XANAX®
(Alprazolam)

1. NAME OF THE MEDICINAL PRODUCT

XANAX®

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each immediate-release (IR) tablet contains 0.25 mg, 0.5 mg, or 1 mg of alprazolam.

3. PHARMACEUTICAL FORM

Immediate-release tablets.

4. 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.

4.2. POSOLOGY AND METHOD OF ADMINISTRATION

Alprazolam 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, especially in elderly or debilitated patients to preclude the development of ataxia or oversedation.

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. The risk of dependence may increase with dose and duration of treatment, therefore, the lowest possible effective dose and duration should be used and the need for continued treatment reassessed frequently.[19] (see section **4.4. Special Warnings and Precautions for Use**).

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.

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

4.3. CONTRAINDICATIONS

XANAX® is contraindicated in patients with known hypersensitivity to benzodiazepines, alprazolam, or to any component of these products' formulations.

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death. Limit dosages and durations to the minimum required.[17]

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

Habituation and emotional/physical dependence may occur with benzodiazepines, including alprazolam. As with all benzodiazepines, the risk of dependence increases with higher doses and long-term use and is further increased in patients with a history of alcoholism or drug abuse. Drug abuse is a known risk for alprazolam and other benzodiazepines, and patients should be monitored accordingly when receiving alprazolam. Alprazolam may be subject to diversion. There have been reports of overdose-related deaths when alprazolam is abused with other central nervous system (CNS) depressants including opioids, other benzodiazepines, and alcohol. These risks should be considered when prescribing or dispensing alprazolam. To reduce these risks the smallest appropriate quantity should be used and patients should be advised on the proper storage and disposal of unused

drug.[19] (see sections **4.2. Posology and Method of Administration, 4.8 Undesirable Effects** and **4.9 Overdose**)

Withdrawal symptoms have occurred following rapid decrease or abrupt discontinuance of benzodiazepines including alprazolam. These can range from mild dysphoria and insomnia to a major syndrome which may include abdominal and muscle cramps, vomiting, sweating, tremor, and convulsions. In addition, withdrawal seizures have occurred upon rapid decrease or abrupt discontinuation of therapy with alprazolam (see sections **4.2. Posology and Method of Administration** – Discontinuation of Treatment and **4.8 Undesirable Effects**).

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 in treating patients with panic disorders as is exercised with the use of any psychotropic drug in treating depressed patients or those in whom there is reason to expect concealed suicidal ideation or plans.

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

Episodes of hypomania and mania have been reported in association with the use of alprazolam in patients with depression.[11]

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

4.5. INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Benzodiazepines produce additive CNS depressant effects, including respiratory depression, when co-administered with opioids, alcohol or other drugs producing CNS depression.[17] (See section **4.4 Special warnings and precautions for use).**

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 co-administration of alprazolam with ketoconazole, itraconazole, or other azole-type antifungals is not recommended.

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

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

- Interactions involving human immunodeficiency virus (HIV) protease inhibitors (e.g., ritonavir) and alprazolam are complex and time dependent.[1,2] 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.

- 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.[14]

4.6. FERTILITY, PREGNANCY AND LACTATION

Pregnancy

The data concerning teratogenicity and effects on post-natal 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.[3] 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.[4] However, nursing should not be undertaken while using benzodiazepines.

4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Patients should be cautioned about using XANAX® 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 and with post-marketing experience are as follows:

Adverse Reactions Table[15]

System Organ Class	**Very Common ≥1/10**	**Common ≥1/100 to <1/10**	**Uncommon ≥1/1000 to <1/100**	**Rare ≥1/10 000 to <1/1 000**	**Very Rare <1/10 000**	**Frequency not known (cannot be estimated from available data)**
Endocrine Disorders						Hyperprolactinaemia*[5,6]
Metabolism and Nutrition Disorders		Decreased appetite				
Psychiatric Disorders	Depression	Confusional state, disorientation[11], libido decreased[11], anxiety, insomnia, nervousness, libido increased*	Mania*[,11] (see section **4.4. Special Warnings and Precautions for Use**), hallucination*, anger*, agitation*, drug dependence[19]			Hypomania*[,11], Aggression*, Hostility*, thinking abnormal*, psychomotor hyperactivity*, drug abuse*[,19]

Adverse Reactions Table[15]						
System Organ Class	**Very Common ≥1/10**	**Common ≥1/100 to <1/10**	**Uncommon ≥1/1000 to <1/100**	**Rare ≥1/10 000 to <1/1 000**	**Very Rare <1/10 000**	**Frequency not known (cannot be estimated from available data)**
Nervous System Disorders	Sedation, somnolence, ataxia, memory impairment, dysarthria, dizziness, headache	Balance disorder[11], coordination abnormal, disturbance in attention, hypersomnia[11], lethargy[11], tremor	Amnesia			Autonomic nervous system imbalance*, dystonia*
Eye Disorders		Vision blurred				
Gastrointestinal Disorders	Constipation[11], dry mouth[11]	Nausea[11]				Gastrointestinal disorder*
Hepatobiliary Disorders						Hepatitis*,[11], hepatic function abnormal* jaundice*
Skin and Subcutaneous Tissue Disorders		Dermatitis*				Angioedema*,[13], photosensitivity reaction*,[14]
Musculoskeletal, Connective Tissue and Bone Disorders			Muscular weakness			
Renal and Urinary Disorders			Incontinence*			Urinary retention*
Reproductive System and Breast Disorders		Sexual dysfunction*	Menstruation irregular*			
General Disorders and Administration Site Conditions	Fatigue, irritability		Drug withdrawal syndrome*,[19]			Oedema peripheral*,[13]
Investigations		Weight decreased, weight increased				Intraocular pressure increased*

*ADR identified post-marketing

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.

4.9. OVERDOSE

Symptoms of overdose with alprazolam are extensions of its pharmacological action and include drowsiness, slurred speech, motor incoordination, coma and respiratory depression.[7] Serious sequela are rare unless other drugs and/or ethanol are concomitantly ingested.[8] Treatment of overdosage is primarily supportive of respiratory and cardiovascular function. The value of dialysis has not been determined.[9] Flumazenil may be used as an adjunct to the management of respiratory and cardiovascular function associated with overdose.[10]

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES

XANAX® tablets contain a triazolobenzodiazepam. The benzodiazepines have qualitatively similar properties: anxiolysis, hypnosedation, myorelaxation, anticonvulsion. There are, however, quantitative differences in their pharmacodynamic properties that have led to varying patterns of therapeutic application. Currently, there is a general agreement that the action of benzodiazepines is a result of the potentiation of the neural inhibition that is mediated by gamma-aminobutyric acid (GABA).

5.2. PHARMACOKINETIC PROPERTIES

Following oral administration, peak concentrations in the plasma occur in 1 to 2 hours following administration. The mean half-life of Alprazolam is 12-15 hours. Alprazolam is mainly oxidized. The predominant metabolites are alpha-hydroxy-alprazolam and a benzophenone derived from alprazolam. Plasma levels of these metabolites are extremely low. The biological activity of alpha-hydroxy-alprazolam is approximately one-half that of alprazolam. Their half-lives appear to be of the same order of magnitude as that of alprazolam. The benzophenone metabolite is essentially inactive.

Alprazolam and its metabolites are excreted primarily in the urine. *In vitro*, alprazolam is bound (80%) to human serum protein.

5.3. PRECLINICAL SAFETY DATA

Mutagenesis

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.[11]

Carcinogenesis

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).[11]

Fertility

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.[11]

Ocular Effects

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.[11]

Effect of anesthetic and sedative drugs

Nonclinical research has shown that administration of anesthetic and sedation drugs that block N-methyl-D-aspartate (NMDA) receptors and/or potentiate gamma-aminobutyric acid (GABA) activity can increase neuronal cell death in the brain and result in long term deficits in cognition and behavior of juvenile animals when administered during the period of peak brain development. Based on comparisons across nonclinical species, the window of vulnerability of the brain to these effects is believed to correlate with human exposures in the third trimester of pregnancy through the first year of life, but may extend to approximately 3 years of age. While there is limited information of this effect with alprazolam, since the mechanism of action includes potentiation of GABA activity, a similar effect may occur. The relevance of these nonclinical findings to human use is unknown.[18]

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS

S. #	**Excipients for Xanax 0.25 mg Tablet**
1.	Alprazolam USP (Milled)
2.	Lactose EP-NF Spray Dried DMV
3.	Colloidal Silicon Dioxide
4.	Docusate Sodium 85% with Sodium Benzoate 15%
5.	Microcrystalline Cellulose PH 101
6.	Magnesium stearate
	Excipients for Xanax 0.5 mg Tablet
1.	Alprazolam USP (Milled)
2.	Lactose EP-NF Spray Dried DMV
3.	Colloidal Silicon Dioxide
4.	Docusate Sodium 85% with Sodium Benzoate 15%
5.	Erythrosine Sodium Aluminum Lake color mixture
6.	Microcrystalline Cellulose PH 101
7.	Magnesium Stearate
	Excipients for Xanax 1.0 mg Tablet
1.	Alprazolam USP (Milled)
2.	Lactose EP-NF Spray Dried DMV
3.	Colloidal Silicon Dioxide
4.	Docusate Sodium 85% with Sodium Benzoate 15%
5.	Lavender Aluminum Lake color mixture
6.	Microcrystalline Cellulose PH 101
7.	Magnesium Stearate.

6.2. INCOMPATIBILITIES

Information not available

6.3. SHELF LIFE

3 years

6.4. SPECIAL PRECAUTIONS FOR STORAGE

Avoid exposure to heat and sunlight. Store below 30°C.

Keep all medicines out of the reach of children.

6.5. NATURE AND CONTENTS OF CONTAINER

XANAX® tablets are supplied in blister pack of 30's.

Xanax LPD/PK-06
According to CDS V 11 Dated 20 November 2018; Supersedes CDS V 10 dated 02 Aug 2018

Manufactured by:
Pfizer Pakistan Limited
B-2, S.I.T.E., Karachi-Pakistan.
*Please visit our website **www.pfizerpro.com.pk** for latest version of Product leaflet.*

7. REFERENCES

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11. 2.5 Clinical Overview to Support Revisions to the Alprazolam Product Labeling dated 13 January 2011.

13. 2.5 Clinical Overview to Support Revisions to the Alprazolam Product Labeling dated May 2011.

14. 2.5 Clinical Overview to Support Revisions to the Alprazolam Product Labeling dated July 2013.

15. 2.5 Clinical Overview to Support Revisions to the Alprazolam Product Labeling dated December 2013.

17. 2.5 Clinical Overview to Support Updates to Sections 4.4 and 4.5 of the Core Data Sheet, May 2017.

18. 2.4 Non Clinical Overview to support Alprazolam CDS update for neuronal death, June 2018.

19. 2.5 Clinical Overview to Support Updates to the Core Data Sheet, November 2018.