

NAME OF THE MEDICINAL PRODUCT

Xanagis 0.25 mg

Xanagis 0.5 mg

Xanagis 1 mg

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet of Xanagis 0.25 mg contains 0.25 mg of alprazolam.

Each tablet of Xanagis 0.5 mg contains 0.5 mg of alprazolam.

Each tablet of Xanagis 1 mg contains 1 mg of alprazolam

PHARMACEUTICAL FORM

Tablets

INDICATIONS AND USAGE

- Treatment of anxiety accompanied by depression.
- Treatment of panic states with or without accompanying phobia.

WARNING: RISKS FROM CONCOMITANT USE WITH OPIOIDS; ABUSE, MISUSE, AND ADDICTION; and DEPENDENCE AND WITHDRAWAL REACTIONS

- Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death.
- Reserve concomitant prescribing of these drugs for patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required.
- Follow patients for signs and symptoms of respiratory depression and sedation (see WARNINGS AND PRECAUTIONS).
- The use of benzodiazepines, including XANAGIS, exposes users to risks of abuse, misuse, and addiction, which can lead to overdose or death. Abuse and misuse of benzodiazepines commonly involve concomitant use of other medications, alcohol, and/or illicit substances, which is associated with an increased frequency of serious adverse outcomes. Before prescribing XANAGIS and throughout treatment, assess each patient's risk for abuse, misuse, and addiction (see WARNINGS AND PRECAUTIONS).
- The continued use of benzodiazepines, including XANAGIS, may lead to clinically significant physical dependence. The risks of dependence and withdrawal increase with longer treatment duration and higher daily dose. Abrupt discontinuation or rapid dosage reduction of XANAGIS after continued use may precipitate acute withdrawal reactions, which can be life-threatening. To reduce the risk of withdrawal reactions, use a gradual taper to discontinue XANAGIS or reduce the dosage (see DOSAGE AND ADMINISTRATION and WARNINGS AND PRECAUTIONS).

DESCRIPTION

XANAGIS Tablets contain alprazolam which is a triazolo analog of the 1,4 benzodiazepine class of central nervous system-active compounds.

The chemical name of alprazolam is 8-Chloro-1-methyl-6-phenyl-4H-s-triazolo [4,3- α] [1,4] benzodiazepine. The structural formula is represented to the right:

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

Each XANAGIS Tablet, for oral administration, contains 0.25, 0.5, 1 mg of alprazolam.

Inactive ingredients:

Lactose monohydrate, microcrystalline cellulose, maize starch, docusate sodium (85%) with sodium benzoate (15%), magnesium stearate, colloidal anhydrous silica.

Xanagis 0.5 mg also contains erythrosine sodium aluminium lake.

Xanagis 1 mg also contains erythrosine sodium aluminium lake and F.D. &C. Blue Nr. 2 aluminium lake.

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Benzoate salt may increase jaundice (yellowing of the skin and eyes) in newborn babies (up to 4 weeks old).

CLINICAL PHARMACOLOGY

Pharmacodynamics

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.

Pharmacokinetics

Absorption

Following oral administration, alprazolam is readily absorbed. Peak concentrations in the plasma occur in 1 to 2 hours following 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. Using a specific assay methodology, the mean plasma elimination half-life of alprazolam has been found to be about 11.2 hours (range: 6.3–26.9 hours) in healthy adults.

Distribution

In vitro, alprazolam is bound (80 percent) to human serum protein. Serum albumin accounts for the majority of the binding.

Metabolism/Elimination

Alprazolam is extensively metabolized in humans, primarily by cytochrome P450 3A4 (CYP3A4), to two major metabolites in the plasma: 4-hydroxyalprazolam and α -hydroxyalprazolam. A benzophenone derived from alprazolam is also found in humans. Their half-lives appear to be similar to that of alprazolam. The plasma concentrations of 4-hydroxyalprazolam and α -hydroxyalprazolam relative to unchanged alprazolam concentration were always less than 4%. The reported relative potencies in benzodiazepine receptor binding experiments and in animal models of induced seizure inhibition are 0.20 and 0.66, respectively, for 4-hydroxyalprazolam and α -hydroxyalprazolam. Such low concentrations and the lesser potencies of 4-hydroxyalprazolam and α -hydroxyalprazolam suggest that they are unlikely to contribute much to the pharmacological effects of alprazolam. The benzophenone metabolite is essentially inactive.

Alprazolam and its metabolites are excreted primarily in the urine.

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.

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

Race

Maximal concentrations and half-life of alprazolam are approximately 15% and 25% higher in Asians compared to Caucasians.

Pediatrics

The pharmacokinetics of alprazolam in pediatric patients have not been studied.

Gender

Gender has no effect on the pharmacokinetics of alprazolam.

Cigarette Smoking

Alprazolam concentrations may be reduced by up to 50% in smokers compared to non-smokers.

Drug-Drug Interactions

Alprazolam is primarily eliminated by metabolism via cytochrome P450 3A (CYP3A). Most of the interactions that have been documented with alprazolam are with drugs that inhibit or induce CYP3A4. potent inhibitors of CYP3A would be expected to increase plasma alprazolam concentrations. Drug products that have been studied in vivo, along with their effect on increasing alprazolam AUC, are as follows: ketoconazole, 3.98 fold; itraconazole, 2.70 fold; nefazodone, 1.98 fold; fluvoxamine, 1.96 fold; and erythromycin, 1.61 fold (see CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS–Drug Interactions).

CYP3A inducers would be expected to decrease alprazolam concentrations and this has been observed in vivo. The oral clearance of alprazolam (given in a 0.8 mg single dose) was increased from 0.90 ± 0.21 mL/min/kg to 2.13 ± 0.54 mL/min/kg and the elimination $t_{1/2}$ was shortened (from 17.1 ± 4.9 h to 7.7 ± 1.7 h) following administration of 300 mg/day carbamazepine for 10 days (see PRECAUTIONS–Drug Interactions). However, the carbamazepine dose used in this study was fairly low compared to the recommended doses (1000–1200 mg/day); the effect at usual carbamazepine doses is unknown.

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.

CLINICAL STUDIES

Anxiety Disorders

Alprazolam Tablets were compared to placebo in double blind clinical studies (doses up to 4 mg/day) in patients with a diagnosis of anxiety or anxiety with associated depressive symptomatology. Alprazolam was significantly better than placebo at each of the evaluation periods of these 4-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.

Panic Disorder

Support for the effectiveness of Alprazolam in the treatment of panic disorder came from three short-term, placebo- controlled studies (up to 10 weeks) in patients with diagnoses closely corresponding to DSM-III-R

criteria for panic disorder.

The average dose of Alprazolam was 5–6 mg/day in two of the studies, and the doses of Alprazolam were fixed at 2 and 6 mg/day in the third study. In all three studies, Alprazolam was superior to placebo on a variable defined as "the number of patients with zero panic attacks" (range, 37–83% met this criterion), as well as on a global improvement score. In two of the three studies, Alprazolam was superior to placebo on a variable defined as "change from baseline on the number of panic attacks per week" (range, 3.3–5.2), and also on a phobia rating scale. A subgroup of patients who were improved on Alprazolam during short-term treatment in one of these trials was continued on an open basis up to 8 months, without apparent loss of benefit.

CONTRAINDICATIONS

XANAGIS Tablets are contraindicated in patients:

- with known hypersensitivity to the active substance or other benzodiazepines or to any of the excipients listed in section "DESCRIPTION".. Angioedema has been reported
- taking strong cytochrome P450 3A (CYP3A) inhibitors (e.g., ketoconazole, itraconazole), except ritonavir (see WARNINGS and PRECAUTIONS–Drug Interactions).

WARNINGS AND PRECAUTIONS

Risks from Concomitant Use with Opioids

Concomitant use of benzodiazepines, including Xanax, and opioids may result in profound sedation, respiratory depression, coma, and death. Because of these risks, reserve concomitant prescribing of these drugs in patients for whom alternative treatment options are inadequate.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioids alone. If a decision is made to prescribe XANAGIS concomitantly with opioids, prescribe the lowest effective dosages and minimum durations of concomitant use, and follow patients closely for signs and symptoms of respiratory depression and sedation. In patients already receiving an opioid analgesic, prescribe a lower initial dose of XANAGIS than indicated in the absence of an opioid and titrate based on clinical response. If an opioid is initiated in a patient already taking XANAGIS, prescribe a lower initial dose of the opioid and titrate based upon clinical response.

Advise both patients and caregivers about the risks of respiratory depression and sedation when XANAGIS is used with opioids. Advise patients not to drive or operate heavy machinery until the effects of concomitant use with the opioid have been determined (see PRECAUTIONS -Drug Interactions).

Abuse, Misuse, and Addiction

The use of benzodiazepines, including XANAGIS, exposes users to the risks of abuse, misuse, and addiction, which can lead to overdose or death. Abuse and misuse of benzodiazepines often (but not always) involve the use of doses greater than the maximum recommended dosage and commonly involve concomitant use of other medications, alcohol, and/or illicit substances, which is associated with an increased frequency of serious adverse outcomes, including respiratory depression, overdose, or death (see DRUG ABUSE AND DEPENDENCE - Abuse).

Before prescribing XANAGIS and throughout treatment, assess each patient's risk for abuse, misuse, and addiction (e.g., using a standardized screening tool). Use of XANAGIS, particularly in patients at elevated risk, necessitates counseling about the risks and proper use of XANAGIS along with monitoring for signs and symptoms of abuse, misuse, and addiction. Prescribe the lowest effective dosage; avoid or minimize concomitant use of CNS depressants and other substances associated with abuse, misuse, and addiction (e.g., opioid analgesics, stimulants); and advise patients on the proper disposal of unused drug. If a substance use disorder is suspected, evaluate the patient and institute (or refer them for) early treatment, as appropriate.

Dependence and Withdrawal Reactions

To reduce the risk of withdrawal reactions, use a gradual taper to discontinue XANAGIS or reduce the dosage (a patient-specific plan should be used to taper the dose) [*see* DOSAGE AND ADMINISTRATION - Discontinuation or *Dosage* Reduction of XANAGIS).

Patients at an increased risk of withdrawal adverse reactions after benzodiazepine discontinuation or rapid dosage reduction include those who take higher dosages, and those who have had longer durations of use.

Acute Withdrawal Reactions

The continued use of benzodiazepines, including XANAGIS, may lead to clinically significant physical dependence. Abrupt discontinuation or rapid dosage reduction of XANAGIS after continued use, or administration of flumazenil (a benzodiazepine antagonist) may precipitate acute withdrawal reactions, which can be life-threatening (e.g., seizures) [*see* DRUG ABUSE AND DEPENDENCE -*Drug Abuse and Dependence*].

Protracted Withdrawal Syndrome

In some cases, benzodiazepine users have developed a protracted withdrawal syndrome with withdrawal symptoms lasting weeks to more than 12 months *see* DRUG ABUSE AND DEPENDENCE *Dependence*

Certain adverse clinical events, some life-threatening, are a direct consequence of physical dependence to XANAGIS. These include a spectrum of withdrawal symptoms; the most important is seizure [*see* DRUG ABUSE AND DEPENDENCE). Even after relatively short-term use at doses of ≤ 4 mg/day, there is some risk of dependence. Spontaneous reporting system data suggest that the risk of dependence and its severity appear to be greater in patients treated with doses greater than 4 mg/day and for long periods (more than 12 weeks).

However, in a controlled postmarketing discontinuation study of panic disorder patients, the duration of treatment (3 months compared to 6 months) had no effect on the ability of patients to taper to zero dose. In contrast, patients treated with doses of Alprazolam greater than 4 mg/day had more difficulty tapering to zero dose than those treated with less than 4 mg/day.

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.

Interdose Symptoms

Early morning anxiety and emergence of anxiety symptoms between doses of XANAGIS have been reported in patients with panic disorder taking prescribed maintenance doses. 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 interdosing interval.

Effects on Driving and Operating Machinery

Because of its CNS depressant effects, patients receiving XANAGIS should be cautioned against engaging in hazardous occupations or activities requiring complete mental alertness such as operating machinery or driving

a motor vehicle. For the same reason, patients should be cautioned about the concomitant use of alcohol and other CNS depressant drugs during treatment with Xanax[see *Drug Interactions*].

Interaction with Drugs that Inhibit Metabolism via Cytochrome P450 3A

The initial step in alprazolam metabolism is hydroxylation catalyzed by cytochrome P450 3A (CYP3A). Drugs that inhibit this metabolic pathway may have a profound effect on the clearance of alprazolam.

Strong CYP3A Inhibitors

Xanax is contraindicated in patients receiving strong inhibitors of CYP3A (such as azole antifungal agents), except ritonavir [see *Contraindications*]. Ketoconazole and itraconazole have been shown in vivo to increase plasma alprazolam concentrations 3.98 fold and 2.70 fold, respectively.

Dosage adjustment is necessary when Xanax and ritonavir are initiated concomitantly or when ritonavir is added to a stable dosage of Xanax [see *Dosage and Administration*, *Drug Interactions*].

Drugs demonstrated to be CYP3A inhibitors on the basis of clinical studies involving alprazolam: nefazodone, fluvoxamine, and cimetidine [see *Drug Interaction*, *Clinical Pharmacology*]. Use caution and consider dose reduction of Xanax, as appropriate, during co-administration with these drugs.

Patients with Depression

Benzodiazepines may worsen depression. Panic disorder has been associated with primary and secondary major depressive disorders and increased reports of suicide among untreated patients. Consequently, appropriate precautions (e.g., limiting the total prescription size and increased monitoring for suicidal ideation) should be considered in patients with depression.

Mania

Episodes of hypomania and mania have been reported in association with the use of XANAGIS in patients with depression [see *Adverse Reactions*].

Neonatal Sedation and Withdrawal Syndrome

Use of Xanax late in pregnancy can result in sedation (respiratory depression, lethargy, hypotonia) and/or withdrawal symptoms (hyperreflexia, irritability, restlessness, tremors, inconsolable crying, and feeding difficulties) in the neonate [see *Use in Specific Populations*]. Monitor neonates exposed to Xanax during pregnancy or labor for signs of sedation and monitor neonates exposed to Xanax during pregnancy for signs of withdrawal; manage these neonates accordingly.

Risk

Use in Patients with Impaired Respiratory Function

There have been reports of death in patients with severe pulmonary disease shortly after the initiation of treatment with Xanax. Closely monitor patients with impaired respiratory function. If signs and symptoms of respiratory depression, hypoventilation, or apnea occur, discontinue Xanax.

ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Risks from Concomitant Use with Opioids [see *Warnings and Precautions*]
- Abuse, Misuse, and Addiction [see *Warnings and Precautions*]
- Dependence and Withdrawal Reactions [see *Warnings and Precautions*]
- Effects on Driving and Operating Machinery [see *Warnings and Precautions*]
- Patients with Depression [see *Warnings and Precautions*]
- Neonatal Sedation and Withdrawal Syndrome [see *Warnings and Precautions*]
- Risks in Patients with Impaired Respiratory Function [see *Warnings and Precautions*]

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data in the two tables below are estimates of adverse reaction incidence among adult patients who participated in:

- 4-week placebo-controlled clinical studies with Xanax dosages up to 4 mg per day for the acute treatment of generalized anxiety disorder (Table 1)
- Short-term (up to 10 weeks) placebo-controlled clinical studies with Xanax dosages up to 10 mg per day for panic disorder, with or without agoraphobia (Table 2).

Table 1: Adverse Reactions Occurring in $\geq 1\%$ in Alprazolam-treated Patients and Greater than Placebo-treated Patients in Placebo-Controlled Trials for Generalized Anxiety

	Alprazolam n=565	Placebo n=505
Nervous system disorders		
Drowsiness	41%	22%
Light-headedness	21%	19%
Dizziness	2%	1%
Akathisia	2%	1%
Gastrointestinal disorders		
Dry mouth	15%	13%
Increased salivation	4%	2%
Cardiovascular disorders		
Hypotension	5%	2%
Skin and subcutaneous tissue disorders		
Dermatitis/Allergy	4%	3%

In addition to the adverse reactions (i.e., greater than 1%) enumerated in the table above for patients with generalized anxiety disorder, the following adverse reactions have been reported in association with the use of benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, transient amnesia or memory impairment, loss of coordination, fatigue, seizures, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

Table 2: Adverse Reactions Occurring in $\geq 1\%$ in Alprazolam-treated Patients and Greater than

Placebo- treated Patients in Placebo-Controlled Trials (Up to 10 Weeks) for Panic Disorder

Number of Patients	Alprazolam n=1388	Placebo n=1231
Drowsiness	77%	43%
Fatigue and Tiredness	49%	42%
Impaired Coordination	40%	18%
Irritability	33%	30%
Memory Impairment	33%	22%
Cognitive Disorder	29%	21%
Decreased Libido	14%	8%
Dysarthria	23%	6%
Confusional state	10%	8%
Increased libido	8%	4%
Change in libido (not specified)	7%	6%
Disinhibition	3%	2%
Talkativeness	2%	1%
Derealization	2%	1%
Gastrointestinal disorders		
Constipation	26%	15%
Increased salivation	6%	4%
Skin and subcutaneous tissue disorders		
Rash	11%	8%
Other		
Increased appetite	33%	23%
Decreased appetite	28%	24%
Weight gain	27%	18%
Weight loss	23%	17%
Micturition difficulties	12%	9%
Menstrual disorders	11%	9%
Sexual dysfunction	7%	4%
Incontinence	2%	1%

In addition to the reactions (i.e., greater than 1%) enumerated in the table above for patients with panic disorder, the following adverse reactions have been reported in association with the use of XANAGIS: seizures, hallucinations, depersonalization, taste alterations, diplopia, elevated bilirubin, elevated hepatic enzymes, and jaundice.

Adverse Reactions Reported as Reasons for Discontinuation in Treatment of Panic Disorder in Placebo-Controlled Trials

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 are shown in Table 3.

Table 3: Discontinuation-Emergent Symptom Incidence Reported in ≥5% of Alprazolam-treated Patients and > Placebo

	-treated Patients n=641
Nervous system disorders	
Insomnia	29.5%
Light-headedness	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 disorders	
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 disorders	
Nausea/Vomiting	16.5%
Diarrhea	13.6%
Decreased salivation	10.6%
Metabolism and nutrition disorders	
Weight loss	13.3%
Decreased appetite	12.8%
Dermatological disorders	
Sweating	14.4%
Cardiovascular disorders	
Tachycardia	12.2%
Special Senses	
Blurred vision	10.0%

n=number of patients.

There have also been reports of withdrawal seizures upon rapid decrease or abrupt discontinuation of Alprazolam Tablets (see WARNINGS).

[see Warning and Precautions) and Drug Abuse and Dependence].

Paradoxical reactions such as stimulation, increased muscle spasticity, sleep disturbances, hallucinations, and other adverse behavioral effects such as agitation, rage, irritability, and aggressive or hostile behavior have been reported rarely. 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. Should any

of the above events occur, alprazolam should be discontinued. Isolated published reports involving small numbers 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 discontinuation of alprazolam in patients with posttraumatic stress disorder.

Postmarketing Experience

The following adverse reactions have been identified during postapproval use of XANAGIS. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Endocrine disorders: Hyperprolactinemia

General disorders and administration site conditions: Edema peripheral

Hepatobiliary disorders: Hepatitis, hepatic failure

Investigations: Liver enzyme elevations

Psychiatric disorders: Hypomania, mania

Reproductive system and breast disorders: Gynecomastia, galactorrhea

Skin and subcutaneous tissue disorders: Photosensitivity reaction, angioedema, Stevens-Johnson syndrome

DRUG INTERACTIONS

Drugs Having Clinically Important Interactions with Xanagis

Table 4 includes clinically significant drug interactions with [see *Clinical Pharmacology*].

Table 4: Clinically Significant Drug Interactions with Xanagis

Opioids	
Clinical implication	The concomitant use of benzodiazepines and opioids increases the risk of respiratory depression because of actions at different receptor sites in the CNS that control respiration. Benzodiazepines interact at gamma-aminobutyric acid(GABA _A) sites and opioids interact primarily at mu receptors. When benzodiazepines and opioids are combined, the potential for benzodiazepines to significantly worsen opioid-related respiratory depression exists.
Prevention or management	Limit dosage and duration of concomitant use of Xanagis and opioids, and monitor patients closely for respiratory depression and sedation [see <i>Warnings and Precautions</i>].
Examples	Morphine, buprenorphine, hydromorphone, oxycodone, fentanyl, methadone, alfentanil, butorphenol, codeine, dihydrocodeine, meperidine, pentazocine, remifentanil, sufentanil, tapentadol, tramadol.
CNS Depressants	
Clinical implication	The benzodiazepines, including alprazolam, produce additive CNS depressant effects when coadministered with other CNS depressants.
Prevention or management	Limit dosage and duration of Xanagis during concomitant use with CNS depressants [see <i>Warnings and Precautions</i>].
Examples	Psychotropic medications, anticonvulsants, antihistaminics, ethanol, and other drugs which themselves produce CNS depression.
Strong Inhibitors of CYP3A (except ritonavir)	

Clinical implication	Concomitant use of Xanax with strong CYP3A inhibitors has a profound effect on the clearance of alprazolam, resulting in increased concentrations of alprazolam and increased risk of adverse reactions [see <i>Clinical Pharmacology</i>].
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Prevention or management	Concomitant use of Xanax with a strong CYP3A4 inhibitor (except ritonavir) is contraindicated [see <i>Contraindications (4), Warnings and Precautions</i>].
Examples	Ketoconazole, itraconazole, clarithromycin

Moderate or Weak Inhibitors of CYP3A

Clinical implication	Concomitant use of Xanax with CYP3A inhibitors may increase the concentrations of Xanax, resulting in increased risk of adverse reactions of alprazolam [see <i>Clinical Pharmacology</i>].
Prevention or management	Avoid use and consider appropriate dose reduction when Xanax is coadministered with a moderate or weak CYP3A inhibitor [see <i>Warnings and Precautions</i>].
Examples	Nefazodone, fluvoxamine, cimetidine, erythromycin

CYP3A Inducers

Clinical implication	Concomitant use of CYP3A inducers can increase alprazolam metabolism and therefore can decrease plasma levels of alprazolam [see <i>Clinical Pharmacology</i>].
Prevention or management	Caution is recommended during coadministration with Xanax.
Examples	Carbamazepine, phenytoin

Ritonavir

Clinical implication	Interactions involving ritonavir and alprazolam are complex and time dependent. Short term administration of ritonavir increased alprazolam exposure due to CYP3A4 inhibition. Following long term treatment of ritonavir (>10 to 14 days), CYP3A4 induction offsets this inhibition. Alprazolam exposure was not meaningfully affected in the presence of ritonavir.
Prevention or management	Reduce Xanax dosage when ritonavir and Xanax are initiated concomitantly, or when ritonavir is added to a regimen where Xanax is stabilized. Increase Xanax dosage to the target dosage after 10 to 14 days of dosing ritonavir and Xanax concomitantly. No dosage adjustment of Xanax is necessary in patients receiving ritonavir for more than 10 to 14 days [see <i>Dosage and Administration</i>]. Concomitant use of Xanax with a strong CYP3A inhibitor, except ritonavir, is contraindicated [see <i>Contraindications, Warnings and Precautions</i>].

Digoxin

Clinical implication	Increased digoxin concentrations have been reported when alprazolam was given, especially in geriatric patients (>65 years of age).
Prevention or management	In patients on digoxin therapy, measure serum digoxin concentrations before initiating Xanax. Continue monitoring digoxin serum concentration and toxicity frequently. Reduce the digoxin dose if necessary.

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.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Neonates born to mothers using benzodiazepines late in pregnancy have been reported to experience symptoms of sedation and/or neonatal withdrawal [*see Warnings and Precautions and Clinical Considerations*]. Available data from published observational studies of pregnant women exposed to benzodiazepines do not report a clear association with benzodiazepines and major birth defects (*see Data*).

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated risk of major birth defects and of miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Fetal/Neonatal adverse reactions

Benzodiazepines cross the placenta and may produce respiratory depression, hypotonia, and sedation in neonates. Monitor neonates exposed to Xanax during pregnancy or labor for signs of sedation, respiratory depression, hypotonia, and feeding problems. Monitor neonates exposed to Xanax during pregnancy for signs of withdrawal. Manage these neonates accordingly [*see Warnings and Precautions*].

Data

Human Data

Published data from observational studies on the use of benzodiazepines during pregnancy do not report a clear association with benzodiazepines and major birth defects. Although early studies reported an increased risk of congenital malformations with diazepam and chlordiazepoxide, there was no consistent pattern noted. In addition, the majority of recent case-control and cohort studies of benzodiazepine use during pregnancy, which were adjusted for confounding exposures to alcohol, tobacco, and other medications, have not confirmed these findings.

Lactation

Risk Summary

Limited data from published literature reports the presence of alprazolam in human breast milk. There are reports of sedation, poor feeding and poor weight gain in infants exposed to benzodiazepines through breast milk. The effects of alprazolam on lactation are unknown.

Because of the potential for serious adverse reactions, including sedation and withdrawal symptoms in breastfed infants, advise patients that breastfeeding is not recommended during treatment with Xanax.

Pediatric Use

Safety and effectiveness of Xanax have not been established in pediatric patients.

Geriatric Use

Xanax-treated geriatric patients had higher plasma concentrations of alprazolam (due to reduced clearance) compared to younger adult patients receiving the same doses. Therefore, dosage reduction of Xanax is

recommended in geriatric patients [*see Dosage and Administration (2.4) and Clinical Pharmacology*].

Hepatic Impairment

Patients with alcoholic liver disease exhibit a longer elimination half-life (19.7 hours), compared to healthy subjects (11.4 hours). This may be caused by decreased clearance of alprazolam in patients with alcoholic liver disease. Dosage reduction of Xanagis is recommended in patients with hepatic impairment [*see Dosage and Administration , Clinical Pharmacology*].

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form <https://sideeffects.health.gov.il>

Additionally, you can also report to www.Padagis.co.il

DRUG ABUSE AND DEPENDENCE

Controlled Substance

XANAGIS contains alprazolam, which is a Schedule IV controlled substance.

Abuse

XANAGIS is a benzodiazepine and a CNS depressant with a potential for abuse and addiction. Abuse is the intentional, non-therapeutic use of a drug, even once, for its desirable psychological or physiological effects. Misuse is the intentional use, for therapeutic purposes, of a drug by an individual in a way other than prescribed by a health care provider or for whom it was not prescribed. Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that may include a strong desire to take the drug, difficulties in controlling drug use (e.g., continuing drug use despite harmful consequences, giving a higher priority to drug use than other activities and obligations), and possible tolerance or physical dependence. Even taking benzodiazepines as prescribed may put patients at risk for abuse and misuse of their medication. Abuse and misuse of benzodiazepines may lead to addiction.

Abuse and misuse of benzodiazepines often (but not always) involve the use of doses greater than the maximum recommended dosage and commonly involve concomitant use of other medications, alcohol, and/or illicit substances, which is associated with an increased frequency of serious adverse outcomes, including respiratory depression, overdose, or death. Benzodiazepines are often sought by individuals who abuse drugs and other substances, and by individuals with addictive disorders [*see Warnings and Precautions*].

The following adverse reactions have occurred with benzodiazepine abuse and/or misuse: abdominal pain, amnesia, anorexia, anxiety, aggression, ataxia, blurred vision, confusion, depression, disinhibition, disorientation, dizziness, euphoria, impaired concentration and memory, indigestion, irritability, muscle pain, slurred speech, tremors, and vertigo.

The following severe adverse reactions have occurred with benzodiazepine abuse and/or misuse: delirium, paranoia, suicidal ideation and behavior, seizures, coma, breathing difficulty, and death. Death is more often associated with polysubstance use (especially benzodiazepines with other CNS depressants such as opioids and alcohol).

Dependence

Xanagis may produce physical dependence from continued therapy. Physical dependence is a state that develops as a result of physiological adaptation in response to repeated drug use, manifested by withdrawal

signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug. Abrupt discontinuation or rapid dosage reduction of benzodiazepines or administration of flumazenil, a benzodiazepine antagonist, may precipitate acute withdrawal reactions, including seizures, which can be life-threatening. Patients at an increased risk of withdrawal adverse reactions after benzodiazepine discontinuation or rapid dosage reduction include those who take higher dosages (i.e., higher and/or more frequent doses) and those who have had longer durations of use [*see Warnings and Precautions*].

To reduce the risk of withdrawal reactions, use a gradual taper to discontinue XANAGIS or reduce the dosage [*see Dosage and Administration*, *Warnings and Precautions*].

Acute Withdrawal Signs and Symptoms

Acute withdrawal signs and symptoms associated with benzodiazepines have included abnormal involuntary movements, anxiety, blurred vision, depersonalization, depression, derealization, dizziness, fatigue, gastrointestinal adverse reactions (e.g., nausea, vomiting, diarrhea, weight loss, decreased appetite), headache, hyperacusis, hypertension, irritability, insomnia, memory impairment, muscle pain and stiffness, panic attacks, photophobia, restlessness, tachycardia, and tremor. More severe acute withdrawal signs and symptoms, including life-threatening reactions, have included catatonia, convulsions, delirium tremens, depression, hallucinations, mania, psychosis, seizures, and suicidality.

Protracted Withdrawal Syndrome

Protracted withdrawal syndrome associated with benzodiazepines is characterized by anxiety, cognitive impairment, depression, insomnia, formication, motor symptoms (e.g., weakness, tremor, muscle twitches), paresthesia, and tinnitus that persists beyond 4 to 6 weeks after initial benzodiazepine withdrawal. Protracted withdrawal symptoms may last weeks to more than 12 months. As a result, there may be difficulty in differentiating withdrawal symptoms from potential re-emergence or continuation of symptoms for which the benzodiazepine was being used.

Tolerance

Tolerance to XANAGIS may develop from continued therapy. Tolerance is a physiological state characterized by a reduced response to a drug after repeated administration (i.e., a higher dose of a drug is required to produce the same effect that was once obtained at a lower dose). Tolerance to the therapeutic effect of XANAGIS may develop; however, little tolerance develops to the amnesic reactions and other cognitive impairments caused by benzodiazepines.

OVERDOSAGE

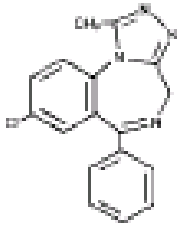
Overdosage of benzodiazepines is characterized by central nervous system depression ranging from drowsiness to coma. In mild to moderate cases, symptoms can include drowsiness, confusion, dysarthria, lethargy, hypnotic state, diminished reflexes, ataxia, and hypotonia. Rarely, paradoxical or disinhibitory reactions (including agitation, irritability, impulsivity, violent behavior, confusion, restlessness, excitement, and talkativeness) may occur. In severe overdosage cases, patients may develop respiratory depression and coma. Overdosage of benzodiazepines in combination with other CNS depressants (including alcohol and opioids) may be fatal [*see Warnings and Precautions*]. Markedly abnormal (lowered or elevated) blood pressure, heart rate, or respiratory rate raise the concern that additional drugs and/or alcohol are involved in the overdosage.

In managing benzodiazepine overdosage, employ general supportive measures, including intravenous fluids and airway management. Flumazenil, a specific benzodiazepine receptor antagonist indicated for the complete or partial reversal of the sedative effects of benzodiazepines in the management of benzodiazepine overdosage, can lead to withdrawal and adverse reactions, including seizures, particularly in the context of mixed overdosage with drugs that increase seizure risk (e.g., tricyclic and tetracyclic antidepressants) and in patients with long-term benzodiazepine use and physical dependency. The risk of withdrawal seizures with flumazenil use may be increased in patients with epilepsy. Flumazenil is contraindicated in patients who have received a benzodiazepine

for control of a potentially life-threatening condition (e.g., status epilepticus). If the decision is made to use flumazenil, it should be used as an adjunct to, not as a substitute for, supportive management of benzodiazepine overdose. See the flumazenil injection Prescribing Information.

Xanax contains alprazolam which is a triazolo analog of the 1,4 benzodiazepine class of central nervous system-active compounds.

The structural formula is:



Xanax 0.25 mg, to 0.5 mg three times daily increasing if required to a total of 3 mg daily .

CLINICAL PHARMACOLOGY

Mechanism of Action

Alprazolam is a 1,4 benzodiazepine. Alprazolam exerts its effect for the acute treatment of generalized anxiety disorder and panic disorder through binding to the benzodiazepine site of gamma-aminobutyric acid-A (GABA_A) receptors in the brain and enhances GABA-mediated synaptic inhibition.

Pharmacokinetics

Plasma levels of alprazolam increase proportionally to the dose over the range of 0.5 to 3.0 mg.

Following oral administration, peak plasma concentration of alprazolam (C_{max}) occurs in 1 to 2 hours post dose.

Alprazolam is 80% bound to human serum protein, and albumin accounts for the majority of the binding.

The mean plasma elimination half-life ($T_{1/2}$) of alprazolam is approximately 11.2 hours (range: 6.3 to 26.9 hours) in healthy adults.

Metabolism

Alprazolam is extensively metabolized in humans, primarily by cytochrome P450 3A4 (CYP3A4), to 2 major active metabolites in the plasma: 4-hydroxyalprazolam and α -hydroxyalprazolam. The plasma circulation levels of the two active metabolites are less than 4% of the parent. The reported relative potencies in benzodiazepine receptor binding experiments and in animal models of induced seizure inhibition are 0.20 and 0.66, respectively, for 4-hydroxyalprazolam and α -hydroxyalprazolam. The low concentrations and low potencies of 4-hydroxyalprazolam and α -hydroxyalprazolam indicate that they unlikely contribute much to the effects of alprazolam. A benzophenone derived from alprazolam is also found in humans. Their half-lives appear to be similar to that of alprazolam.

Excretion

Specific Populations

Geriatric Patients

The mean $T_{1/2}$ of alprazolam was 16.3 hours (range: 9.0 to 26.9 hours) in healthy elderly subjects compared to 11.0 hours (range: 6.3 to 15.8 hours, n=16) in healthy younger adult subjects.

Obese Patients

The mean $T_{1/2}$ of alprazolam was 21.8 hours (range: 9.9 to 40.4 hours) in a group of obese subjects.

Patients with Hepatic Impairment

The mean $T_{1/2}$ of alprazolam was 19.7 hours (range: 5.8 to 65.3 hours) in patients with alcoholic liver disease.

Racial or Ethnic Groups

Maximal concentrations and $T_{1/2}$ of alprazolam are approximately 15% and 25% higher in Asians compared to Caucasians.

Drug Interaction Studies

In Vivo Studies

Most of the interactions that have been documented with alprazolam are with drugs that modulate CYP3A4 activity.

Compounds that are inhibitors or inducers of CYP3A would be expected to increase or decrease plasma alprazolam concentrations, respectively. Drug products that have been studied in vivo, along with their effect on increasing alprazolam AUC, are as follows: ketoconazole, 3.98 fold; itraconazole, 2.66 fold; nefazodone, 1.98 fold; fluvoxamine, 1.96 fold; and erythromycin, 1.61 fold [*see Contraindications, Warnings and Precautions, Drug Interactions*]. Other studied drugs include:

Cimetidine: Coadministration of cimetidine increased the maximum plasma concentration of alprazolam by 82%, decreased clearance by 42%, and increased $T_{1/2}$ by 16%.

Fluoxetine: Coadministration of fluoxetine with alprazolam increased the maximum plasma concentration of alprazolam by 46%, decreased clearance by 21%, increased $T_{1/2}$ by 17%, and decreased measured psychomotor performance.

Oral Contraceptives: Coadministration of oral contraceptives increased the maximum plasma concentration of alprazolam by 18%, decreased clearance by 22%, and increased $T_{1/2}$ by 29%.

Carbamazepine: The oral clearance of alprazolam (given in a 0.8 mg single dose) was increased from 0.90 ± 0.21 mL/min/kg to 2.13 ± 0.54 mL/min/kg and the elimination $T_{1/2}$ was shortened (from 17.1 ± 4.9 to 7.7 ± 1.7 hour) following administration of 300 mg per day carbamazepine for 10 days [see *Drug Interactions*]. However, the carbamazepine dose used in this study was fairly low compared to the recommended doses (1000-1200 mg per day); the effect at usual carbamazepine doses is unknown.

Ritonavir: Interactions involving HIV protease inhibitors (e.g., ritonavir) and alprazolam are complex and time dependent. Short-term low doses of ritonavir (4 doses of 200 mg) increased mean AUC of alprazolam by about 2.5-fold, and did not significantly affect C_{max} of alprazolam. The elimination $T_{1/2}$ was prolonged (30 hours versus 13 hours). However, upon extended exposure to ritonavir (500 mg, twice daily for 10 days), CYP3A induction offset this inhibition. Alprazolam AUC and C_{max} was reduced by 12% and 16%, respectively, in the presence of ritonavir. The elimination $T_{1/2}$ of alprazolam was not significantly changed [see *Warnings and Precautions*].

Sertraline: A single dose of alprazolam 1 mg and steady state dose of sertraline (50 mg to 150 mg per day) did not reveal any clinically significant changes in the pharmacokinetics of alprazolam.

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 Xanaxis in doses up to 4 mg per day.

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

In Vitro Studies

Data from in vitro studies of alprazolam suggest a possible drug interaction of alprazolam with paroxetine.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

No evidence of carcinogenic potential was observed in rats or mice administered alprazolam for 2-years at doses up to 30 and 10 mg/kg day respectively. These doses are 29 times and 4.8 times the maximum recommended human dose of 10 mg/day based on mg/m^2 body surface area, respectively.

Mutagenesis

Alprazolam was negative in the in vitro Ames bacterial reverse mutation assay and DNA Damage/Alkaline Elution Assay and in vivo rat micronucleus genetic toxicology assays.

Impairment of Fertility

Alprazolam produced no impairment of fertility in rats at doses up to 5 mg/kg per day, which is approximately 5 times the maximum recommended human dose of 10 mg per day based on mg/m^2 body surface area.

Animal Toxicology and/or Pharmacology

When rats were treated with alprazolam at oral doses of 3 mg, 10 mg, and 30 mg/kg day (3 to 29 times the maximum recommended human dose based on mg/m^2 body surface area) for 2 years, a tendency for a dose related increase in the number of cataracts was observed in females and a tendency for a dose related increase in corneal vascularization was observed in males. These lesions did not appear until after 11 months of treatment.

DOSAGE AND ADMINISTRATION Generalized Anxiety Disorder

Xanax was compared to placebo in double-blind clinical studies (doses up to 4 mg per day) in patients with a diagnosis of anxiety or anxiety with associated depressive symptomatology. Xanax was significantly better than placebo at each of the evaluation periods of these 4-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.

Panic Disorder

The effectiveness of Xanax in the treatment of panic disorder was studied in 3 short-term, placebo-controlled studies (up to 10 weeks) in patients with diagnoses closely corresponding to DSM-III-R criteria for panic disorder.

The average dose of Xanax was 5 mg to 6 mg per day in 2 of the studies, and the doses of Xanax were fixed at 2 mg and 6 mg per day in the third study. In all 3 studies, Xanax was superior to placebo on a variable defined as "the number of patients with zero panic attacks" (range, 37% to 83% met this criterion), as well as on a global improvement score. In 2 of the 3 studies, Xanax was superior to placebo on a variable defined as "change from baseline on the number of panic attacks per week" (range, 3.3 to 5.2), and also on a phobia rating scale. A subgroup of patients who improved on Xanax during short-term treatment in 1 of these trials was continued on an open basis up to 8 months, without apparent loss of benefit.

HOW SUPPLIED

XANAGIS Tablets are available as follows:

Xanax 0.25 mg: white, elliptical full oval tablet with "UPJOHN 29" on one side and a score on the other side.

Xanax 0.5 mg: Pink, elliptical full oval tablet with "UPJOHN 55" on one side and a score on the other side.

Xanax 1 mg: Lavender, elliptical full oval scored tablet with "UPJOHN 90" on one side and a score on the other side.

All tablets are packed in blister strips of 10 tablets. Box containing 10 tablets, 30 tablets, 50 tablets.

Storage: Store in a cool place below 25°C. Protect from light.

Shelf Life: The expiry date of the product is indicated on the packaging materials

MANUFACTURER and MARKETING AUTHORIZATIONS HOLDER:

Padagis Israel Pharmaceuticals LTD, 1st Rakefet St. , Shoham.

REGISTRATION NUMBERS:

Xanax 0.25 mg: 063 48 26906.

Xanax 0.5 mg: 063 46 26908.

Xanax 1 mg: 063 47 26907.

Revised on September 2023