ALPRANAX® TABLET 0.5MG

Ingredient(s):
Each tablet contains:
Alprazolam 0.5mg

Pharmacodynamics:
Alprazolam is a triazolo analog of the 1,4 benzodiazepine class of central nervous system-active compounds. The chemical name is 8-chloro-1-methyl-6-phenyl-4H-s-triazolo (4,3-α)(1,4) benzodiazepine.

Pharmacokinetics:
1. Alprazolam is readily absorbed from the gastrointestinal tract following oral administration with peak plasma concentrations being achieved within 1-2 hours. The mean half-life in plasma is 12 to 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. Alprazolam and its metabolites are excreted primarily in the urine.
2. Alprazolam did not affect the prothrombin times or plasma warfarin levels in male volunteers administered sodium warfarin orally.

Indication(s):
Anxiety States: Symptoms 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.
Neurotic or Reactive Depression: Patients show a depressed mood or a pervasive loss of interest or pleasure. Symptoms include anxiety, psychomotor agitation and insomnia. Other characteristics are appetite disturbances, changes in weight, somatic complaints, cognitive disturbances, decreased energy, feeling of worthlessness or guilt or thoughts of death or suicide.
Alprazolam should not be used in patients whose primary symptom of depression is psychomotor retardation; with a diagnosis of bipolar depression; with psychotic symptoms.
Anxiety states, mixed anxiety-depression or neurotic depression associated with other diseases, eg the chronic phase of alcohol withdrawal and functional or organic disease, particularly certain gastrointestinal, cardiovascular or dermatological disorders.
Alprazolam is also indicated for the treatment of panic disorder, with or without agoraphobia.
The effectiveness of Alprazolam for long-term use exceeding 6 months has not been established.
The physician should reassess the usefulness of the drug for the individual patient from time to time.

Dosage and Administration:
The optimum dosage of Alprazolam should be individualized based on the severity of the symptoms and patient response for maximum beneficial effect.
The usual daily dosage (refer table) will meet the needs of most patients. Dosage should be increased cautiously to avoid adverse effects. The evening dose should be increased before the daytime doses.
Patients who have not previously received psychotropic medications will require lower doses than those previously treated with minor tranquilizers, antidepressants or hypnotics or those with a history of chronic alcoholism. The general principle of using the lowest effective dosage should be followed to preclude the development of oversedation or ataxia.

	Usual Starting Dosage*	Usual Dosage Range
Anxiety	0.25-0.5mg given 3 times daily	0.5-4mg daily, given in divided dose
Depression	0.5mg given 3 times daily	1.5-4.5mg daily, given in divided dose
Geriatric patients or in the presence of debilitating disease	0.25mg, given 2-3 times daily	0.5-0.75mg daily, given in divided dosage; to be gradually increased if needed and tolerated
Panic-related disorders	0.5-1mg, given at bedtime	The dose should be adjusted to patient response. Dosage adjustments should be in increments no greater than 1 mg every 3-4 days. Additional doses can be added until 3 or 4 times daily schedule is achieved. The mean dose in a large multi-clinic study was 5.7 ± 2.3mg/day with rare patients requiring a maximum of 10mg daily.
* If side effects occur, the dose should be lowered		

Route of Administration: Oral

Contraindication(s):
Patients with known sensitivity to the benzodiazepines.

Side Effect(s) / Adverse Reaction(s):
Side effects are generally observed at the beginning of therapy and usually disappear upon continued medication or decreased dosage. The most common adverse reaction to Alprazolam was drowsiness. Other less common adverse reactions include lightheadedness, blurred vision, coordination disorders, various gastrointestinal symptoms and autonomic manifestations.
Withdrawal symptoms have occurred following rapid decrease or abrupt discontinuance of 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 rapid decrease or abrupt discontinuation of therapy with alprazolam.
Anterograde amnesia may occur at therapeutic dosages and the risk increasing at higher dosages. Amnesic effects may be associated with inappropriate behaviour.
Pre-existing depression may be unmasked during benzodiazepam use.
Paradoxical reactions, eg stimulation, agitation, concentration difficulties, confusion, hallucinations or other adverse behavioural effects, may occur in rare instances and in a random fashion. They are more likely to occur in children and the elderly. Patients who have borderline personality disorder, a prior history of violent or aggressive behaviour, or alcohol or substance abuse may be at risk of adverse behavioural effects. Instances of irritability, hostility and intrusive thoughts have been reported during discontinuance of alprazolam in patients with post-traumatic stress disorder.
Use of alprazolam (even at therapeutic doses) may lead to the development of physical dependence. Discontinuation of the therapy may result in withdrawal or rebound phenomena. Psychic dependence may also occur.

Precaution(s) / Warning(s):
1. Alprazolam is not recommended in patients whose primary diagnosis is schizophrenia.
2. Due to the predisposition to habituation and dependence, individuals who are prone to abuse drugs eg. alcoholics and known drug addicts, should be under surveillance.
3. Abrupt discontinuation of Alprazolam must be avoided. Gradual tapering of the dosage must be performed to preclude sequelae of rapid withdrawal. These can range from mild dysphoria and insomnia to a major syndrome including abdominal and muscle cramps, vomiting, sweating, tremor and occasionally convulsions. These signs and symptoms are generally more common in patients on excessive doses over an extended period. However, withdrawal symptoms have also been reported following abrupt discontinuance of benzodiazepines taken at therapeutic levels. Consequently, abrupt discontinuation should be avoided and a gradual tapering in dosage followed.

4. The usual precautions for treating patients with renal or hepatic impairment should be exercised. Benzodiazepines are not indicated to treat patients with severe hepatic insufficiency as they may precipitate encephalopathy.
5. Effects on the Ability to Drive or Operate Machinery: Patients should be advised not to operate motor vehicles or dangerous machinery until it is established that they do not become drowsy or dizzy while receiving Alprazolam.
6. Use in Children: The safety and efficacy of Alprazolam in children <18 years has not been established. Benzodiazepines should not be given to children without careful assessment of the need to do so; the duration of treatment must be kept to a minimum.
7. Use in elderly or debilitated patients: It is recommended that the dosage be limited to the smallest effective dose to preclude the development of ataxia or oversedation which may be a particular problem in elderly or debilitated patients.
8. A lower dose is also recommended for patients with chronic respiratory insufficiency due to risk of respiratory depression.
9. Benzodiazepines should not be used alone to treat depression of anxiety associated with depression (suicide may be precipitated in such patients). Administration to severely depressed or suicidal patients should be done with appropriate precautions and appropriate size of the prescription.
10. Risks from Concomitant Use with Opioids

    Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Alprazolam with opioids. Observational studies have demonstrated that concomitant use of opioids and benzodiazepines increases the risk of drug-related mortality compared to use of opioids alone. Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. If the decision is made to newly prescribe a benzodiazepine and an opioid together, prescribe the lowest effective dosages and minimum durations of concomitant use.

    If the decision is made to prescribe a benzodiazepine in a patient already receiving an opioid, prescribe a lower initial dose of the benzodiazepine than indicated in the absence of an opioid, and titrate based on clinical response.

    If the decision is made to prescribe an opioid in a patient already taking a benzodiazepine, prescribe a lower initial dose of the opioid, and titrate based on clinical response.

    Follow patients closely for signs and symptoms of respiratory depression and sedation. 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 of the opioid have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of opioids (See Drug Interactions).

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)

Caution - This preparation may be habit forming on prolonged use.

Interaction with Other Medicaments:
The sedative effects may be enhanced when alprazolam is used in combination with alcohol. This affects the ability to drive or use machines. Therefore it is not recommended to take alprazolam and alcohol concomitantly.
Alprazolam produces additive CNS depressant effects when co-administered with antipsychotics (neuroleptics), hypnotics, anxiolytics/sedatives, antidepressant agents, narcotic analgesics, anti-epileptic drugs, anaesthetics and sedative antihistamines.
The CYP3A isoenzymes are involved in the metabolism of Alprazolam. Concurrent use with drugs that inhibit CYP3A isoenzymes, eg. nefazodone, fluvoxamine and cimetidine, should be undertaken with caution, and reduction in Alprazolam dosage should be considered. Caution should be exercised when Alprazolam is co-administered with fluoxetine, propoxyphene, oral contraceptives, sertraline, diltiazem, or macrolide antibiotics such as erythromycin and troleandomycin. The co-administration of alprazolam with ketoconazole, itraconazole, or other azole-type antifungals is not recommended. Interactions involving HIV protease inhibitors (eg. ritonavir) and alprazolam are complex and time dependent. Low doses of ritonavir caused a large impairment of alprazolam clearance, prolonged its elimination half-life and thereby enhanced the clinical effects. However, upon extended exposure to ritonavir, CYP3A induction offset this inhibition. A dose adjustment or discontinuation of alprazolam will be required.
Opioids
Due to additive pharmacologic effect, the concomitant use of opioids with benzodiazepines increases the risk of respiratory depression, profound sedation, coma and death.
The concomitant use of opioids and benzodiazepines increases the risk of respiratory depression because of actions at different receptor sites in the central nervous system that control respiration. Opioids interact primarily at μ-receptors, and benzodiazepines interact at GABAA sites. When opioids and benzodiazepines are combined, the potential for benzodiazepines to significantly worsen opioid-related respiratory depression exists.
Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate (see Warnings and Precautions).
Limit dosage and duration of concomitant use of benzodiazepines and opioids, and follow patients closely for respiratory depression and sedation.

Pregnancy and Lactation:
Alprazolam should be avoided during pregnancy except when clearly needed and the anticipated benefit to the patient outweighs the potential risk to the fetus. Nursing should not be undertaken while receiving Alprazolam.

Symptoms and Treatment for Overdosage and Antidote(s):
As with other benzodiazepines, overdose should not present a threat to life unless combined with other CNS depressants (including alcohol). Manifestations of Alprazolam overdosage include extensions of its pharmacologic activity eg. slurring of speech, motor incoordination and degrees of central nervous system depression ranging from drowsiness to coma. In mild cases, symptoms include drowsiness, mental confusion and lethargy. In more serious cases, symptoms may include ataxia, hypotonia, hypotension, respiratory depression, rarely coma and very rarely death.
The treatment includes induced vomiting and/or gastric lavage. If there is no advantage in emptying the stomach, activated charcoal should be given to reduce absorption. Respiration and cardiovascular functions eg. respiration pulse and blood pressure should be monitored and supported by general measures when necessary. IV fluids may be administered and an adequate airway maintained.
Flumazenil may be useful as an antidote.
Animal experiments have suggested that forced diuresis or hemodialysis is probably of little value in treating overdosage. The physician should bear in mind that multiple agents may have been ingested.

Shelf-life:
3 years from the date of manufacture.

Storage Condition(s):
Store at temperature below 30° C. Protect from light and moisture.

Product description and Packing(s):
An elliptical light-pink color tablet in the shape of "YS | 2" " ".
Blister packing of 10's x 50 and 10's x 100.

Y. S. P.®
Manufacturer and Product Registration Holder:
Y.S.P. INDUSTRIES (M) SDN. BHD. (199001001034)
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