]*.
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 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 Clinical Pharmacology (12.3)]*.
Prevention or management	Concomitant use of alprazolam with a strong CYP3A4 inhibitor (except ritonavir) is contraindicated *[see Contraindications (4), Warnings and Precautions (5.5)]*.
Examples	Ketoconazole, itraconazole, clarithromycin
Moderate or Weak Inhibitors of CYP3A	
Clinical implication	Concomitant use of alprazolam with CYP3A inhibitors may increase the concentrations of alprazolam, resulting in increased risk of adverse reactions of alprazolam *[see Clinical Pharmacology (12.3)]*.
Prevention or management	Avoid use and consider appropriate dose reduction when alprazolam is coadministered with a moderate or weak CYP3A inhibitor *[see Warnings and Precautions (5.5)]*.
Examples	Nefazodone, fluvoxamine, cimetidine, erythromycin
CYP3A Inducers	
Clinical implication	Concomitant use of CYP3A inducers can increase alprazolam metabolism and therefore can decease

Clinical implication	plasma levels of alprazolam *[see Clinical Pharmacology (12.3)]*.
Prevention or management	Caution is recommended during coadministration with alprazolam.
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 dosage when ritonavir and alprazolam are initiated concomitantly, or when ritonavir is added to a regimen where alprazolam is stabilized. Increase alprazolam dosage to the target dosage after 10 to 14 days of dosing ritonavir and alprazolam concomitantly. No dosage adjustment of alprazolam is necessary in patients receiving ritonavir for more than 10 to14 days *[see Dosage and Administration (2.6)]*. Concomitant use of alprazolam with a strong CYP3A inhibitor, except ritonavir, is contraindicated *[see Contraindications (4), Warnings and Precautions (5.5)]*.
Digoxin	
Clinical implication	Increased digoxin concentrations have been reported when 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. 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 psychiatric medications, including alprazolam, during pregnancy. Healthcare providers are encouraged to register patients by calling the National Pregnancy Registry for Psychiatric Medications at 1-866-961-2388 or visiting online at https://womensmentalhealth.org/research/pregnancyregistry/.

Risk Summary

Neonates born to mothers using benzodiazepines late in pregnancy have been reported to experience symptoms of sedation and/or neonatal withdrawal *[see Warnings and Precautions (5.8) and Clinical Considerations)]*. Available data from published observational studies of pregnant women exposed to benzodiazepines do not report a clear association with benzodiazepines and major birth defects *(see Data)*.

The 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, hypotonia, and sedation in neonates. Monitor neonates exposed to alprazolam during pregnancy or labor for signs of sedation, respiratory depression, hypotonia, and feeding problems. Monitor neonates exposed to alprazolam during pregnancy for signs of withdrawal. Manage these neonates accordingly *[see Warnings and Precautions (5.8)].*

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.

8.2 Lactation

Risk Summary

Limited data from published literature reports the presence of alprazolam in human breast milk. There are reports of sedation, poor feeding and poor weight gain in infants exposed to benzodiazepines through breast milk. The effects of alprazolam on lactation are unknown.

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

8.4 Pediatric Use

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

10 OVERDOSAGE

Overdosage of benzodiazepines is characterized by central nervous system depression ranging from drowsiness to coma. In mild to moderate cases, symptoms can include drowsiness, confusion, dysarthria, lethargy, hypnotic state, diminished reflexes, ataxia, and hypotonia. Rarely, paradoxical or disinhibitory reactions (including agitation, irritability, impulsivity, violent behavior, confusion, restlessness, excitement, and talkativeness) may occur. In severe overdosage cases, patients may develop respiratory

depression and coma. Overdosage of benzodiazepines in combination with other CNS depressants (including alcohol and opioids) may be fatal *[see Warnings and Precautions (5.2)]*. Markedly abnormal (lowered or elevated) blood pressure, heart rate, or respiratory rate raise the concern that additional drugs and/or alcohol are involved in the overdosage.

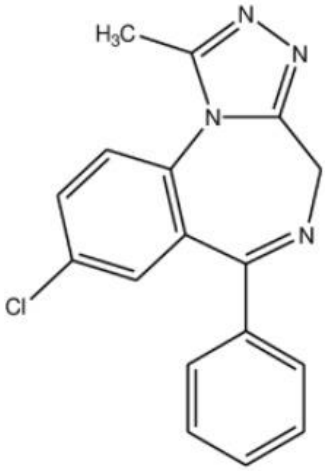
In managing benzodiazepine overdosage, employ general supportive measures, including intravenous fluids and airway management. Flumazenil, a specific benzodiazepine receptor antagonist indicated for the complete or partial reversal of the sedative effects of benzodiazepines in the management of benzodiazepine overdosage, can lead to withdrawal and adverse reactions, including seizures, particularly in the context of mixed overdosage with drugs that increase seizure risk (e.g., tricyclic and tetracyclic antidepressants) and in patients with long-term benzodiazepine use and physical dependency. The risk of withdrawal seizures with flumazenil use may be increased in patients with epilepsy. Flumazenil is contraindicated in patients who have received a benzodiazepine for control of a potentially life-threatening condition (e.g., status epilepticus). If the decision is made to use flumazenil, it should be used as an adjunct to, not as a substitute for, supportive management of benzodiazepine overdosage. See the flumazenil injection Prescribing Information.

Consider contacting the Poison Help Line (1-800-222-1222), or a medical toxicologist for additional overdosage management recommendations.

11 DESCRIPTION

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

The chemical name of alprazolam, USP is 8-Chloro-1-methyl-6-phenyl-4H-s-triazolo [4,3-α] [1,4] benzodiazepine. The structural formula is:



$C_{17}H_{13}ClN_4$ M.W. 308.76

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 tablet, for oral administration, contains 0.25 mg, 0.5 mg, 1 mg, or 2 mg of alprazolam, USP. The 2 mg tablets are multi-scored and may be divided in half to provide two 1 mg segments, or quarters to provide four 0.5 mg segments.

Inactive ingredients: colloidal silicon dioxide, corn starch, docusate sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and sodium benzoate. The 0.5 mg tablet also contains FD&C Yellow #6 Aluminum Lake (Sunset Yellow Lake). The 1 mg tablet also contains FD&C Blue #2 Aluminum Lake. The 2 mg tablet also contains D&C Yellow #10 Aluminum 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 (1,000 to 1,200 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 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 was 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 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 was 5 mg to 6 mg per day in 2 of the studies, and the doses of alprazolam were fixed at 2 mg and 6 mg per day in the third study. In all 3 studies, alprazolam was 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 was 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 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 are supplied as follows:

0.25 mg — Each white, round tablet imprinted with ℞ on one side and 027 and bisect on the other side contains 0.25 mg of alprazolam, USP. Tablets are supplied in bottles of 100 (NDC 0228-2027-10), 500 (NDC 0228-2027-50), and 1000 (NDC 0228-2027-96).

0.5 mg — Each peach, round tablet imprinted with ℞ on one side and 029 and bisect on the other side contains 0.5 mg of alprazolam, USP. Tablets are supplied in bottles of 100 (NDC 0228-2029-10), 500 (NDC 0228-2029-50), and 1000 (NDC 0228-2029-96).

1 mg — Each blue, round tablet imprinted with ℞ on one side and 031 and bisect on the other side contains 1 mg of alprazolam, USP. Tablets are supplied in bottles of 100 (NDC 0228-2031-10), 500 (NDC 0228-2031-50), and 1000 (NDC 0228-2031-96).

2 mg — Each yellow, rectangle shaped, flat faced, beveled edge tablet imprinted with ℞ and 039 on one side and multi-scored on both sides contains 2 mg of alprazolam, USP. Tablets are supplied in bottles of 100 (NDC 0228-2039-10).

Dispense in tight, light-resistant containers as defined in the USP.

Keep container tightly closed.

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

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

Advise pregnant females that use of alprazolam late in pregnancy can result in sedation (respiratory depression, lethargy, hypotonia) and/or withdrawal symptoms (hyperreflexia, irritability, restlessness, tremors, inconsolable crying, and feeding difficulties) in newborns *[see Warnings and Precautions (5.8), Use in Specific Populations (8.1)]*. Instruct patients to inform their healthcare provider if they are pregnant.

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 patients that breastfeeding is not recommended during treatment with alprazolam tablets *[see Use in Specific Populations (8.2)]*.

Dispense with Medication Guide available at: www.tevausa.com/medguides

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MEDICATION GUIDE

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MEDICATION GUIDE
Alprazolam (al pra' zoe lam) Tablets CIV

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 (CIV) because it contains 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.
  - Taking alprazolam tablets late in pregnancy may cause your baby to have symptoms of sedation (breathing problems, sluggishness, low muscle tone), and/or withdrawal symptoms (jitteriness, irritability, restlessness, shaking, excessive crying, feeding problems).
  - Tell your healthcare provider right away if you become pregnant or think you are pregnant during treatment with alprazolam tablets.
  - There is a pregnancy registry for women who take alprazolam tablets during pregnancy. The purpose of the registry is to collect information about the health of you and your baby. If you become pregnant during treatment with alprazolam tablets, talk to your healthcare provider about registering with the National Pregnancy Registry for Psychiatric Medications. You can register by calling 1-866-961-2388 or visiting https://womensmentalhealth.org/pregnancyregistry/.
- are breastfeeding or plan to breastfeed. Alprazolam passes into your breast milk.
  - Talk to your healthcare provider about the best way to feed your baby if you take alprazolam tablets.
  - Breastfeeding is not recommended during treatment with 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 it. Your healthcare provider will tell you how much alprazolam tablets to take and when to take it.
- If you take too many 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 they were not prescribed.
- Do not give alprazolam tablets to other people, even if they have the same symptoms that you have. They 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: colloidal silicon dioxide, corn starch, docusate sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and sodium benzoate. The 0.5 mg tablet also contains FD&C Yellow #6 Aluminum Lake (Sunset Yellow Lake). The 1 mg tablet also contains FD&C Blue #2 Aluminum Lake. The 2 mg tablet also contains D&C Yellow #10 Aluminum Lake.
Manufactured In India By: **Watson Pharma Private Limited**, Verna, Salcette Goa 403 722 INDIA
Manufactured For: **Teva Pharmaceuticals**, Parsippany, NJ 07054
For more information call Teva at 1-888-838-2872.

This Medication Guide has been approved by the U.S. Food and Drug Administration. Rev. C 1/2023

Principal Display Panel

NDC 0228-2027-10

Alprazolam Tablets, USP CIV

0.25 mg

PHARMACIST: Dispense the accompanying Medication Guide to each patient.

Rx only

100 Tablets

Principal Display Panel

NDC 0228-2029-10

Alprazolam Tablets, USP CIV

0.5 mg

PHARMACIST: Dispense the accompanying Medication Guide to each patient.

Rx only

100 Tablets

Principal Display Panel

NDC 0228-2031-10

Alprazolam Tablets, USP CIV

1 mg

PHARMACIST: Dispense the accompanying Medication Guide to each patient.

Rx only

100 Tablets

Principal Display Panel

NDC 0228-2039-10

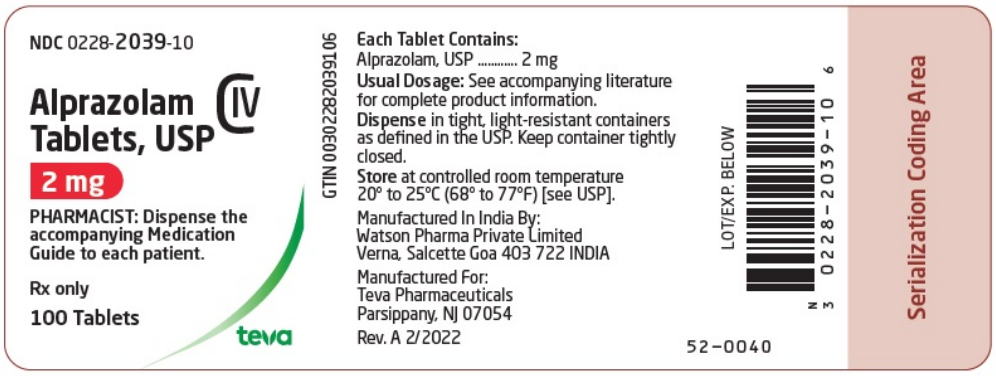
Alprazolam Tablets, USP CIV

2 mg

PHARMACIST: Dispense the accompanying Medication Guide to each patient.

Rx only

100 Tablets



ALPRAZOLAM

alprazolam tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0228-2027
Route of Administration	ORAL	**DEA Schedule**	CIV

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
ALPRAZOLAM (UNII: YU55MQ3IZY) (ALPRAZOLAM - UNII:YU55MQ3IZY)	ALPRAZOLAM	0.25 mg

Inactive Ingredients	
Ingredient Name	**Strength**
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
STARCH, CORN (UNII: O8232NY3SJ)	
DOCUSATE SODIUM (UNII: F05Q2T2JA0)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
SODIUM BENZOATE (UNII: OJ245FE5EU)	

Product Characteristics			
Color	white	**Score**	2 pieces
Shape	ROUND	**Size**	7mm
Flavor		**Imprint Code**	R;027
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:0228-2027-10	100 in 1 BOTTLE; Type 0: Not a Combination Product	10/01/1993	
2	NDC:0228-2027-50	500 in 1 BOTTLE; Type 0: Not a Combination Product	10/01/1993	
3	NDC:0228-2027-96	1000 in 1 BOTTLE; Type 0: Not a Combination Product	10/01/1993	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA074342	10/01/1993	

ALPRAZOLAM

alprazolam tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0228-2029
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
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
STARCH, CORN (UNII: O8232NY3SJ)	
DOCUSATE SODIUM (UNII: F05Q2T2JA0)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
SODIUM BENZOATE (UNII: OJ245FE5EU)	
FD&C YELLOW NO. 6 ALUMINUM LAKE (UNII: GYP6Z2JR6Q)	

Product Characteristics

Color	orange (peach)	**Score**	2 pieces
Shape	ROUND	**Size**	7mm
Flavor		**Imprint Code**	R;029
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0228-2029-10	100 in 1 BOTTLE; Type 0: Not a Combination Product	10/01/1993	
2	NDC:0228-2029-50	500 in 1 BOTTLE; Type 0: Not a Combination Product	10/01/1993	
3	NDC:0228-2029-96	1000 in 1 BOTTLE; Type 0: Not a Combination Product	10/01/1993	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA074342	10/01/1993	

ALPRAZOLAM

alprazolam tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0228-2031
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)	
STARCH, CORN (UNII: O8232NY3SJ)	
DOCUSATE SODIUM (UNII: F05Q2T2JA0)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
SODIUM BENZOATE (UNII: OJ245FE5EU)	
FD&C BLUE NO. 2 ALUMINUM LAKE (UNII: 4AQJ3LG584)	

Product Characteristics

Color	blue	**Score**	2 pieces
Shape	ROUND	**Size**	7mm
Flavor		**Imprint Code**	R;031
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0228-2031-10	100 in 1 BOTTLE; Type 0: Not a Combination Product	10/01/1993	
2	NDC:0228-2031-50	500 in 1 BOTTLE; Type 0: Not a Combination Product	10/01/1993	
3	NDC:0228-2031-96	1000 in 1 BOTTLE; Type 0: Not a Combination Product	10/01/1993	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA074342	10/01/1993	

ALPRAZOLAM

alprazolam tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0228-2039
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)	
STARCH, CORN (UNII: O8232NY3SJ)	
DOCUSATE SODIUM (UNII: F05Q2T2JA0)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
SODIUM BENZOATE (UNII: OJ245FE5EU)	
D&C YELLOW NO. 10 ALUMINUM LAKE (UNII: CQ3XH3DET6)	

Product Characteristics

Color	yellow	**Score**	4 pieces
Shape	RECTANGLE	**Size**	15mm

Flavor		**Imprint Code**	R;039
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0228-2039-10	100 in 1 BOTTLE; Type 0: Not a Combination Product	10/01/1993	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA074342	10/01/1993	

Labeler - Actavis Pharma, Inc. (119723554)

Revised: 1/2023 Actavis Pharma, Inc.