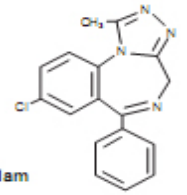
PRAZ™ (Alprazolam)

Tablets
0.25mg, 0.5mg, 1.0mg

DESCRIPTION

PRAZ (Alprazolam) is a triazolo analog of the 1,4 benzodiazepine class of central nervous system active compounds indicated for the short-term treatment of anxiety and anxiety accompanying depression.
Alprazolam is described chemically as 8-Chloro-1-methyl-6-phenyl-4H-s-triazolo [4,3 α 1,4] benzodiazepine. The molecular formula is $C_{17}H_{13}ClN_4$ and the structural formula is:



Alprazolam

QUALITATIVE & QUANTITATIVE COMPOSITION

PRAZ (Alprazolam) is available for oral administration as:

1. PRAZ Tablets 0.25mg
   Each tablet contains:
   Alprazolam USP 0.25mg
2. PRAZ Tablets 0.5mg
   Each tablet contains:
   Alprazolam USP 0.5mg
3. PRAZ Tablets 1.0mg
   Each tablet contains:
   Alprazolam USP 1.0mg

CLINICAL PHARMACOLOGY

Mechanism of action:
The central therapeutic action of benzodiazepines including alprazolam is a result of the potentiation of the neuronal inhibition that is mediated by gamma-aminobutyric acid (GABA). Clinically, all benzodiazepines cause a dose-related central nervous system depressant activity varying from mild impairment of task performance to hypnosis.

Pharmacokinetics:
Alprazolam is well absorbed from the gastrointestinal tract following oral administration, with peak plasma concentrations being achieved within 1–2 hours of a dose. The mean plasma half-life is 11–15 hours. Alprazolam is 70% – 80% bound to plasma protein. It is metabolized in the liver primarily to α-hydroxyalprazolam, which is reported to be approximately half as active as the parent compound, and to an inactive benzophenone; Plasma concentrations of metabolites are very low and it is excreted in urine as unchanged drug and metabolites.

Special Populations:
Changes in the absorption, distribution, metabolism and excretion of benzodiazepines have been reported in a variety of disease states including alcoholism, impaired hepatic function and impaired renal function. Changes have also been demonstrated in geriatric patients. Dosage adjustment may be recommended in these populations.

THERAPEUTIC INDICATIONS

PRAZ (Alprazolam) is indicated for the treatment of:
Anxiety disorder or the short-term relief of symptoms of anxiety;
- *Anxiety states (Anxiety Neuroses)*
  Symptoms, which occur in such patients include anxiety, tension, agitation, insomnia, apprehension, irritability and/or autonomic hyperactivity resulting in a variety of somatic complaints.
- *Mixed Anxiety-Depression*
  Symptoms of both anxiety and depression occur simultaneously in such patients.
- *Neurotic or Reactive Depression*
  Such patients primarily exhibit a depressed mood or a pervasive loss of interest or pleasure. Symptoms of anxiety, psychomotor agitation and insomnia are usually present.
- *Anxiety States, Mixed Anxiety-Depression, Neurotic or Reactive Depression* associated with other diseases such as the chronic phase of alcohol withdrawal and functional or organic disease, particularly certain gastrointestinal, cardiovascular, or dermatological disorders.

Panic disorders
PRAZ (Alprazolam) is indicated for the management of panic disorders (an illness characterized by recurrent panic attacks) with or without agoraphobia.

DOSAGE AND ADMINISTRATION

The optimum dosage of PRAZ (Alprazolam) should be individualized for maximum beneficial effect. The usual daily doses will meet the needs of most patients. In patients who require higher doses, the dosage should be increased cautiously to avoid adverse effects.
When higher dosage is required, the evening dose should be increased before the daytime doses. In general, patients who have not previously received psychotropic medication will require lower doses than those previously treated with minor tranquillizers, antidepressants, hypnotics, or those with the history of chronic alcoholism.

Indication or Population	Usual starting dosage	Maximum dosage
Anxiety	0.25 to 0.5mg, given three times daily	4.0mg daily, given in divided doses at intervals of 3-4 days
Depression	0.5mg, given three times daily	4.5mg daily, given in divided doses
Geriatric patients, patients with advanced liver disease, patients with debilitating disease	0.25mg, given two to three times daily	0.5 to 0.75mg daily, given in divided doses; to be gradually increased if needed and tolerated
Panic disorders	0.5mg to 1mg at bed time or 0.5mg three times a day	4mg-10mg daily. Dosage should be increased at intervals or 3-4 day in increment of no more than 1mg/day.

For patients receiving doses greater than 4mg daily, periodic reassessment and consideration of dose reduction is advised. If side effects occur, the dose should be lowered.

Duration of treatment
Effectiveness of alprazolam by systematic clinical studies are limited to four months duration for anxiety disorder and four to ten weeks duration for panic disorder. However, patients with panic disorder have been treated up to eight months without apparent loss of benefit. The physician should periodically reassess the usefulness of the drug for individual patients.

Discontinuation therapy
Dosage should be reduced gradually in keeping with good medical practice. It is suggested that the daily dosage of PRAZ (Alprazolam) be decreased by no more than 0.5mg every three days. Some patients may require an even slower dose reduction.

ADVERSE REACTIONS

Side effects to alprazolam if they occur, are generally observed at the beginning of therapy and usually disappear upon continued medication.

Patients treated for Anxiety disorders
Most frequent: Drowsiness, light-headedness

Less frequent: Blurred vision, headache, depression, insomnia, nervousness, tremor, change in weight, amnesia, coordination disorders, various gastrointestinal symptoms and autonomic manifestations. In addition, the following adverse effects have been observed in association with the use of benzodiazepines including alprazolam: Dystonia, irritability, concentration difficulties, anorexia, fatigue, slurred speech, jaundice, musculoskeletal weakness, changes in libido, menstrual irregularities, incontinence, urinary retention, and abnormal liver functions.

Patients treated for Panic disorders
Most frequent: Drowsiness, fatigue, impaired coordination, slurred speech.
Less frequent: Altered mood, gastrointestinal symptoms, dermatitis, memory problems, sexual dysfunction, intellectual impairment and confusion.
As with other benzodiazapines, reactions such as concentration difficulties, confusion, hallucinations, stimulation, an adverse behavioral effect such as irritability, agitation, rage and regressive or hostile behavior have been reported rarely.

CONTRAINDICATIONS

- Alprazolam is contraindicated in patients with known hypersensitivity to this drug or other benzodiazepines.
- Alprazolam is contraindicated in patients with acute narrow angle glaucoma.

PRECAUTIONS

General

As with other psychotropic medications, the usual precautions with respect to administration of the drug and size of the prescription are indicated for severely depressed patients or those in whom there is reason to expect concealed suicidal ideation or plans.

Impaired Renal or Hepatic Function

If treatment is necessary in patients with impaired hepatic or renal function, therapy should be initiated at a very low dose and the dosage increased only to the extent that it is compatible with the degree of residual function of these organs. Such patients should be followed closely and should have periodic laboratory assessments.

Drug Abuse and Dependence

Physical and psychological dependence may occur with benzodiazepines, including alprazolam. Patients who are prone to abuse drugs should be under careful surveillance when receiving alprazolam. Patients with a history of alcohol or drug abuse are at higher risk for developing psychological dependence.
It may be difficult to differentiate between relapse and withdrawal upon discontinuation of alprazolam, since symptoms may be similar to those for which the patient is being treated. Dosage must be gradually tapered to minimize withdrawal reactions, in keeping with good medical practice.

Pregnancy

The safety of the use of alprazolam in pregnancy has not been established. Therefore, alprazolam is not recommended for use during pregnancy.

Nursing mothers

Benzodiazepines are known to be excreted in human milk. It should be assumed that alprazolam is as well. As a general rule, nursing should not be undertaken by mothers who use alprazolam.

Pediatric use

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

Geriatrics

Elderly and debilitated patients have been found to be prone to the CNS depressant activity of benzodiazepines, even after low doses. Manifestations of this CNS depressant activity include ataxia, over sedation and hypotension. Therefore, alprazolam should be administered with caution to these patients, particularly if a drop in blood pressure might lead to cardiac complications. Initial doses should be low and increments should be made gradually, depending on the response of the patient, in order to avoid over sedation, neurological impairment and other possible adverse reactions.

Drug Interactions:

- The benzodiazepines, including alprazolam, produce additive CNS depressant effects when co-administered with other psychotropic medications, alcohol, narcotics, barbiturates, anticonvulsants or antihistamines and other drugs which themselves produce CNS depression.
- The steady state plasma concentrations of imipramine and desipramine have been reported to be increased in an average of 31% and 20%, respectively, by the concomitant administration of alprazolam in doses up to 4mg/day. The clinical significance of these changes is unknown.
- Clearance of alprazolam can be delayed by the co-administration of following drugs: fluoxetine, propoxyphene, cimetidine, fluvoxamine, macrolide antibiotics and oral contraceptives.
- Co-administration of alprazolam with ketoconazole and itraconazole is not recommended because these are potent cytochrome P450 3A (CYP 3A) inhibitors.

OVERDOSAGE

Manifestations of alprazolam over-dosage include somnolence, confusion, impaired coordination, diminished reflexes and coma. Overdose reports with alprazolam are limited. As in all cases of drug overdose, respiration, pulse rate and blood pressure should be monitored. General supportive measures should be employed, along with immediate gastric lavage. Intravenous fluids should be administered and an adequate airway maintained. If hypotension occurs, it may be combated by the use of vasopressors. Dialysis is of limited value. As with the management of intentional overdosing with any drug, it should be borne in mind that multiple agents may have been ingested.

HOW SUPPLIED

PRAZ (Alprazolam) Tablets 0.25mg are available in blister pack of 30's.

PRAZ (Alprazolam) Tablets 0.5mg are available in blister pack of 30's.

PRAZ (Alprazolam) Tablets 1.0mg are available in blister pack of 30's.

STORAGE

Store below 30°C.
Protect from sunlight and moisture.
The expiration date refers to the product correctly stored at the required conditions.

Keep out of reach of children.

To be sold on prescription of a registered medical practitioner only.

Please read the contents carefully before use.
This package insert is continually updated from time to time.

Manufactured by:
Getz Pharma (Pvt.) Limited, 29-30/27,
K.I.A., Karachi - 74900, Pakistan.

Marketed by:

SCILIFE | Scilife Pharma (Pvt.) Ltd.,
16 - K.O.C.H.S., Amir Khusro Road,
Karachi - 75350, Pakistan.

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