Prescribing Information

1. NAME OF THE MEDICINAL PRODUCT

Xanagis 0.25 mg
Xanagis 0.5 mg
Xanagis 1 mg

WARNING: RISKS FROM CONCOMITANT USE WITH OPIOIDS OR OTHER CNS DEPRESSANTS

Concomitant use of benzodiazepines with opioids or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death [see Warnings, Drug Interactions].
Reserve concomitant prescribing of these drugs for use in 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.

2. 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.

3. PHARMACEUTICAL FORM

Tablets

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

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

4.2. Posology and method of 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.

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. (See section 4.4 Special warnings and precautions for use)

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.

4.3. Contraindications

Alprazolam is contraindicated in patients with known hypersensitivity to benzodiazepines, alprazolam, or to any component of the product's formulation. Benzodiazepines are also contraindicated in patients with myasthenia gravis, severe respiratory insufficiency, sleep apnoea syndrome, severe hepatic insufficiency. Alprazolam may be used in patients with open angle glaucoma who are receiving appropriate therapy, but is contraindicated in patients with acute narrow angle glaucoma.

Alprazolam is contraindicated with ketoconazole and itraconazole, since these medications significantly impair the oxidative metabolism mediated by cytochrome P450 3A (CYP3A).

4.4. Special warnings and precautions for use

Caution is recommended when treating patients with impaired renal function or mild to moderate hepatic insufficiency.

In patients presenting with major depression or anxiety associated with depression benzodiazepines and benzodiazepine-like agents should not be prescribed alone to treat depression as they may precipitate or increase the risk of suicide. Panic disorder has been associated with primary and secondary major depressive disorders and increased reports of suicide among untreated patients.

Therefore alprazolam should be used with caution and the prescription size should be limited in patients with signs and symptoms of a depressive disorder or suicidal tendencies.

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.

It is recommended that general principle of using the lowest effective dose to be followed in elderly and /or debilitated patients to preclude development of ataxia or oversedation (See section 4.2 Posology and method of administration). A lower dose is also recommended for patients with chronic respiratory insufficiency due to risk of respiratory depression. There have been rare reports of death in patients with severe pulmonary disease shortly after the initiation of treatment with alprazolam.

Benzodiazepines should be used with extreme caution in patients with a history of alcohol or drug abuse (See section 4.5 Interactions with other medicinal products and other form of interactions). A decreased systemic alprazolam elimination rate (eg, increased plasma half-life) has been observed in both alcoholic liver disease patients and obese patients receiving alprazolam.

Dependence

Use of benzodiazepines may lead to the development of physical and psychic dependence upon these products. The risk of dependence increases with dose and duration of treatment; it is also greater in patients with a history of alcohol and drug abuse. Pharmacodependency may occur at therapeutic doses and/or in patients with no individualized risk factor. There is an increased risk of pharmacodependency with the combined use of several benzodiazepines regardless of the anxiolytic or hypnotic indication. Cases of abuse have also been reported.

The importance of dose and the risks of alprazolam as a treatment for panic disorder: Because the management of panic disorder often requires the use of average daily doses of alprazolam above 4 mg, the risk of dependence among panic disorder patients may be higher than that among those treated for less severe anxiety.

Withdrawal symptoms: Once physical dependence has developed, abrupt termination of treatment will be accompanied by withdrawal symptoms. These may consist of headaches, muscle pain, extreme anxiety, tension, restlessness, confusion, irritability and insomnia. In severe cases the following symptoms may occur: derealization, depersonalization, hyperacusis, numbness and tingling of the extremities, hypersensitivity to light, noise and physical contact, hallucinations or epileptic seizures. (See section 4.2 Posology and method of administration)

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.

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 even slower dosage reduction.

Rebound insomnia and anxiety: a transient syndrome whereby the symptoms that led to treatment with a benzodiazepine recur in an enhanced form may occur on withdrawal of treatment. It may be accompanied by other reactions including mood changes, anxiety or sleep disturbances and restlessness. Since the risk of withdrawal phenomena/rebound phenomena is greater after abrupt discontinuation of treatment, it is recommended that the dosage be decreased gradually by no more than 0.5 mg every three days. Some patients may require an even slower dose reduction. (See section 4.2 Posology and method of administration)

Interdose Symptoms

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

Duration of treatment

The duration of treatment should be as short as possible (See section 4.2 Posology and method of administration) depending on the indication, but should not exceed eight to twelve weeks including tapering off process. Extension beyond these periods should not take place without re-evaluation of the situation.

It may be useful to inform the patient when treatment is started that it will be of limited duration and to explain precisely how the dosage will be progressively decreased. Moreover it is important that the patient should be aware of the possibility of rebound phenomena, thereby minimizing anxiety over such symptoms should they occur while the medicinal product is being discontinued. There are indications, that in the case of benzodiazepines with a short duration of action, withdrawal phenomena can become manifest within the dosage interval, especially when the dosage is high. When benzodiazepines with a long duration of action are being used it is important to warn against changing to a benzodiazepine with a short duration of action, as withdrawal symptoms may develop.

Amnesia

Benzodiazepines may induce anterograde amnesia. The condition occurs most often several hours after ingesting the product and therefore to reduce the risk patients should ensure that they will be able to have uninterrupted sleep of 7-8 hours. (See section 4.8. Undesirable Effects)

Psychiatric and paradoxical reactions

Reactions like restlessness, agitation, irritability, aggressiveness, delusion, rages, nightmares, hallucinations, psychoses, inappropriate behaviour and other adverse behavioural effects are known to occur when using benzodiazepines. Should this occur, use of the medicinal product should be discontinued. They are more likely to occur in children and the elderly.

Tolerance

Some loss of efficacy to the hypnotic effects of benzodiazepines may develop after repeated use for a few weeks.

Episodes of hypomania and mania have been reported in association with the use of alprazolam in patients with depression. Benzodiazepines are not recommended for the primary treatment of psychotic illness.

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

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 alprazolam.

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

Benzodiazepines produce an additive effect when co-administered with alcohol or other CNS depressants. Concomitant intake with alcohol is not recommended. Alprazolam should be used with caution when combined with CNS depressants.

Enhancement of the central depressive effect may occur in cases of concomitant use with antipsychotics (neuroleptics), hypnotics, anxiolytics/sedatives, antidepressant agents, narcotic analgesics, anti-epileptic drugs, anaesthetics, ethanol and sedative antihistamines. In the case of narcotic analgesics enhancement of the euphoria may also occur leading to an increase in psychic dependence.
Pharmacokinetic interactions can occur when alprazolam is administered along with drugs that interfere with its metabolism.
CYP3A Inhibitors
Compounds that inhibit certain hepatic enzymes (particularly cytochrome P450 3A4) may increase the concentration of alprazolam and enhance its activity. Data from clinical studies with alprazolam, in-vitro studies with alprazolam and clinical studies with drugs metabolized similarly to alprazolam provide evidence for varying degrees of interaction and possible interaction with alprazolam for a number of drugs. Based on the degree of interaction and the type of data available, the following recommendations are made:The co-administration of alprazolam with ketoconazole, itraconazole, or other azole-type antifungals is not recommended.

The co-administration of nefazodone or fluvoxamine increases the AUC of alprazolam by approximately 2-fold. Caution and consideration of dose reduction is recommended when alprazolam is co-administered with nefazodone, fluvoxamine and cimetidine.

Caution is recommended when alprazolam is co-administered with fluoxetine, propoxyphene, oral contraceptives, sertraline, diltiazem, or macrolide antibiotics such as erythromycin, clarithromycin and troleandomycin.

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%.

Caution and consideration of appropriate alprazolam dose reduction are recommended during coadministration with Cimetidine—Coadministration of cimetidine increased the maximum plasma concentration of alprazolam by 86%, decreased

clearance by 42%, and increased half-life by 16%.

CYP3A4 Inducers

Since alprazolam is metabolized by CYP3A4, inducers of this enzyme may enhance the metabolism of alprazolam. Interactions involving HIV protease inhibitors (e.g. ritonavir) and alprazolam are complex and time dependent. Short term, low doses of ritonavir resulted in a large impairment of alprazolam clearance, prolonged its elimination half-life and enhanced clinical effects. However, upon extended exposure to ritonavir, CYP3A induction offset this inhibition. This interaction will require a dose-adjustment or discontinuation of alprazolam. Carbamazepine can increase alprazolam metabolism and therefore can decrease plasma levels of 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.

4.6. Fertility, pregnancy and lactation

Pregnancy

The data concerning teratogenicity and effects on postnatal development and behavior following benzodiazepine treatment are inconsistent. A large amount of data based on cohort studies indicate that first trimester exposure to benzodiazepine is not associated with an increase in the risk of major malformation. However, some early case-control epidemiological studies have found a twofold increased risk of oral clefts.

Benzodiazepine treatment at high dose, during the second and/or the third trimester of pregnancy, has revealed a decrease of fetal active movements and a variability of fetal cardiac rhythm.

When treatment has to be administered for medical reasons during the last part of pregnancy, even at low doses, floppy infant syndrome such as axial hypotonia, sucking troubles leading to a poor weight gain may be observed. These signs are reversible but they may last from 1 up to 3 weeks, according to the half-life of the product. At high doses, respiratory depression or apnoea and hypothermia in newborn may appear. Moreover, neonatal withdrawal symptoms with hyperexcitability, agitation and tremor may be observed a few days after birth, even if no floppy infant syndrome is observed. The apparition of withdrawal symptoms after birth depends on the half-life of the substance.

Alprazolam should not be used during pregnancy unless the clinical condition of the woman requires treatment with alprazolam. If alprazolam is used during pregnancy, or of the patient becomes pregnant while taking alprazolam, the patient should be apprised of the potential hazard to the fetus.

If alprazolam treatment is necessary during last part of pregnancy, high doses should be avoided and withdrawal symptoms and/or floppy infant syndrome should be monitored in newborn.

Breastfeeding

Alprazolam is excreted in breast milk at low level. However, alprazolam is not recommended during breastfeeding.

4.7. Effects on ability to drive and use machines

Sedation, amnesia, impaired concentration and impaired muscle function may adversely affect the ability to drive or use machines. If insufficient sleep occurs, the likelihood of impaired alertness may be increased (See section 4.5 Interactions with other Medical Products and other forms of Interaction).

These effects are potentiated by alcohol (See section 4.5 Interactions with other Medical Products and other forms of Interaction).

Patients should be cautioned about operating motor vehicles or engaging in other dangerous activities while taking

alprazolam.

4.8. Undesirable effects

Adverse events, if they occur, are generally observed at the beginning of therapy and usually disappear upon continued medication or decreased dosage.

The following undesirable effects have been observed and reported during treatment with alprazolam with the following frequencies: Very common (>1/10); common (>1/100 to <1/10); uncommon (>1/1,000 to <1/100); rare (>1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

MedDRA System Organ Class	Frequency	Undesirable Effects
Endocrine disorders	Uncommon	Hyperprolactinaemia
Metabolism and nutrition disorders	Common	Decreased appetite
Psychiatric disorders	Common	Confusional state, depression, disorientation, libido decreased
	Uncommon	Anxiety, insomnia, nervousness, hypomania, mania (see section 4.4 Special warnings and precautions for use), hallucination, anger, aggression, hostility, agitation, libido disorder, thinking abnormal, psychomotor hyperactivity
Nervous system disorders	Very common	Sedation, somnolence
	Common	Ataxia, balance disorder, coordination abnormal, memory impairment, dysarthria, disturbance in attention, hypersomnia, lethargy, dizziness, headache
	Uncommon	Amnesia, tremor, dystonia
	Not Known	Autonomic nervous system imbalance
Eye disorders	Common	Vision blurred
Gastrointestinal disorders	Common	Constipation, dry mouth, nausea
	Uncommon	Gastrointestinal disorder
Hepatobiliary disorders	Uncommon	Hepatitis, hepatic function abnormal, jaundice
Skin and subcutaneous tissue disorders	Uncommon	Dermatitis
	Not Known	Angioedema
Musculoskeletal and connective tissue disorders	Uncommon	Muscular weakness
Renal and urinary disorders	Uncommon	Incontinence, urinary retention
Reproductive system and breast	Uncommon	Sexual dysfunction, menstruation

disorders		irregular
General disorders and administration site conditions	Common	Fatigue, irritability
	Not Known	Peripheral oedema
Investigations	Uncommon	Change in weight, intraocular pressure increased

Withdrawal symptoms have occurred following rapid decrease or abrupt discontinuance of benzodiazepines including alprazolam. These can range from mild dysphoria and insomnia to a major syndrome, which may include abdominal and muscle cramps, vomiting, sweating, tremor and convulsions. In addition, withdrawal seizures have occurred upon rapid decrease or abrupt discontinuation of therapy with alprazolam.

Panic disorder has been associated with primary and secondary major depressive disorders and increased reports of suicide among untreated patients.

Amnesia

Anterograde amnesia may occur at therapeutic dosages, the risk increasing at higher dosages. Amnesic effects may be associated with inappropriate behaviour. (See section 4.4 Special warnings and precautions for use).

Depression
Pre-existing depression may be unmasked during benzodiazepine use.

Psychiatric and paradoxical reactions
Reactions like restlessness, agitation, irritability, aggressiveness, delusion, rages, nightmares, hallucinations, psychoses, inappropriate behaviour and other adverse behavioural effects are known to occur when using benzodiazepines or benzodiazepine-like agents. They may be quite severe with this product. They are more likely to occur in the elderly.

In many of the spontaneous case reports of adverse behavioural effects, patients were receiving other CNS drugs concomitantly and/or were described as having underlying psychiatric conditions. Patients who have borderline personality disorder, a prior history of violent or aggressive behaviour, or alcohol or substance abuse may be at risk of such events. Instances of irritability, hostility and intrusive thoughts have been reported during discontinuance of alprazolam in patients with post-traumatic stress disorder.

Dependence

Use (even at therapeutic doses) may lead to the development of physical dependence: discontinuation of the therapy may result in withdrawal or rebound phenomena (See section 4.4 Special warnings and precautions for use). Psychic dependence may occur. Abuse of benzodiazepines has been reported.

4.9. Overdose

As with other benzodiazepines, overdose should not present a threat to life unless combined with other CNS depressants (including alcohol). In the management of overdose with any medicinal product, it should be borne in mind that multiple agents have been taken.

Following overdose with oral benzodiazepines, vomiting may be induced (within 1 hour) if the patient is conscious or gastric lavage undertaken with the airway protected if the patient is unconscious. If there is no advantage in emptying the stomach, activated charcoal should be given to reduce absorption.

Special attention should be paid to respiratory and cardiovascular functions in intensive care.

Overdose of benzodiazepines is usually manifested by degrees of central nervous system depression ranging from drowsiness to coma. In mild cases, symptoms include drowsiness, mental confusion and lethargy, in more serious cases, symptoms may include ataxia, hypotonia, hypotension, respiratory depression, rarely coma and very rarely death.

Flumazenil may be useful as an antidote.

5. Pharmacological properties

5.1. Pharmacodynamic properties

Alprazolam, like other benzodiazepines, has a high affinity for the benzodiazepine binding site in the brain. It facilitates the inhibitory neurotransmitter action of gamma-aminobutyric acid, which mediates both pre- and post-synaptic inhibition in the central nervous system (CNS).

5.2. Pharmacokinetic properties

Alprazolam is readily absorbed. Following oral administration peak concentration in the plasma occurs after 1 - 2 hours.

The mean half-life is 12 - 15 hours. Repeated dosage may lead to accumulation and this should be borne in mind in elderly patients and those with impaired renal or hepatic function. Alprazolam and its metabolites are excreted primarily in the urine.

In vitro alprazolam is bound (80%) to human serum protein.

5.3. Preclinical safety data

Non-clinical data reveal no special hazarchildren

d for humans based on conventional studies of genotoxicity and carcinogenic potential.

When rats were treated orally with alprazolam for 2 years, a tendency for a dose related increase in the number of cataracts (females) and corneal vascularization (males) was observed. These lesions did not appear until after 11 months of treatment.

In reproductive toxicity studies administration of alprazolam in rats and rabbits is associated at very high doses with developmental delay and an increased incidence of fetal death and skeletal malformations. In fertility studies, treatment of male rats at high doses prior to mating resulted in a decrease in the percentage of dams conceiving.

6. Pharmaceutical particulars

6.1. List of excipients

The adjuvants are::Lactose, microcrystalline cellulose, docusate sodium with sodium benzoate, colloidal anhydrous silica, maize starch, magnesium stearate. Xanagis 0.5 mg also contains: colouring agent erythrosine sodium aluminium lake
Xanagis 1 mg also contains: colouring agents erythrosine sodium aluminium lake and F.D. and C. Blue Nr. 2 aluminium lake.

6.2. Incompatibilities

None known.

6.3. Shelf life

36 months

6.4. Special precautions for storage

Store at room temperature 20-25°C.
Store in a cool and dry place.

6.5. Presentations

Xanagis 0,25 mg: Blister strips of 10 tablets. Box containing 10 tablets, 30 tablets, 50 tablets
Xanagis 0,5 mg: Blister strips of 10 tablets. Box containing 10 tablets, 30 tablets, 50 tablets.
Xanagis 1 mg: Blister strips of 10 tablets. Box containing 10 tablets, 30 tablets, 50 tablets.

6.6. Special precautions for disposal and other handling

Not applicable

7. **Manufacturer:**

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

8. **License Nos.;**

Xanagis 0,25 mg: 063 48 26906 00.
Xanagis 0,5 mg: 063 46 26908 00.
Xanagis 1 mg: 063 47 26907 00.

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