For the use of a Registered Medical Practitioner or Hospital or a Laboratory only

ALPRAX 0.25, ALPRAX 0.5, ALPRAX 1

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

- **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.**
- **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.**
- **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.**

1. Generic Name

Alprazolam Tablets I.P.

2. Qualitative and quantitative Composition:

ALPRAX 0.25 mg

Each uncoated tablet contains:

Alprazolam I.P. …….....…..0.25 mg

Colour: Tartrazine

The excipients used are Lactose Monohydrate, Starch, Polyvinyl Pyrrolidone (K-30), Dioctyl Sodium Sul.Suc., Tartrazine YEl.Food Grade, Magnesium Stearate, Talc.

ALPRAX 0.5 mg

Each uncoated tablet contains:

Alprazolam I.P. …….....…..0.5 mg

Colour: Sunset Yellow

The excipients used are Lactose Monohydrate, Starch, Polyvinyl Pyrrolidone (K-30), Dioctyl Sodium Sul.Suc., Sunset Yellow Colour, Talc, Magnesium Stearate.

ALPRAX 1 mg

Each uncoated tablet contains:

Alprazolam I.P. …….....…..1 mg

The excipients used are Lactose, Starch, Magnesium Stearate, Talc, Polyvinyl Pyrrolidone (K-30), Dioctyl Sodium Sul.Suc.

3. Dosage form and strength

Dosage form: Uncoated tablet

Strength: 0.25 mg, 0.5 mg, 1 mg

4. Clinical particulars

4.1. Therapeutic indication

Anxiolytic agent- Indicated in the treatment of anxiety associated with depression.

4.2. Posology and method of administration

Posology

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.

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.

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.

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.

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.

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.

Method of administration

For oral use.

4.3. Contraindications

Alprazolam is contraindicated in patients:

- With known hypersensitivity to alprazolam or other benzodiazepines. Angioedema has been reported.
- Taking strong cytochrome P450 3A (CYP3A) inhibitors (e.g., ketoconazole, itraconazole), except ritonavir.

4.4. Special warnings and precautions for use

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.

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.

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.

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).

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).

Protracted Withdrawal Syndrome

In some cases, benzodiazepine users have developed a protracted withdrawal syndrome with withdrawal symptoms lasting weeks to more than 12 months.

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. 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).

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.

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. 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.

Drugs demonstrated to be CYP3A inhibitors on the basis of clinical studies involving alprazolam: nefazodone, fluvoxamine, and cimetidine. Use caution and consider dose reduction of alprazolam, as appropriate, during co-administration with these drugs.

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.

Mania

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

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. 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.

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.

4.5. Drugs interactions

Table: Drugs Having Clinically Important 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.
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 co-administered with other CNS depressants.
Prevention or management	Limit dosage and duration of alprazolam during concomitant use with CNS depressants.
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.
Prevention or management	Concomitant use of alprazolam with a strong CYP3A4 inhibitor (except ritonavir) is contraindicated.
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.
Prevention or management	Avoid use and consider appropriate dose reduction when alprazolam is coadministered with a moderate or weak CYP3A inhibitor.
Examples	Nefazodone, fluvoxamine, cimetidine, erythromycin
CYP3A Inducers	
Clinical implication	Concomitant use of CYP3A inducers can increase alprazolam metabolism and therefore can decease plasma levels of alprazolam

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. Concomitant use of alprazolam with a strong CYP3A inhibitor, except ritonavir, is contraindicated.
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.

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.

4.6. Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Pregnancy

Risk Summary

Neonates born to mothers using benzodiazepines late in pregnancy have been reported to experience symptoms of sedation and/or neonatal withdrawal. Available data from published

observational studies of pregnant women exposed to benzodiazepines do not report a clear association with benzodiazepines and major birth defects.

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.

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.

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.

Pediatric Use

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

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.

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.

4.7. Effects on ability to drive and use machines

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.

4.8. Undesirable effects

Summary of the safety profile

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

- Risks from Concomitant Use with Opioids.
- Abuse, Misuse, and Addiction.
- Dependence and Withdrawal Reactions.
- Effects on Driving and Operating Machinery.
- Patients with Depression.
- Neonatal Sedation and Withdrawal Syndrome.
- Risks in Patients with Impaired Respiratory Function.

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: 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%	11%
Light-headedness	21%	19%
Dizziness	2%	1%
Akathisia	2%	1%
Gastrointestinal disorders		
Dry mouth	15%	13%

Increase 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.

Postmarketing Experience

The following adverse reactions have been identified during post-approval 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, Steven Johnson syndrome

Drug abuse and dependence

Controlled Substance

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

Abuse

Alprazolam is 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.

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

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

Dependence

Alprazolam 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.

To reduce the risk of withdrawal reactions, use a gradual taper to discontinue alprazolam or reduce the dosage.

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.

Reporting of adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Report suspected adverse reactions via any point of contact available at www.torrentpharma.com.

4.9. Overdose

Overdose 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 Overdose cases, patients may develop respiratory depression and coma. Overdose of benzodiazepines in combination with other CNS depressants (including alcohol and opioids) may be fatal. 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 overdose.

In managing benzodiazepine Overdose, 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 Overdose, can lead to withdrawal and adverse reactions, including seizures, particularly in the context of mixed Overdose 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.

5. Pharmacological properties

5.1. Mechanism of Action

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

5.2. Pharmacodynamic properties

Alprazolam, like other benzodiazepines, has a high affinity for the benzodiazepine binding site in the brain. It facilitates the inhibitory neurotransmitter action of gamma- aminobutyric

acid, which mediates both pre- and post-synaptic inhibition in the central nervous system (CNS).

5.3.Pharmacokinetic properties

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 (Cmax) 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 (T1/2) 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 nonsmokers.

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. Other studied drugs include:

Cimetidine:

Coadministration of cimetidine increased the maximum plasma concentration of alprazolam by 82%, decreased clearance by 42%, and increased T1/2 by 16%.

Fluoxetine:

Coadministration of fluoxetine with alprazolam increased the maximum plasma concentration of alprazolam by 46%, decreased clearance by 21%, increased T1/2 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 T1/2 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 T1/2 was shortened (from 17.1±4.9 to 7.7±1.7 hour) following administration of 300 mg per day carbamazepine for 10 days. 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 Cmax of alprazolam. The elimination T1/2 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 Cmax was reduced by 12% and 16%, respectively, in the presence of ritonavir. The elimination T1/2 of alprazolam was not significantly changed.

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.

6. Nonclinical properties

6.1. Animal Toxicology 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.

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 body surface area, respectively.

Mutagenesis

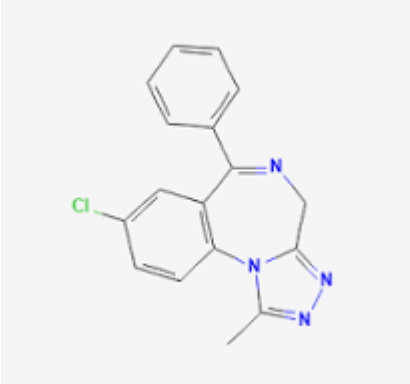
Alprazolam was negative in the in vitro Ames bacterial reverse mutation assay and DNA Damage/Alkaline Elution Assay and in vivo rat micronucleus genetic toxicology assays.

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 body surface area.

7. Description

Alprazolam is 8-choloro-1-methyl-6-phenyl-4H-1,2,4-triazolo[4,3-α] [1,4] benzodiazepine. The molecular formula is $C_{17}H_{13}ClN_4$. The chemical structure of Alprazolam is:



Alprazolam is a White to off white crystalline powder with a molecular weight of 308.8 g/mol. Freely soluble in chloroform; soluble in ethanol (95 per cent); sparingly soluble in acetone; slightly soluble in ethyl acetate; insoluble in water.

ALPRAX 0.25 mg

Light yellow coloured, round, flat uncoated tablets one side plain and other side break line.

The excipients used are Lactose Monohydrate, Starch, Polyvinyl Pyrrolidone (K-30), Dioctyl Sodium Sul.Suc., Tartrazine YEl.Food Grade, Magnesium Stearate, Talc.

ALPRAX 0.5 mg

Light orange coloured, round, flat uncoated tablets on one side break line and plain on other side.

The excipients used are Lactose Monohydrate, Starch, Polyvinyl Pyrrolidone (K-30), Dioctyl Sodium Sul.Suc., Sunset Yellow Colour, Talc, Magnesium Stearate.

ALPRAX 1 mg

White coloured, round, flat uncoated tablets debossed with 'ALPRAX' on one side and bisecting line on other side.

The excipients used are Lactose, Starch, Magnesium Stearate, Talc, Polyvinyl Pyrrolidone (K-30), Dioctyl Sodium Sul.Suc.

8. Pharmaceutical particulars

8.1. Incompatibilities

Not applicable

8.2. Shelf-life

Do not use later than date of expiry.

8.3. Packaging information

ALPRAX 0.25 is available in 20 composite packs of 6×15 tablets each.

ALPRAX 0.5 is available in 20 composite packs of 5 x 15 tablets each.

ALPRAX 1 is available in 10 composite packs of 5 x 15 tablets each.

8.4. Storage and handing instructions

Store at a temperature not exceeding 30°c, protected from light and moisture.

9. Patient Counselling Information

Ask the patients to inform the treating physicians in case of any of the below:

- Have any allergies.
- Have kidney or liver problems.
- Are pregnant or plan to become pregnant.
- Are breastfeeding or plan to breastfeed.
- Have any serious illness.
- Are taking any medicines (prescription, over the counter, vitamins, or herbal products).

10. Details of manufacturer

ALPRAX 0.25 mg, 0.5 mg, 1 mg

Torrent Pharmaceuticals Ltd.

32 No. Middle Camp, NH-10,

East District, Gangtok,

Sikkim-737135, India

11. Details of permission or licence number with date

ALPRAX 0.25 mg, 0.5 mg, 1 mg

M/563/2010 issued on 06.12.2021.

12. Date of revision

NA

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

Torrent House, Off Ashram Road,

Ahmedabad-380 009, INDIA

IN/ALPRAX 0.25 mg, 0.5 mg & 1 mg /DEC 2025/01/PI