Alpraline Tablets 0.5mg "S.T."

INGREDIENT

Each Tablet contains:

Alprazolam .....0.5 mg

DESCRIPTION

It is a pale pink, oval-shaped, biconvex tablet.

PHARMACOLOGICAL PROPERTIES

(1) 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).

(2) Pharmacokinetic properties
Alprazolam is readily absorbed. Following oral administration peak concentration in the plasma occurs after 1 – 2 hours. The mean half-life is 12 – 15 hours. Repeated dosage may lead to accumulation and this should be borne in mind in elderly patients and those with impaired renal or hepatic function. Alprazolam and its metabolites are excreted primarily in the urine.

In vitro alprazolam is bound (80%) to human serum protein.

INDICATIONS

Alprazolam is indicated for the short-term treatment of moderate or severe anxiety states and anxiety associated with depression. It is only indicated when the disorder is severe, disabling or subjecting the individual to extreme distress.

Alprazolam should not be used to treat short-term mild anxiety, such as anxiety or tension associated with the stress of everyday life. As the efficacy of Alprazolam in depression and in phobic or obsessional states has yet to be established, specific treatment may have to be considered.

DOSAGE AND ADMINISTRATION

Oral administration

Treatment should be as short as possible. It is recommended that the patient be reassessed at the end of no longer than 4 weeks' treatment and the need for continued treatment established, especially in case the patient is symptom free. The overall duration of treatment should not be more than 8-12 weeks, including a tapering off process.

In certain cases extension beyond the maximum treatment period may be necessary; if so, it should not take place without re-evaluation of the patient's status with special expertise. As with all benzodiazepines, physicians should be aware that long-term use might lead to dependence in certain patients.

The optimum dosage of Alprazolam should be based upon the severity of the symptoms and individual patient response. The lowest dose which can control symptoms should be used. Dosage should be reassessed at intervals of no more than 4 weeks. The usual dosage is stated below; in the few 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 medications will require lower doses than those so treated, or those with a history of chronic alcoholism.

Treatment should always be tapered off gradually. During discontinuation of alprazolam treatment, 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 three days.

Some patients may require an even slower dosage reduction

There is a reduced clearance of the drug and, as with other benzodiazepines, an increased sensitivity to the drug in elderly patients. Anxiety: 250 micrograms (0.25 mg) to 500 micrograms (0.5 mg) three times daily increasing if required to a total of 3 mg daily.

Geriatric patients or in the presence of debilitating disease: 250 micrograms (0.25 mg) two to three times daily to be gradually increased if needed and tolerated.

Children: Not recommended.

If side-effects occur, the dose should be lowered. It is advisable to review treatment regularly and to discontinue use as soon as possible. Should longer term treatment be necessary, then intermittent treatment may be considered to minimize the risk of dependence.

SIDE EFFECTS

Sedation/drowsiness, light-headedness, numbed emotions, reduced alertness, confusion, fatigue, headache, dizziness, muscle weakness, ataxia, double or blurred vision, insomnia, nervousness/anxiety, tremor, change in weight. These phenomena occur predominantly at the start of therapy and usually disappear with repeated administration. Other side effects like gastrointestinal disturbances, changes in libido or skin reactions have been reported occasionally.

In addition, the following adverse events have been reported in association with the use of alprazolam: dystonia, anorexia, slurred speech, jaundice, musculoskeletal weakness, sexual dysfunction/changes in libido, menstrual irregularities, incontinence, urinary retention, abnormal liver function and hyperprolactinaemia. Increased intraocular pressure have been rarely reported.

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 rapid decrease or abrupt discontinuation of therapy with alprazolam.

Amnesia

Anterograde amnesia may occur at therapeutic dosages, the risk increasing at higher dosages. Amnesic effects may be associated with inappropriate behaviour (see warnings and precautions).

Depression

Pre-existing depression may be unmasked during benzodiazepam use.

Psychiatric and 'paradoxical' reactions

Reactions like restlessness, agitation, irritability, aggressiveness, delusion, rages, nightmares, hallucinations, psychoses, inappropriate behaviour and other adverse behavioural effects are known to occur when using benzodiazepines or benzodiazepine-like agents. They may be quite severe with this product. They are more likely to occur in children and the elderly.

In many of the spontaneous case reports of adverse behavioural effects, patients were receiving other CNS drugs concomitantly and/or were described as having underlying psychiatric conditions. Patients who have borderline personality disorder, a prior history of violent or aggressive behaviour, or alcohol or substance abuse may be at risk of such events. Instances of irritability, hostility and intrusive thoughts have been reported during discontinuance of alprazolam in patients with post-traumatic stress disorder.

Dependence

Use (even at therapeutic doses) may lead to the development of physical dependence: discontinuation of the therapy may result in withdrawal or rebound phenomena (see warnings and precautions). Psychic dependence may occur. Abuse of benzodiazepines have been reported.

Effects on ability to drive and use machines

Sedation, amnesia, impaired concentration and impaired muscle function may adversely affect the ability to drive or use machines. If insufficient sleep occurs, the likelihood of impaired alertness may be increased.

These effects are potentiated by alcohol.

Patients should be cautioned about operating motor vehicles or engaging in other dangerous activities while taking Alprazolam.

CONTRAINDICATIONS

Myasthenia gravis

Hypersensitivity to benzodiazepines or any of the other constituents of the tablet

Severe respiratory insufficiency

Sleep apnoea syndrome

Severe hepatic insufficiency

PRECAUTIONS/WARNINGS:

- **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**

Risks from Concomitant Use with Opioids

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Alpraline 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 Alpraline 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 Interaction with other medicinal products and other forms of interaction).

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Tolerance

Some loss of efficacy to the hypnotic effects of benzodiazepines may develop after repeated use for a few weeks.

Dependence

Use of benzodiazepines may lead to the development of physical and psychic dependence upon these products. The risk of dependence increases with dose and duration of treatment; it is also greater in patients with a history of alcohol and drug abuse.

Once physical dependence has developed, abrupt termination of treatment will be accompanied by withdrawal symptoms. These may consist of headaches, muscle pain, extreme anxiety, tension, restlessness, confusion and irritability. In severe cases the following symptoms may

occur: derealization, depersonalisation, hyperacusis, numbness and tingling of the extremities, hypersensitivity to light, noise and physical contact, hallucinations or epileptic seizures.

Rebound insomnia and anxiety: a transient syndrome whereby the symptoms that led to treatment with a benzodiazepine recur in an enhanced form, may occur on withdrawal of treatment. It may be accompanied by other reactions including mood changes, anxiety or sleep disturbances and restlessness. Since the risk of withdrawal phenomena/rebound phenomena is greater after abrupt discontinuation of treatment, it is recommended that the dosage be decreased gradually by no more than 0.5 mg every three days. Some patients may require an even slower dose reduction.

Duration of treatment

The duration of treatment should be as short as possible (see posology) depending on the indication, but should not exceed eight to twelve weeks including tapering off process. Extension beyond these periods should not take place without re-evaluation of the situation.

It may be useful to inform the patient when treatment is started that it will be of limited duration and to explain precisely how the dosage will be progressively decreased. Moreover it is important that the patient should be aware of the possibility of rebound phenomena, thereby minimising anxiety over such symptoms should they occur while the medicinal product is being discontinued.

There are indications, that in the case of benzodiazepines with a short duration of action, withdrawal phenomena can become manifest within the dosage interval, especially when the dosage is high. When benzodiazepines with a long duration of action are being used it is important to warn against changing to a benzodiazepine with a short duration of action, as withdrawal symptoms may develop.

Amnesia

Benzodiazepines may induce anterograde amnesia. The condition occurs most often several hours after ingesting the product and therefore to reduce the risk patients should ensure that they will be able to have uninterrupted sleep of 7-8 hours (see also undesirable effects).

Psychiatric and 'paradoxical' reactions

Reactions like restlessness, agitation, irritability, aggressiveness, delusion, rages, nightmares, hallucinations, psychoses, inappropriate behaviour and other adverse behavioural effects are known to occur when using benzodiazepines. Should this occur, use of the drug should be discontinued.

They are more likely to occur in children and the elderly.

Specific patient groups

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. The elderly should be given a reduced dose (see posology). A lower dose is also recommended for patients with chronic respiratory insufficiency due to risk of respiratory depression.

Benzodiazepines are not indicated to treat patients with severe hepatic insufficiency as they may precipitate encephalopathy. Caution is recommended when treating patients with impaired renal or hepatic function.

Benzodiazepines are not recommended for the primary treatment of psychotic illness.

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.

Benzodiazepines should be used with extreme caution in patients with a history of alcohol or drug abuse.

PREGNANCY AND LACTATION

If the product is prescribed to a woman of childbearing potential, she should be warned to contact her physician regarding discontinuance of the product if she intends to become or suspects that she is pregnant. The data concerning teratogenicity and effects on postnatal development and behaviour following benzodiazepine treatment are inconsistent. There is evidence from some early studies with other members of the benzodiazepine class that in utero exposure may be associated with malformations. Later studies with the benzodiazepine class of drugs have provided no clear evidence of any type of defect.

If, for compelling medical reasons, the product is administered during the late phase of pregnancy, or during labour, effects on the neonate, such as hypothermia, hypotonia and moderate respiratory depression, can be expected, due to the pharmacological action of the compound. Infants born to mothers who took benzodiazepines chronically during the latter stages of pregnancy may have developed physical dependence and may be at some risk of developing withdrawal symptoms in the postnatal period.

Since benzodiazepines are found in the breast milk, benzodiazepines should not be given to breast feeding mothers.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Not recommended: Concomitant intake with alcohol

The sedative effects may be enhanced when the product is used in combination with alcohol. This affects the ability to drive or use machines.

Take into account: Combination with CNS depressants

Enhancement of the central depressive effect may occur in cases of concomitant use with antipsychotics (neuroleptics), hypnotics, anxiolytics/sedatives, antidepressant agents, narcotic analgesics, anti-epileptic drugs, anaesthetics and sedative antihistamines.

Pharmacokinetic interactions can occur when alprazolam is administered along with drugs that interfere with its metabolism. Compounds that inhibit certain hepatic enzymes (particularly cytochrome P450 3A4) may increase the concentration of alprazolam and enhance it's 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:

The 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 and cimetidine.

Caution is recommended when alprazolam is co-administered with fluoxetine, propoxyphene, oral contraceptives, sertraline, diltiazem, or macrolide antibiotics such as erythromycin and troleandomycin.

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 offset this inhibition. This interaction will require a dose-adjustment or discontinuation of alprazolam.

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 $GABA_A$ 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 Precautions/Warnings).

Limit dosage and duration of concomitant use of benzodiazepines and opioids, and follow patients closely for respiratory depression and sedation.

OVERDOSE

Clinical Experience

Manifestations of alprazolam overdosage include somnolence, confusion, impaired coordination, diminished reflexes and coma. Death has been reported in association with overdoses of alprazolam by itself, as it has with other benzodiazepines. In addition, fatalities have been reported in patients who have overdosed with a combination of a single benzodiazepine, including alprazolam, and alcohol; alcohol levels seen in some of these patients have been lower than those usually associated with alcohol-induced fatality.

The acute oral LD_{50} in rats is 331 - 2171 mg/kg. Other experiments in animals have indicated that cardiopulmonary collapse can occur following massive intravenous doses of alprazolam (over 195 mg/kg; 975 times the maximum recommended daily human dose of 10 mg/day). Animals could be resuscitated with positive mechanical ventilation and the intravenous infusion of norepinephrine bitartrate.

Animal experiments have suggested that forced diuresis or hemodialysis are probably of little value in treating overdosage.

General Treatment of Overdose

Overdosage reports with alprazolam are limited. As in all cases of drug overdosage, 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. Flumazenil, a specific benzodiazepine receptor antagonist, is indicated for the complete or partial reversal of the sedative effects of benzodiazepines and may be used in situations when an overdose with a benzodiazepine is known or suspected. Prior to the administration of flumazenil, necessary measures should be instituted to secure airway, ventilation and intravenous access. Flumazenil is intended as an adjunct to, not as a substitute for, proper management of benzodiazepine overdose. Patients treated with flumazenil should be monitored for re-sedation, respiratory depression, and other residual benzodiazepine effects for an appropriate period after treatment. **The prescriber should be aware of a risk of seizure in association with flumazenil treatment, particularly in long-term benzodiazepine users and in cyclic antidepressant overdose.**

SHELF LIFE:
3 Years

STORAGE CONDITION:
Store below 30°C and away from excess heat and moisture.

PACKAGE:
10 x 10 tablets in PVC/foil blister strip / box

REGISTRATION NO.: MAL07090924AZ

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TAIWAN BIOTECH CO., LTD.
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Product Registration Holder:
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