1. NAME OF THE MEDICINAL PRODUCT

XANAX™
(ALPRAZOLAM TABLETS)

XANAX™ XR
(ALPRAZOLAM EXTENDED-RELEASE TABLETS)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

- XANAX™ 0.25 mg Tablets
Each tablet contains:
Alprazolam 0.25 mg - Microcrystalline cellulose - Lactose - Starch - Docusate sodium (85%) + Sodium benzoate (15%) - Colloidal silicon dioxide - Magnesium stearate.

- XANAX™ 0.5 mg Tablets
Each tablet contains:
Alprazolam 0.5 mg - Microcrystalline cellulose - Lactose - Starch - Docusate sodium (85%) + Sodium benzoate (15%) - Colloidal silicon dioxide - Magnesium stearate - Erythrosine sodium aluminum lake.

- XANAX™ 1 mg Tablets
Each tablet contains:
Alprazolam 1 mg - Microcrystalline cellulose - Lactose - Starch - Docusate sodium (85%) + Sodium benzoate (15%) - Colloidal silicon dioxide - Magnesium stearate - Erythrosine sodium aluminum lake - F.D. & C. blue no. 2 aluminum lake.

- XANAX™ 2 mg Tablets
Each tablet contains:
Alprazolam 2 mg - Microcrystalline cellulose - Lactose - Starch - Docusate sodium (85%) + Sodium benzoate (15%) - Colloidal silicon dioxide - Magnesium stearate.

- XANAX™ XR 0.5 mg Extended-release tablets
Each tablet contains:
Alprazolam 0.5 mg - Lactose - Hydroxypropyl methylcellulose - Colloidal silicon dioxide – Magnesium stearate - F.D. & C. blue no. 2 aluminum lake.

- XANAX™ XR 1 mg Extended-release tablets
Each tablet contains:
Alprazolam 1 mg - Lactose - Hydroxypropyl methylcellulose - Colloidal silicon dioxide – Magnesium stearate.

- XANAX™ XR 2 mg Extended-release tablets
Each tablet contains:
Alprazolam 2 mg - Lactose - Hydroxypropyl methylcellulose - Colloidal silicon dioxide – Magnesium stearate - F.D. & C. blue no. 2 aluminum lake.

- XANAX™ XR 3 mg Extended-release tablets
Each tablet contains:
Alprazolam 3 mg - Lactose - Hydroxypropyl methylcellulose - Colloidal silicon dioxide – Magnesium stearate.

3. PHARMACEUTICAL FORM

XANAX™ Tablets are available in 0.25 mg, 0.5 mg, 1 mg and 2 mg.

XANAX™ XR Extended-release tablets are available in 0.5 mg, 1 mg, 2 mg and 3 mg.

ROUTE OF ADMINISTRATION

Oral

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

XANAX™ Tablets (alprazolam) are indicated for the treatment of:

- Anxiety states (anxiety neuroses)
Symptoms which occur in such patients include anxiety, tension, agitation, insomnia, apprehension, irritability and/or autonomic hyperactivity resulting in a variety of somatic complaints.

- Mixed anxiety-depression
Symptoms of both anxiety and depression occur simultaneously in such patients.

- Neurotic or reactive depression
Such patients primarily exhibit a depressed mood or a pervasive loss of interest or pleasure. Symptoms of anxiety, psychomotor agitation and insomnia are usually present. Other characteristics include appetite disturbances, changes in weight, somatic complaints, cognitive disturbances, decreased energy, feeling of worthlessness or guilt, or thoughts of death or suicide.

- Anxiety states, mixed anxiety-depression, or depression associated with other diseases, such as the **chronic phase** of alcohol withdrawal and functional or organic disease, particularly certain gastrointestinal, cardiovascular, or dermatological disorders.

- Panic related disorders
XANAX™ is indicated in the treatment of panic disorder with or without some phobic avoidance. XANAX™ is also indicated for the blocking or attenuation of panic attacks and phobias in patients who have agoraphobia with panic attacks. The effectiveness of XANAX™ in the treatment of anxiety, anxiety associated with depression and neurotic (reactive) depression for long-term use exceeding six months has not been established by systematic clinical trials; however, patients with panic-related disorders have been effectively treated for up to eight months. The physician should periodically reassess the usefulness of the drug for the individual patient.

4.2 Posology and method of administration

The optimum dosage of XANAX™ (alprazolam) 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 oversedation or ataxia.

If XANAX™ XR 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.

Dosage recommendations for XANAX™ XR Tablets for use in panic disorders are based on short term clinical trials in patients with panic disorders and a comparable pharmacokinetic profile in normal subjects, between XANAX™ Tablets given three or four times daily and XANAX™ XR Tablets given twice daily.

Dosing recommendations for XANAX™ XR Tablets for use in anxiety, depression, mixed anxiety-depression and in geriatric patients are based on a comparable pharmacokinetic profile in normal subjects between XANAX™ Tablets given three or four times daily and XANAX™ XR Tablets given twice daily.

When equal daily doses of XANAX™ Tablets, dosed three or four times daily, and XANAX™ XR Tablets, dosed twice daily, were given, the steady-state serum concentration levels of alprazolam achieved with XANAX™ XR fell between the steady-state peak and trough serum concentration levels obtained with XANAX™ Tablets. The total amount of alprazolam absorbed is equivalent for XANAX™ Tablets and XANAX™ XR Tablets.

XANAX™ tablets	**Usual starting dosage***	**Usual dosage range**
Anxiety	0.25 to 0.5 mg given three times daily.	0.5 to 4.0 mg daily, given in divided doses.
Depression	0.5 mg given three times daily.	1.5 to 4.5 mg daily, given in divided doses.
Geriatric patients or in the presence of debilitating disease	0.25 mg given two to three times daily.	0.5 to 0.75 mg daily, given in divided doses; to be gradually increased if needed and tolerated.
Panic-related disorders	0.5 - 1.0 mg, given at bedtime or 0.5 mg three times daily.	The dose should be adjusted to patient response. Dosage adjustments should be in increments not greater than 1 mg every 3 or 4 days. Additional doses can be added until a TID or QID schedule is achieved. The mean dose in a large multiclinic study was 5.7 ± 2.27 mg/day with rare patients requiring a maximum of 10 mg daily.

XANAX™ XR Extended-release tablets	Usual starting dosage*	Usual dosage range
Anxiety	1 mg daily given in one or two doses.	0.5 to 4.0 mg daily, given in one or two doses.
Depression	1 mg daily given in one or two doses.	0.5 to 4.5 mg daily, given in one or two doses.
Geriatric patients	0.5 to 1 mg daily, given in one or two doses.	0.5 to 1.0 mg daily, may be gradually increased if needed and tolerated.
Panic-related disorders	0.5 - 1.0 mg given at bedtime or 0.5 mg two times daily.	In clinical trials the mean maintenance dose was between 5 and 6 mg/day given as a single daily dose or divided into two doses daily, with occasional patients needing up to 10 mg/day. The dose should be adjusted to patient response, with dose increments of not greater than 1 mg in the daily dose every three to four days.

* If side effects occur, the dose should be lowered.

The safety and efficacy of XANAX™ in children less than 18 years of age has not been established.

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 therapy

To discontinue alprazolam treatment, the dosage should be reduced slowly in keeping with good medical practice. It is suggested that the daily dosage of XANAX™ be decreased by not 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**).

4.3. Contraindications

XANAX™ is contraindicated in patients with known hypersensitivity to the 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.

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

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 (see section **4.2 Posology and method of administration**, section **4.8 Undesirable effects** and section **4.9 Overdosage**).

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 section **4.2 Posology and method of administration - Discontinuation therapy** and section **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 XANAX™ 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.

The 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 abrupt discontinuance of benzodiazepines taken at therapeutic levels. Consequently, abrupt discontinuation should be avoided and a gradual tapering in dosage followed (see section **4.2 Posology and method of administration - Discontinuation therapy**). 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.

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

Usage has not been established in depression with psychiatric features, in bipolar disorders or in "endogenous" depression (i.e., severely depressed in-patients) (see section **4.1 Therapeutic indications**).

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

Benzodiazepines, including alprazolam, produce additive CNS depressant effects, including respiratory depression, when co-administered with opioids, other psychotropic medications, anticonvulsants, antihistaminics, alcohol 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™ Tablets 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, sertraline, 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

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.

If XANAX™ 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 use of these drugs is rarely a matter of urgency, their use during the first trimester should almost always be avoided.

Breast-feeding

Benzodiazepines are known to be excreted in human milk. As a general rule, nursing should not be undertaken by mothers who must use XANAX™.

4.7. Effects on ability to drive and use machines

As with other CNS active drugs, patients receiving XANAX™ should be advised not to operate motor vehicles or engage in dangerous activities until it is established that they do not become impaired while receiving XANAX™.

4.8. Undesirable effects

Side effects, 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*
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*, altered mood, 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*			
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. Isolated published reports involving small number of patients have suggested that 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 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 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

Properties

Alprazolam is chemically 8-chloro-1-methyl-6-phenyl-4H-s-triazolo [4,3-a] [1,4] benzodiazepine.

5.1. Pharmacodynamic properties

XANAX™ Tablets contain a triazolobenzodiazepine. 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 of XANAX™ Tablets in plasma occur in one to two hours following administration. The mean half-life of alprazolam is 12-15 hours.

Following oral administration, peak concentrations of XANAX™ XR in plasma occur between 5 and 11 hours following administration. The mean half-life of alprazolam is 11.2 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.

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 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.

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.

6. PHARMACEUTICAL PARTICULARS

6.1. Shelf life

The expiry date (month/year) is mentioned on the package after "EXP.:" (EXP. = expiry date).

6.2. Special precautions for storage

XANAX™: Do not store above 25°C.
XANAX™ XR: Do not store above 30°C.

6.3. Nature and contents of container

XANAX™ Tablets 0.25 mg, 0.5 mg, 1 mg and 2 mg are supplied in packages of 100 tablets.

XANAX™ XR Extended-release tablets in 0.5 mg, 1 mg, 2 mg and 3 mg are supplied in packages of 30 tablets.

Not all strengths and presentations are available in all countries.

7. PRODUCT OWNER

Viatris Inc
1000 Mylan Blvd
Canonsburg PA 15317
United States

XAN-SIN-0321/0
Date of last revision: March 2021