PRODUCT MONOGRAPH

[Pr]NTP-ALPRAZOLAM
(Alprazolam)
0.25 mg and 0.5 mg Tablets
USP

Anxiolytic/Sedative

Teva Canada Limited
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THERAPEUTIC CLASSIFICATION

Anxiolytic/Sedative

ACTION AND CLINICAL PHARMACOLOGY

NTP-ALPRAZOLAM (alprazolam) is a benzodiazepine with anxiolytic properties.

In man, orally administered alprazolam is readily absorbed and reaches peak plasma concentrations within 1 to 2 hours. Alprazolam has a mean half-life of 6 to 20 hours after the administration of a single dose. When multiple doses given 3 times daily are administered, a steady state is reached within 7 days. The primary route of excretion for alprazolam and its metabolites is urinary with approximately 80% recovery. Fecal elimination accounts for about 7%. The primary metabolites, alpha-hydroxy-alprazolam and a benzophenone derivative, are the result of oxidation which is the main route degradation. Further transformation of the alpha-hydroxy metabolite yields demethylalprazolam. The metabolites, demethylalprazolam and alpha-hydroxy-alprazolam, are active and appear to have half-lives similar to that of alprazolam; however, these metabolites are present in the plasma at low levels. Alprazolam is 80% protein-bound.

In human sleep laboratory studies, alprazolam was shown to decrease sleep latency and the number of nocturnal awakenings and to increase the duration of sleep. Stage 3, stage 4 and REM sleep were all slightly reduced by alprazolam. A dose related increase in REM latency was also observed.

The administration of alprazolam 0.5 mg 3 limes daily for 14 days had no effect on prothrombin times or plasma warfarin levels in male volunteers given oral sodium warfarin.

A single-dose two-way, crossover study was conducted in order to compare the rate and extent of absorption and bioequivalence of NTP-ALPRAZOLAM 0.5 mg tablets with Xanax® 0.5 mg tablets. The pharmacokinetic plasma data (mean ± standard deviation) calculated for the two products are tabulated below:

Pharmacokinetic Indices for Alprazolam:

	NTP-ALPRAZOLAM (2 x 0.5 mg Tablets)	**Xanax® (2 x 0.5 mg Tablets)**	**Percentage of Xanax®**
AUC_T* (ng·h/mL)	182.1 (30)	180.2 (31)	101
AUC_I* (ng·h/mL)	195.0 (31)	195.0 (30)	100
Cmax* (ng/mL)	13.49 (21)	13.49 (17)	100
$Tmax^+$ (h)	1.33 (0.92)	1.67 (0.89)	- -
$T½^+$ (h)	10.58 (3.96)	10.36 (3.07)	- -

* Geometric means (CV)
\+ Arithmetic means (SD)

INDICATIONS AND CLINICAL USE

NTP-ALPRAZOLAM (alprazolam) is indicated for the short-term symptomatic treatment of excessive anxiety in patients with anxiety neurosis.

CONTRAINDICATIONS

Patients who are known to be hypersensitive to alprazolam other benzodiazepines should not be given NTP-ALPRAZOLAM (alprazolam). NTP-ALPRAZOLAM is also contraindicated in pregnancy, in infants and in patients with myasthenia gravis and acute narrow angle glaucoma.

WARNINGS

The use of NTP-ALPRAZOLAM (alprazolam) is not recommended in patients whose primary diagnosis is psychosis or depression.

Driving and Hazardous Activities:
As with other drugs which act on the CNS, patients receiving NTP-ALPRAZOLAM should be cautioned not to undertake activities which require mental alertness, judgement and physical coordination such as driving or operating machinery. This is especially important during the early periods of dose adjustment and until it has been determined that the patient does not become drowsy or dizzy during NTP-ALPRAZOLAM treatment. When combined, alcohol and benzodiazepines have unpredictable CNS depressant effects and should therefore never be mixed when driving.

Use in Pregnancy:
Alprazolam is not recommended for use during pregnancy as its safety during this time has not been established. Several studies have suggested that during the first trimester of pregnancy, the risk of congenital malformations is increased with the use of the benzodiazepines, chlordiazepoxide and diazepam, and meprobamate. Alprazolam is also a benzodiazepine; therefore, its administration is rarely justified in women of childbearing potential. Women of childbearing potential receiving alprazolam should be warned to consult their physician regarding the discontinuation of the drug if they intend to become or suspect that they are pregnant.

Use in Nursing Mothers:
Benzodiazepines are excreted in breast milk and it should be assumed that the same is true for alprazolam. Since there is a potential for adverse reactions from these drugs in nursing infants, nursing should not be undertaken by mothers receiving alprazolam therapy.

Use in Children and Adolescents:
The safety and effectiveness of alprazolam have not been determined in patients under the age of 18 years.

PRECAUTIONS

Use in the Elderly:
It has been found that elderly and debilitated patients, and those with organic brain syndrome are more susceptible to the CNS depressant activity is manifested as ataxia, oversedation and hypotension. Caution should be exercised when administering medication to these patients especially if a drop in blood pressure might result in cardiac complications. Depending on the response of the patient, initial doses should be low and increments should be made gradually in order to avoid oversedation, neurological impairment and other possible adverse reactions.

Dependence Liability:
Alprazolam should not be used in individuals prone to drug abuse. Caution should be exercised with all patients considered to have potential for psychological dependence. Abrupt discontinuation of benzodiazepines has produced withdrawal symptoms including irritability, nervousness, insomnia, agitation, tremors, convulsions, diarrhea, abdominal cramps, vomiting, mental impairment and seizures. Upon discontinuation of treatment, it may appear that the patient has suffered a relapse since the withdrawal symptoms may be similar to those for which the patient is being treated. It is therefore suggested that if the individual is suspected of having become dependent or the drug has been used in high doses for prolonged periods, alprazolam should be gradually withdrawn.

Use in Mental and Emotional Disorders:
Suicidal tendencies may be present in patients with emotional disorders, especially when depressed; therefore, it may be necessary to initiate protective measures and appropriate treatment without delay.

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

Benzodiazepines are not effective in patients with disorders of the character or personality or with obsessive-compulsive disorders. Alprazolam is also not recommended in the treatment of depressive or psychotic disorders.

Use in Patients with Impaired Renal or Hepatic Function:
If alprazolam treatment is necessary in patients with impaired hepatic or renal function, therapy should be instituted at a very low dose and the dosage increased only to the extent that it is compatible with the degree of residual function in these organs. These patients should be observed carefully and have laboratory assessments periodically.

Laboratory Tests:
It is advisable to perform blood counts and liver function tests periodically if alprazolam is used for repeated cycles of therapy.

Epileptic Patients:

When alprazolam is used in epileptic patients, caution is necessary. An adjustment in their anticonvulsive medication may also be required since grand mal seizures may occasionally be exacerbated by benzodiazepines. Alprazolam should not be withdrawn abruptly.

Drug Interactions:
Benzodiazepines may potentiate or interact with the effects of other CNS-acting drugs such as alcohol, narcotics, barbiturates, nonbarbiturate hypnotics, antihistamines, phenothtazines, butyrophenones, monoamine oxidase lnhibitors, tricyclic antidepressants and anticonvulsants. If alprazolam is to be combined with other CNS-acting drugs, the pharmacology of the agent involved should be considered carefully because of the possibility of additive or potentiating effects. During the administration of alprazolam patients should also be advised not to take alcohol or simultaneously use other CNS depressant drugs.

ADVERSE REACTIONS

The adverse reactions that are most frequently reported with alprazolam include drowsiness (36%), coordination difficulties, lightheadedness (18.6%) and dizziness. Also known to occur with the use of benzodiazepines are the release of hostility and other paradoxical effects such as irritability, excitability and hallucinations.

Other less frequently reported adverse reactions include the following:

Neurologic: Blurred vision (7%), headache (14.9%), seizures, slurred speech, difficulty in depth perception, tremor (4.6%), rigidity/stiffness (3.6%), akathisia (1.2%), dystonia (1 %), syncope (3%).

Psychiatric: Agitation, mental confusion (9.3%), depression (11.9%), irritability, nervousness (7%), sleep disturbances (9%), euphoria, lethargy, stupor.

Gastrointestinal: Dry mouth (13%), nausea/vomiting (9.3), constipation (9.3%), diarrhea (8.5%) and nonspecific gastrointestinal disturbances.
Musculoskeletal: Muscle spasm, muscle weakness.

Cardiovascular: Tachycardia/palpitations (8.1%), hypotension (3.4%).

Dermatologic: Pruritus, rash, dermatitis/allergy (4.5%).

Genitourinary: Incontinence, change in libido.

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

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

Miscellaneous: Nasal congestion (7.6%), weight loss (3.5%), increased salivation (3.5%), weight gain (2.5%) increased and decreased blood sugar levels.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptoms: As with the management of intentional overdosage with any drug, it should be borne in mind that more than one agent may have been ingested. Manifestations of alprazolam overdosage are an extension of its pharmacologic activity. Thus, varying levels of CNS depressant effects such as somnolence and hypnosis can occur. Manifestations of overdosage may also include muscle weakness, ataxia, dysarthria and paradoxical excitement, especially in children. Diminished reflexes, confusion and coma may be present in cases of greater severity.

Benzodiazepine overdosage rarely results in fatality, except when other drugs, alcohol or aggravating factors are involved.

Treatment: If the patient is completely awake, emesis may be induced. Vital signs should be monitored and general support measures should be carried out as indicated. Gastric lavage should be initiated as soon as possible. An adequate airway should be maintained. Fluids may be administered intravenously.

Animal experimentation has demonstrated that massive doses of alprazolam given intravenously can cause cardiopulmonary collapse. The animals could be resuscitated by the intravenous infusion of levarterenol and positive mechanical respiration.

Animal experiments with alprazolam and related compounds have indicated that hemodialysis and forced diuresis probably have little value.

DOSAGE AND ADMINISTRATION

In order to avoid excessive sedation or mental and motor impairment, the dosage of NTP-ALPRAZOLAM (alprazolam) must be individualized and carefully titrated. As with other anxiolytic-sedatives, short courses of treatment are the general rule for the symptomatic relief of excessive anxiety. The initial treatment period should not exceed one week without reassessment of the need for a limited extension. After one week of treatment, the dose of the drug can be adjusted if necessary. Initially, no more than one week supply of the drug should be provided and prescriptions should not be automatically renewed. When required, subsequent prescriptions should be limited to short periods of therapy.

Usual Adult Dosage: The initial adult dosage of NTP-ALPRAZOLAM 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.

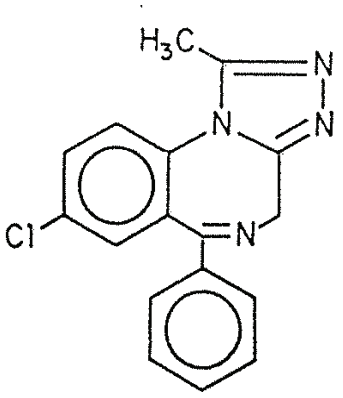
Elderly and Debilitated Patients: The initial dosage is 0.125 mg 2 or 3 times daily. If necessary, this dosage may be increased gradually depending on patient tolerance and response.

PHARMACEUTICAL INFORMATION

Trade Name: NTP-ALPRAZOLAM

Proper Name: Alprazolam

Structural Formula:



Molecular Weight: 308.77

Chemical Name: 4H-(1,2,4)Triazolo(4,3-a)(1,4)benzodiazepine,8-chloro-1-methyl-6-phenyl.

Description: Alprazolam is a benzodiazepine which occurs as a white to off-white crystalline powder. The drug is insoluble in water and soluble in alcohol.

Stability and Storage Recommendations: Store tablets between 15°C and 30°C.

AVAILABILITY

NTP-ALPRAZOLAM (alprazolam) is available as white, oval, single-scored, compressed tablets, engraved no/vo on one side, 0.25 on the other side, containing 0.25 mg of alprazolam.

NTP-ALPRAZOLAM is also available as peach-coloured, oval, single-scored, compressed tablets, engraved no/vo on one side, 0.5 on the other side, containing 0.5 mg of alprazolam.

Supplied in bottles of 100and 1000 tablets.

PHARMACOLOGY

Pharmacokinetics:

Hydroxylation of the 1-methyl group is an important metabolic pathway in man, yielding alpha-hydroxy-alprazolam and accounting for 14.96% of the urinary 14_C. The next most significant metabolic pathway involves the hydrolysis of the azomethine bond yielding the corresponding benzophenone. Approximately 30 different metabolites have been found in human urine.

Protein binding is extensive, approximately 80%, and not saturated by 1000 ng/mL alprazolam, a concentration 42 times higher than the steady state level after 0.5 mg administered three times daily (t.i.d.) and 25 times higher than the level after a single 3 mg dose. Considerable amounts of alprazolam would have to be ingested before appreciable increases in free drug would occur.

Drug Disposition:

After administration of 14_C labelled alprazolam i.v., label reached an apparent maximum concentration within one minute in the rat brain in 15 minutes after oral administration. The concentration of label was equal to the concentration in the blood for up to 15 minutes, after which, label was cleared from the brain more rapidly than the blood. In general, alprazolam and/or its metabolites are widely distributed in most tissues usually within one hour of dosing.

Animal Pharmacology:

Analysis of cortical EEG was carried out in the Rhesus monkey. Alprazolam at 0.01 - 0.03 mg/kg i.p. caused an increase in the 30-50 cps component. Ten times more diazepam was required to yield a similar change.

Alprazolam produced motor incoordination and muscle relaxation. In the rat it is estimated to be of the same order of potency a diazepam. In the decerebrate cat, it is approximately 10 to 30 times potent than diazepam.

A significant difference in route of excretion exists between humans and either the dog or rat. This is ascribed to a more active biliary secretion of alprazolam by the dog rat.

Alprazolam did not alter the level of noradrenaline in the rat brain. Incorporation of 14_C tyrosine into catecholamines in the brain was reduced by alprazolam treatment. The rate of turnover of noradrenaline and dopamine was reduced by alprazolam and diazepam.

Alprazolam has little effect on arterial blood pressure. Rapid i.v. injection of alprazolam in the anesthetized dog produced only a transient fall in arterial blood pressure.

Alprazolam was submitted for general pharmacological screening. The results essentially substantiated what was already determined by other studies. Alprazolam was found to be devoid of cardiotrophic or beta stimulatory/inhibitory activity.

TOXICOLOGY

Acute Toxicity:

Species	Route	LD50 (mg/kg)
Mouse	i.p.	500
Mouse	i.p.	509 – 582
		564 – 647
		652 – 712
Rat	i.p.	409 – 819
	p.o.	709 - 2171

Sedative effects, depression and ataxia were noted at these high doses, with death from respiratory depression and convulsions.

Subacute Toxicity:

Rats: In a six day study of rats given a fixed dose of 300 mg/kg, prolonged depression and ataxia were found in both male and female animals. In addition, 4 out of 5 female animals developed ulcers.

Dogs: In a 10 day oral toxicity study 3 dogs were tested at doses up to 300 mg/kg/day under a fixed, increasing dosage schedule. Doses up to 100 mg/kg were well tolerated.

Two 1-month studies were conducted in which Sprague-Dawley rats of both sexes were given alprazolam 0, 10, 30, 100 or 300 mg/kg/day administered by gavage. A dose dependent depression and ataxia was observed in all treated animals which resulted in a dose dependent reduction of weight in the animals receiving 30, 100 and 300 mg/kg/day. At 300 mg/kg/day, survival was poor and all females died at the end of the first week and only 2 of the 5 males survived to the end of the study. High oral doses via gavage in this study produced stomach lesions and hemorrhage. This did not occur in a 2 year rat study where animals were administered alprazolam via the diet instead of by gavage.

In a 3 month toxicity study, 4 groups of Beagle dogs (4 per group) were tested at doses of 0, 1, 10 and 100 mg/kg/day. Alprazolam was judged to be slightly toxic at the 100 mg/kg dose but non-toxic at 1 and 10 mg/kg. Brief convulsions were seen at the 2 higher dose levels with dose related severity.

Chronic Toxicity:

In a 2 year study, 4 groups of pregnant Sprague-Dawley rats received alprazolam 0, 3, 10 and 30 mg/kg/day via stomach tube from the 15th day of gestation through weaning. The dams in the 10 and 30 mg/kg/day groups were sacrificed after weaning but the dams receiving 0 and 30 mg/kg/day continued to receive alprazolam in the diet for the duration of the study. After weaning, the offspring were divided into 4 groups of 55 males and 55 females and were given alprazolam 0, 3, 10 and 30 mg/kg/day in the diet.

Aggressive behaviour was common among both males and females and was most prevalent at the 30 mg/kg/day dosage level. Convulsions were observed and were dose related in both frequency and time of onset. The first convulsions were observed in the high dose group during the third treatment month. Convulsions were noted in the mid dose group at 9 months and only 1

rat had convulsions in the low dose group at 12 months. High dose rats that appeared normal during the day were found dead the next morning with lesions of hemorrhage around the nostrils, congestion and hemorrhage of the lungs, liver and brain which were suggestive of convulsions prior to death. No convulsions were observed in dams given 30 mg/kg/day for 2 years.

A dose related trend towards and increase in the incidence of cataracts was observed at the end of the study in female but not male offspring. Dams treated with 30 mg/kg/day for 2 years also showed an increase in the incidence of cataracts compared to control dams. The males showed a linear increase in corneal vascularization with dose. No ophthalmic lesions were evident at 11 months.

There were no significant differences in body weight during the first year; however, by the end of the second year the high dose males showed a 10 to 20% decrease in weight gain compared to controls. Several animals showed abnormal hematology values, such as elevated WBC counts and occasional anemia associated with malignant lymphoma. Treatment related pathology was also evident in the kidneys, thyroid and stomach.

During two 1 year chronic toxicity studies in Beagle dogs, doses of 1 and 0.3 mg/kg/day orally produced no convulsions. Doses of 3 mg/kg/day or higher resulted in a dose dependent increase in the number of convulsions reported. Abnormal clinical signs were observed in the top 3 dose levels (i.e. 3, 10 and 30 mg/kg). Moderate loss of coordination and lethargy was observed for several months. As the lethargy subsided, the animals became hyperexcitable. In addition, convulsions occurred in all dogs at the 10 and 30 mg/kg level. These convulsions resulted in death in 4 dogs at 30 mg/kg, 4 dogs at 10 mg/kg and 1 dog at 3 mg/kg. Toxicity studies have shown similar convulsions for equivalent doses of diazepam. Since the anxiolytic potency of alprazolam appears to be approximately 10 times that of diazepam in humans, lower doses of alprazolam are employed therapeutically in humans. The margin of safety for alprazolam therefore, should be at least of the same magnitude as that for diazepam, with regard to convulsive potential. No drug related ophthalmic lesions were reported.

Carcinogenicity:
In a 24 month study of male and female rats, alprazolam at doses of 3-30 mg/kg/day administered in the diet, showed no significant potential for carcinogenicity.

Mutagenicity:
Alprazolam, at doses up to 1250 times the human dose, was not shown to be mutagenic in the rat micronucleus test.

Reproduction Studies: Two segment II rat studies were conducted with doses of 0, 5 and 10 mg/kg/day orally. In one study, some retarded ossification, agenesis and asymmetrical sternabrae were observed but this observation was not substantiated in a second study. When maximum human therapeutic dose is taken into consideration in a comparison of alprazolam with diazepam, alprazolam appears to have a greater margin of safety with regard to teratology and adverse effects on reproductive ability. No teratogenic activity or significant effect on reproductive ability was reported in any other segment I, II or III study.

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