APO-ALPRAZ

0.25 mg and 0.5 mg alprazolam

Anxiolytic-Sedative

Pharmacology :

APO-ALPRAZ (alprazolam) is a benzodiazepine with anxiolytic properties. Orally administered alprazolam is readily absorbed in man with peak plasma concentrations occurring 1 to 2 hours following administration. The halflife range of alprazolam is 6 to 20 hours following single dose administration. With multiple doses, given 3 times daily, steady state is reached within 7 days. Alprazolam and its metabolites are excreted primarily in the urine. Degradation of alprazolam occurs mainly by oxidation yielding the primary metabolites α-hydroxy-alprazolam and a benzophenone derivative. The α-hydroxy-metabolite is further transformed to demethylalprazolam. The α-hydroxy-alprazolam and demethylalprazolam are active and appear to have half-lives similar to alprazolam but are present at only low levels in the plasma. Alprazolam is 80% protein-bound.

In sleep laboratory studies in man, alprazolam decreased sleep latency, increased duration of sleep and decreased the number of nocturnal awakenings. Alprazolam produced small decreases in both stage 3 and 4 and REM sleep. Alprazolam increased REM latency in a dose-related manner.

Alprazolam 0.5mg, administered 3 times a day for 14 days, did not affect prothrombin times or plasma warfarin levels in male volunteers administered sodium warfarin orally.

Indications : APO-ALPRAZ (alprazolam) is indicated for the short-term symptomatic relief of excessive anxiety in patients with anxiety neurosis.

Adverse Effects : The most frequently reported adverse reactions with **APO-ALPRAZ** (alprazolam) were drowsiness, coordination difficulties and dizziness. Release of hostility and other paradoxical effects such as irritability, excitability and hallucinations are known to occur with the use of benzodiazepines.

Other side effects less frequently reported, listed by body systems, include the following :

Neurologic : Blurred vision, headache, seizures, slurred speech, difficulty in depth perception.

Psychiatric : Agitation, mental confusion, depression, irritability, nervousness, sleep disturbances, euphoria, lethargy, stupor.

Gastrointestinal : Dry mouth, nausea, non-specific gastrointestinal disturbances, vomiting.

Musculoskeletal : Muscle spasm, muscle weakness.

Cardiovascular : Hypotension, palpitations, tachycardia.

Dermatologic : Pruritus, rash.

Genitourinary : Incontinence, change in libido.

Hematologic : Decreased hemoglobin and hematocrit, increased and decreased WBC.

Hepatic : Elevations of alkaline phosphatase, bilirubin, SGOT, SGPT.

Miscellaneous : Increased and decreased blood sugar levels.

Precautions / Warnings :

Use in the Elderly : Elderly and debilitated patients, or those with organic brain syndrome, 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, medication 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.

Dependence Liability : Alprazolam should not be administered to individuals prone to drug abuse. Caution should be observed in all patients who are considered to have potential for psychological dependence. Withdrawal symptoms have been observed after abrupt discontinuation of benzodiazepines. These include irritability, nervousness, insomnia, agitation, tremors, convulsions, diarrhea, abdominal cramps, vomiting and mental impairment. Since these symptoms may be similar to those for which the patient is being treated, it may appear that he has suffered a relapse upon discontinuation. It is suggested that alprazolam should be withdrawn gradually if the individual is suspected of having become dependent, or the drug perhaps has been used in prolonged high doses.

Use in Mental and Emotional Disorders : It should be recognized that suicidal tendencies may be present in patients with emotional disorders, particularly when depressed and that protective measures and appropriate treatment may be necessary and should be instituted without delay.

Since excitement and other paradoxical reactions can result from the use of anxiolytic-sedatives in psychotic patients, alprazolam should not be used in patients suspected of having psychotic tendencies. As with other benzodiazepines, alprazolam should not be used in individuals with physiological anxiety or normal stress of daily living but only in the presence of disabling manifestations of an appropriate pathological anxiety disorder.

The drugs are not effective in patients with characterological and personality disorders or those with obsessive-compulsive disorders. Alprazolam is not recommended for the management of depressive or psychotic disorders.

Use in Patients with 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 have periodic laboratory assessments.

Laboratory Tests :If alprazolam is administered for repeated cycles of therapy, periodic blood counts and liver function tests are advisable.

Epileptic Patients : Since benzodiazepines may occasionally exacerbate grand mal seizures, caution is required when alprazolam is used in epileptic patients and an adjustment may be necessary in their anticonvulsive medication. Abrupt withdrawal of alprazolam should be avoided.

APO-ALPRAZ (alprazolam) is not recommended for use in patients whose primary diagnosis is psychosis or depression.

Anaphylaxis (severe allergic reaction) and angioedema (severe facial swelling) which can occur as early as the first time the product is taken. Complex sleep-related behaviors which may include sleep driving, making phone calls, preparing and eating food (while asleep).

Driving and Hazardous Activities : As with other CNSactive drugs, patients receiving alprazolam should be cautioned not to undertake activities requiring mental alertness, judgment and physical coordination such as driving or operating machinery, particularly in the early phases of dose adjustment, and until it has been established that they do not become drowsy or dizzy while taking alprazolam. Alcohol and benzodiazepines should never be mixed when driving because of the unpredictable CNS depressant effects of this combination.

Use in Pregnancy : The safety of the use of alprazolam in pregnancy has not been established. Therefore, alprazolam is not recommended for use during pregnancy. Several studies have suggested an increased risk of congenital malformations associated with the use of the benzodiazepines, chlordiazepoxide and diazepam, and meprobamate, during the first trimester of pregnancy. Since alprazolam is also a benzodiazepine derivative, its administration is rarely justified in women of child-bearing potential. If the drug is prescribed to a woman of childbearing potential she should be warned to consult her physician regarding the discontinuation of the drug if she intends to become or suspects that she is pregnant.
Use in Nursing Mother : Studies in rats have indicated that alprazolam and its metabolites are secreted into the milk. Therefore, nursing should not be undertaken while a patient is receiving the drug.
Use in Children and Adolescents : The safety and efficacy of alprazolam in patients under the age of 18 years has not been established.

Contraindications : APO-ALPRAZ (alprazolam) is contraindicated in patients with known hypersensitivity to alprazolam or other benzodiazepines. Alprazolam is also contraindicated in pregnancy, in infants and in patients with myasthenia gravis and acute narrow angle glaucoma.

Drug Interactions : Benzodiazepines may potentiate or interact with effects of other CNS-acting drugs such as alcohol, narcotics, barbiturates, non-barbiturate hypnotics, antihistamines, phenothiazines, butyrophenones, monoamine oxidase inhibitors, tricyclic antidepressants and anticonvulsants. Therefore, if alprazolam is to be combined with other drugs acting on the CNS, careful consideration should be given to the pharmacology of the agent involved because of the possible additive or potentiating effects. Patients should also be advised against the simultaneous use of other CNS depressant drugs and should be cautioned not to take alcohol during the administration of alprazolam.

Dosage : The dosage of **APO-ALPRAZ** (alprazolam) must be individualized and carefully titrated in order to avoid excessive sedation or mental and motor impairment. As with other anxiolytic-sedatives, short courses of treatment should usually be the rule for the symptomatic relief of excessive anxiety and the initial course of treatment should not last longer than one week without reassessment of the need for a limited extension. If necessary, drug dosage can be adjusted after one week of treatment. Initially, not more than one week's supply of the drug should be provided and automatic prescription renewals should not be allowed. Subsequent prescriptions, when required, should be limited to short courses of therapy.
Usual Adult Dosage : The initial adult dosage of **APO-ALPRAZ** is 0.25 mg given 2 or 3 times daily. If required, increases may be made in 0.25 mg increments according to the severity of symptoms and patient response. It is recommended that the evening dose be increased before the daytime doses. Very severe manifestations of anxiety may require larger initial daily doses. The optimal dosage is one that permits symptomatic control of excessive anxiety without impairment of mental and motor function. Exceptionally, it may be necessary to increase dosage to a maximum of 3.0 mg daily, given in divided doses.

Elderly and Debilitated Patients : The initial dosage is 0.125 mg 2 or 3 times daily. If necessary, this dosage may be increased gradually depending on patient tolerance and response.

Symptoms and Treatment of Overdosage : Symptoms : As in the management of overdose with any drug, it should be remembered that multiple agents may have been ingested. Overdose of **APO-ALPRAZ** (alprazolam) is manifested as an extension of its pharmacological activity. Thus, varying degrees of CNS depressant effects such as somnolence and hypnosis can occur. Other manifestations of overdosage may include muscle weakness, ataxia, dysarthria and particularly in children paradoxical excitement. In more severe cases diminished reflexes, confusion and coma may ensue.
Fatalities with benzodiazepines rarely occur except when other drugs, alcohol or aggravating factors are involved.
Treatment : Vomiting may be induced if the patient is fully awake. Vital signs should be monitored and general supportive measures should be employed as indicated. Gastric lavage should be instituted as soon as possible. Intravenous fluids may be administered and an adequate airway should be maintained.
Experiments in animals have indicated that cardiopulmonary collapse can occur with massive intravenous doses of alprazolam. This could be reversed with positive mechanical respiration and the intravenous infusion of levarterenol.
Animal experiments with alprazolam and related compounds have suggested that haemodialysis and forced diuresis are probably of little value.

Mode of Administration: Oral

Availability of Dosage Forms :
APO-ALPRAZ (alprazolam) is available in 0.25 mg (white, oval, biconvex, scored and engraved ALP over 0.25 on one side) and 0.5 mg (peach, oval, biconvex, scored and engraved ALP over 0.5 on one side). Available in PVC Blisters of 1000 tablets. 0.5mg is also available in PVC Blisters of 500 tablets.
Storage Conditions: Store below 30°C.

Manufacturer: Apotex Inc., 150 Signet Drive, Weston, Ontario, Canada M9L 1T9.

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