PRODUCT MONOGRAPH

APO-ALPRAZ

alprazolam tablets USP

0.25 mg, 0.5 mg and 1.0 mg tablets

APO-ALPRAZ TS

alprazolam tablets USP

2 mg triscored tablets

ANXIOLYTIC-ANTIPANIC

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Alprazolam Tablets USP

APO-ALPRAZ TS
Alprazolam Tablets USP

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route Of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
oral	tablet 0.25 mg, 0.5 mg and 1.0 mg	Microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, magnesium stearate. The 0.5 mg tablet also contains FD&C yellow #6. The 1 mg tablet also contains D&C red #30 and FD&C blue #2
oral	triscored tablet 2 mg	Microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, magnesium stearate.

INDICATIONS AND CLINICAL USE

Adults:

APO-ALPRAZ and APO-ALPRAZ TS (alprazolam) are indicated for the management of Anxiety Disorders or the short-term symptomatic relief of symptoms of excessive anxiety. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic.

Generalized Anxiety Disorder

APO-ALPRAZ and APO-ALPRAZ TS are indicated for the treatment of Generalized Anxiety Disorder (GAD). GAD is characterized by unrealistic or excessive anxiety and worry (apprehensive expectation) about two or more life circumstances, for a period of six months or longer, during which the person has been bothered more days than not by these concerns. At least 6 of the following 18 symptoms are often present in these patients: *Motor Tension* (trembling, twitching, or feeling shaky; muscle tension, aches, or soreness; restlessness; easy fatigability); *Autonomic Hyperactivity* (shortness of breath or smothering sensations; palpitations or accelerated heart rate; sweating, or cold clammy hands; dry mouth; dizziness or lighthead-edness; nausea, diarrhea, or other abdominal distress; flushes or chills; frequent urination; trouble swallowing or "lump in throat"); *Vigilance and Scanning* (feeling keyed up or on edge; exaggerated startle response; difficulty concentrating or "mind going blank" because of anxiety; trouble falling or staying asleep; irritability). These symptoms must not be secondary to another psychiatric disorder or caused by some organic factor.

Panic Disorder with/without Agoraphobia

APO-ALPRAZ and APO-ALPRAZ TS are also indicated for the management of Panic Disorder with or without Agoraphobia. Panic disorder is an illness characterized by recurrent panic attacks. Panic attacks are discrete periods of intense fear or discomfort, with at least four of the following symptoms: dyspnea; dizziness, unsteady feelings, or faintness; tachycardia; trembling or shaking; sweating; choking; nausea or abdominal distress; depersonalization or derealization; paresthesias; flushes or chills; chest pain or discomfort, fear of dying; fear of going crazy or of doing something uncontrolled.

Attacks are usually of a few minutes duration but can, more rarely, last up to a few hours.

The diagnosis of Panic Disorders requires that either four attacks must have occurred within a four week period, or one or more attacks must have been followed by a period of at least one month of persistent fear of having another attack. The symptoms must not be attributable to known organic factors.

The panic attacks, at least initially, are unexpected. Later in the course of this disturbance certain situations, eg, driving a car or being in a crowded place, may become associated with having a panic attack. These panic attacks are not triggered by situations in which the person is the focus of others' attention (as in social phobia).

During the natural course of the illness, the patient often develops symptoms of Agoraphobia. Agoraphobia is a fear of being in situations from which escape might be difficult or in which help might not be available in the event of an unexpected panic attack. As a result of this fear, the patient either restricts travel or needs a companion when away from home, or else endures agoraphobic situations despite intense anxiety. The severity varies from mild (able to travel to work or to shop), to severe (completely housebound).

Demonstrations of the effectiveness of alprazolam by systematic clinical studies are limited to four months duration for Anxiety Disorder and four to ten weeks duration for Panic Disorder; however, patients with Panic Disorder have been treated on an open basis for up to eight months without apparent loss of benefit. The physician should periodically reassess the usefulness of drug treatment in all patients.

Geriatrics (≥65 years of age):

Elderly patients may be especially sensitive to the effects of benzodiazepines and lower doses of APO-ALPRAZ and APO-ALPRAZ TS are recommended (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics; WARNINGS AND PRECAUTIONS, Special Populations - Geriatrics; and DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment, Anxiety Disorders - Elderly and Debilitated Patients).

Pediatrics (< 18 years of age):

APO-ALPRAZ and APO-ALPRAZ TS are not recommended for use in patients under the age of 18 years (see WARNINGS AND PRECAUTIONS, Special Populations - Pediatrics).

CONTRAINDICATIONS

APO-ALPRAZ and APO-ALPRAZ TS (alprazolam) are contraindicated in patients with known hypersensitivity to alprazolam or to any component of the product's formulation, or other benzodiazepines. APO-ALPRAZ and APO-ALPRAZ TS are also contraindicated in in patients with myasthenia gravis or acute narrow angle glaucoma. However, APO-ALPRAZ and APO-ALPRAZ TS may be used in patients with open angle glaucoma who are receiving appropriate treatment.

Co-administration of APO-ALPRAZ and APO-ALPRAZ TS with ketoconazole and itraconazole are contraindicated because these medications significantly impair the metabolism of alprazolam by CYP3A4 (see DRUG INTERACTIONS, Drug-Drug Interactions).

WARNINGS AND PRECAUTIONS

General

APO-ALPRAZ and APO-ALPRAZ TS (alprazolam) are not effective in patients with Personality Disorders. APO-ALPRAZ and APO-ALPRAZ TS are not recommended for the management of Mood or Psychotic Disorders.

Dependence/Tolerance

Dependence Liability: Physical and psychological dependence may occur with benzodiazepines, including APO-ALPRAZ and APO-ALPRAZ TS. The risk of dependence increases with higher doses and long-term use. Patients who are prone to abuse drugs should be under careful surveillance when receiving APO-ALPRAZ and APO-ALPRAZ TS. Patients with a history of alcohol or drug abuse are at higher risk for developing psychological dependence.

Dependence and Withdrawal Reactions Including Seizures:

Physical dependence with withdrawal symptoms may occur with benzodiazepine discontinuation and can be severe (eg, seizures) if benzodiazepines are suddenly discontinued or upon rapid dose decrease (see DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment - Discontinuation). Even after relatively short-term use (eg, for several weeks) at the doses recommended for the treatment of transient anxiety and anxiety disorder (ie, 0.75 to 3.0 mg per day), there is some risk of dependence, as withdrawal symptoms, including seizures, have been reported . Post-marketing surveillance data suggest that the risk of dependence and its severity appear to be greater in patients treated with relatively high doses (above 4 mg per day) and for long periods (more than 8-12 weeks).

Withdrawal symptoms can range from mild dysphoria and insomnia to a major syndrome that may include irritability, nervousness, insomnia, agitation, diarrhea, abdominal cramps, vomiting, sweating, tremors and convulsions. Since symptoms may be similar to those for which the patient is being treated, it may be difficult to differentiate between relapse and withdrawal upon discontinuation.

Abrupt Discontinuations to be Avoided, Even With Short Duration of Treatment

Since the risk of withdrawal symptoms is greater after abrupt discontinuation of treatment, abrupt withdrawal of the drug should be avoided and treatment - even if only of short duration - should be terminated by gradually reducing the daily dose to minimize withdrawal reactions.

To discontinue treatment in patients taking APO-ALPRAZ and APO-ALPRAZ TS, the dosage should be reduced slowly in keeping with good medical practice. (see DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment - Discontinuation).

Risk of Withdrawal with Dose Reduction: Withdrawal reactions may occur when dosage reduction occurs for any reason. This includes purposeful tapering, but also includes inadvertent reduction of dose (eg, the patient forgets, the patient is admitted to a hospital, etc.). Therefore, the dosage of APO-ALPRAZ and APO-ALPRAZ TS should be reduced or discontinued gradually (See DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment - Discontinuation).

Status Epilepticus and its Treatment: The medical event voluntary reporting system shows that withdrawal seizures have been reported in association with the discontinuation of alprazolam. In most cases, only a single seizure was reported; however, multiple seizures and status epilepticus were reported as well. Ordinarily, the treatment of status epilepticus of any etiology involves use of intravenous benzodiazepines plus phenytoin or barbiturates, maintenance of a patent airway and adequate hydration. For additional details regarding therapy, consultation with an appropriate specialist may be considered.

Withdrawal and Rebound in Treating Panic Disorder: Because the management of Panic Disorder often requires the use of average daily doses of alprazolam above 3 mg, the risk of dependence among Panic Disorder patients may be higher than that among those treated for less severe anxiety. Randomized placebo-controlled discontinuation studies showed a high rate of rebound and withdrawal symptoms in patients treated with alprazolam compared to placebo-treated patients.

Relapse or return of illness was defined as a return of symptoms characteristic of Panic Disorder (primarily panic attacks) to levels approximately equal to those seen at baseline before active

treatment was initiated. *Rebound* refers to a return of symptoms of Panic Disorder to a level substantially greater in frequency, or more severe in intensity, than seen at baseline. *Withdrawal* symptoms were identified as those which were generally not characteristic of Panic Disorder and which occurred for the first time more frequently during discontinuation than at baseline.

In a controlled clinical trial in which 63 patients were randomized to alprazolam and where withdrawal symptoms were specifically sought, the following were identified as symptoms of withdrawal: heightened sensory perception, impaired concentration, dysosmia, clouded sensorium, paresthesias, muscle cramps, muscle twitch, diarrhea, blurred vision, appetite decrease and weight loss. Other symptoms, such as anxiety and insomnia, were frequently seen during discontinuation, but it could not be determined if they were due to return of illness, rebound or withdrawal.

In a larger database comprised of both controlled and uncontrolled studies in which 641 patients received alprazolam, discontinuation-emergent symptoms which occurred at a rate of over 5% in patients treated with alprazolam and at a greater rate than the placebo-treated group were as follows:

Discontinuation-Emergent Symptom Incidence		
Body System	**Event**	**Percentage of alprazolam-treated patients reporting event (N=641)**
Neurologic	Insomnia	29.5
	Lightheadedness	19.3
	Abnormal involuntary movement	17.3
	Headache	17.0
	Muscular twitching	6.9
	Impaired coordination	6.6
	Muscle tone disorders	5.9
	Weakness	5.8
Psychiatric	Anxiety	19.2
	Fatigue and tiredness	18.4
	Irritability	10.5
	Cognitive disorder	10.3
	Memory impairment	5.5
	Depression	5.1
	Confusional state	5.0
Gastrointestinal	Nausea/vomiting	16.5
	Diarrhea	13.6
	Decreased salivation	10.6
Metabolic-Nutritional	Weight Loss	13.3
	Decreased appetite	12.8
Dermatological	Sweating	14.4
Cardiovascular	Tachycardia	12.2
Special Senses	Blurred vision	10.0

From the studies cited, it has not been determined whether these symptoms are clearly related to the dose and duration of therapy with alprazolam in patients with Panic Disorder. In two controlled trials of six to eight weeks duration where the ability of patients to discontinue medication was measured, 71 %-93% of patients treated with alprazolam tapered completely off

therapy compared to 89%-96% of placebo treated patients. The ability of patients to completely discontinue therapy with alprazolam after long-term therapy has not been reliably determined.

Seizures attributable to alprazolam were seen after drug discontinuance or dose reduction in 8 of 1980 patients with Panic Disorder or in patients participating in clinical trials where doses of alprazolam greater than 4 mg daily for over 3 months were permitted. Five of these cases clearly occurred during abrupt dose reduction or discontinuation from daily doses of 2 to 10 mg. Three cases occurred in situations where there was not a clear relationship to abrupt dose reduction or discontinuation. In one instance, seizure occurred after discontinuation from a single dose of 1 mg after tapering at a rate of 1 mg every three days, from 6 mg daily. In two other instances, the relationship to taper is indeterminate; in both of these cases the patients had been receiving doses of 3 mg daily prior to seizure. The duration of use in the above 8 cases ranged from 4 to 22 weeks. There have been occasional voluntary reports of patients developing seizures while apparently tapering gradually from alprazolam. The risk of seizure seems to be greatest 24-72 hours after discontinuation. (see DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment - Discontinuation; ADVERSE REACTIONS, Post-Market Adverse Drug Reactions).

Treating Interdose Symptoms in Panic Disorder

Interdose Symptoms: Early morning anxiety and emergence of anxiety symptoms between doses of alprazolam have been reported in patients with Panic Disorder taking prescribed maintenance doses of alprazolam. These symptoms may reflect the development of tolerance or a time interval between doses which is longer than the duration of clinical action of the administered dose. In either case, it is presumed that the prescribed dose is not sufficient to maintain plasma levels above those needed to prevent relapse, rebound or withdrawal symptoms over the entire course of the inter-dosing interval. In these situations, it is recommended that the same total daily dose be given, divided as more frequent administrations (See DOSAGE AND ADMINISTRATION).

Psychiatric

Depression and Suicide: Panic-related disorders have been associated with primary and secondary major depressive disorders and increased reports of suicide among untreated patients. Therefore, the same precaution that is exercised with the use of any psychotropic drug in treating depressed patients or those in whom there is reason to suspect concealed suicidal ideation or plans must be exercised when using the higher doses of APO-ALPRAZ and APO-ALPRAZ TS in treating patients with panic-related disorders. Prescriptions for APO-ALPRAZ and APO-ALPRAZ TS should be written for the smallest quantity of drug consistent with good patient management.

Mania: Episodes of hypomania and mania have been reported in association with the use of alprazolam in patients with depression. New onset hypomania or mania were also reported with

alprazolam treatment in the absence of a history of significant psychiatric disorders or concomitant medications.

Hepatic

Hepatic Impairment: If treatment is necessary in patients with impaired hepatic function, therapy should be initiated at a very low dose and the dosage increased only to the extent that it is compatible with the degree of residual function of these organs. Such patients should be followed closely and have periodic laboratory assessments. (see DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY).

Renal

Renal Impairment: If treatment is necessary in patients with renal function, therapy should be initiated at a very low dose and the dosage increased only to the extent that it is compatible with the degree of residual function of these organs. Such patients should be followed closely and have periodic laboratory assessments. (see and DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY).

Special Populations

Pregnant Women: APO-ALPRAZ and APO-ALPRAZ TS are not recommended for use during pregnancy.

Teratogenic Effects: Benzodiazepines can potentially cause fetal harm when administered to pregnant women. Because of experience with other members of the benzodiazepine class, alprazolam is assumed to be capable of causing an increased risk of congenital abnormalities when administered to a pregnant woman during the first trimester. Because use of these drugs is rarely a matter of urgency, the administration of APO-ALPRAZ or APO-ALPRAZ TS is rarely justified in women of child-bearing potential. Women of child-bearing potential should be warned to consult their physician regarding the discontinuation of the drug due to the potential hazard to the fetus if they are pregnant or intend to become pregnant.

Nonteratogenic effects: It should be considered that the child born of a mother who is receiving benzodiazepines may be at some risk for withdrawal symptoms from the drug during the postnatal period. Also, neonatal flaccidity and respiratory problems have been reported in children born of mothers who have been receiving benzodiazepines during late third trimester of pregnancy or during labour.

APO-ALPRAZ and APO-ALPRAZ TS have no established use in labor or delivery.

Nursing Women: Studies in rats have indicated that alprazolam and its metabolites are secreted into the milk. Levels of benzodiazepines, including alprazolam, in breast milk are low. Therefore, nursing should not be undertaken while a patient is receiving APO-ALPRAZ or APO-ALPRAZ TS.

Pediatrics (< 18 years of age): The safety and efficacy of alprazolam in patients under the age of 18 years have not been established. APO-ALPRAZ or APO-ALPRAZ TS are not recommended for use in patients under the age of 18 years.

Geriatrics (≥ 65 years of age): Elderly and debilitated patients have been found to be prone to the CNS depressant activity of benzodiazepines, even after low doses. Manifestations of this CNS depressant activity include ataxia, over sedation and hypotension. Therefore, medication should be administered with caution to these patients, particularly if a drop in blood pressure might lead to cardiac complications. Initial doses should be low and increments should be made gradually, depending on the response of the patient, in order to avoid over sedation, neurological impairment and other possible adverse reactions. (see DOSAGE AND ADMINISTRATION , Special Population – Geriatrics and ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics).

Use in Patients with Concomitant Illness

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 (see DOSAGE AND ADMINISTRATION). The usual precautions in treating patients with impaired renal, hepatic, or pulmonary function should be observed. There have been rare reports of death in patients with severe pulmonary disease shortly after the initiation of treatment with alprazolam tablets. A decreased systemic alprazolam elimination rate (eg, increased plasma half-life) has been observed in both alcoholic liver disease patients and obese patients receiving alprazolam tablets (see CLINICAL PHARMACOLOGY).

Monitoring and Laboratory Tests:

If APO-ALPRAZ or APO-ALPRAZ TS is administered for repeated cycles of therapy, periodic blood counts and liver function tests are advisable.

Information for Patients

To assure safe and effective use of APO-ALPRAZ or APO-ALPRAZ TS, the physician should provide the patient with the following guidance.

1. Inform your physician about any alcohol consumption and medicine you are taking now, including medication you may buy without a prescription. Alcohol should generally not be used during treatment with benzodiazepines.

2. Not recommended for use in pregnancy. Therefore, inform your physician if you are pregnant, if you are planning to have a child, or if you become pregnant while you are taking this medication.

3. Inform your physician if you are nursing.

4. Until you experience how this medication affects you, do not drive a car or operate potentially dangerous machinery, etc.

5. Do not increase the dose even if you think the medication "does not work anymore" without consulting your physician. Benzodiazepines, even when used as recommended, may produce emotional and/or physical dependence.

6. Do not stop taking this medication abruptly or decrease the dose without consulting your physician, since withdrawal symptoms can occur.

7. Some patients may find it very difficult to discontinue treatment with APO-ALPRAZ or APO-ALPRAZ TS due to severe emotional and physical dependence. Discontinuation symptoms, including possible seizures, may occur following discontinuation from any dose, but the risk may be increased with extended use at doses greater than 4 mg/day, especially if discontinuation is too abrupt. It is important that you seek advice from your physician to discontinue treatment in a careful and safe manner. Proper discontinuation will help to decrease the possibility of withdrawal reactions that can range from mild reactions to severe reactions such as seizure.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Side effects to alprazolam if they occur, are generally observed at the beginning of therapy and usually disappear upon continued medication or decreased dosage.

As with all benzodiazepines, paradoxical reactions such as stimulation, agitation, rage, aggressive or hostile behaviour, increased muscle spasticity, sleep disturbances, hallucinations and other adverse behavioural effects may occur in rare instances and in a random fashion. Should these occur, use of the drug should be discontinued.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The data cited in the following two tables are estimates of untoward clinical event incidence among patients who participated under the following clinical conditions:

- For the Anxiety Disorders Table: relatively short duration (ie, four weeks) placebo-controlled clinical studies with dosages up to 4 mg/day of alprazolam (for the management of anxiety disorders or for the short-term relief of the symptoms of anxiety)

- For the Panic Disorders Table: short-term (up to ten weeks) placebo-controlled clinical studies with dosages up to 10 mg/day of alprazolam in patients with panic disorder, with or without agoraphobia.

Anxiety Disorders

Treatment-Emergent Symptom Incidence (% of Patients Reporting)			
Body System	**Event**	**Alprazolam (N=565)**	**Placebo (N=505)**
Central Nervous System	Drowsiness	41.0	21.6
	Lightheadedness	20.8	19.3
	Depression	13.9	18.1
	Headache	12.9	19.6
	Confusion	9.9	10.0
	Insomnia	8.9	18.4
	Nervousness	4.1	10.3
	Syncope	3.1	4.0
	Dizziness	1.8	0.8
	Akathisia	1.6	1.2
Gastrointestinal	Dry mouth	14.7	13.3
	Constipation	10.4	11.4
	Diarrhea	10.1	10.3
	Nausea/vomiting	9.6	12.8
	Increased salivation	4.2	2.4
Cardiovascular	Tachycardia/ palpitations	7.7	15.6
	Hypotension	4.7	2.2
Sensory	Blurred vision	6.2	6.2
Musculoskeletal	Rigidity	4.2	5.3
	Tremor	4.0	8.8
Cutaneous	Dermatitis/allergy	3.8	3.1
Other	Nasal congestion	7.3	9.3
	Weight gain	2.7	2.7
	Weight loss	2.3	3.0

Panic Disorders

Treatment-Emergent Symptom Incidence (% of Patients Reporting)			
Body System	**Event**	**Alprazolam (N=1388)**	**Placebo (N=1231)**
Central Nervous System	Drowsiness	76.8	42.7
	Fatigue & Tiredness	48.6	42.3
	Impaired Coordination	40.1	17.9
	Irritability	33.1	30.1
	Memory Impairment	33.1	22.1
	Lightheadedness/ Dizziness	29.8	36.9
	Insomnia	29.4	41.8
	Headache	29.2	35.6
	Cognitive Disorder	28.8	20.5
	Dysarthria	23.3	6.3
	Anxiety	16.6	24.9
	Abnormal Involuntary Movement	14.8	21.0
	Decreased Libido	14.4	8.0
	Depression	13.8	14.0
	Confusional State	10.4	8.2
	Muscular Twitching	7.9	11.8
	Increased Libido	7.7	4.1
	Change in Libido (Not Specified)	7.1	5.6
	Weakness	7.1	8.4
	Muscle Tone Disorders	6.3	7.5
	Syncope	3.8	4.8
	Akathisia	3.0	4.3
	Agitation	2.9	2.6
	Disinhibition	2.7	1.5
	Paresthesia	2.4	3.2
	Talkativeness	2.2	1.0
	Vasomotor Disturbances	2.0	2.6
	Derealization	1.9	1.2
	Dream Abnormalities	1.8	1.5
	Fear	1.4	1.0
	Feeling Warm	1.3	0.5
Gastrointestinal	Decreased Salivation	32.8	34.2
	Constipation	26.2	15.4
	Nausea/vomiting	22.0	31.8
	Diarrhea	20.6	22.8
	Abdominal Distress	18.3	21.5
	Increased Salivation	5.6	4.4
Cardio-Respiratory	Nasal Congestion	17.4	16.5
	Tachycardia	15.4	26.8
	Chest Pain	10.6	18.1
	Hyperventilation	9.7	14.5
	Upper Respiratory Infection	4.3	3.7
Sensory	Blurred vision	21.0	21.4
	Tinnitus	6.6	10.4
Musculoskeletal	Muscular Cramps	2.4	2.4
	Muscle Stiffness	2.2	3.3
Cutaneous	Sweating	15.1	23.5

Treatment-Emergent Symptom Incidence (% of Patients Reporting)			
Body System	**Event**	**Alprazolam (N=1388)**	**Placebo (N=1231)**
	Rash	10.8	8.1
Other	Increased Appetite	32.7	22.8
	Decreased Appetite	27.8	24.1
	Weight Gain	27.2	17.9
	Weight Loss	22.6	16.5
	Micturition Difficulties	12.2	8.6
	Menstrual Disorders	10.4	8.7
	Sexual Dysfunction	7.4	3.7
	Edema	4.9	5.6
	Incontinence	1.5	0.6
	Infection	1.3	1.7

Less Common Clinical Trial Adverse Drug Reactions (<1%)

In addition to the relatively common (i.e., greater than 1%) untoward events listed in the tables, the following events have been reported to occur with alprazolam and other benzodiazepines: seizures, loss of coordination, concentration difficulties, memory impairment/transient amnesia, hallucinations, depersonalization, taste alterations, dystonia, irritability, anorexia, fatigue, sedation, slurred speech, musculoskeletal weakness, changes in libido, menstrual irregularities, incontinence, urinary retention, abnormal hepatic function, elevated hepatic enzymes, elevated bilirubin, jaundice, pruritus, diplopia and hyperprolactinemia. Increased intraocular pressure has been rarely reported.

Post-Market Adverse Drug Reactions

Various adverse events have been reported in association with the use of alprazolam since market introduction. The majority of these reactions were reported through the medical event voluntary reporting system. Because of the spontaneous nature of the reporting of medical events and the lack of controls, a causal relationship to the use of alprazolam cannot be readily determined. Events include: gastrointestinal disorder, hypomania, mania, hepatitis, angioedema, peripheral edema, liver enzyme elevations, hepatic failure, Stevens-Johnson syndrome, gynecomastia, galactorrhea, aggression, anger, libido disorder, psychomotor hyperactivity, dystonia, autonomic nervous system imbalance, dermatitis, and photosensitivity reaction.

In some of the spontaneous case reports of adverse behavioural effects such as stimulation, agitation, concentration difficulties, confusion and hallucinations, patients were receiving other CNS drugs concomitantly and/or were described as having underlying psychiatric conditions. Patients with 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 discontinuation of alprazolam in patients with post-traumatic stress disorder.

Withdrawal seizures have been reported for patients taking alprazolam alone.

DRUG INTERACTIONS

Drug-Drug Interactions

Pharmacodynamic Drug-Drug Interactions

CNS – Acting Drugs
Benzodiazepines, including alprazolam, may potentiate or produce additive central nervous system depressant effects when combined with other psychotropic medication, alcohol, narcotics, barbiturates, antihistamines or anticonvulsants. Therefore, if APO-ALPRAZ or APO-ALPRAZ TS (alprazolam) is to be combined with other drugs acting on the CNS, careful consideration should be given to the pharmacology of the agents involved because of the possible additive or potentiating effects. Patients should also be advised against the simultaneous use of other CNS depressant drugs and should be cautioned not to take alcohol during the administration of APO-ALPRAZ or APO-ALPRAZ TS.

Pharmacokinetic Drug-Drug Interactions

CYP3A Inhibitors
Pharmacokinetic interactions can occur when alprazolam is administered along with drugs that interfere with its metabolism. Compounds which inhibit certain hepatic enzymes (particularly cytochrome P450 3A4) 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 metabolized similarly to alprazolam provide evidence for varying degrees of interaction and possible interaction with alprazolam for a number of drugs.

Antifungal agents
Ketoconazole and itraconazole are potent inhibitors of CYP3A. The co-administration of alprazolam with ketoconazole, itraconazole, or other azole-type antifungals is not recommended (see CONTRAINDICATIONS). This is based on results of drug interaction studies of triazolam and midazolam, benzodiazepines metabolized similarly to alprazolam, with ketoconazole and itraconazole. In addition, an *in vitro* study showed ketoconazole to be a potent inhibitor of alprazolam metabolism.

Caution and consideration of dose reduction is recommended when alprazolam is coadministered with nefazodone, fluvoxamine, and cimetidine.

Nefazodone
When alprazolam tablets (1 mg bid) and nefazodone (200 mg bid) were co-administered to steady state, peak concentrations, AUC and half-life values for alprazolam tablets increased by approximately 2 fold. Nefazodone plasma concentrations were unaffected by alprazolam, although levels of the mCPP metabolite were increased. The concomitant use of alprazolam and nefazodone was also associated with an increase in psychomotor impairment presumably due to increased alprazolam plasma concentrations.

If alprazolam is co-administered with nefazodone, a reduction in the alprazolam dosage may be appropriate; no dosage adjustment is required for nefazodone. The interactive effects of higher doses of these agents, such as the dosage levels of alprazolam used in panic disorder, have not been studied.

Fluvoxamine
When alprazolam 1.0 mg and fluvoxamine (50 mg qd for 3 days followed by 100 mg qd for 7 days) were co-administered the AUC of alprazolam was approximately doubled, the Cmax of alprazolam increased by about 50% and the half life of alprazolam increased from 19.8 hours to 33.9 hours. Cmax and AUC of fluvoxamine were decreased by about 25%. Psychomotor performance tests on day 10 showed significant decreases in performance.

Cimetidine
In healthy volunteers, a single 1 mg dose of alprazolam was administered with and without concurrent administration of cimetidine (300 mg) every 6 hours. Cimetidine significantly impaired the clearance of alprazolam and prolonged its half-life. Cimetidine significantly reduced total metabolic clearance (1.05 versus 1.66 ml/min/kg). Co-administration of alprazolam and cimetidine resulted in an approximate doubling of the Cmax of alprazolam and a statistically significant increase in the AUC of alprazolam. The half-life of alprazolam increased from 12.2 hours to 14.2 hours.

Oral contraceptives
The effect of oral contraceptives on the pharmacokinetics of a single 1 mg dose of alprazolam was studied in healthy women. Alprazolam clearance was lower in subjects taking oral contraceptives (0.95 ml/min/kg) than in the control group (1.21 ml/min/kg) while its half-life was prolonged (12.4 hours versus 9.6 hours). Caution is recommended when alprazolam is coadministered with oral contraceptives.

HIV Protease Inhibitors
Interactions involving HIV protease inhibitors (eg, ritonavir) and alprozolam 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.

<u>CYP3A Inducers</u>
Carbamazepine
A pharmacokinetic interaction has been noted between alprazolam and carbamazepine; significant reductions in alprazolam concentration have been noted after carbamazepine treatment has been initiated. Pharmacokinetic interactions between alprazolam and phenytoin have not been observed.

<u>Other Drugs</u>
Imipramine and desipramine
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.

Warfarin
Alprazolam 0.5 mg, administered 3 times a day for 14 days, did not affect prothrombin times or plasma warfarin levels in male volunteers administered sodium warfarin orally.

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

Digoxin
Increased digoxin concentrations have been reported when alprazolam was given, especially in elderly (>65 years of age). Patients who receive alprazolam and digoxin should therefore be monitored for signs and symptoms related to digoxin toxicity.

Drug-Food Interactions
Alcohol should not be ingested during treatment with APO-ALPRAZ or APO-ALPRAZ TS (see also CNS-Acting Drugs, above)

Drug-Lifestyle Interactions

Driving and Hazardous Activities: Because of its central nervous system depressant effect, patients receiving APO-ALPRAZ or APO-ALPRAZ TS should be cautioned not to undertake activities requiring mental alertness, judgment and physical coordination such as driving or operating machinery.
This is particularly true in the early phases of dose adjustment, and until it has been established that they do not become drowsy or dizzy while taking APO-ALPRAZ or APO-ALPRAZ TS.

Alcohol and other CNS-depressant drugs: Alcohol or central nervous system depressant drugs should not be ingested during treatment with APO-ALPRAZ or APO-ALPRAZ TS.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Dosage should be individualized for maximal benefit. The lowest possible effective dose should be administered and the need for continued treatment reassessed frequently. The risk of dependence may increase with dose and duration of treatment. In general, patients who have not previously received psychotropic medication will require somewhat lower doses than those previously treated with minor tranquilizers, antidepressants, or hypnotics.

Both APO-ALPRAZ and APO-ALPRAZ TS are immediate-release formulations. APO-ALPRAZ TS is scored in three places ("tri-scored") and can be broken into 4 equal parts of 0.5 mg each.

Recommended Dose and Dosage Adjustment

Anxiety Disorders

Adults:

The initial adult dosage of APO-ALPRAZ (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 or Debilitated Patients: 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. The initial dosage is 0.125 mg given 2 or 3 times daily. If necessary, this dosage may be increased gradually depending on patient tolerance and response. The elderly may be especially sensitive to the effects of benzodiazepines.

Hepatic or Renal Impairment: In patients with advanced liver or renal disease, the usual dose is 0.125 to 0.25 mg, given two or three times daily. This may be gradually increased if needed and tolerated.

Panic Disorders

The usual starting dose is 0.5 mg to 1.0 mg at bedtime or 0.5 mg three times daily. The dose should be adjusted until the patient is free of panic attacks. Dosage adjustments should be in increments no greater than 1 mg every three to four days. Interdose symptoms presumed to reflect insufficient plasma levels, may be lessened by using the same dose, but a schedule that provides for administration 3 or 4 times per day.

In controlled trials conducted to establish the efficacy of alprazolam in Panic Disorders, doses in the range of 1 to 10 mg daily were used. The mean dosage employed was approximately 5 to 6 mg daily. Among the approximately 1700 patients participating in the Panic Disorder development program, about 300 received maximum alprazolam doses of greater than 7 mg per day, including approximately 100 patients who received maximum dosages of greater than 9 mg per day. Occasional patients required as much as 10 mg per day to receive a successful response.

Because the management of Panic Disorder often requires the use of average daily doses of alprazolam above 3 mg, the risk of rebound and withdrawal symptoms may be higher than in patients treated for anxiety. (See also **WARNINGS AND PRECAUTIONS, Withdrawal and Rebound in Treating Panic Disorder)**

The necessary duration of treatment for Panic Disorder is unknown at this time. After a period of extended freedom from panic attacks, a supervised tapered discontinuation may be attempted.

Discontinuation:
To discontinue treatment in patients taking APO-ALPRAZ and APO-ALPRAZ TS, the dosage should be reduced slowly in keeping with good medical practice. It is suggested that the daily dosage of APO-ALPRAZ or APO-ALPRAZ TS be decreased by no more than 0.5 mg every 3 days. Some patients may require an even slower dosage reduction. A decrease of 0.5 mg every 2 to 3 weeks is more appropriate when a dose of 6 mg daily or more has been administered even for only a few months. Once a dose of 2 mg daily is achieved, the dose should be decreased by 0.25 mg per 2 to 3 weeks. The ability of patients to completely discontinue therapy with alprazolam after long-term therapy has not been reliably determined. (see also WARNINGS AND PRECAUTIONS, Dependence/Tolerance)

OVERDOSAGE

Symptoms

Overdose of alprazolam is manifested as an extension of its pharmacologic activity. Thus, varying degrees of CNS depression effects such as somnolence, confusion, drowsiness, slurred speech, impaired coordination, diminished reflexes, respiratory depression and coma may ensue. As in the management of overdose with any drug, the possibility of multiple drug ingestion should be considered.

Serious sequela are rare unless other drugs and/or ethanol are concomitantly ingested. 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.

Treatment
Vomiting may be induced if the patient is fully awake. Vital signs should be monitored and general supportive measures should be employed as indicated. Gastric lavage should be instituted as soon as possible. Intravenous fluids may be administered and an adequate airway should be maintained.
Experiments in animals have indicated that cardiopulmonary collapse can occur with massive intravenous doses of alprazolam. This could be reversed with positive mechanical respiration and the intravenous infusion of levarterenol. Animal experiments with alprazolam and related compounds have suggested that hemodialysis and forced diuresis are probably of little value.

Treatment of overdosage is primarily supportive of respiratory and cardiovascular function.

Flumazenil, a benzodiazepine receptor antagonist, may be used as an adjunct to the management of respiratory and cardiovascular function associated with overdose.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Alprazolam, a triazolo 1,4 benzodiazepine analog, binds with high affinity to the GABA benzodiazepine receptor complex. Considerable evidence suggests that the central pharmacologic/therapeutic actions of alprazolam are mediated via interaction with this receptor complex.

Pharmacokinetics

Absorption: Orally administered alprazolam is readily absorbed in man. Plasma levels are proportional to the dose given; over the dose range of 0.5 to 3 mg, peak levels of 8.0 to 37 ng/ml were observed. The mean elimination half-life of alprazolam is about 11 hours in healthy adults. With multiple doses, given 3 times daily, steady state is reached within 7 days.

Metabolism / Excretion: Alprazolam is extensively metabolized in humans, primarily by cytochrome P450 3A4 (CYP3A4). Degradation of alprazolam occurs mainly by oxidation yielding the primary metabolites αhydroxy-alprazolam and a benzophenone derivative. The αhydroxy-metabolite is further transformed to demethylalprazolam. Both αhydroxy-alprazolam and demethylalprazolam are active and appear to have half-lives similar to alprazolam but their plasma levels are low. Alprazolam metabolites are excreted primarily in the urine.

Special Populations and Conditions

The table below summarizes some pharmacokinetic parameters in healthy adults and healthy elderly subjects (mean age 70 years, range 62 to 78 years), as well as in obese subjects and in patients with impaired hepatic or renal function. Clearance was decreased and half-lives were increased in all special patient populations except in patients on hemodialysis. Time to peak plasma concentration was increased in patients with liver disease and CAPD.

Alprazolam pharmacokinetics in special patient populations following the administration of single oral doses. Values are means with the ranges in parentheses.

	Patient Population					
					End Stage Renal Disease	
Parameter	**Adults**	**Elderly**	**Obese**	**Alcoholic Liver Disease**	**Hemodialysis**	**CAPD[a]**
No.	16	16	12	17	7	5
Dose(mg)	1.0	1.0	1.0	1.0	0.5	0.5
C_{max} (ng/mL)	17.9 *(8.5-29.5)*	22.9 *(12.4-36.3)*	Not reported	17.3 *(8.6-26.0)*	8.1 *(5.9-14.4)*	8.6 *(6.8-10.5)*

T_{max} (hr)	1.6 *(0.25-6.0)*	0.9 *(0.5-2.0)*	Not reported	3.3 *(0.5-8.0)*	1.1 *(0.5-2.0)*	3.0 *(0.5-6.0)*
Cl (mL/min/kg)	1.33 (0.90-2.23)	0.86 (0.40-1.84)	0.59 (not available)	0.56 (0.17-1.46)	not reported	not reported
$T_{1/2}$(hr)	11.0 *(6.3-15.8)*	16.3 *(9.0-26.9)*	21.8 *(9.9-40.5)*	19.7 *(5.8-65.3)*	11.2 *(7.1-19.1)*	19.2 *(8.8-33.8)*
Unbound fraction in plasma (%)	29.0 *(25.0-32.8)*	29.8 *(25.0-35.4)*	30.3 *(26.4-35.4)*	23.2 *(16.9-32.8)*	27.6 *(22.7-30.7)*	30.9 *(28.0-34.2)*

[a]CAPD: Continuous Ambulatory Peritoneal Dialysis
C_{max}: peak plasma concentration
T_{max}: time of peak concentration
Cl total clearance
$T_{1/2}$ elimination half-life

STORAGE AND STABILITY

APO-ALPRAZ and APO-ALPRAZ TS should be stored at room temperature (15°C-30°C).

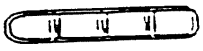
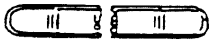
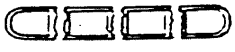
DOSAGE FORMS, COMPOSITION AND PACKAGING

APO-ALPRAZ (alprazolam) is available in :

- 0.25 mg (oval, white, biconvex, side scored and engraved "APO" over ".25" one side, other side plain) tablets in bottles of 100 and 500,
- 0.5 mg (oval, peach, biconvex, side scored and engraved "APO" over "0.5" one side, other side plain) tablets in bottles of 100 and 500, and
- 1 mg (oval, lavender, biconvex, scored and engraved "APO" over "1" one side, and plain on the other side) tablets in bottles of 100 and 500.

APO-ALPRAZ TS is available in white, rectangular, 2 mg triscored tablets (3 scores) engraved "APO 2" on one side and plain on the other side and can be broken into 4 equal parts of 0.5 mg each. APO-ALPRAZOLAM TS tablets are available in bottles of 100 & 500 tablets

complete 2 mg tablet two 1 mg segments four 0.5 mg segments

Each 0.25 mg tablet of APO-ALPRAZ contains 0,25 mg alprazolam and includes the following inactive ingredients microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, magnesium stearate.

Each 0.5 mg tablet of APO-ALPRAZ contains 0,5 mg alprazolam and includes the following inactive ingredients microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, magnesium stearate, FD&C yellow #6.

Each 1 mg tablet of APO-ALPRAZ contains 1 mg alprazolam and includes the following inactive ingredients microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, magnesium stearate, FD&C blue #2, D&C red #30.

Each 2 mg tablet of APO-ALPRAZ TS contains 2 mg alprazolam and includes the following inactive ingredients microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, magnesium stearate.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper/Common Name: Alprazolam

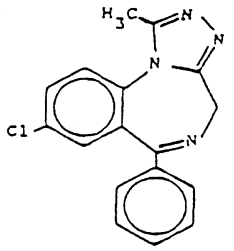
Chemical Name: (1) 4H-{1,2,4}Triazolo[4,3-a][1,4]benzodiazepine, 8 chloro-1-methyl-6-phenyl-;

(2) 8-Chloro-1-methyl-6-phenyl-4H-s-triazolo[4,3-a][1,4]benzodiazepine

Molecular Formula

and molecular mass: $C_{17}H_{13}ClN_4$ and 308.76

Structural Formula:



Description: Alprazolam is a white crystalline powder, soluble in methanol or ethanol but with no appreciable solubility in water and a melting point of 225-231°C

CLINICAL TRIALS

In a placebo-controlled, 8-week trial, which included 526 patients with diagnoses of Panic Disorder with or without Agoraphobia, alprazolam in a dosage range of 1 to 10 mg per day (with a mean daily dosage of 5.7 ± 2.27 mg at the end of the treatment period) was found effective in blocking or attenuating panic attacks and reducing phobic avoidance.

Comparative Bioavailability

A comparative bioavailability study was performed using healthy human volunteers. The rate and extent of absorption of alprazolam was measured and compared following oral administration of Apo-Alpraz or Xanax (1x1 mg) tablet. The results from measured data are summarized as follows:

Summary Table of the Comparative Bioavailability Data
Alprazolam (Dose: 1 x 1 mg) From Measured Data

Parameter	Geometric Mean Arithmetic Mean (CV%) Apo-Alprazolam 1 mg/XC452A	Geometric Mean Arithmetic Mean (CV%) Xanax† 1 mg/DR63	% Ratio of Geometric Means** (Cl)
AUC_T (ng•hr/mL)	201 215 (31)	217 223 (22)	92.5 (82.4 - 103.8)
AUC_I (ng•hr/mL)	228 247 (35)	246 256 (28)	92.7 (82.4 - 104.4)
C_{max} (ng/mL)	12.7 13.4 (28)	13.6 13.7 (14)	93.3 (82.6 - 105.3)
T_{max} (hr)*	1.44 (62)	1.31 (50)	-
$t_{1/2}$ (hr)*	15.7 (25)	15.6 (25)	-

* Expressed as arithmetic means (CV%) only.

** Based on the least squares estimate.

† Xanax (Upjohn Company of Canada) was purchased at a Canadian retail pharmacy.

DETAILED PHARMACOLOGY

The anxiolytic activity of alprazolam was demonstrated in various tests in the mouse, rat, cat and monkey. Although alprazolam appeared qualitatively similar to diazepam, it was about 3 to 5 times more potent on an overall basis. In the mouse, alprazolam prolonged hypoxic survival, reduced rearing in the open-field test, and reduced footshock or isolation-induced aggression. Pentylenetetrazol induced seizures were antagonized by alprazolam in the mouse, rat and cat. Alprazolam attenuated conflict behavior in rats and reduced plasma corticosteroid levels in stressed rats. In the cat and monkey alprazolam produced increased beta activity in the EEG similar to diazepam.

Alprazolam had CNS depressant relaxation activity in all species tested. These effects were observed over a large range of doses giving the compound an extremely flat dose response curve. Except at near lethal doses, little change was observed in physiological measures such as heart rate, respiratory rate and body temperature.

In mice, alprazolam potentiated the actions of pentobarbital, chlorprothixene, ethanol and butyrolactone. Alprazolam promoted sleep in the monkey at doses that caused observable motor incoordination.

As with other benzodiazepines, direct physical dependence was induced when large doses of alprazolam were administered on a continuing basis to rats and mice. Alprazolam had weak but measurable reinforcing properties and showed very poor cross-dependence in phenobarbital-dependent animals.

Alprazolam increased the toxicity of glutethimide, methaqualone, pentobarbital, chlorpromazine, thioridazine, phenytoin and d-amphetamine in the mouse. Attempts to eliminate alprazolam by hemodialysis in nephrectomized dogs were unsuccessful.

Alprazolam readily entered the CNS in mice and rats. Alprazolam had no apparent effect on the cholinergic system. Brain levels of dopamine and serotonin were only slightly elevated in mice treated with alprazolam. When catecholamine synthesis was blocked, dopamine utilization was slowed. Alprazolam decreased the incorporation of tyrosine into brain dopamine and norepinephrine of rats.

Cardiopulmonary studies in the dog showed that supratherapeutic intravenous doses of alprazolam decreased blood pressure by a modest amount but had little effect on other cardiovascular measures. Respiratory function was modestly decreased in these studies.

In rats, large doses of alprazolam and diazepam tended to prolong prothrombin times and lower plasma warfarin levels.

Pharmacokinetics

When alprazolam was administered orally as a compressed tablet formulation, the average time of peak plasma concentration in several studies ranged from 0.9 to 2.4 hours. Based on urinary ^{14}C excretion after oral alprazolam-^{14}C, the minimal drug absorption was 79%. Over a dosage range of 0.5 mg dose to 2.0 mg, serum alprazolam levels were proportional to dose. Average peak serum levels of alprazolam ranged from 8.0 ng/mL for a 0.5 mg dose to 26.5 ng/mL for a 2.0 mg dose. Average elimination half-life values in several studies ranged from 9.5 to 15.0 hr., based on serum levels fit to a one-compartment model. Protein binding studies with human serum, at 37°C showed that over a concentration range of 30 to 1000 ng/mL, alprazolam binding

was independent of concentration and amounted to 80%; alprazolam was 68% bound to human serum albumin.

Alprazolam serum levels increased after daily three times a day dosing and reached steady-state levels within 7 days.

Drug-related materials were excreted predominantly in the urine. After a 2.0 mg dose of alprazolam-^{14}C, average recoveries of ^{14}C in urine and feces were 79% and 7%, respectively. Average renal clearance of alprazolam was 371 mL/hr compared to a normal glomerular filtration rate of 7500 mL/hr. Renal excretion apparently involves glomerular filtration with extensive reabsorption.

Alprazolam was extensively metabolized and evidence was obtained for 29 metabolites in urine. Three pathways of metabolism have been identified: (1) oxidation of the 1-methyl group to yield the major metabolite, α-hydroxyalprazolam, followed by further oxidation and decarboxylation to yield 1-demethylalprazolam, (2) oxidation of the C-4 methylene to yield 4-hydroxyalprazolam, and (3) cleavage of the 5,6 azomethine bond with subsequent oxidation to yield a 3-hydroxymethyl-5-methyl-triazolyl-substituted benzophenone. These metabolites of alprazolam are present in only very low levels in the plasma, thus precluding rigorous pharmacokinetic treatment of the data. However, their excretion half-lives are likely to be similar to that of alprazolam.

Tissue distribution of alprazolam-^{14}C was studied in mice by whole body-slice autoradiography after 2.2 mg/kg oral and intravenous doses. Drug-related material penetrated the central nervous system rapidly and was widely distributed in other tissues without long-term retention. In pregnant mice, low levels of drug-related materials were observed in the fetus. Following a 0.3 mg/kg oral dose of alprazolam-^{14}C in lactating rats, average drug equivalent levels of 17 and 18 ng/mL were found in milk 6 and 12 hours, respectively, after dosing.

Special Populations

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. A mean half-life of alprazolam of 16.3 hours has been observed in healthy elderly subjects (range: 9.0–26.9 hours, n=16) compared to 11.0 hours (range: 6.3–15.8 hours, n=16) in healthy adult subjects. In patients with alcoholic liver disease the half-life of alprazolam ranged between 5.8 and 65.3 hours (mean: 19.7 hours, n=17) as compared to between 6.3 and 26.9 hours (mean=11.4 hours, n=17) in healthy subjects. In an obese group of subjects the half-life of alprazolam ranged between 9.9 and 40.4 hours (mean=21.8 hours, n=12) as compared to between 6.3 and 15.8 hours (mean=10.6 hours, n=12) in healthy subjects.

TOXICOLOGY

Acute Toxicity:

In studies in mice, the LD_{50} of intraperitoneal alprazolam was found to be 500 to 682 mg/kg. In studies in the rat, the oral LD_{50} and intraperitoneal LD_{50} ranged from 331 to 2171 mg/kg and 409 to 819 mg/kg, respectively. Signs of toxicity were rapid sleep induction and convulsions.

Subacute and Chronic Toxicity:

Rat:

Alprazolam was administered orally to rats at a dosage of 300 mg/kg/day for 6 days. Depression and ataxia were observed in all treated rats and ulcers were found in 4 of 5 treated female rats.

In two 1-month studies (0, 10, 30,100 and 300 mg/kg/day oral alprazolam), depression and ataxia resulting in decreased food consumption and lower body weights were observed at all dose levels. Stomach ulcers were observed at 100 and 300 mg/kg/day, and at 300 mg/kg/day hemorrhages from the stomach lesions resulted in lower hematocrit and hemoglobin levels and the presence of nucleated red blood cells in blood smears. Multinucleated giant cells in the testicular tubules (2 of 4 males) and degeneration of the testicular tubular cells (4 of 4 males) were observed at the 300 mg/kg/day dose level.

In two-3 month studies (0, 10, 30 and 100 mg/kg/day oral alprazolam) depression and ataxia were seen at all dose levels. Atrophy of the thymus, stomach ulcers and reduced hemoglobin, hematocrit and red blood cell counts secondary to hemorrhages from these stomach lesions, were observed in the 100 mg/kg/day group. In one study, testicular atrophy (15 of 15 males) and a reduced number of spermatozoa in the epididymis (11 of 15 males) were observed at the 100 mg/kg/day dose. In the other study, atrophy of a few testicular tubules (1 of 2 males) and multinucleated giant cells in the tubules (2 of 2 males) were observed at this dose.

In a 2-year study (0, 3, 10 and 30 mg/kg/day oral alprazolam), treatment was associated with dose and time-related convulsions at 10 and 30 mg/kg/day. A significantly shorter survival period for males and females at 30 mg/kg/day and for males at 10 mg/kg/day was observed. Atrophy of the testes and decreased mature spermatozoa in the epididymis were seen in 18 of 44 males at the 30 mg/kg/day dose level. There was a significant positive dose trend of telangiectasis in females. Telangiectasis appeared grossly as sporadic red spots, about I mm in diameter. Histologically, the hepatic sinusoids were dilated and filled with blood. A tendency for a dose related increase in the number of cataracts (females) and corneal vascularization (males) was observed. These lesions did not appear until after 11 months of treatment.

Dog:

Dogs were administered alprazolam orally for 10 days at dose levels of 10 to 300 mg/kg/day. Sedation and ataxia were seen at all dose levels and cholesterol, glucose, alkaline phosphatase and SGPT were slightly elevated.

In a three-month study, alprazolam was administered orally to dogs at dosage levels of 0,1,10 and 100 mg/kg/day. Incoordination and ataxia were seen at the 10 and 100 mg/kg/day dose. In the high dose group (100 mg/kg/day) alkaline phosphatase was elevated, red blood cell count, hematocrit and hemoglobin were reduced and an increased number of foci in the liver containing degenerate hepatocytes with neutrophils and lymphocytes were observed. Convulsions occurred in 2 of 4 dogs at this dose level.

In a twelve-month study, dogs were administered alprazolam orally at doses of 0, 0.3, 1.0, 3, 10 and 30 mg/kg/day. A slight to moderate impairment of coordination was noted in dogs treated with 3, 10 and 30 mg/kg/day. Convulsions occurred in all dogs at the 10 and 30 mg/ kg/day dose level and in 4 of 6 dogs at the 3 mg/kg/day dose level. At the end of the treatment, the dogs were put on a 5-day withdrawal to evaluate drug dependence liability. Some inappetence and weight loss were encountered following drug withdrawal. Body temperature had dose-related increases. All of the 10 and 30 mg/kg/day dogs that were alive during the withdrawal period convulsed, while only 1of 5 dogs receiving 3 mg/kg/day convulsed.

Reproductive And Teratologic Studies: Alprazolam was given by gastric intubation to pregnant rats on gestation days 6 through 15 at 5, 10, 30 and 100 mg/kg/day. All fetuses at 100 mg/kg/day were resorbed. There was a dose related incidence of resorptions and a decrease in pup weights. The incidence of missing metacarpals at the 10 and 30 mg/kg/day doses and agenesis of sternebrae at the 5 and 10 mg/kg/day doses were significantly increased. However, there was no evidence of skeletal immaturity and all bones were present in two week old pups from dams that were allowed to deliver and nurse the offspring for that period. Cardiovascular abnormalities were observed in 4 of the 35 animals in one study at 30 mg/kg/day. These were not observed in two other studies at the same dose.

Alprazolam was administered at 2 and 5 mg/kg/day in the diet of female rats for 14 days prior to mating and throughout the subsequent pregnancy and for 21 days post-parturition. A slight increase in the average number of resorptions per litter was noted at the 5 mg/kg/day level and a slight increase in the average number of dead pups per litter was observed at both dose levels. Pup weights at birth were lower and postnatal survival was slightly decreased at the 5 mg/kg/day dose. Treatment of male rats at 2 and 5 mg/kg/day for 60 days prior to mating resulted in a decrease in the percentage of dams conceiving at the 5 mg/kg/day dose.

Pregnant rabbits were administered alprazolam by gastric intubation at 10 and 30 mg/kg/day on gestation days 6 through 18. The 30 mg/kg/day level resulted in the death of 6 of 27 rabbits. The majority of fetuses were resorbed and those which survived had a lower birth weight. A dose-related increase in the number of animals with extra ribs was observed. A low incidence of rib malformations and fused vertebrae and sternebrae were noted in treated animals. The majority of the fetuses at the 30 mg/kg/day level had no ossification centers for the phalanges of

the first digit on the forepaw and/or missing metacarpals on the same digit. Short tails and the reduction in the number of caudal vertebrae were observed at both dose levels. Five of 21 fetuses at the 30 mg/kg/day level had asymmetrical caudal vertebrae.

Pregnant rabbits were administered alprazolam by gastric intubation at 2 and 5 mg/kg/day on gestation days 6 through 18. An increase in the incidence rates of extra ribs was observed at the 5 mg/kg/day dose and first metacarpal agenesis and first proximal phalanx agenesis on the forelimb was observed at both dose levels. Fused ribs and vertebrae were noted at the 2 mg/kg/day level and vertebrae fusion and malposition were noted at the 5 mg/kg/day level.

Pregnant rabbits were administered alprazolam by gastric intubation at 2 and 5 mg/kg/day on gestation days 6 through 18. In this study, the does were allowed to kindle and nurse the pups for 4 days. There were no consistent drug or dose-related anomalies observed in the gross visceral and skeletal examinations.

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46. Product Monograph - XANAX (alprazolam) tablets (0.25 mg, 0.5 mg and 1.0 mg) & XANAX TS. (alprazolam) triscored tablets (2 mg) , Pharmacia & Upjohn, Pfizer Canada Inc. Licencee, Date of Revision: October 21, 2014, Control number: 175541

PART III: CONSUMER INFORMATION

APO-ALPRAZ AND APO-ALPRAZ TS
(alprazolam tablets USP)

This leaflet is part III of a three-part "Product Monograph" published when **APO-ALPRAZ and APO-ALPRAZ TS** (alprazolam tablets) was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about **APO-ALPRAZ and APO-ALPRAZ TS**. Contact a member of your healthcare team if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
APO-ALPRAZ has been prescribed to you by your doctor to relieve your symptoms of the following conditions:

- Generalized anxiety disorder (excessive anxiety or worry)
- Panic disorder (repeated, unexpected panic attacks of extreme fear and worry about these attacks)

What it does:
APO-ALPRAZ contains the active ingredient alprazolam, which belongs to a group of medicines known asbenzodiazepines. APO-ALPRAZ has sedative properties which help in the treatment of anxiety and panic.

When it should not be used:
Do not take APO-ALPRAZ if you:

- are allergic to the group of medicines known as benzodiazepines (examples: clonazepam, chlordiazepoxide, diazepam, or flurazepam).
- are allergic to APO-ALPRAZ or any of the ingredients listed in the section "What the nonmedicinal ingredients are".have acute narrow angle glaucoma, a condition that may associated with increased pressure in the eye cause loss of sight.
- have myasthenia gravis, a chronic disease characterized by weakness of the skeletal muscles.
- have a liver condition.
- have lung disease or breathing problems.
- have a sleep disorder that causes pauses in breathing or shallow breathing while sleeping (sleep apnea).
- are taking ketoconazole (eg., Nizoral) or itraconazole (eg., Sporanox), medicines used to treat fungal infections.

APO-ALPRAZ should not be used in patients under 18 years of age.

What the medicinal ingredient is:
Alprazolam

What the nonmedicinal ingredients are:
All tablets contain ingredients microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, magnesium stearate. The 0.5 mg tablet also contains FD&C yellow #6. The 1 mg tablet also contains D&C red #30 and FD&C blue #2

What dosage forms it comes in:
APO-ALPRAZ 0.25 mg tablet: oval, white, biconvex tablet, are side scored and engraved "APO" over ".25" one side, other side plain.
APO-ALPRAZ 0.5 mg tablet: oval, peach, biconvex tablet, are side scored and engraved "APO" over "0.5" one side, other side plain.
APO-ALPRAZ 1 mg tablet: oval, lavender, biconvex tablet, scored and engraved "APO" over "1" one side, and plain on the other side.
APO-ALPRAZ TS 2 mg tablet: white, rectangular, triscored tablets and engraved "APO 2" on one side, triscored and plain on the other. This can be broken into 4 individual 0.5 mg segments.

WARNINGS AND PRECAUTIONS

BEFORE you use APO-ALPRAZ talk to your doctor or pharmacist if you:

- have a lung, liver or kidney condition.
- have a history of alcohol or drug abuse.
- have a history of depression and/or suicide attempts.
- are pregnant, think you may be pregnant, or are planning to become pregnant.
- are breast feeding.
- regularly drink alcohol.
- have lactose intolerance.

Mental alertness
APO-ALPRAZ can cause drowsiness and affect your ability to be alert.
You should not perform activities that require mental alertness such as driving or operating machinery until you know how this drug will affect you. This effect of APO-ALPRAZ may be made worse if you take alcoholic drinks. If your doctor has increased your dose or if you have changed the timings of when you take your medication this may also change how the drug affects you.

Risk of falls, memory loss
There have been reports of falls and fractures in people who take benzodiazepenes such as alprazolam. Memory loss has also been reported. These have occurred in people taking the usual doses.

Worsening of side effects with alcohol and other drugs
APO-ALPRAZ may have more pronounced sedative effects when taken with alcohol or other drugs that can make you sleep, such as: narcotic pain relievers, sleeping pills, antihistamines, medications to control seizures, antidepressants or

antipsychotics. **Do not** take APO-ALPRAZ if you drink alcohol. **Do not** use APO-ALPRAZ with these other medications without first discussing with your doctor.

Withdrawal symptoms
Always contact your doctor before stopping or reducing your dosage of APO-ALPRAZ. Suddenly stopping treatment or a large decrease in dose can cause withdrawal symptoms. This can happen with drugs of this type even when taking for only a few weeks.

Symptoms of withdrawal may include mild symptoms, such as a feeling of dissatisfaction, restlessness or trouble sleeping.

In severe cases of withdrawal, symptoms may include irritability, nervousness, insomnia, agitation, diarrhea, stomach pains, vomiting, sweating, shaking, numbness and tingling of the extremities, hallucinations (seeing or hearing things that are not there), being unusually sensitive to light, noise and physical contact and seizures.
Therefore, always follow the treatment as prescribed by your doctor.

Dependence
Benzodiazepines such as alprazolam have caused dependence (addiction) and withdrawal symptoms can occur when treatment is stopped suddenly. The risk of dependence (addiction) increases with higher doses and longer duration of treatment, or after suddenly stopping treatment.

Pregnancy
Some benzodiazepines have been linked to birth defects when taken during the early months of pregnancy. Babies born to mothers who have taken benzodiazepines during the last weeks of pregnancy or during labour have been known to have overly relaxed muscles and breathing problems, and may also have withdrawal symptoms after birth.
Do not take this medicine if you are pregnant (or think you may be pregnant), unless advised by your doctor. Consult with your doctor before taking APO-ALPRAZ if you are planning to become pregnant.

Breast feeding
APO-ALPRAZ may pass into breast milk. Therefore, if you are breast feeding, this medicine should be avoided.

INTERACTIONS WITH THIS MEDICATION

Tell your doctor if you are taking any other medicines including any that you have bought from a pharmacy, supermarket or health food store without a prescription.

APO-ALPRAZ may have more pronounced side effects when taken with alcohol or other drugs that affect the central nervous system.

Do not drink alcohol while taking APO-ALPRAZ. **Do not** use APO-ALPRAZ with the following other medicines without first discussing with your doctor:

- narcotic pain relievers (e.g., morphine, codeine)
- sleeping pills
- antihistamines (medicines used for relief of allergy
- symptoms)
- anticonvulsants (medications used to control seizures)
- antidepressants (medicines used to treat anxiety or depression)
- antipsychotics (medicines used to treat mental illnesses such as schizophrenia)

APO-ALPRAZ should not be taken with ketoconazole or itraconazole (medicines used to treat fungal infections) because these medicines can cause an increase in the amount of APO-ALPRAZ in your blood and can enhance side effects.

Other medicines that can affect the amount of APO-ALPRAZ in your blood include cimetidine, fluvoxamine, carbamazepine, HIV protease inhibitors, and birth control pills.

Talk to your doctor if you are using APO-ALPRAZ with digoxin, as APO-ALPRAZ may affect the amount of digoxin in your blood.

Always tell your doctor about any other medicines you are taking or plan to take.

PROPER USE OF THIS MEDICATION

Always take the tablets exactly as your doctor tells you to. Your doctor will prescribe a suitable dose for you. The dose your doctor prescribes will depend on your illness and how you respond to the medicine. The table below shows the different doses that your doctor may prescribe according to your illness.

Usual Daily Dose

	Usual Daily Dose
Anxiety disorders	0.25 mg, two to three times per day. Maximum 3 mg/day.
Panic disorders	0.5 mg, three times per day. Maximum 10 mg/day.

The total daily dose should be taken as advised by your doctor.

Do not change the prescribed dose yourself.
If you think the effect of your medicine is too weak or too strong, talk to your doctor.

Your doctor will advise you when to stop taking the medicine. Your doctor will slowly decrease the dosage as sudden discontinuation of treatment can cause the appearance of withdrawal symptoms.

Because elderly patients can be more sensitive to the effects of APO-ALPRAZ, lower doses may be prescribed.

Overdose:

Contact your doctor, regional Poison Control Centre or pharmacist immediately if you suspect you have taken an overdose or someone else accidentally takes your APO-ALPRAZ. If you are unable to contact them, go to a hospital emergency department for medical help, even though you may not feel sick.
Show the doctor your bottle of tablets.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medications APO-ALPRAZ can cause some side effects. For most patients, these side effects are likely to be minor and temporary as your body adjusts to the medicine. However, some may be serious. Consult your doctor or pharmacist as soon as you can if you do not feel well while taking APO-ALPRAZ.

The most common side effects are:

- Feeling drowsy or tired, especially at the start of treatment.
- Dizziness
- Loss of some balance and coordination
- Memory problems
- Constipation
- Slurred speech

Less common possible side effects are:

- Agitation
- Changes in sex drive (increased or decreased)
- Changes in weight (gain or loss)
- Increased appetite
- Difficulty urinating
- Bladder control problems

In rare cases, APO-ALPRAZ can affect liver function, and disorders such as hepatitis or liver failure may occur. Your doctor will monitor your blood for effects of APO-ALPRAZ on your liver.

Elderly patients may be especially susceptible to side effects. Excessive drowsiness or loss of balance may increase the risk of falls and fractures in elderly patients.

All patients should be cautious about performing hazardous activities that require complete mental alertness, such as operating machinery or driving a car.

Withdrawal-related side effects:
If treatment is stopped suddenly or there is a large decrease in dose, symptoms of withdrawal may occur, including: restlessness and trouble sleeping. In severe cases of withdrawal, symptoms may include: irritability, nervousness, trouble sleeping, diarrhea, stomach pains, vomiting, sweating, tremors, numbness and tingling of the extremities, hallucinations (seeing or hearing things that are not there), being unusually sensitive to light, noise and physical contact and seizures.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek emergency help
		Only if severe	In all cases	
Rare	Unusual behavioural problems (aggression, rage), sudden anxiety or excitation, restlessness, agitation, irritability; hallucinations (see or hear things that are not there) or delusions, severe sleep disturbances, nightmares, inappropriate behaviour		*	
	Allergic reactions (red skin, skin rashes, hives, itching, swelling of the lips, face, tongue, throat, trouble breathing, wheezing, shortness of breath)			*
	Depression. Symptoms may include: Difficulty sleeping, changes in weight, feelings of worthlessness, guilt, regret, helplessness or hopelessness, withdrawal from social situations, family gatherings and activities with friends, reduced libido (sex drive), and thoughts of death or suicide		*	
	Hepatitis, liver failure (yellow skin and eyes, nausea, vomiting, pain in upper right abdomen, loss of appetite, dark colored urine)			*
	Serious skin reactions (rash that may be severe, red skin, blistering of the lips, eyes or mouth, peeling skin)			*
	Increased pressure in the eyes (change in side vision, sudden severe pain in the eye, decreased or cloudy vision, seeing rainbow-like halos around lights, eyes feeling swollen)			*

This is not a complete of side effects. For any unexpected effects while taking APO-ALPRAZ, contact your doctor or pharmacist.

HOW TO STORE IT

APO-ALPRAZ should be stored at room temperature (15 - 30ºC).

Keep out of the reach of children.

Reporting Side Effects
You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

- Online at MedEffect;
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 0701E
    Ottawa, ON
    K1A 0K9

    Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

For more information, please contact your doctor, pharmacist or other healthcare professional.

This leaflet plus the full product monograph, prepared for health professionals, can be obtained by contacting Apotex Inc. at: 1-800-267-1438

This leaflet was prepared by Apotex Inc., Toronto, Ontario, M9L 1T9.

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