PRAZOLEX

Tablets

Composition

Prazolex 0.25, 0.5 & 1 mg

Each tablet contains Alprazolam 0.25, 0.5 & 1 mg.

Action

Alprazolam is an anti-anxiety drug. It is a benzodiazepine derivative, chemically and pharmacologically related to other drugs of this class. Presumably, benzodiazepines exert their effects by binding at stereo-specific receptors at several sites within the central nervous system (CNS). Their exact mechanism of action is unknown.

All benzodiazepines cause a dose-related CNS depressant activity, varying from mild impairment of task performance to hypnosis. Pharmacological properties of Alprazolam in animals appear similar to those of other benzodiazepines, that is, it produces significant anxiolytic, muscle relaxant, sleep promoting and anticonvulsant effects in appropriate animal models.

Clinical studies in healthy volunteers at doses up to 4 mg/day, and in patients with panic disorder at doses up to 10 mg/day, produce only effects that can be considered to be extensions of its pharmacological activities. No clinically significant effects on the cardiovascular or respiratory systems were observed. Alprazolam doses up to 10 mg/day do not clinically affect laboratory parameters or vital signs.

Sleep laboratory studies in man showed that Alprazolam decreased sleep latency, increased duration of sleep, and decreased the number of nocturnal awakenings. Alprazolam produced small decreases in both stages 3 to 4 and rapid eye movement (REM) sleep.

Pharmacokinetics

Absorption

Following oral administration to fasting subjects, Alprazolam is rapidly absorbed with nearly complete bioavailability. Peak concentrations in the plasma occur in 0.3 to 3 hours following administration. Plasma levels are proportionate to the dose given.

Over the dose range of 0.5 to 3.0 mg, peak levels of 8.0 to 37 mg/ml were observed. Peak plasma levels can show a two- to three-fold variation within individual treatment groups. The plasma half-life of Alprazolam after single doses in healthy subjects has ranged from 7 to 22 hours. The mean half-life of individual treatment groups ranged only from 10 to 14 hours. Plasma levels of the drug reach steady-state within 7 days after starting or altering dosage size. The steady-state level is 3 to 4 times that achieved with a single dose. During multiple dose administration of 1.5 to 10 mg/day in divided doses, steady-state plasma levels of 18.3 to 100 ng/ml were observed.

Distribution

Alprazolam is bound (80%) to human serum protein.

Metabolism

About 21 metabolites of Alprazolam were detected in humans. The predominant metabolites are α-hydroxyalprazolam and a benzophenone derived from Alprazolam. The biological activity of α-hydroxyalprazolam is approximately one-half that of Alprazolam. The benzophenone metabolite is essentially inactive. Plasma levels of these metabolites are extremely low, thus precluding precise pharmacokinetic description. However, their half-lives appear to be of the same order of magnitude as that of Alprazolam.

Elimination

Alprazolam and its metabolites are excreted primarily in the urine. About 50% of the dose is excreted within 24 hours, and 94% after 72 hours. With chronic dosing, the apparent elimination half-life increases by about 50%, possibly because of compartmentalization effects. The mean percentage

excreted over a two-week period following a single ^{14}C Alprazolam dose was 78.8 ± 2.1% in urine and 7.02 ± 0.6% in feces.

Special patient groups
Changes in the absorption, distribution, metabolism and excretion of benzodiazepines have been reported in a variety of disease states including alcoholism, impaired hepatic function and impaired renal function. Changes have also been demonstrated in elderly patients. It has not yet been determined if similar changes occur in the pharmacokinetics of Alprazolam.

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

Indications
Prazolex is indicated for the treatments of anxiety and anxiety associated conditions in adults over 18 years old as follows:

Anxiety states (anxiety neuroses)
Symptoms that occur in such patients include anxiety, tension, fear, insomnia, apprehension, restlessness, concentration difficulties, irritability and/or autonomic hyperactivity resulting in a variety of somatic complaints.

Mixed anxiety-depression
Symptoms of both anxiety and depression occur concurrently in such patients.

Neurotic or reactive depression
such patients primarily exhibit a depressed mood or a pervasive loss of interest or pleasure. Other characteristics include anxiety, appetite disturbances, and changes in weight, cognitive disturbances, decreased energy, feeling of worthlessness or guilt, insomnia, somatic complaints, or thoughts of death or suicide.

Anxiety states, mixed anxiety-depression, or neurotic depression
Prazolex is indicated when these conditions are associated with other diseases, such as the chronic phase of alcohol withdrawal and functional or organic disease, particularly certain gastrointestinal, cardiovascular, or dermatological disorders.

Contraindications
- Hypersensitivity to benzodiazepines or to any component of the product
- Myasthenia gravis
- Chronic obstructive airways disease with incipient respiratory failure.

Adverse Reactions
Side effects are generally observed at the beginning of therapy and usually disappear upon continued medication or decreased dosage. In patients treated for anxiety, anxiety associated with depression, the most common side-effects to (Alprazolam) were drowsiness, sedation and ataxia. Drowsiness is more common in elderly and debilitated patients and in patients receiving high doses.

<u>Less common side-effects are:</u>
Co-ordination disorders, tremor, lethargy, ataxia, blurred vision, memory impairment/amnesia, insomnia, nervousness/anxiety, depression, headache, autonomic manifestations, change in mass and various gastrointestinal symptoms.

<u>The following side-effects have also been reported:</u>
Stimulation, agitation, irritability, concentration difficulties, confusion, hallucinations, other adverse behavioral effects, musculoskeletal weakness, dystonia, fatigue, slurred speech, anorexia, changes in

salivation, changes in libido, menstrual irregularities, incontinence, urinary retention, abnormal liver function, jaundice, blood disorders, increased intra-ocular pressure and hypersensitivity reactions.

Amnesia and paradoxical excitation may occur. In the case of acute, hyper-excitability states, the medicine should be discontinued.

Warnings and Precautions

In general, benzodiazepines should be prescribed for short periods only (e.g. 2 to 4 weeks). With the exception of the use of Alprazolam for the treatment of panic disorder, continuous long-term use is not recommended. There is evidence that tolerance develops to the sedative effects of benzodiazepines. After as little as one week therapy with recommended doses, withdrawal symptoms can appear following cessation of treatment, e.g. rebound anxiety following the cessation of an anxiolytic benzodiazepine.

Habituation and emotional or physical dependence may occur with benzodiazepines, including Alprazolam. As with all benzodiazepines, the risk of dependence increases with higher doses and long-term use and is further increased in patients with a history of alcoholism or drug abuse.

Following the prolonged use of Alprazolam at therapeutic doses, withdrawal from the medication should be gradual in keeping with good medical practice. An individualized withdrawal timetable needs to be planned for each patient in whom dependence is known or suspected (periods from four weeks to four months have been suggested). It is suggested that the daily dosage of Arrow - Alprazolam be decreased by no more that 0.5 mg every 3 days. Some patients may require an even slower dosage reduction.

Withdrawal symptoms have occurred following rapid decrease or abrupt discontinuance of benzodiazepines including Alprazolam. These can range from mild dysphoria and insomnia to a major syndrome, which may include abdominal and muscle cramps, vomiting, sweating, tremor and convulsions. In addition, withdrawal seizures have occurred upon a rapid decrease or abrupt discontinuation of therapy with Alprazolam.

Depression, psychosis and schizophrenia

The use of Alprazolam has not been established in certain types of depression. Thus, it is not recommended as a primary therapy in patients with depression and psychosis. In such conditions, psychiatric assessment and supervision are necessary if benzodiazepines are indicated. Benzodiazepines may increase depression in some patients and may contribute to deterioration in severely disturbed schizophrenics with confusion and withdrawal. Suicidal tendencies may be present or uncovered, and protective measures may be required.

Panic-related disorders have been associated with depression, and an increased frequency of suicide amongst untreated patients has been reported. Therefore, the same precaution must be exercised when using the higher doses of Alprazolam in treating patients with panic disorders, as is exercised with the use of any psychotropic drug in treating depressed patients or those in whom there is reason to expect concealed suicidal ideation or plans.

Administration to severely depressed or suicidal patients should be done with appropriate precautions and appropriate size of the prescription.

Withdrawal and dependence

The use of benzodiazepines may lead to dependence as defined by the presence of a withdrawal syndrome on discontinuation of the drug. Tolerance as defined by a need to increase the dose in order to achieve the same therapeutic effect seldom occurs in patients receiving the recommended dose under medical supervision. Tolerance to sedation may occur with benzodiazepines, especially in those with drug-seeking behavior.

The result of withdrawal symptoms is a direct consequence of physical dependence to Alprazolam. Signs and symptoms of withdrawal are similar in character to those noted with barbiturates and alcohol, and are more prominent after a rapid decrease of dosage or abrupt discontinuation. These symptoms range from insomnia, anxiety, dysphoria, palpitations, panic attacks, vertigo, myoclonus, akinesia, hypersensitivity to light, sound and touch, abnormal body sensations (e.g. feelings of motion, metallic taste), depersonalization, derealisation, delusional beliefs, hyper-reflexia and loss of short-term memory, to a major syndrome that may include convulsions, tremor, abdominal and muscle cramps, confusional state, delirium, hallucinations, hyperthermia, psychosis, vomiting and sweating. Such manifestations of withdrawal, especially the more serious ones, are more common in patients who have received excessive doses over a prolonged period. However, withdrawal symptoms have been reported following abrupt discontinuation of benzodiazepines taken continuously at therapeutic levels.

Signs and symptoms of withdrawal are more prominent after a rapid decrease of dosage or abrupt discontinuation of benzodiazepines. Hence, abrupt discontinuation of therapy with Alprazolam should be avoided. It is recommended that all patients on Alprazolam who require a dosage reduction be gradually tapered under close supervision to minimize the incidence or severity of withdrawal problems. It is important to advise patients not to increase the dose of, or abruptly discontinue, their medication without first consulting a physician.

The discontinuation of therapy with Alprazolam may not only result in withdrawal symptoms, but also in relapse of the anxiety and panic symptoms of the original disorder and rebound effect. The term relapse refers to the return of symptoms characteristic of the original disorder, at levels approximately equal to those seen at baseline before active treatment was initiated. Rebound phenomenon refers to the return of symptoms characteristic of the original disorder, at levels greater than originally seen at baseline.

In general, rebound phenomenon reflects the re-emergence of pre-existing conditions combined with withdrawal symptoms described earlier. Withdrawal or rebound phenomenon may follow high doses of benzodiazepines for relatively short periods of time. It was found that the majority of Alprazolam treated patients (66.9%) were able to taper dose to zero. A minority of patients were unable to successfully stop Alprazolam after long-term therapy.

Abuse
Physical and psychological dependence have occurred with recommended doses of benzodiazepines. Caution must therefore be exercised in administering Alprazolam to individuals known to be addiction prone, or those whose history suggesting they may increase the dosage on their own initiative. In such patients, it is therefore desirable to limit repeat prescriptions without adequate medical supervision. Such individuals should be under careful surveillance when receiving benzodiazepines because of their predisposition to habituation and dependence.

Paradoxical reactions
Paradoxical reactions such as acute rage, stimulation or excitement may occur in rare instances. Should such reactions occur, Alprazolam should be discontinued.

Elderly or debilitated patients
Such patients may be particularly susceptible to the sedative effects of benzodiazepines and associated giddiness, ataxia and confusion, which may increase the possibility of a fall. Therefore, the dosage should be limited to the smallest effective amount to preclude such effects.

Effects on ability to drive or use machinery
Patients receiving Alprazolam should be warned not to operate dangerous machinery or motor vehicles until it is known that they do not become drowsy or dizzy while taking Alprazolam. Abilities may be impaired on the day following use.

Impaired renal or hepatic function

Patients with impaired renal or hepatic function should use benzodiazepine medication with caution and a reduction in dosage, or a decision not to prescribe, may be necessary in such patients. In rare instances, some patients taking benzodiazepines have developed blood dyscrasias, and some have had elevations of liver enzymes. As with other benzodiazepines, periodic blood counts and liver function tests are recommended.

Impaired respiratory function
Caution in the use of Alprazolam is recommended in patients with respiratory depression. In patients with chronic obstructive pulmonary disease, benzodiazepines can cause increased arterial carbon dioxide tension and decreased oxygen tension.

Acute narrow-angle glaucoma
Caution should be used in the treatment of patients with acute narrow-angle glaucoma because of atropine-like side effects of Alprazolam.

Hypotension
Although hypotension has occurred rarely, benzodiazepines should be administered with care to patients in whom a drop in blood pressure may lead to cardiac or cerebral complications. This is particularly important in elderly patients.

Epilepsy
Abrupt withdrawal of benzodiazepines in persons with convulsive disorders may be associated with a temporary increase in the frequency and/or severity of seizures. Patients with convulsive disorder should not be abruptly withdrawn from Alprazolam.

Amnesia
Transient amnesia or memory impairment has been reported in association with the use of benzodiazepines.

Alcohol and other CNS drugs
Patients should be advised that their tolerance for alcohol and other CNS depressants will be diminished and that these drugs should either be eliminated or given in reduced dosage in the presence of Arrow - Alprazolam.

Use in pregnancy
Category C
Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

Use in lactation
Benzodiazepines, including Alprazolam, are known to be excreted in human milk. Although the levels in breast milk are low, benzodiazepines generally show increased toxicity in neonates, and may cause drowsiness, lethargy, weight loss, hypotonia and/or feeding difficulties in the infant. Therefore, unless there are compelling circumstances to the contrary, Alprazolam is not recommended for use while breast feeding.

Children
Safety and efficacy of Alprazolam in children under 18 years of age have not been established

Drug Interactions
Benzodiazepines, including Alprazolam, produce additive CNS depressant effects when co-administered with drugs such as barbiturates, alcohol, sedatives, tricyclic antidepressants, and non-selective monoamine oxidase inhibitors and other antipsychotics, skeletal muscle relaxants, antihistamines, narcotic analgesics and anesthetics.

Pharmacokinetic interactions can occur when Alprazolam is administered along with drugs that interfere with its metabolism. Compounds that inhibit certain hepatic enzymes (particularly cytochrome P4503A4) may increase the concentration of Alprazolam and enhance its activity. Data from clinical studies with Alprazolam, in vitro studies with Alprazolam, and clinical studies with drugs metabolised similarly to Alprazolam provide evidence for varying degrees of interaction and possible interaction with Alprazolam for a number of drugs. Based on the degree of interaction and the type of data available, the following recommendations are made:

- Co-administration of Alprazolam with ketoconazole, Itraconazole, or other azole-type antifungals is not recommended.
- Caution and consideration of dose reduction is recommended when Alprazolam is co-administered with nefazodone, fluvoxamine, cimetidine or disulfiram.
- Caution is recommended when Alprazolam is co-administered with fluoxetine, propoxyphene, oral contraceptives, sertraline, diltiazem, erythromycin or other macrolide antibiotics. Increased levels of Alprazolam have been observed with co-administration of erythromycin.
- Interactions involving HIV protease inhibitors (e.g. ritonavir) and Alprazolam are complex and time dependent. Low doses of ritonavir resulted in a large impairment of Alprazolam clearance, prolonged its elimination half-life and enhanced clinical effects. However, upon extended exposure to ritonavir, CYP3A induction offsets this inhibition. This interaction will require a dose-adjustment or discontinuation of Alprazolam.
- The anticholinergic effects of other drugs, including atropine and similar drugs, antihistamines and antidepressants, may be potentiated when taken in conjunction with benzodiazepines.
- Interactions have been reported between some benzodiazepines and anticonvulsants, with changes in the serum concentration of the benzodiazepine or the anticonvulsant. It is recommended that patients be observed for altered responses when benzodiazepines and anticonvulsants are prescribed together, and that serum level monitoring of the anticonvulsant be performed more frequently.
- Minor EEG changes, usually low voltage fast activity, of no known clinical significance, have been reported with benzodiazepine administration.
- The steady-state plasma concentrations of imipramine and desipramine have been reported to increase by an average of 31 and 20%, respectively, when Alprazolam was given in doses up to 4 mg/day concomitantly. The clinical significance of these changes is unknown.
- Alprazolam causes a small decrease (7%) in lithium clearance. Caution should be exercised with close monitoring of lithium concentrations to avoid toxicity.
- Oral contraceptives may increase the elimination half-life of Alprazolam. A 20% increase in the Alprazolam steady-state plasma concentration may be expected in women taking Alprazolam and oral contraceptives concurrently.
- Pharmacokinetic interactions of benzodiazepines with other drugs have been reported. Clearance of Alprazolam and certain other benzodiazepines can be delayed by the co-administration of cimetidine or macrolide antibiotics. The clinical significance of this is unclear.

Dosage and Administration

The optimum dose should be individualized based upon the severity of the symptoms and individual patient's response. The usual dose will meet the needs of most patients. In patients who require higher doses, dosage should be increased cautiously to avoid adverse effects. In general, patients who have not previously received psychotropic medications will require somewhat lower doses than those previously treated with minor tranquilizers, antidepressants or hypnotics, or those with a history of chronic alcoholism.

It is recommended that the general principle of using the lowest effective dose be followed, particularly in elderly or debilitated patients, to preclude the development of ataxia or over-sedation. In patients who experience early morning anxiety and emergence of anxiety symptoms, it is recommended that the same total daily dose be given as more frequent administration.

Conditions	**Usual starting dosage ***	**Usual dosage range**

Anxiety	0.25 to 0.5 mg, given three times daily	0.5 to 4.0 mg daily, given in divided doses
Anxiety with depressive symptoms	0.5 mg, given three times daily	1.5 to 4.5 mg daily, given in divided doses
Elderly patients or in the presence of debilitating disease	0.25 mg, given two to three times daily	0.5 to 0.75 mg daily, given in divided doses; to be gradually increased if needed and tolerated

* If side effects occur, the dose should be lowered.

Administration Prazolex tablets immediately after meals do not affect the extent of absorption compared to administration on an empty stomach. Food does, however, delay the onset of absorption and decrease the rate of absorption of Prazolex tablets. As a direct consequence, side effects such as somnolence are less pronounced.

Duration of treatment
Data is available to support a usage of up to 6 months for anxiety and anxious patients with some symptoms of depression.

Discontinuation therapy
The dosage should be reduced slowly in keeping with good medical practice. It is suggested that the daily dosage of Alprazolam be decreased by no more than 0.5 mg every 3 days in order to minimize any possible withdrawal symptoms. Some patients may require an even slower dosage reduction.

Over Dosage

Symptoms
Symptoms of overdosage with Alprazolam are extensions of its pharmacological actions including central nervous system depression ranging from drowsiness to coma. In mild cases, symptoms include drowsiness, mental confusion, slurred speech and lethargy. In more serious cases, symptoms may include ataxia, hypotonia, hypotension, respiratory depression, coma and, very rarely, death. Serious sequelae occur when Alprazolam is taken with other drugs and/or ethanol is concomitantly ingested.

Treatment
In management of overdosage, it should be borne in mind that multiple agents may have been taken. Following overdosage with Alprazolam, activated charcoal should be given to reduce absorption. Hypotension and respiratory depression should be managed according to general supportive procedures.

Haemoperfusion, forced diuresis and haemodialysis are generally not useful in benzodiazepine intoxication. The benzodiazepine antagonist flumazenil may be useful in hospitalized patients for the reversal of acute benzodiazepine effects on the respiratory and cardiovascular systems. Consult the flumazenil data sheet prior to use.

Presentation

Prazolex 0.25, 0.5 & 1 Tablet
Box of 50 tablets