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

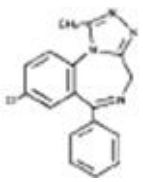
WARNING: RISKS FROM CONCOMITANT USE WITH OPIOIDS; ABUSE, MISUSE, AND ADDICTION; and DEPENDENCE AND WITHDRAWAL REACTIONS

- 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).
- 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).

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.

Compounds that are 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±4.9h 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.

INDICATIONS AND USAGE

Treatment of anxiety accompanied by depression.

Treatment of panic states with or without accompanying phobia.

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".

XANAGIS is contraindicated with ketoconazole and itraconazole, since these medications significantly impair the oxidative metabolism mediated by cytochrome P450 3A (CYP3A) (see WARNINGS and PRECAUTIONS–Drug Interactions).

WARNINGS

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 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 - 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 the doses recommended for the treatment of transient anxiety and anxiety disorder (i.e., 0.75 to 4.0 mg per 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.

The importance of dose and the risks of XANAGIS as a treatment for panic disorder

Because the management of panic disorder often requires the use of average daily doses of XANAGIS above 4 mg, the risk of dependence among panic disorder patients may be higher than that among those treated for less severe anxiety. Experience in randomized placebo-controlled discontinuation studies of patients with panic disorder showed a high rate of rebound and withdrawal symptoms in patients treated with Alprazolam compared to placebo-treated patients.

Relapse or return of illness was defined as a return of symptoms characteristic of panic disorder (primarily panic attacks) to levels approximately equal to those seen at baseline before active treatment was initiated. Rebound refers to a return of symptoms of panic disorder to a level substantially greater in frequency, or more severe in intensity than seen at baseline. Withdrawal symptoms were identified as those which were generally not characteristic of panic disorder and which occurred for the first time more frequently during discontinuation than at baseline.

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.

In two controlled trials of 6 to 8 weeks duration where the ability of patients to discontinue medication was measured, 71%–93% of patients treated with Alprazolam tapered completely off therapy compared to 89%–96% of placebo-treated patients. 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.

Seizures attributable to Alprazolam were seen after drug discontinuance or dose reduction in 8 of 1980 patients with panic disorder or in patients participating in clinical trials where doses of Alprazolam greater than 4 mg/day for over 3 months were permitted. Five of these cases clearly occurred during abrupt dose reduction, or discontinuation from daily doses of 2 to 10 mg. Three cases occurred in situations where there was not a clear relationship to abrupt dose reduction or discontinuation. In one instance, seizure occurred after discontinuation from a single dose of 1 mg after tapering at a rate of 1 mg every 3 days from 6 mg daily. In two other instances, the relationship to taper is indeterminate; in both of these cases the patients had been receiving doses of 3 mg daily prior to seizure. The duration of use in the above 8 cases ranged from 4 to 22 weeks. There have been occasional voluntary reports of patients developing seizures while apparently tapering gradually from Alprazolam.

The risk of seizure seems to be greatest 24–72 hours after discontinuation

(see DOSAGE AND ADMINISTRATION - Discontinuation or Dosage Reduction of XANAGIS).

Status Epilepticus and its Treatment

The medical event voluntary reporting system shows that withdrawal seizures have been reported in association with the discontinuation of XANAGIS. In most cases, only a single seizure was reported; however, multiple seizures and status epilepticus were reported as well.

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 of XANAGIS. 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. In these situations, it is recommended that the same total daily dose be given divided as more frequent administrations (see DOSAGE AND ADMINISTRATION).

CNS Depression and Impaired Performance

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 simultaneous ingestion of alcohol and other CNS depressant drugs during treatment with XANAGIS.

Risk of Fetal Harm

Benzodiazepines can potentially cause fetal harm when administered to pregnant women. If XANAGIS is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Because of experience with other members of the benzodiazepine class, XANAGIS is assumed to be capable of causing an increased risk of congenital abnormalities when administered to a pregnant woman during the first trimester. Because use of these drugs is rarely a matter of urgency, their use during the first trimester should almost always be avoided. . The possibility that a woman of childbearing potential may be pregnant at the time of institution of therapy should be considered. Patients should be advised that if they become pregnant during therapy or intend to become pregnant they should communicate with their physicians about the desirability of discontinuing the drug.

Alprazolam Interaction with Drugs that Inhibit Metabolism via Cytochrome P4503A

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. Consequently, alprazolam should be avoided in patients receiving very potent inhibitors of CYP3A. With drugs inhibiting CYP3A to a lesser but still significant degree, alprazolam should be used only with caution and consideration of appropriate dosage reduction. For some drugs, an interaction with

alprazolam has been quantified with clinical data; for other drugs, interactions are predicted from *in vitro* data and/or experience with similar drugs in the same pharmacologic class.

The following are examples of drugs known to inhibit the metabolism of alprazolam and/or related benzodiazepines, presumably through inhibition of CYP3A.

Potent CYP3A Inhibitors

Azole antifungal agents

Ketoconazole and itraconazole are potent CYP3A inhibitors and have been shown in vivo to increase plasma alprazolam concentrations 3.98 fold and 2.70 fold, respectively. The coadministration of alprazolam with these agents is not recommended. Other azole-type antifungal agents should also be considered potent CYP3A inhibitors and the coadministration of alprazolam with them is not recommended (see CONTRAINDICATIONS).

Drugs demonstrated to be CYP 3A inhibitors on the basis of clinical studies involving alprazolam (caution and consideration of appropriate alprazolam dose reduction are recommended during coadministration with the following drugs)

Nefazodone

Coadministration of nefazodone increased alprazolam concentration two-fold.

Fluvoxamine

Coadministration of fluvoxamine approximately doubled the maximum plasma concentration of alprazolam, decreased clearance by 49%, increased half-life by 71%, and decreased measured psychomotor performance.

Cimetidine

Coadministration of cimetidine increased the maximum plasma concentration of alprazolam by 86%, decreased clearance by 42%, and increased half-life by 16%.

Other drugs possibly affecting alprazolam metabolism

Other drugs possibly affecting alprazolam metabolism by inhibition of CYP3A are discussed in the PRECAUTIONS section (see PRECAUTIONS–Drug Interactions).

PRECAUTIONS

General

Suicide

As with other psychotropic medications, the usual precautions with respect to administration of the drug and size of the prescription are indicated for severely depressed patients or those in whom there is reason to expect concealed suicidal ideation or plans. Panic disorder has been associated with primary and secondary major depressive disorders and increased reports of suicide among untreated patients.

Mania

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

Uricosuric Effect

Alprazolam has a weak uricosuric effect. Although other medications with weak uricosuric effect have been reported to cause acute renal failure, there have been no reported instances of acute renal failure attributable to therapy with XANAGIS.

Use in Patients with Concomitant Illness

It is recommended that the dosage be limited to the smallest effective dose to preclude the development of ataxia or oversedation which may be a particular problem in elderly or debilitated patients. (see DOSAGE AND ADMINISTRATION.) The usual precautions in treating patients with impaired renal, hepatic or pulmonary function should be observed. There have been rare reports of death in patients with severe pulmonary disease shortly after the initiation of treatment with XANAGIS. A decreased systemic alprazolam elimination rate (e.g., increased plasma half-life) has been observed in both alcoholic liver disease patients and obese patients receiving XANAGIS (see CLINICAL PHARMACOLOGY).

Laboratory Tests

Laboratory tests are not ordinarily required in otherwise healthy patients. However, when treatment is protracted, periodic blood counts, urinalysis, and blood chemistry analyses are advisable in keeping with good medical practice.

Drug Interactions

Use with Opioids

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 $GABA_A$ 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. Limit dosage and duration of concomitant use of benzodiazepines and opioids and monitor patients closely for respiratory depression and sedation.

Use with Other CNS Depressants

If XANAGIS Tablets are to be combined with other psychotropic agents or anticonvulsant drugs, careful consideration should be given to the pharmacology of the agents to be employed, particularly with compounds which might potentiate the action of benzodiazepines. The benzodiazepines, including alprazolam, produce additive CNS depressant effects when co-administered with other psychotropic medications, anticonvulsants, antihistaminics, ethanol and other drugs which themselves produce CNS depression.

Use with 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 Tablets in doses up to 4 mg/day. The clinical significance of these changes is unknown.

Drugs that inhibit alprazolam metabolism via cytochrome P450 3A

The initial step in alprazolam metabolism is hydroxylation catalyzed by cytochrome P450 3A (CYP3A). Drugs which inhibit this metabolic pathway may have a profound effect on the clearance of alprazolam (see CONTRAINDICATIONS and WARNINGS for additional drugs of this type).

Drugs demonstrated to be CYP3A inhibitors of possible clinical significance on the basis of clinical studies involving alprazolam (caution is recommended during coadministration with alprazolam)

Fluoxetine

Coadministration of fluoxetine with alprazolam increased the maximum plasma concentration of alprazolam by 46%, decreased clearance by 21%, increased half-life by 17%, and decreased measured psychomotor performance.

Propoxyphene

Coadministration of propoxyphene decreased the maximum plasma concentration of alprazolam by 6%, decreased clearance by 38%, and increased half-life by 58%.

Oral Contraceptives

Coadministration of oral contraceptives increased the maximum plasma concentration of alprazolam by 18%, decreased clearance by 22%, and increased half-life by 29%.

Drugs and other substances demonstrated to be CYP 3A inhibitors on the basis of clinical studies involving benzodiazepines metabolized similarly to alprazolam or on the basis of in vitro studies with alprazolam or other benzodiazepines (caution is recommended during coadministration with alprazolam)

Available data from clinical studies of benzodiazepines other than alprazolam suggest a possible drug interaction with alprazolam for the following: diltiazem, isoniazid, macrolide antibiotics such as erythromycin and clarithromycin, and grapefruit juice. Data from *in vitro* studies of alprazolam suggest a possible drug interaction with alprazolam for the following: sertraline and paroxetine. However, data from an in vivo drug interaction study involving a single dose of alprazolam 1 mg and steady state dose of sertraline (50 to 150 mg/day) did not reveal any clinically significant changes in the pharmacokinetics of alprazolam. Data from *in vitro* studies of benzodiazepines other than alprazolam suggest a possible drug interaction for the following: ergotamine, cyclosporine, amiodarone, nicardipine, and nifedipine. Caution is recommended during the coadministration of any of these with alprazolam (see WARNINGS).

Drugs demonstrated to be inducers of CYP3A

Carbamazepine can increase alprazolam metabolism and therefore can decrease plasma levels of alprazolam.

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.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of carcinogenic potential was observed during 2-year bioassay studies of alprazolam in rats at doses up to 30 mg/kg/day (150 times the maximum recommended daily human dose of 10 mg/day) and in mice at doses up to 10 mg/kg/day (50 times the maximum recommended daily human dose).

Alprazolam was not mutagenic in the rat micronucleus test at doses up to 100 mg/kg, which is 500 times the maximum recommended daily human dose of 10 mg/day. Alprazolam also was not mutagenic *in vitro* in the DNA Damage/Alkaline Elution Assay or the Ames Assay.

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

Pregnancy

Teratogenic Effects Pregnancy Category D (See WARNINGS section).

Nonteratogenic Effects: It should be considered that the child born of a mother who is receiving benzodiazepines may be at some risk for withdrawal symptoms from the drug during the postnatal period. Also, neonatal flaccidity and respiratory problems have been reported in children born of mothers who have been receiving benzodiazepines.

Labor and Delivery

XANAGIS has no established use in labor or delivery.

Nursing Mothers

Benzodiazepines are known to be excreted in human milk. It should be assumed that alprazolam is as well. Chronic administration of diazepam to nursing mothers has been reported to cause their infants to become lethargic and to lose weight. As a general rule, nursing should not be undertaken by mothers who must use XANAGIS.

Pediatric Use

Safety and effectiveness of XANAGIS in individuals below 18 years of age have not been established.

Geriatric Use

The elderly may be more 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. The smallest effective dose of XANAGIS should be used in the elderly to preclude the development of ataxia and oversedation (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

Side effects to XANAGIS Tablets, if they occur, are generally observed at the beginning of therapy and usually disappear upon continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacological activity of alprazolam, e.g., drowsiness or light-headedness.

The data cited in the two tables below are estimates of untoward clinical event incidence among patients who participated under the following clinical conditions: relatively short duration (i.e., four weeks) placebo-controlled clinical studies with dosages up to 4 mg/day of Alprazolam (for the management of anxiety disorders or for the short-term relief of the symptoms of anxiety) and short-term (up to ten weeks) placebo-controlled clinical studies with dosages up to 10 mg/day of Alprazolam in patients with panic disorder, with or without agoraphobia.

These data cannot be used to predict precisely the incidence of untoward events in the course of usual medical practice where patient characteristics, and other factors often differ from those in clinical trials. These figures cannot be compared with those obtained from other clinical studies involving related drug products and placebo as each group of drug trials are conducted under a different set of conditions.

Comparison of the cited figures, however, can provide the prescriber with some basis for estimating the relative contributions of drug and non-drug factors to the untoward event incidence in the population studied. Even this use must be approached cautiously, as a drug may relieve a symptom in one patient but induce it in others. (For example, an anxiolytic drug may relieve dry mouth [a symptom of anxiety] in some subjects but induce it [an untoward event] in others.)

Additionally, for anxiety disorders the cited figures can provide the prescriber with an indication as to the frequency with which physician intervention (e.g., increased surveillance, decreased dosage or discontinuation of drug therapy) may be necessary because of the untoward clinical event.

Treatment-Emergent Adverse Events Reported in Placebo-Controlled Trials of Anxiety Disorders

ANXIETY DISORDERS

	Treatment-Emergent Symptom Incidence*		**Incidence of Intervention Because of Symptom**
	Alprazolam	**PLACEBO**	**Alprazolam**
Number of Patients	565	505	565
% of Patients Reporting:			
Central Nervous System			
Drowsiness	41.0	21.6	15.1
Light-headedness	20.8	19.3	1.2

Depression	13.9	18.1	2.4
Headache	12.9	19.6	1.1
Confusion	9.9	10.0	0.9
Insomnia	8.9	18.4	1.3
Nervousness	4.1	10.3	1.1
Syncope	3.1	4.0	†
Dizziness	1.8	0.8	2.5
Akathisia	1.6	1.2	†
Tiredness/Sleepiness	†	†	1.8
Gastrointestinal			
Dry Mouth	14.7	13.3	0.7
Constipation	10.4	11.4	0.9
Diarrhea	10.1	10.3	1.2
Nausea/Vomiting	9.6	12.8	1.7
Increased Salivation	4.2	2.4	†
Cardiovascular			
Tachycardia/Palpitations	7.7	15.6	0.4
Hypotension	4.7	2.2	†
Sensory			
Blurred Vision	6.2	6.2	0.4
Musculoskeletal			
Rigidity	4.2	5.3	†
Tremor	4.0	8.8	0.4
Cutaneous			
Dermatitis/Allergy	3.8	3.1	0.6
Other			
Nasal Congestion	7.3	9.3	†
Weight Gain	2.7	2.7	†
Weight Loss	2.3	3.0	†

* *Events reported by 1% or more of Alprazolam patients are included.*

† *None reported*

In addition to the relatively common (i.e. greater than 1%) untoward events enumerated in the table above, the following adverse events 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.

Treatment-Emergent Adverse Events Reported in Placebo-Controlled Trials of Panic Disorder

PANIC DISORDER

	Treatment-Emergent Symptom Incidence *	
	Alprazolam	**PLACEBO**
Number of Patients	1388	1231
% of Patients Reporting:		
Central Nervous System		
Drowsiness	76.8	42.7
Fatigue and Tiredness	48.6	42.3

Impaired Coordination	40.1	17.9
Irritability	33.1	30.1
Memory Impairment	33.1	22.1
Light-headedness/Dizziness	29.8	36.9
Insomnia	29.4	41.8
Headache	29.2	35.6
Cognitive Disorder	28.8	20.5
Dysarthria	23.3	6.3
Anxiety	16.6	24.9
Abnormal Involuntary Movement	14.8	21.0
Decreased Libido	14.4	8.0
Depression	13.8	14.0
Confusional State	10.4	8.2
Muscular Twitching	7.9	11.8
Increased Libido	7.7	4.1
Change in Libido (Not Specified)	7.1	5.6
Weakness	7.1	8.4
Muscle Tone Disorders	6.3	7.5
Syncope	3.8	4.8
Akathisia	3.0	4.3
Agitation	2.9	2.6
Disinhibition	2.7	1.5
Paresthesia	2.4	3.2
Talkativeness	2.2	1.0
Vasomotor Disturbances	2.0	2.6
Derealization	1.9	1.2
Dream Abnormalities	1.8	1.5
Fear	1.4	1.0
Feeling Warm	1.3	0.5
Gastrointestinal		
Decreased Salivation	32.8	34.2
Constipation	26.2	15.4
Nausea/Vomiting	22.0	31.8
Diarrhea	20.6	22.8
Abdominal Distress	18.3	21.5
Increased Salivation	5.6	4.4
Cardio-Respiratory		
Nasal Congestion	17.4	16.5
Tachycardia	15.4	26.8
Chest Pain	10.6	18.1
Hyperventilation	9.7	14.5
Upper Respiratory Infection	4.3	3.7
Sensory		
Blurred Vision	21.0	21.4
Tinnitus	6.6	10.4
Musculoskeletal		
Muscular Cramps	2.4	2.4
Muscle Stiffness	2.2	3.3
Cutaneous		
Sweating	15.1	23.5
Rash	10.8	8.1

Other		
Increased Appetite	32.7	22.8
Decreased Appetite	27.8	24.1
Weight Gain	27.2	17.9
Weight Loss	22.6	16.5
Micturition Difficulties	12.2	8.6
Menstrual Disorders	10.4	8.7
Sexual Dysfunction	7.4	3.7
Edema	4.9	5.6
Incontinence	1.5	0.6
Infection	1.3	1.7

**Events reported by 1% or more of Alprazolam patients are included.*

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

Panic disorder has been associated with primary and secondary major depressive disorders and increased reports of suicide among untreated patients (see PRECAUTIONS, General).

Adverse Events 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 were as follows:

DISCONTINUATION-EMERGENT SYMPTOM INCIDENCE

Percentage of 641 - Alprazolam Treated Panic Disorder Patients Reporting Events Body System/Event			
Neurologic		**Gastrointestinal**	
Insomnia	29.5	Nausea/Vomiting	16.5
Light-headedness	19.3	Diarrhea	13.6
Abnormal involuntary movement	17.3	Decreased salivation	10.6
Headache	17.0	**Metabolic-Nutritional**	
Muscular twitching	6.9	Weight loss	13.3
Impaired coordination	6.6	Decreased appetite	12.8
Muscle tone disorders	5.9		
Weakness	5.8	**Dermatological**	
Psychiatric		Sweating	14.4
Anxiety	19.2		
Fatigue and Tiredness	18.4	**Cardiovascular**	
Irritability	10.5	Tachycardia	12.2
Cognitive disorder	10.3		
Memory impairment	5.5	**Special Senses**	
Depression	5.1	Blurred vision	10.0
Confusional state	5.0		

From the studies cited, it has not been determined whether these symptoms are clearly related to the dose and duration of therapy with Alprazolam in patients with panic disorder. There have also been reports of withdrawal seizures upon rapid decrease or abrupt discontinuation of Alprazolam Tablets (see WARNINGS).

To discontinue treatment in patients taking XANAGIS, the dosage should be reduced slowly in keeping with good medical practice. It is suggested that the daily dosage of XANAGIS be decreased by no more than 0.5 mg every three days (see DOSAGE AND ADMINISTRATION). Some patients may benefit from an even slower dosage reduction. In a controlled post marketing discontinuation study of panic disorder patients which compared this recommended taper schedule with a slower taper schedule, no difference was observed between the groups in the proportion of patients who tapered to zero dose; however, the slower schedule was associated with a reduction in symptoms associated with a withdrawal syndrome.

As with all benzodiazepines, 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.

Post Introduction Reports

Various adverse drug reactions have been reported in association with the use of XANAGIS since market introduction. The majority of these reactions were reported through the medical event voluntary reporting system. Because of the spontaneous nature of the reporting of medical events and the lack of controls, a causal relationship to the use of XANAGIS cannot be readily determined. Reported events include: gastrointestinal disorder, hypomania, mania, liver enzyme elevations, hepatitis, hepatic failure, Stevens-Johnson syndrome, angioedema, peripheral edema, hyperprolactinemia, gynecomastia, and galactorrhea (see PRECAUTIONS).

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.perrigo-pharma.co.il.

DRUG ABUSE AND DEPENDENCE

Controlled Substance

XANAGIS contains alprazolam, 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 - Abuse, Misuse, and Addiction).

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

Physical 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 - Dependence and Withdrawal Reactions).

To reduce the risk of withdrawal reactions, use a gradual taper to discontinue XANAGIS or reduce the dosage (see DOSAGE AND ADMINISTRATION - Discontinuation or Dosage Reduction of XANAGIS and WARNINGS - Dependence and Withdrawal Reactions).

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

Clinical Experience

Manifestations of alprazolam overdosage include somnolence, confusion, impaired coordination, diminished reflexes and coma. Death has been reported in association with overdoses of alprazolam by itself, as it has with other benzodiazepines. In addition, fatalities have been reported in patients who have overdosed with a combination of a single benzodiazepine, including alprazolam, and alcohol; alcohol levels seen in some of these patients have been lower than those usually associated with alcohol-induced fatality.

The acute oral LD_{50} in rats is 331–2171 mg/kg. Other experiments in animals have indicated that cardiopulmonary collapse can occur following massive intravenous doses of alprazolam (over 195 mg/kg; 975 times the maximum recommended daily human dose of 10 mg/day). Animals could be resuscitated with positive mechanical ventilation and the intravenous infusion of norepinephrine bitartrate.

Animal experiments have suggested that forced diuresis or hemodialysis are probably of little value in treating overdosage.

General Treatment of Overdose

Overdosage reports with XANAGIS Tablets are limited. As in all cases of drug overdosage, respiration, pulse rate, and blood pressure should be monitored. General supportive measures should be employed, along with immediate gastric lavage. Intravenous fluids should be administered and an adequate airway maintained. If hypotension occurs, it may be combated by the use of vasopressors. Dialysis is of limited value. As with the management of intentional overdosing with any drug, it should be borne in mind that multiple agents may have been ingested.

Flumazenil, a specific benzodiazepine receptor antagonist, is indicated for the complete or partial reversal of the sedative effects of benzodiazepines and may be used in situations when an overdose with a benzodiazepine is known or suspected. Prior to the administration of flumazenil, necessary measures should be instituted to secure airway, ventilation and intravenous access. Flumazenil is intended as an adjunct to, not as a substitute for, proper management of benzodiazepine overdose. Patients treated with flumazenil should be monitored for re-sedation, respiratory depression, and other residual benzodiazepine effects for an appropriate period after treatment. **The prescriber should be aware of a risk of seizure in association with flumazenil treatment, particularly in long-term benzodiazepine users and in cyclic antidepressant overdose.** The complete flumazenil package insert including CONTRAINDICATIONS, WARNINGS and PRECAUTIONS should be consulted prior to use.

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.

ANIMAL STUDIES

When rats were treated with alprazolam at 3, 10, and 30 mg/kg/day (15 to 150 times the maximum recommended human dose) orally 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.

MANUFACTURER and MARKETING AUTHORIZATIONS HOLDER:

Perrigo Israel Pharmaceuticals LTD, P.O.B 16, Yeruham

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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