

DATA SHEET

XANAX[®]

Alprazolam 0.25 mg, 0.5 mg and 1.0 mg tablets

PRESENTATION

XANAX 0.25mg tablets are white, scored, ovoid shaped tablets coded "Upjohn 29". Length 9.1mm, Width 5.5mm, Thickness 3.5mm.

XANAX 0.5mg tablets are pink coloured, scored, ovoid shaped tablets coded "Upjohn 55". Length 9.1mm, Width 5.5mm, Thickness 3.5mm.

XANAX 1.0mg tablets are lavender coloured, scored, ovoid shaped tablets coded "Upjohn 90". Length 9.1mm, Width 5.5mm, Thickness 3.5mm.

USES

Actions

CNS agents of the 1.4 benzodiazepine class presumably exert their effects by binding at stereo specific receptors at several sites within the central nervous system. Their exact mechanism of action is unknown.

Clinically, all benzodiazepines cause a dose-related central nervous system depressant activity varying from mild impairment of task performance to hypnosis.

Pharmacokinetics

Following oral administration, alprazolam is readily absorbed. Peak concentrations in the plasma occur in one to two hours following administration. Plasma levels are proportionate to the dose given; over the dose range of 0.5 to 3.0mg, peak levels of 8.0 to 37 mg/mL were observed. The mean elimination half-life of alprazolam is 12 - 15 hours. The predominant metabolites are α -hydroxy alprazolam and a benzophenone derived from alprazolam. The biological activity of α -hydroxy-alprazolam is approximately one-half that of alprazolam. The benzophenone metabolite is essentially inactive. Plasma levels of these metabolites are extremely low, thus precluding precise pharmacokinetic description. However, their half-lives appear to be of the same order of magnitude as alprazolam. Alprazolam and its metabolites are excreted primarily in the urine. The mean percentage excreted over a two week period following a single ¹⁴C alprazolam dose was 78.8 +/- 2.1% in urine and 7.02 +/- 0.6% in faeces.

The ability of alprazolam to induce human hepatic enzyme systems has not yet been determined. However, this is not a property of benzodiazepines in general. Further, alprazolam did not affect

the prothrombin or plasma warfarin levels in male volunteers administered sodium warfarin orally.

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

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. It has not yet been determined if similar changes occur in the pharmacokinetics of alprazolam.

INDICATIONS

XANAX (alprazolam) is indicated for the treatment of:

1. **Anxiety states (anxiety neuroses).**
Symptoms which occur in such patients include anxiety, tension, fear, insomnia, apprehension, restlessness, concentration difficulties, irritability and/or autonomic hyperactivity resulting in a variety of somatic complaints.
2. **Mixed anxiety-depression.**
Symptoms of both anxiety and depression occur concurrently in such patients.
3. **Neurotic or reactive depression.**
Such patients primarily exhibit a depressed mood or a pervasive loss of interest or pleasure. Other characteristics include anxiety, appetite disturbances, changes in weight, cognitive disturbances, decreased energy, feeling of worthlessness or guilt, insomnia, somatic complaints, or thoughts of death or suicide.
4. **Anxiety states, mixed anxiety-depression, or neurotic 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.

The effectiveness of XANAX 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.

The physician should periodically reassess the usefulness of the drug for the individual patient.

DOSAGE AND ADMINISTRATION

The optimum dose should be individualised, based upon the severity of the symptoms and individual patient response. The usual dose will meet the needs of most patients. 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 in elderly or debilitated patients to preclude the development of ataxia or oversedation.

<i>Indication or population</i>	Usual starting dosage (if side effects occur dose should be lowered)	<i>Usual dosage range</i>
Anxiety	0.25 to 0.5mg, given three times daily	0.5 to 4.0mg daily, given in divided doses
Depression	0.5mg, given three times daily	1.5 to 4.5mg daily, given in divided doses
Geriatric patients or in the presence of 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

Duration of Treatment

Data are available to support usage of up to 6 months for anxiety and depression.

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 XANAX be decreased by no more than 0.5 mg every three days. Some patients may require an even slower dosage reduction.

Use in Children

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

CONTRAINDICATIONS

XANAX is contraindicated in patients with known hypersensitivity to benzodiazepines, alprazolam or to any component of the product's formulation.

WARNINGS AND PRECAUTIONS

Caution is recommended when treating patients with impaired renal or hepatic function.

Habituation and emotional/physical dependence may occur with benzodiazepines, including alprazolam. As with all benzodiazepines, the risk of dependence increases with higher doses and long-term use and is further increased in patients with a history of alcoholism or drug abuse.

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 XANAX be decreased by no more than 0.5mg every three days. Some patients may require an even slower dosage reduction.

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.

Panic disorders have been associated with primary and secondary major depressive disorders and increased reports of suicide among untreated patients. Therefore, the same precaution must be exercised when using the higher doses of XANAX in treating patients with panic disorders as is exercised with the use of any psychotropic drug in treating depressed patients or those in whom there is reason to expect concealed suicidal ideation or plans.

Administration to severely depressed or suicidal patients should be done with appropriate precautions and appropriate size of the prescription.

Episodes of hypomania and mania have been reported in association with the use of alprazolam in patients with depression.

The use of alprazolam has not been established in certain types of depression.

Pregnancy and Lactation

Pregnancy - Category C

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. Infants exposed to benzodiazepines during late third trimester of pregnancy or during labour have been reported to exhibit either the floppy infant syndrome or neonatal withdrawal symptoms. If alprazolam is used during pregnancy, or if the patient becomes pregnant while taking alprazolam, the patient should be apprised of the potential hazard to the foetus.

Lactation

Levels of benzodiazepines, including alprazolam, in breast milk are low. However, nursing should not be undertaken while using benzodiazepines.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of carcinogenic potential was observed during 2-year bioassay studies of alprazolam in rats at doses up to 30 mg/kg/day (150 times the maximum recommended) and in mice at doses up to 10 mg/kg/day (50 times the maximum recommended daily human dose).

Alprazolam was not mutagenic in the rat micronucleus test at doses up to 100 mg/kg, which is 500 times the maximum recommended daily human dose of 10 mg/day. Alprazolam also was not mutagenic *in vitro* in the DNA Damage/Alkaline Elution Assay or the Ames Assay.

Alprazolam produced no impairment of fertility in rats at doses up to 5 mg/kg/day, which is 25 times the maximum recommended daily human dose of 10 mg/day.

Effects on ability to drive and use machinery

Patients should be cautioned about using alprazolam while operating motor vehicles or engaging in other dangerous activities until it is established that they do not become drowsy or dizzy while receiving the drug.

ADVERSE EFFECTS

Adverse effects, if they occur, are generally observed at the beginning of therapy and usually disappear upon continued medication or decreased dosage. The most common adverse effects of alprazolam were sedation/drowsiness and lightheadedness/dizziness. Common adverse effects include disorientation, decreased libido, balance disorder, hypersomnia, lethargy, constipation, dry mouth and nausea. Less common adverse effects were blurred vision, headache, depression, insomnia, nervousness/anxiety, tremor, change in weight, memory impairment/amnesia, ataxia/coordination disorders, various gastrointestinal symptoms, dermatitis, and autonomic manifestations.

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

As with other benzodiazepines, adverse effects such as concentration difficulties, confusion, hallucinations, stimulation, and adverse behavioural effects such as irritability, agitation, rage and aggressive or hostile behaviour have been reported rarely. 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 for such events. Instances of irritability, hostility and intrusive thoughts have been reported during discontinuance of alprazolam in patients with post-traumatic stress disorder.

Post-Marketing Experience

The following additional adverse effects have been reported:

Psychiatric disorders	Uncommon	Hypomania, mania
Hepatobiliary disorders	Uncommon	Hepatitis
Skin and subcutaneous tissue disorders	Not known	Angioedema
General disorders and administration site conditions	Not Known	Oedema peripheral

INTERACTIONS

Benzodiazepines produce additive CNS depressant effects when co-administered with alcohol or other drugs producing CNS depression.

Pharmacokinetic interactions can occur when alprazolam is administered along with drugs that interfere with its metabolism. Compounds which inhibit certain hepatic enzymes (particularly cytochrome P4503A4) may increase the concentration of alprazolam and enhance its 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 offsets this inhibition. This interaction will require a dose-adjustment or discontinuation of alprazolam.

OVERDOSAGE

Overdosage of benzodiazepines is usually manifested by an extension of their pharmacologic activity, including respiratory depression and central nervous system depression ranging from drowsiness to coma. In mild cases, symptoms may include drowsiness, mental confusion and lethargy, impaired coordination, diminished reflexes, slurred speech, dilated pupils, absent bowel sounds, and tachycardia. In more serious cases symptoms may include ataxia, hypotonia, hypotension, hypothermia, rhabdomyolysis, atrio-ventricular block, coma and very rarely death. Serious sequelae occur when Xanax is taken with other drugs and/or ethanol is concomitantly ingested. Deep coma, marked hypotension and respiratory depression may indicate other drugs have been ingested as well. In terms of duration, most obtunded patients become arousable within 12 to 36 hours following an acute overdose.

Treatment: In the management of overdose it should be borne in mind that multiple agents may have been taken. Treatment of overdose is primarily supportive of respiratory and cardiovascular function. Following overdose with Xanax tablets, activated charcoal should be given to reduce absorption. Activated charcoal is most effective when administered within 1-hour of ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via nasogastric tube once the airway is protected.

The benzodiazepine antagonist flumazenil may be useful in hospitalised patients for the reversal of CNS actions of benzodiazepines. 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. Please consult the flumazenil product information prior to usage.

Haemoperfusion, forced diuresis and haemodialysis are generally not useful in benzodiazepine intoxication. Ipecac-induced emesis is not recommended due to the potential for CNS depression.

Contact the Poisons Information Centre for advice on the management of an overdose.

PHARMACEUTICAL PRECAUTIONS

Shelf life

Store at or below 25° C.

MEDICINE CLASSIFICATION

Controlled Drug C5

PACKAGE QUANTITIES

XANAX tablets 0.25mg, 0.5mg and 1.0mg are available in quantities of 50 or 100 (not all presentations available).

FURTHER INFORMATION

Nil

NAME AND ADDRESS

Pfizer New Zealand Ltd
P O Box 3998
Auckland, New Zealand, 1140.

Toll Free Number: 0800 736 363

DATE OF PREPARATION

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