1.0 THERAPEUTIC CATEGORY

Anxiolytic

2.0 DESCRIPTION

Xanor® Tablets contain alprazolam which is a triazolo analog of the 1,4 benzodiazepine class of central nervous system active compound.

The chemical name of the alprazolam is 8-chloro-1-methyl-6-phenyl-4H-s-triazolo [-4.3-a] 1,4] benzodiazepine.

The structural formula is represented below:

![Structural formula of Alprazolam]

Alprazolam is a white crystalline powder, soluble in methanol or ethanol but with no appreciable solubility in water at physiological pH.

3.0 FORMULATION

Alprazolam (Xanor) tablets:
Each tablet contains 250 mcg alprazolam
Each tablet contains 500 mcg alprazolam
Each tablet contains 1 mg alprazolam

Alprazolam (Xanor XR) extended-release tablets:
Each extended-release tablet contains 500 mcg of alprazolam

4.0 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Alprazolam is indicated for the treatment of:
- Anxiety
- Depression (usage has not been established in depression with psychotic features, in bipolar disorders, or in “endogenous” depression).
- Mixed anxiety-depression
- Anxiety, mixed anxiety-depression, or depression associated with other functional or organic disease
- Panic disorders

Demonstrations of the effectiveness of Alprazolam (Xanor) by systematic clinical study are limited to four month duration of anxiety disorder and four to ten week 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 the drug for the individual patient.

4.2 DOSAGE AND METHOD OF ADMINISTRATION

Dosage should be individualized for maximum beneficial effect. While the usual daily dosages given below will meet the needs of most patients, there will be some who require higher doses. In such cases, dosage should be increased cautiously to avoid adverse effects. Dosage should be reduced gradually when terminating therapy or decreasing daily dose. Although clinical studies have not been conducted to determine a tapering regimen, it is suggested that dosage be decreased no more than one milligram every three days.

Dosage Schedule

Alprazolam (Xanor) Tablets: The optimum dose should be individualized based upon the severity of the symptoms and individual patient response. In patients who require higher doses, dosage should be increased cautiously to avoid adverse effects. In general, patients who have not previously received psychotropic medications will require somewhat lower doses than those previously treated with minor tranquilizers, antidepressants, or hypnotics. It is recommended that the general principle of using the lowest effective dose be followed in elderly or debilitated patients to preclude the development of ataxia or oversedation.

Alprazolam (Xanor XR) extended-release Tablets: If alprazolam (Xanor XR) extended-release tablet is to be given once daily, it is preferable to administer the dose in the morning. The tablets should be taken intact; they should not be chewed, crushed, or broken.

Dosing recommendations for alprazolam (Xanor XR) extended-tablets are based on a comparable pharmacokinetic profile in normal subjects given
alprazolam (Xanor) tablets three or four times daily and in those given alprazolam (Xanor XR) extended-release tablets twice daily.

## Dosage

<table>
<thead>
<tr>
<th>Indication or Population</th>
<th>Alprazolam (Xanor) Tablets</th>
<th>Alprazolam (Xanor XR) extended-release Tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Usual Starting Dose</td>
<td>Usual Dose Range</td>
</tr>
<tr>
<td></td>
<td>(if side effects occur,</td>
<td>(if side effects occur,</td>
</tr>
<tr>
<td></td>
<td>dose should be lowered)</td>
<td>dose should be lowered)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>0.75 to 1.5 mg daily</td>
<td>1 mg daily in one or two doses</td>
</tr>
<tr>
<td></td>
<td>given in divided doses</td>
<td>0.5 to 4 mg daily,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>in one or two doses</td>
</tr>
<tr>
<td>Depression</td>
<td>1.5 mg daily given in</td>
<td>1 mg daily in one or two doses</td>
</tr>
<tr>
<td></td>
<td>divided doses</td>
<td>0.5 to 4.5 mg daily,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>in one or two doses</td>
</tr>
<tr>
<td>Panic Disorders</td>
<td>0.5 to 1.0 mg given at</td>
<td>0.5 to 1.0 mg given at</td>
</tr>
<tr>
<td></td>
<td>bedtime or 0.5 mg three</td>
<td>bedtime or 0.5 mg two times daily</td>
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<tr>
<td></td>
<td>times daily</td>
<td>Dose should be adjusted to patient response</td>
</tr>
<tr>
<td></td>
<td></td>
<td>with increments no greater than 1 mg/day</td>
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<tr>
<td></td>
<td></td>
<td>every 3 to 4 days.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Additional doses can be added until a schedule</td>
</tr>
<tr>
<td></td>
<td></td>
<td>of three or four times daily is achieved.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>[The mean dose in a large multi-clinic study</td>
</tr>
<tr>
<td></td>
<td></td>
<td>was 5.7 ± 2.27 mg, with occasional patients</td>
</tr>
<tr>
<td></td>
<td></td>
<td>requiring a maximum of 10 mg/day.]</td>
</tr>
<tr>
<td>Geriatric Patients</td>
<td>0.5 to 0.75 mg daily</td>
<td>0.5 to 1 mg daily in one or two doses</td>
</tr>
<tr>
<td></td>
<td>given in divided doses</td>
<td>0.5 to 1 mg/day;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>may be gradually increased if needed and</td>
</tr>
<tr>
<td></td>
<td></td>
<td>tolerated.</td>
</tr>
</tbody>
</table>

**Duration of Treatment:** Data are available to support usage for up to 6 months for anxiety and depression and for up to 8 months in the treatment of panic disorder.
Discontinuation of Treatment: To discontinue alprazolam treatment, the dosage should be reduced slowly in keeping with good medical practice. It is suggested that the daily dosage of alprazolam be decreased by no more than 0.5 mg every 3 days. Some patients may require an even slower dosage reduction. (See section 4.4 Special warnings and precautions for use)

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

4.3 Contraindications

Xanor tablets are contraindicated in patients with known sensitivity to this drug or other benzodiazepines. Xanor may be used in patients with open angle glaucoma who are receiving appropriate therapy but is contraindicated in acute narrow angle glaucoma.

4.4 Special Warnings and Precautions for Use

Alprazolam (Xanor) tablets are not of value in the treatment of psychotic patients and should not be employed in lieu of appropriate treatment for psychosis. Because of its depressant CNS effects, patients receiving Alprazolam (Xanor) should be cautioned against engaging in hazardous occupations requiring complete mental alertness such as operating machinery or driving a motor vehicle. For the same reason, patients should be cautioned about the simultaneous ingestion of alcohol and other CNS depressant drugs during treatment with Alprazolam (Xanor).

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

Benzodiazepines can potentially cause fetal harm when administered to pregnant women. If Alprazolam (Xanor) is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Because of experience with other members of the benzodiazepine class, Alprazolam (Xanor) 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 this drug is rarely a matter of urgency, their use during the first trimester should almost always be avoided. The possibility that a woman of childbearing potential may be pregnant at the time of institution of therapy should be considered. Patients should be advised that if they
become pregnant during therapy or intend to become pregnant, they should communicate with their physicians about the desirability of discontinuing the drug.

**Precautions**

**General**

In some patients receiving recommended (or higher) doses of Alprazolam (Xanor) tablets for relatively brief periods of time (e.g. one week to four months) withdrawal seizures have been reported upon rapid decrease of dosage or abrupt discontinuation. Therefore, the dosage of Alprazolam (Xanor) should be reduced or withdrawn gradually (See 4.2 Dosage and Method of Administration).

If Alprazolam (Xanor) tablets are to be combined with other psychotropic agents or anticonvulsant drugs, careful consideration should be given to the pharmacology of the agents to be employed particularly with compounds which might potentiate the action of benzodiazepines (See 4.5 Interaction with Other Drugs and Other Forms of Interaction).

As with other psychotropic medications, the usual precautions with respect to administration of the drug and site of the prescription are indicated for severely depressed patients or those in whom there is reason to expect concealed suicidal ideation or plans.

In elderly and debilitated patients, it is recommended that the dosage be limited to the smallest effective amount to preclude the development of ataxia or oversedation. (See 4.2 Dosage and Method of Administration). The usual precautions in treating patients with impaired renal or hepatic function should be observed.

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

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

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

The use of alprazolam has not been established in certain types of depression. (See section 4.1 Therapeutic Indications)

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

Withdrawal symptoms (similar in character to those noted with barbiturates and alcohol) have occurred following abrupt discontinuance of benzodiazepines including alprazolam. These can range from mild dysphoria and insomnia to a major syndrome which may include abdominal and muscle cramps, vomiting, sweating, tremor and convulsions. In addition, withdrawal seizures have occurred upon rapid decrease or abrupt discontinuation of therapy with alprazolam. It is recommended that all patients on alprazolam who require a dosage reduction be gradually tapered under dose supervision (See 4.2 Dosage and Method of Administration).

Patients with a history of seizures or epilepsy regardless of their concomitant anti-seizure drug therapy, should not be abruptly withdrawn from any CNS depressant agent including alprazolam (Xanor) tablets. Addiction-prone individuals (such as drug addicts or alcoholics) should be under careful surveillance when receiving alprazolam or other psychotrophic agents because of the predisposition of such patients to habituation and dependence.

**Information for Patients**

To assure safe and effective use of benzodiazepines, the following information and instructions should be given to patients.

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

2) Inform your physician if you are planning to become pregnant, if you are pregnant, or if you become pregnant while 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) If benzodiazepines are used in large doses and/or for extended periods of time, they may produce habituation and emotional and physical dependence. Therefore, do not increase the dose even if you think the drug does not work anymore.
6) Do not stop taking the drug abruptly or decrease the dose without consulting your physician, since withdrawal symptoms can occur.

4.5 Interaction with other medicinal products and other forms of interaction

Benzodiazepines produce additive CNS depressant effects when coadministered with alcohol or other drugs producing CNS depression.

Pharmacokinetic interactions can occur when alprazolam is administered along with drugs that interfere with its metabolism. Compounds which inhibit certain hepatic enzymes (particularly cytochrome P4503A4) may increase the concentration of alprazolam and enhance its activity. Data from clinical studies with alprazolam, in vitro studies with alprazolam, and clinical studies with drugs metabolized similarly to alprazolam provide evidence for varying degrees of interaction and possible interaction with alprazolam for a number of drugs. Based on the degree of interaction and the type of data available, the following recommendations are made:

- The coadministration of alprazolam with ketoconazole, itraconazole, or otherazole-type antifungals is not recommended.
- Caution and consideration of dose reduction is recommended when alprazolam is co-administered with nefazodone, fluvoxamine, and cimetidine.
- Caution is recommended when alprazolam is coadministered with fluoxetine, propoxyphene, oral contraceptives, diltiazem, or macrolide antibiotics such as erythromycin and troleandomycin.
- Interactions involving HIV protease inhibitors (eg, ritonavir) and alprazolam are complex and time dependent. Low doses of ritonavir resulted in a large impairment of alprazolam clearance, prolonged its elimination half-life and enhanced clinical effects. However, upon extended exposure to ritonavir, CYP3A induction offset this inhibition. This interaction will require a dose-adjustment or discontinuation of alprazolam.

The benzodiazepines including alprazolam, produce additive CNS depressant effects when co-administered with other psychotropic medications, anticonvulsants, and histaminic ethanol and other drugs which themselves produce CNS depression.

Pharmacokinetic interactions of benzodiazepines with other drugs have been reported. For example, the clearance of alprazolam and certain other benzodiazepines can be delayed by the co-administration of cimetidine or macrolide antibiotics. The clinical significance of this is unclear.

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 (Xanor) Tablets in doses up to 4 mg/day. The clinical significance of these changes is unknown.
Drug/Laboratory Test Interactions:

Although interactions between benzodiazepines and commonly employed clinical laboratory tests have occasionally been reported, there is no consistent pattern for a specific drug or specific test.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

No evidence of carcinogenic potential was observed in rats during a 24-month study with alprazolam in doses up to 375 times the human dose.

Alprazolam was not mutagenic in the rat micronudeus test at doses up to 1250 times the human dose.

Alprazolam produced no impairment of fertility in rats at doses up to 62.5 times the human dose.

4.6 Pregnancy and Lactation

Pregnancy

The data concerning teratogenicity and effects on postnatal development and behavior following benzodiazepine treatment are inconsistent. There is evidence from some early studies with other members of the benzodiazepine class that in utero exposure may be associated with malformations. Later studies with the benzodiazepine class of drugs have provided no clear evidence of any type of defect. Infants exposed to benzodiazepines during late third trimester of pregnancy or during labor have been reported to exhibit either the floppy infant syndrome or neonatal withdrawal symptoms. If alprazolam is used during pregnancy, or if the patient becomes pregnant while taking alprazolam, the patient should be apprised of the potential hazard to the fetus.

Breastfeeding

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

Teratogenic effects: Pregnancy Category D: (See 4.4 Special Warning and Special Precaution for Use)

Nonteratogenic Effects:

It is to be considered that the child born of a mother who is on benzodiazepines may be at some risk for withdrawal symptoms from the drug during the postnatal period. Also, neonatal flaccidity has been reported in children born of a mother who has been receiving benzodiazepines.
Labor and Delivery: Alprazolam (Xanor) has no established use in labor or delivery.

Nursing Mother: Benzodiazepines are known to be excreted in human milk. It is to be assumed that alprazolam is as well. Chronic administration of diazepam to nursing mothers has been reported to cause their infants to become lethargic and lose weight. As a general rule, nursing should not be undertaken by mothers who must use Alprazolam (Xanor).

Pediatric Use:

Safety and effectiveness in children below the age of 18 have not been established.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable Effects

Adverse events, if they occur, are generally observed at the beginning of therapy and usually disappear upon continued medication or decreased dosage.

Undesirable effects associated with alprazolam therapy in patients participating in controlled clinical studies were as follows:

<table>
<thead>
<tr>
<th>MedDRA System Organ Class</th>
<th>Frequency</th>
<th>Undesirable Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Common</td>
<td>Decreased appetite</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Common</td>
<td>Confusional state, depression, disorientation, libido decreased</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Anxiety, insomnia, nervousness</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Very common</td>
<td>Sedation, somnolence</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td>Ataxia, balance disorder, coordination abnormal, memory impairment, dysarthria, disturbance in attention, hypersomnia, lethargy, dizziness, headache</td>
</tr>
<tr>
<td>MedDRA System Organ Class</td>
<td>Frequency</td>
<td>Undesirable Effects</td>
</tr>
<tr>
<td>--------------------------</td>
<td>-----------</td>
<td>---------------------</td>
</tr>
<tr>
<td>Endocrine disorders</td>
<td>Uncommon</td>
<td>Hyperprolactinaemia.</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Uncommon</td>
<td>Hypomania, mania (see section 4.4 Special warnings and precautions for use), hallucination, anger, aggression, hostility, agitation, libido disorder, thinking abnormal, psychomotor hyperactivity</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Uncommon</td>
<td>Dystonia</td>
</tr>
<tr>
<td></td>
<td>Not Known</td>
<td>Autonomic nervous system imbalance</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Uncommon</td>
<td>Gastrointestinal disorder</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>Uncommon</td>
<td>Hepatitis, hepatic function abnormal, jaundice</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Uncommon</td>
<td>Dermatitis</td>
</tr>
<tr>
<td></td>
<td>Not Known</td>
<td>Angioedema</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Uncommon</td>
<td>Incontinence, urinary retention</td>
</tr>
</tbody>
</table>
### Reproductive system and breast disorders

| Uncommon                  | Sexual dysfunction, menstruation irregular |

### General disorders and administration site conditions

| Not known                  | Oedema peripheral |

### Investigations

| Uncommon                  | Intraocular pressure increased |

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

Side effects to Alprazolam (Xanor) tablets, if they occur, are generally observed at the beginning of therapy and usually disappear upon continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacological activity of alprazolam, e.g. drowsiness or lightheadedness.

#### 4.9 Overdosage

Symptoms of overdose with alprazolam are extensions of its pharmacological action and include drowsiness, slurred speech, motor incoordination, coma and respiratory depression. Serious sequela are rare unless other drugs and/or ethanol are concomitantly ingested. Treatment of overdose is primarily supportive of respiratory and cardiovascular function. The value of dialysis has not been determined. Flumazenil may be used as an adjunct to the management of respiratory and cardiovascular function associated with overdose.

#### 5.0 PHARMACOLOGICAL PROPERTIES

#### 5.1 Pharmacodynamic Properties

CNS agents of the 1,4 benzodiazepine class presumably exert their effects by binding at stereo specific receptors at several sites within the central nervous system. Their exact mechanism of action is unknown. Clinically all
benzodiazepines cause a dose-related central nervous system depressant activity varying from mild impairment of task performance to hypnosis.

Clinical Studies

Alprazolam (Xanor) tablets were compared to placebo in double blind clinical trials in patients with a diagnosis of anxiety or anxiety with associated depressive symptomatology. Alprazolam (Xanor) was significantly better than placebo at each of the evaluation periods of these four week studies as judged by the following psychometric instruments: Physician’s Global Impressions, Hamilton Anxiety Rating Scale, Target Symptoms, Patient’s Global Impressions and Self-Rating Symptom Scale.

5.2 Pharmacokinetic Properties

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

The ability of alprazolam to induce human hepatic enzyme systems has not yet been determined. However, this is not a property of benzodiazepines in general. Further, alprazolam did not affect the prothrombin or plasma warfarin levels in male volunteers administered sodium warfarin orally.

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

Changes in the absorption, distribution, metabolism and excretion of benzodiazepines have been reported in a variety of disease states including alcoholism, impaired hepatic function and impaired renal function changes have also been demonstrated in geriatric patients. It has not yet been determined if similar changes occur in the pharmacokinetics of alprazolam.

Because of its similarity to other benzodiazepines, it is assumed that alprazolam undergoes transplacental passage and is excreted in human milk.

5.3 Preclinical Safety Data
Mutagenesis, Carcinogenesis, Fertility, and Ocular Effects

Alprazolam was not mutagenic in the in vitro Ames test. Alprazolam did not produce chromosomal aberrations in the in vivo micronucleus assay in rats up to the highest dose tested of 100 mg/kg, which is 500 times greater than the maximum recommended daily human dose of 10 mg/day.

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

Alprazolam did not impair fertility in rats up to the highest dose tested of 5 mg/kg/day, which is 25 times the maximum recommended daily human dose of 10 mg/day.

When rats were treated orally with alprazolam at 3, 10, and 30 mg/kg/day (15 to 150 times the maximum recommended daily human dose of 10 mg/day) for 2 years, 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.

6.0 PHARMACEUTICAL PARTICULARS

6.1 Shelf Life

Please see outer package for the expiry date of the product.

6.2 Storage

Alprazolam (Xanor) 250 mcg Tablet: Store at temperature not exceeding 30ºC.

Alprazolam (Xanor XR) 500 mcg, Alprazolam (Xanor) 500 mcg and 1 mg Tablets: Store at temperature not exceeding 25 ºC.

Keep out of reach of children.

6.3 Availability

Alprazolam (Xanor) 250 mcg Tablet is available as white elliptical full oval scored tablet in blister pack x 10’s (Box of 100’s)

Alprazolam (Xanor) 500 mcg Tablet is available as light orange elliptical full oval scored tablet, with “Upjohn 55” or “F” on one side and a score on the other side, in blister pack x 10’s (Box of 100’s)
Alprazolam (Xanor) 1 mg Tablet is available as blue elliptical full oval scored tablet with “Upjohn 90” or “F” on one side and a score on the other side, in blister pack x 10’s (Box of 100’s)

Alprazolam (Xanor XR) 500 mcg Extended-Release Tablet is available as round blue convex tablet, with “P&U 57” on one side and plain on the other side, in alu-alu blister pack x 10’s (Box of 100’s)

**CAUTION:** Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

**Alprazolam (Xanor) 250 mcg Tablet and Alprazolam (Xanor XR) 500 mcg Extended Release Tablet:**
Manufactured by: Pfizer Italia S.r.l.
Localita Marino Del Tronto
63100 Ascoli Piceno, Italy

**Alprazolam (Xanor) 500 mcg and 1 mg Tablets:**
Manufactured by: Pfizer Pharmaceuticals LLC
Road # 2 KM 58.2 Barceloneta, Puerto Rico 00617

Packed by: Pfizer Italia S.r.l.
Localita Marino del Tronto
63100 Ascoli Piceno, Italy

Imported by: PFIZER, INC.
23/F Ayala Life-FGU Center
6811 Ayala Avenue, Makati City, Philippines
Under Authority of PFIZER, INC.
New York, N.Y., U.S.A.

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Reference Date: 26 May 2011