ASOLAN TABLET 0.5MG

DESCRIPTION: A round pink, 7 mm diameter tablet with marking "DUOMA/DUOMA" and "DUO 2"

COMPOSITION: Each tablet contains Alprazolam 0.5 mg

PHARMACODYNAMICS:

In general, benzodiazepines act as depressants of the central nervous system (CNS), producing all levels of CNS depression from mild sedation to hypnosis to coma depending on dose. The precise sites and mechanisms of action have not been completely established. Although various mechanisms of action have been proposed, it is believed that benzodiazepines enhance or facilitate the inhibitory neurotransmitter action of gamma-aminobutyric acid (GABA), which is one of the major inhibitory neurotransmitters in the brain and mediates both pre- and post-synaptic inhibition in all regions of the CNS, following interaction between the benzodiazepine and a specific neuronal membrane receptor.
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.

PHARMACOKINETICS:

Following oral administration to fasting subjects, alprazolam is rapidly absorbed with nearly complete bioavailability. Alprazolam exhibits linear kinetics; after single dose administration of 0.5 – 3.0 mg plasma levels of 8.0p 40 mg/mL were observed; during multiple dose administration of 1.5 – 10 mg/day in divided doses, steady state plasma levels of 18.3 – 100 mg/mL were observed. Peak plasma levels showed a two- to three-fold variation within individual treatment groups. The plasma half life of alprazolam after single doses in health subjects has ranged from 6 to 25 hours. The mean half life of individual treatment groups ranged only from 10 to 14 hours. Alprazolam and its metabolites are excreted primarily in the urine. About 50 percent of the dose is excreted within 24 hours, and 94 percent after 72 hours. With chronic dosing, the apparent elimination half life increases by about 50 percent, possibly because of compartmentalization effects.
Plasma levels of 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.
Some 21 metabolites of alprazolam were detected in man. In addition to alprazolam, the major drug-related materials excreted in urine are alpha-hydroxyalprazolam, and a benzophenone analog. The biological activity of alpha-hydroxyalprazolam is approximately one-half that of alprazolam. The benzophenone metabolite is essentially inactive. Plasma level of these metabolites is extremely low. However, their half-lives appear to be of the same order of magnitude as that of alprazolam. In vitro alprazolam is bound (80%) to human serum protein. When alprazolam-14C was administered to pregnant mice, drug-related materials appeared uniformly distributed in the foetus with 14C concentration approximately the same as in the blood and skeletal muscle of the mother.
Of the known alprazolam metabolites, only alpha-hydroxy-alprazolam shows significant pharmacologic activity (in animals); however, only very low levels of this metabolite are found in human plasma.
Alprazolam tablets did not affect the prothrombin times or plasma warfarin levels in male volunteers administered sodium warfarin orally.

INDICATION:

Anxiety States (Anxiety Neurosis): 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. Other characteristics include appetite disturbances, changes in weight, somatic complaints, cognitive disturbances, decreased energy, feeling of worthlessness or guilt or thoughts of death or suicide.
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.
Panic related disorders: Alprazolam is indicated in the treatment of panic disorder with or without some phobic avoidance. Alprazolam is also indicated for the blocking or attenuation of panic attacks and phobias in patients who have agoraphobia with panic attacks. The effectiveness of alprazolam in the treatment of anxiety, anxiety associated with depression and neurotic (reactive) depression for long-term use exceeding six months has not been established by systematic clinical trials; however, patients with panic-related disorders have been effectively treated for up to eight months.
The physician should periodically reassess the usefulness of the drug for the individual patient.

RECOMMENDED DOSAGE:

The optimum dose should be individualized based upon the severity of the symptoms and individual patient response. 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. It is recommended that the general principle of using the lowest effective dose be followed, especially in elderly or debilitated patients to preclude the development of ataxia or oversedation.

Duration of Treatment:
The overall duration of treatment should not be more than 8-12 weeks, including a tapering off process.

Discontinuation of Treatment:
To discontinue 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 3 days. Some patients may require an even slower dosage reduction (see section Warnings and Precautions).

Pediatric Use:
Safety and efficacy have not been established in children under 18 years of age.

Indication or Population	Usual starting Dosage (If side effects occur, the dose should be lowered.	Usual Dosage Range
Anxiety	0.75 to 1.5 mg daily given in divided doses	0.5 to 4.0 mg daily, given in divided doses
Depression	1.5 mg daily, given in divided doses	1.5 to 4.5 mg daily given in divided doses
Panic Disorders	0.5 to 1.0 mg given at bedtime or 0.5 mg three times daily	Dose should be adjusted to patient response with increments no greater than 1mg/day every 3 to 4 days. Additional doses can be added until a schedule of three or four times daily is achieved. [The mean dose in a large multi-clinic study was 5.7 ± 2.27 mg, with occasional patients requiring a maximum of 10 mg/day.]
Geriatric patients	0.5 to 0.75mg daily given in divided doses	0.5 to 0.75 mg/day, given in divided doses; may be gradually increased if needed and tolerated.

ROUTE OF ADMINISTRATION: Oral

CONTRAINDICATIONS: Hypersensitivity to benzodiazepines; myasthenia gravis; chronic obstructive airways disease with incipient respiratory failure.

WARNINGS & PRECAUTIONS:

CAUTION: THIS PREPARATION MAY BE HABIT FORMING ON PROLONGED USE.
Abilities may be impaired on the day following use. Patients should be advised that their tolerance for alcohol and other CNS depressants will be diminished and that these medications should either be eliminated or given in reduced dosage in the presence of alprazolam.
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).
Following the prolonged use of Alprazolam at therapeutic doses, withdrawal from the medication should be gradual. An individualized withdrawal timetable needs to be planned for each patient in whom dependence is known or suspected (periods form four weeks to four months have been suggested). As with other benzodiazepines, when treatment is suddenly withdrawn, a temporary increase in sleep disturbance can occur after use of Alprazolam (see Precautions, Withdrawal and Dependence).
In general, benzodiazepines should be prescribed for short periods only (eg. 2-4 weeks). With the exception of the use of Alprazolam for the treatment of Panic Disorder (see Indications), continuous longterm use of alprazolam 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, eg. rebound anxiety following the cessation of an anxiolytic benzodiazepine – see Precautions, Withdrawal and Dependence.

Precautions:
Depression, Psychosis and Schizophrenia: Alprazolam is not recommended as 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 precautions exercised when using any psychotropic drug in depressed or potentially suicidal patients should be applied when using higher doses of alprazolam in patients with panic related disorders.
Paradoxical Reactions: Paradoxical reactions such as acute rage, stimulation or excitement may occur in rare instances; should such reactions occur, alprazolam should be discontinued.
Geriatric of 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. For elderly or debilitated patients the dosage should be limited to the smallest effective amount to preclude such effects.
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.
Impaired renal /liver function: Patients with impaired renal of 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).
Amnesia: Transient amnesia or memory impairment has been reported in association with the use of benzodiazepines.
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 suggests 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.

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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 behaviour.

The result of withdrawal symptoms is a direct consequence of physical dependence to Alprazolam tablets. 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 (eg. feelings of motion, metallic taste), depersonalization, derealisation, delusional beliefs, hyperreflexia and loss of short term memory, to a major syndrome which 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 tablets who require a dosage reduction be gradually tapered under close supervision (see Discontinuation of treatment) to minimize the incidence of 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 therapy with alprazolam tablets 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 base line before active treatment was initiated. Rebound phenomena refer to the return of symptoms characteristic of the original disorder, at levels greater than originally seen at base line.

In general rebound phenomena reflect the re-emergence of pre-existing conditions combined with withdrawal symptoms described earlier. Withdrawal/rebound phenomena may follow high doses of benzodiazepines for relatively short periods of time.

Risks from Concomitant Use with Opioids :

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Asolan 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 Asolan 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) .

Use in paediatrics: The safety and efficacy of alprazolam in children has not been established.

INTERACTION WITH OTHER MEDICAMENTS:

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.

The benzodiazepines including alprazolam tablets, produce additive CNS depressant effects when co-administered with drugs such as barbiturates, alcohol, sedatives, tricyclic antidepressants, non-selective MAO inhibitors and other antipsychotics, skeletal muscle relaxants, antihistamines, narcotic analgesics and anaesthetics (see Warnings).

Alprazolam undergoes oxidative metabolism, and consequently may interact with disulfiram or cimetidine resulting in increased plasma levels. Increased levels of alprazolam have also been observed with co-administration of erythromycin. Patients should be observed closely for evidence of enhanced benzodiazepine response during concomitant treatment with disulfiram, cimetidine, erythromycin or other macrolide antibiotics; some patients may require a reduction in dosage 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, has been reported with benzodiazepine administration.

The steady state plasma concentrations of imipramine and desipramine have been reported to be increased an average of 31% and 20% respectively, by the concomitant administration of alprazolam tablets in doses up to 4 mg/day. The clinical significance of these changes is unknown.

Alprazolam causes a small decrease (7%) in lithium clearance. Caution should be exercised with the 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 tablets and oral contraceptives concurrently.

Interaction with Anti-HIV drugs: Ritonavir: A significant decrease in mean alprazolam Cmax values (16%) but not in mean AUC values (12%). Similarly, a significant effect was observed on the sedation effect curve but not on the extent of sedation. Mild psychomotor impairment was confounded by a learning effect. These pharmacokinetic and pharmacodynamic results are inconsistent with considering the pharmacologic effect of alprazolam. These results were not considered clinically significant. Indinavir: Competitive inhibition of the metabolism of these drugs and creates potential for serious and or life threatening adverse events such as prolonged sedation or respiratory depression. Amprenavir: Serum concentrations may increased which could increase the activity of alprazolam. Although specific studies have not been performed, co-administration with amprenavir should be avoided due to the potential for prolonged sedation.

USE IN PREGNANCY & LACTATION:

Use in pregnancy: Benzodiazepines cross the placenta and may cause hypotonia, respiratory depression and hypothermia in the newborn infant. Continuous treatment during pregnancy and administration of high doses in connection with delivery should be avoided. Withdrawal symptoms in newborn infants have been reported with this class of drug.

Use in lactation: Human studies on the excretion of alprazolam in breast milk have not been performed. Studies in mice, however, indicated that alprazolam and its metabolites are excreted in breast milk. Benzodiazepines generally show increased toxicity in neonates, and the excretion of benzodiazepines in breast milk may cause drowsiness 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.

SIDE EFFECTS:

Side effects if they occur, are generally observed at the beginning of therapy and usually disappear upon continued medication or decreased dosage. In patients treated for anxiety associated with depression, the most common adverse reactions to alprazolam tablets were drowsiness and light-headedness/dizziness. Less common adverse reactions were blurred vision, headache, depression, insomnia, nervousness/anxiety, tremor, change in weight, memory impairment/amnesia, coordination disorders, various gastrointestinal symptoms, and autonomic manifestations. As with other benzodiazepines, reactions such as stimulation, agitation, concentration difficulties, confusion, hallucinations, or other adverse behavioural effects, have been reported with alprazolam. Increased intra-ocular pressure has been rarely reported.

In addition, the following adverse events have been reported in association with the use of anxiolytic benzodiazepines, including alprazolam: dystonia, irritability, anorexia, fatigue, slurred speech, jaundice, musculoskeletal weakness, changes in libido, menstrual irregularities, incontinence, urinary retention, and abnormal liver function.

The most common adverse reactions in patients with panic related disorders were sedation/drowsiness; fatigue, ataxia/impaired coordination and slurred speech. Less common adverse reactions were altered mood, GI symptoms, dermatitis, memory problems, sexual dysfunction, intellectual impairment and confusion.

Rarely, jaundice or abnormal liver function tests occur during alprazolam therapy, with recovery of function after cessation of use.

Episodes of hypomania, mania and other adverse behavioural effects may occur in rare instances with the use of alprazolam, and may necessitate the discontinuation of therapy. Such discontinuation should follow the recommended daily dosage reduction regimen (see Dosage and Administration).

SYMPTOMS AND TREATMENT OF OVERDOSE:

Overdosage: Overdosage of benzodiazepines is usually manifested by an extension of their pharmacologic activity, including central nervous system depression ranging from drowsiness to coma. In more serious cases, symptoms may include drowsiness, mental confusion and lethargy. In more serious cases symptoms may include ataxia, hypotonia, hypotension, respiratory depression, coma and very rarely death.

Treatment: In the management of overdosage it should be borne in mind that multiple agents may have been taken. Following overdosage with alprazolam tablets, vomiting should be induced (within one hour) if the patient is conscious or gastric lavage undertake with the airways protected if the patient is comatose. If there is no advantage in emptying the stomach, activated charcoal should be given to reduce absorption. Hypotension and respiratory depression should be managed according to general 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. Please consult the flumazenil product information prior to usage.

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 dose of 10 mg/day). Animals could be resuscitated with positive mechanical ventilation and the intravenous infusion of noradrenaline.

STORAGE CONDITIONS:

Store below 30°C. Protect from light. Keep out of reach of children. Jauhkan daripada kanak-kanak

SHELF LIFE:

Please refer to outer package.

PACK SIZE:

Pack in 10 x 10's and 50x10's of blister pack.

PRODUCT REGISTRATION HOLDER & MANUFACTURER:

DUOPHARMA (M) SDN BHD
Lot 2599, Jalan Seruling 59 Kawasan 3,
Taman Klang Jaya, 41200 Klang, Selangor, MALAYSIA.

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