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

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

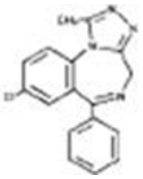
- Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death.
- Reserve concomitant prescribing of these drugs for patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required.
- Follow 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).

INDICATIONS AND USAGE

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

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:



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).

CONTRAINDICATIONS

XANAGIS Tablets are contraindicated in patients:

- with known hypersensitivity to the active substance or other benzodiazepines .Angioedema has been reported *[see Adverse Reactions]*.
  with known hypersensitivity to any of the excipients listed in section "DESCRIPTION"..
- 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 Xanagis , 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 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).

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) .

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*]*

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*)*

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 who received Alprazolam, 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 Xanagis*[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
Xanagis 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 Xanagis and ritonavir are initiated concomitantly or when ritonavir is added to a stable dosage of Xanagis.

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 Xanagis, 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 Xanagis 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. Monitor neonates exposed to Xanagis during pregnancy or labor for signs of sedation and monitor neonates exposed to Xanagis during pregnancy for signs of withdrawal; manage these neonates accordingly.

Risk 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 Xanagis. Closely monitor patients with impaired respiratory function. If signs and symptoms of respiratory depression, hypoventilation, or apnea occur, discontinue Xanagis.

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 Alprazolam 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 withAlprazolam dosages up to 10 mg per day for panic disorder, with or without agoraphobia (Table 2).

Table 1: Adverse Reactions Occurring in ⩾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 Occuring in ⩾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%
Fatique and Tiredness	49%	42%
Impaired Coordination	40%	18%
Irritability	33%	30%
Memory Impairment	33%	22%
Cognitive Disorder	29%	21%
Decreased Libido	14%	8%
Dysartharia	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 alprazolam: 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

	Alprazolam-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%
Memoryimpairment	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%
Decreasedappetite	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 XANAGIS

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 Warnings and Precautions].*
Examples	Morphine, buprenorphine, hydromorphone, oxymorphone, oxycodone, fentanyl, methadone, alfentanil, butorpenol, 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 Warnings and Precautions].*
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 Xanagis 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 Clinical Pharmacology].*

Prevention or management	Concomitant use of Xanagis with a strong CYP3A4 inhibitor (except ritonavir) is contraindicated *[see Contraindications, Warnings and Precautions]*.
Examples	Ketoconazole, itraconazole, clarithromycin
Moderate or Weak Inhibitors of CYP3A	
Clinical implication	Concomitant use of Xanagis with CYP3A inhibitors may increase the concentrations of Xanagis, resulting in increased risk of adverse reactions of alprazolam *[see Clinical Pharmacology]*.
Prevention or management	Avoid use and consider appropriate dose reduction when Xanagis is coadministered with a moderate or weak CYP3A inhibitor *[see Warnings and Precautions]*.
Examples	Nefazodone, fluvoxamine, cimetidine, erythromycin
CYP3A Inducers	
Clinical implication	Concomitant use of CYP3A inducers can increase alprazolam metabolism and therefore can decease plasma levels of alprazolam *[see Clinical Pharmacology]*.
Prevention or management	Caution is recommended during coadministration with Xanagis.
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 Xanagis dosage when ritonavir and Xanagis are initiated concomitantly, or when ritonavir is added to a regimen where Xanagis is stabilized. Increase Xanagis dosage to the target dosage after 10 to 14 days of dosing ritonavir and Xanagis concomitantly. No dosage adjustment of Xanagis is necessary in patients receiving ritonavir for more than 10 to14 days Concomitant use of Xanagis with a strong CYP3A inhibitor, except ritonavir, is contraindicated *[see Contraindications, Warnings and Precautions]*.
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 Xanagis. 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 Xanagis during pregnancy or labor for signs of sedation, respiratory depression, hypotonia, and feeding problems. Monitor neonates exposed to Xanagis 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 Xanagis.

Pediatric Use
Safety and effectiveness of Xanagis have not been established in pediatric patients.

Geriatric Use
Xanagis-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 Xanagis is recommended in geriatric patients *[see 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 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 amnestic 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 overdosage. See the flumazenil injection Prescribing Information..

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.

Absorption

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

Distribution

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

Elimination

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

Alprazolam and its metabolites are excreted primarily in the urine.

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.

Smoking

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

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 Xanagis 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. The ability of alprazolam to induce human hepatic enzyme systems has not yet been determined.

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.

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.

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DOSAGE AND ADMINISTRATION
Treatment should be as short as possible. It is recommended that the patient be reassessed at the end of no longer than 4 weeks' treatment and the need for continued treatment established, especially in case the patient is symptom free. The overall duration of treatment should not be more than 8-12 weeks, including a tapering off process.
In certain cases, extension beyond the maximum treatment period may be necessary; if so, it should not take place without re-evaluation of the patient's status with special expertise. As with all benzodiazepines, physicians should be aware that long-term use might lead to dependence in certain patients.

The optimum dosage of alprazolam should be based upon the severity of the symptoms and individual patient response. The lowest dose which can control symptoms should be used. Dosage should be reassessed at intervals of no more than 4 weeks. The usual dosage is stated below; in the few patients who require higher doses, the 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 so treated, or those with a history of chronic alcoholism.

Discontinuation or Dosage Reduction of XANAGIS
To reduce the risk of withdrawal reactions, treatment should always be tapered off gradually. During discontinuation of alprazolam treatment, the dosage should be reduced slowly in keeping with good medical practice. It is suggested that the daily dosage of alprazolam be decreased by no more than 0.5 mg every three days. Some patients may require an even slower dosage reduction. If a patient develops withdrawal reactions, consider pausing the taper or increasing the dosage to the previous tapered dosage level. Subsequently decrease the dosage more slowly (see WARNINGS - Dependence and Withdrawal Reactions and DRUG ABUSE AND DEPENDENCE - Dependence).
There is a reduced clearance of the drug and, as with other benzodiazepines, an increased sensitivity to the drug in elderly patients.

Anxiety: 0.25 mg to 0.5 mg three times daily increasing if required to a total of 3 mg daily.
The dose may be increased to achieve a maximum therapeutic effect, at intervals of 3 to 4 days, to a maximum daily dose of 4 mg, given in divided doses. The lowest possible effective dose should be employed and the need for continued treatment reassessed frequently. The risk of dependence may increase with dose and duration of treatment.

In all patients, dosage should be reduced gradually when discontinuing therapy or when decreasing the daily dosage. Although there are no systematically collected data to support a specific discontinuation schedule, it is suggested that the daily dosage be decreased by no more than 0.5 mg every 3 days. Some patients may require an even slower dosage reduction.

Panic Disorder: The successful treatment of many panic disorder patients has required the use of alprazolam at doses greater than 4 mg daily.
Treatment may be initiated with a dose of 0.5 mg three times daily. Depending on the response, the dose may be increased at intervals of 3 to 4 days in increments of no more than 1 mg per day. Generally, therapy should be initiated at a low dose to minimize the risk of adverse responses in patients especially sensitive to the drug. Dose should be advanced until an acceptable therapeutic response (i.e., a substantial reduction in or total elimination of panic attacks) is achieved, intolerance occurs, or the maximum recommended dose is attained. Because of the danger of withdrawal, abrupt discontinuation of treatment should be avoided. In all patients, dosage should be reduced gradually when discontinuing therapy or when decreasing the daily dosage.

Paediatric patients: Safety and efficacy of alprazolam have not been established in children and adolescents below the age of 18 years; therefore alprazolam should not be used in children and adolescent under age of 18.
Geriatric patients or in the presence of debilitating disease: 0.25 mg two to three times daily to be gradually increased if needed and tolerated. The elderly may be especially sensitive to the effects of benzodiazepines. They exhibit higher plasma alprazolam concentrations due to reduced clearance of the drug as compared with a younger population receiving the same doses.
If side-effects occur, the dose should be lowered. It is advisable to review treatment regularly and to discontinue use as soon as possible. Should longer term treatment be necessary, then intermittent treatment may be considered to minimize the risk of dependence.

HOW SUPPLIED

XANAGIS Tablets are available as follows:
Xanagis 0.25 mg: white, elliptical full oval tablet with “UPJOHN 29” on one side and a score on the other side.
Xanagis 0.5 mg: Pink, elliptical full oval tablet with "UPJOHN 55" on one side and a score on the other side.
Xanagis 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:
Xanagis 0.25 mg: 063 48 26906.
Xanagis 0.5 mg: 063 46 26908.
Xanagis 1 mg: 063 47 26907.

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