PT PFIZER INDONESIA
Local Product Document

Generic Name: Alprazolam
Trade Name: XANAX SL
CDS Effective Date: November 20, 2018
Supersedes: December 12, 2013

1. NAME OF THE MEDICINAL PRODUCT

XANAX SL

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sublingual (SL) tablet contains 0.5 mg or 1 mg of alprazolam.

3. PHARMACEUTICAL FORM

Sublingual tablets.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

XANAX SL is indicated for the treatment of:

- Anxiety – including anxiety neurosis, anxiety disorders, symptoms of anxiety, etc.
- Mixed anxiety-depression – including anxiety associated with depression.
- Panic disorders – including panic disorder with or without agoraphobia. The essential feature of panic disorder is the unexpected panic attack, a sudden onset of intense apprehension, fear or terror.

4.2. Posology and method of administration

The optimum dose should be individualized based upon the severity of the symptoms and individual patient response. The daily dosage (see Table) will meet the needs of most patients. In the few patients who require higher doses, dosage should be increased cautiously to avoid adverse effects. When higher dosage is required, the evening dose should be increased before the daytime doses. In general, patients who have not previously received psychotropic medications will require lower doses than those previously treated with minor tranquilizers, antidepressants, or hypnotics or those with a history of chronic alcoholism. Patients should be periodically reassessed and dosage adjustments made, as appropriate.

Dosing recommendations for XANAX SL tablets are based on a comparable pharmacokinetic profile in normal subjects given alprazolam IR tablets and XANAX SL tablets. Patients requiring dosing that cannot be managed by XANAX SL tablets are recommended to use the alprazolam IR tablets or oral solution formulation.

XANAX SL tablets should be placed under the tongue for at least two minutes. The tablets should be allowed to completely disintegrate under the tongue before swallowing. XANAX SL tablets should not be divided, chewed, or swallowed.

Duration of Treatment:
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. (See section **4.4 Special warnings and precautions for use**)

Discontinuation of 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**).

Posology		
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 daily given in divided doses
Panic Disorders	0.5 to 1.0 mg given at bedtime or 0.5 mg three times daily	The dose should be adjusted to response. Dosage adjustments should be in increments no greater than 1 mg every three to four days. Additional doses can be added until a three times daily or four times daily schedule 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 daily.
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 SL tablets are contraindicated in patients with known hypersensitivity to benzodiazepines, alprazolam, or to any component of these products' formulations. XANAX SL may be used in patients with open angle glaucoma who are receiving appropriate therapy, but is contraindicated in patients with acute narrow angle glaucoma.

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.

Usage has not been established in depression with psychosis features, in bipolar disorders or in "endogenous" depression (i.e., severely depressed in-patients).

Habituation and emotional/physical dependence may occur with benzodiazepines, including alprazolam. Caution should be particularly used when prescribing benzodiazepines to patients who are prone to abuse drugs (e.g., alcoholics and drug addicts) because of their predisposition to habituation and dependence. 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. (See section **4.2 Posology and method of administration**, section **4.8 Undesirable effects** and section **4.9 Overdose**)

XANAX SL tablets are not recommended for use in patients whose primary diagnosis is schizophrenia.

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

Withdrawal symptoms have occurred following rapid decrease or abrupt discontinuance of benzodiazepines including alprazolam. Therefore, dosage must be gradually tapered to preclude sequelae of rapid withdrawal. These can range from mild dysphoria and insomnia to a major syndrome which may include abdominal and muscle cramps, vomiting, sweating, tremor and convulsions. These signs and symptoms, especially the more serious ones, are generally more common in those patients who have received excessive doses over an extended period of time. However, withdrawal symptoms have also been reported following rapid decrease or abrupt discontinuance of alprazolam. Consequently, abrupt discontinuation should be avoided and a gradual tapering in dosage followed (See section **4.2 Posology and method of administration** – Discontinuation of Treatment and section **4.8 Undesirable effects**). When therapy is discontinued in patients with panic-related disorders, the symptoms associated with recurrence of panic attacks often mimic those of withdrawal.

Administration to severely depressed or suicidal patients should be done with appropriate precautions and appropriate size of prescription. 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 must be exercised when using the higher doses of XANAX SL tablets in treating patients with panic-related 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.

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. The usual precautions for treating patients with impaired renal or hepatic function should be observed.

The safety and efficacy of XANAX SL tablets in children under 18 years of age have not been established.

4.5. Interaction with other medicinal products and other forms of interaction

The benzodiazepines, including alprazolam, produce additive CNS depressant effects, including respiratory depression, when co-administered with opioids, other psychotropic medications, anticonvulsants, antihistaminics, ethanol and other drugs which themselves produce CNS depression (See section **4.4 Special warnings and precautions for use)**.

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 XANAX caplets in doses up to 4 mg/day. The clinical significance of these changes is unknown.

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. 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.

4.6. Fertility, pregnancy and lactation

Pregnancy
An increased risk congenital malformations associated with minor tranquilizers (chlordiazepoxide, diazepam and meprobamate) during the first trimester of pregnancy has been suggested in several studies. 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. Because the use of these drug is rarely a matter of urgency, the use of XANAX SL tablets during this period 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 they should communicate with their physician about the desirability of discontinuing the drug.

Breast-feeding
As a general rule, nursing should not be undertaken while a patient is on a drug, since many drugs are excreted in human milk.

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 or drowsy 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

System Organ Class	Very Common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 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 *

Adverse Reactions Table

System Organ Class	Very Common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 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)
Metabolism and Nutrition Disorders		Decreased appetite				
Psychiatric Disorders	Depression	Confusional state, disorientation, libido decreased, anxiety, insomnia, nervousness, libido increased*	Mania* (See section **4.4 Special warnings and precautions for use**), hallucination*, anger*, agitation*, drug dependence			Hypomania*, aggression*, hostility*, thinking abnormal*, psychomotor hyperactivity*, drug abuse*
Nervous System Disorders	Sedation, somnolence, ataxia, memory impairment, dysarthria, dizziness, headache	Balance disorder, coordination abnormal, disturbance in attention, hypersomnia, lethargy, tremor	Amnesia			Autonomic nervous system imbalance*, dystonia*
Eye Disorders		Vision blurred				
Gastrointestinal Disorders	Constipation, dry mouth	Nausea				Gastrointestinal disorder*
Hepatobiliary Disorders						Hepatitis*, hepatic function abnormal*, jaundice*
Skin and Subcutaneous Tissue Disorders		Dermatitis*				Angioedema* , photosensitivity reaction*
Musculoskeletal, Connective Tissue and Bone Disorders			Muscular weakness			
Renal and Urinary Disorders			Incontinence*			Urinary retention*
Reproductive System and Breast Disorders		Sexual dysfunction*	Menstruation irregular*			

Adverse Reactions Table

System Organ Class	Very Common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 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)
General Disorders and Administration Site Conditions	Fatigue, irritability		Drug withdrawal syndrome*			Oedema peripheral*
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.

In addition, the following adverse events have been reported in association with the use of anxiolytic benzodiazepines including alprazolam: anorexia, fatigue, and slurred speech.

The most common adverse reactions in patients with panic-related disorders were drowsiness, and slurred speech. Less common adverse reactions were altered mood, and intellectual impairment confusion.

4.9. Overdose

Manifestation of alprazolam overdosage include somnolence, confusion, impaired coordination, slurred speech, respiratory depression, diminished reflexes and coma. 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.

Experiments in animals have indicated that cardiopulmonary collapse can occur following massive intravenous doses of alprazolam (over 195 mg/kg; 975 times the maximum recommended daily human dose of 10 mg/day). Animals could be resuscitated with positive mechanical ventilation and the intravenous infusion of norepinephrine bitartrate.

Treatment of overdosage 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. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Alprazolam is an effective anxiolytic, antidepressant, and antipanic agent.

5.2. Pharmacokinetic properties

Absorption
Following oral administration, Alprazolam is readily absorbed. Peak concentrations in the plasma occur in one or two hours following administration. After single-dose administration, plasma levels are proportionate to the dose given; over the dose range of 0.5 to 3.0 mg peak levels of 8.0 to 37 ng/ml were observed. The mean plasma elimination half life of Alprazolam has been found to be about 11.2 hours (range: 6.3-26.9 hours).

Distribution
In vitro alprazolam is bound (80%) to human serum protein. When alprazolam-14C was administered to pregnant mice, drug-related materials appeared uniformly distributed in the fetus with 14C concentration approximately the same as in the blood and skeletal muscle of the mother. Because of its similarity to other benzodiazepines, it is assumed that alprazolam undergoes transplacental passage, and that it is excreted in human milk.

Metabolism/Elimination
Alprazolam and its metabolites are excreted primarily in the urine. The predominant metabolites are alpha-hydroxy-alprazolam, 4-hydroxy alprazolam, and a benzophenone derived from alprazolam. The biological activity of alpha-hydroxy-alprazolam is approximately one-half that of alprazolam. The benzophenone metabolite is essentially inactive. Plasma levels of these metabolites are extremely low. However, their half lives appear to be of the same order of magnitude as that of alprazolam.

Alprazolam did not affect the prothrombin or plasma warfarin levels in male volunteers administered sodium warfarin orally.

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. The co-administration of oral contraceptives to healthy woman increased the half-life of alprazolam as compared to that in healthy control woman (mean: 12.4 hours, n = 11 vs. 9.6 hours, n = 9). There was a prolongation in the mean half-life of

alprazolam from 12.4 hours (range: 7.2-18.4 hours, n = 9) to 16.6 hours (range: 10.0-24.3 hours, n = 9) by the co-administration of cimetidine to the same healthy adults. 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.

5.3. Preclinical safety data

Mutagenesis

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

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).

Fertility

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

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.

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.

HOW SUPPLIED

XANAX SL tablets 0.5 mg
Box, 2 blisters @ 15 sublingual tablets
Reg. No. DPI1754201074A1

XANAX SL tablets 1 mg
Box, 2 blisters @ 15 sublingual tablets
Reg. No. DPI1754201074B1

Store at temperature below 30°C.

HARUS DENGAN RESEP DOKTER

Manufactured by:
Pfizer Italia, S.r.l., 63100 Ascoli Piceno (AP), Italy

Imported by:
PT. Pfizer Indonesia
Jakarta, Indonesia