Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Xanax 500 microgram Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 500 micrograms alprazolam.

Excipient(s) with known effect:
Each tablet contains 96 mg lactose monohydrate.
Each tablet contains 0.11 mg sodium benzoate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

Pink, oval, biconvex tablets scored on one side and marked 'Upjohn 55' on the other.
The scoreline is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Anxiety
Xanax is indicated for short-term symptomatic treatment of anxiety in adults. Xanax is only indicated when the disorder is severe, disabling or subjecting the individual to extreme distress.

4.2 Posology and method of administration

Posology

Duration of treatment
Xanax should be used in the lowest possible effective dose, for the shortest possible time and for a maximum of 2-4 weeks. The need for continued treatment should be reassessed frequently. Long-term treatment is not recommended. The risk of dependence may increase with dose and duration of treatment (see section 4.4).

It is usual to commence with a dose of 500 micrograms to 1 mg daily in divided doses, with increments (no greater than 1 mg every 3-4 days), to the level of optimal control usually 3 to 4 mg daily.

The dose must be gradually reduced to avoid withdrawal symptoms.

Elderly
In the elderly or debilitated patient a regimen of 250 micrograms twice daily should be used initially with gradual increments if required and tolerance is assured.

Paediatric population
Safety and efficacy of alprazolam have not been established in children and adolescents below the age of 18 years; therefore use of alprazolam is not recommended.

Method of administration
For oral use.

Treatment should be started with the lower recommended dose. The maximum dose should not be exceeded.

Initial doses may be given at bedtime to minimise daytime lethargy. If side effects occur with the starting dose, the dose should be lowered.

4.3 Contraindications

Hypersensitivity to benzodiazepines, alprazolam or to any of the excipients listed in section 6.1. Benzodiazepines are also contraindicated in patients with myasthenia gravis, severe respiratory insufficiency, sleep apnoea syndrome and severe hepatic insufficiency.

4.4 Special warnings and precautions for use

Duration of treatment
The length of treatment should be as short as possible and not more than 2-4 weeks (see section 4.2). An extension of the treatment time beyond this must not be made without a reassessment of the situation.

It may be appropriate to inform the patient on initiation of treatment that the treatment is time-limited and to explain exactly how the dosage will be gradually decreased. There is evidence to suggest that withdrawal symptoms may occur within the dosage interval when using short-acting benzodiazepines, especially at high doses. When long-acting benzodiazepines are used it is important to inform the patient that he/she should not change to a short-acting benzodiazepine, as withdrawal symptoms may then develop.

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

Benzodiazepines and benzodiazepine-like agents should not be prescribed alone to treat depression as they may precipitate or increase the risk of suicide. Xanax 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 use of alprazolam is not recommended.

Benzodiazepines should be used with extreme caution in patients with a history of alcohol or drug abuse (see section 4.5).

A lower dose is also recommended for patients with chronic respiratory insufficiency due to the risk of respiratory depression.

Concomitant use of Xanax and opioids may result in sedation, respiratory depression, coma, and death. Because of these risks, concomitant prescribing of sedative medicines such as benzodiazepines or related drugs such as Xanax with opioids should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe Xanax concomitantly with opioids, the lowest effective dose should be used and the duration of treatment should be as short as possible (see also general dose recommendation in section 4.2).
The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers (where applicable) to be aware of these symptoms (see section 4.5).

Elderly
Benzodiazepines and related products should be used with caution in elderly, due to the risk of sedation and / or musculoskeletal weakness that can promote falls, often with serious consequences in this population.

It is recommended that the general principle of using the lowest effective dose be followed, especially in elderly and/or debilitated patients to preclude the development of ataxia or oversedation.

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 or drug abuse. Pharmacodependency may occur at therapeutic doses and/or in patients with no individualised risk factor. There is an increased risk of pharmacodependency with the combined use of several benzodiazepines regardless of the anxiolytic or hypnotic indication. Drug abuse is a known risk for alprazolam and other benzodiazepines, and patients should be monitored accordingly when receiving alprazolam. Alprazolam may be subject to diversion. There have been reports of overdose-related deaths when alprazolam is abused with other central nervous system (CNS) depressants including opioids, other benzodiazepines, and alcohol. These risks should be considered when prescribing or dispensing alprazolam. To reduce these

risks the smallest appropriate quantity should be used and patients should be advised on the proper storage and disposal of unused drug (see section 4.2, 4.8 and 4.9).

Withdrawal symptoms: Once 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: derealisation, depersonalisation, hyperacusis, numbness and tingling of the extremities, hypersensitivity to light, noise and physical contact, hallucinations or epileptic seizures (see section 4.2 and 4.8).

During discontinuation of alprazolam treatment, the dosage should be reduced slowly in keeping with good medical practice.

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, mild dysphoria, anxiety or sleep disturbances, abdominal and muscle cramps, vomiting, sweating, tremor and restlessness. Since the risk of withdrawal phenomena/rebound phenomena is greater after abrupt discontinuation of treatment, it is recommended that the dosage is decreased gradually (see section 4.2).

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 an uninterrupted sleep of 7-8 hours (see section 4.8).

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 the hypnotic effects of benzodiazepines may develop after repeated use for a few weeks.

Administration to severely depressed or suicidal patients should be done with appropriate precautions and appropriate size of the prescription.

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

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

Xanax contains sodium benzoate
This medicine contains 0.11 mg sodium benzoate in each tablet.

Xanax contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Opioids
The concomitant use of sedative medicines such as benzodiazepines or related drugs such as Xanax with opioids increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effects. The dosage and duration of concomitant use should be limited (see section 4.4). 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 and sedative antihistamines. In the case of narcotic analgesics enhancement of the euphoria may also occur leading to an increase in psychic dependence.

CYP3A Inhibitors

Compounds which 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 data available currently, 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, diltiazem, or macrolide antibiotics such as erythromycin, clarithromycin and troleandomycin.

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.

Digoxin
Increased digoxin concentrations have been reported when alprazolam was given, especially in elderly (>65 years of age). Patients who receive alprazolam and digoxin should therefore be monitored for signs and symptoms related to digoxin toxicity.

4.6 Fertility, pregnancy and lactation

Pregnancy

The data concerning teratogenicity and effects on postnatal development and behaviour 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.

Benzodiazepines including Xanax should only be used during pregnancy or lactation if considered essential by the physician. Animal studies with benzodiazepines have shown minor effects on the foetus while a few studies have reported late behavioural disturbance in offspring exposed *in utero*.

Benzodiazepine treatment at high dose, during the second and/or the third trimester of pregnancy, has revealed a decrease of foetal active movements and a variability of foetal 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 if the patient becomes pregnant while taking alprazolam, the patient should be apprised of the potential hazard to the foetus.
If alprazolam treatment is necessary during last part of pregnancy, or during labour high doses should be avoided and withdrawal symptoms and/or floppy infant syndrome should be monitored in newborn.

Breast-feeding

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

4.7 Effects on ability to drive and use machines

Sedation, amnesia, impaired concentration and impaired muscular function may adversely affect the ability to drive and use machines. If sufficient sleep duration occurs, the likelihood of impaired alertness may be increased (see section 4.5).

These effects are potentiated by alcohol (see section 4.5). Patients should be cautioned about operating motor vehicles or engaging in other dangerous activities while taking Xanax.

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	**Not Known**	Hyperprolactinaemia*
Metabolism and nutrition disorders	**Common**	Decreased appetite
Psychiatric disorders	**Very Common**	Depression
	Common	Confusional state, disorientation, libido decreased, anxiety, insomnia, nervousness, libido increased*
	Uncommon	Mania* (see section 4.4), hallucination*, anger*, agitation*, drug dependence
	Not Known	Hypomania*, aggression*, hostility*, thinking abnormal*, psychomotor hyperactivity*, drug abuse*
Nervous system disorders	**Very Common**	Sedation, somnolence, ataxia, memory impairment, dysarthria, dizziness, headache
	Common	Balance disorder, coordination abnormal, disturbance in attention, hypersomnia, lethargy, tremor
	Uncommon	Amnesia
	Not Known	Autonomic nervous system imbalance*, dystonia*
Eye disorders	**Common**	Vision blurred
Gastrointestinal disorders	**Very Common**	Constipation, dry mouth
	Common	Nausea
	Not Known	Gastrointestinal disorder*
Hepatobiliary disorders	**Not Known**	Hepatitis*, hepatic function abnormal*, jaundice*
Skin and subcutaneous tissue disorders	**Common**	Dermatitis*
	Not Known	Angioedema*, photosensitivity reaction*
Musculoskeletal and connective tissue disorders	**Uncommon**	Muscular weakness
Renal and urinary disorders	**Uncommon**	Incontinence*
	Not Known	Urinary retention*
Reproductive system and breast disorders	**Common**	Sexual dysfunction*
	Uncommon	Menstruation irregular*
General disorders and administration site conditions	**Very Common**	Fatigue, irritability
	Uncommon	Drug withdrawal syndrome*
	Not Known	Oedema peripheral*
Investigations	**Common**	Weight increased, weight decreased
	Not known	Intraocular pressure increased*

* ADR identified post-marketing

Withdrawal symptoms
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.

Amnesia
Anterograde amnesia may occur using therapeutic dosages, the risk increasing at higher dosages. Amnesic effects may be associated with inappropriate behaviour. (see section 4.4).

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 benzodiazepine or benzodiazepine-like agents. They may be quite severe with this product. They are more likely to occur in children and the elderly.

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). Psychic dependence may occur. Abuse of benzodiazepines has been reported.

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. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance. Website: www.hpra.ie.

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 may have been taken.

Following overdose with oral benzodiazepines, vomiting should be induced (within one 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. The value of dialysis has not been determined. 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, slurred speech, 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 used as an adjunct to the management of respiratory and cardiovascular function associated with overdose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Benzodiazepine derivatives, ATC code: N05BA12

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

Following oral administration, peak plasma concentrations are reached in about 1.7 hours. After a single oral dose of 500 micrograms, the average maximal concentration was 7.1 ng/ml. There is a linear relationship between the dose and plasma

concentration. At least 80 % of the oral dose is absorbed.About 70% of the absorbed dose is bound to plasma proteins. Alprazolam is extensively metabolised in the liver, primarily to hydroxylated metabolites, but about 20% of the dose is excreted as unchanged alprazolam. Elimination occurs mostly via the kidneys; 80% of the dose is excreted into the urine and only 7% into the faeces. The mean elimination half-life is 10-12 hours.

5.3 Preclinical safety data

Mutagenesis
Alprazolam was not mutagenic in the in vitro Ames test. Alprazolam did not produce chromosomal aberrations in the in vivo micronucleus assay in rats up to the highest dose tested of 100 mg/kg, which is 500 times greater than the maximum recommended daily human dose of 10 mg/day.

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

Fertility
Alprazolam did not impair fertility in rats up to the highest dose tested of 5 mg/kg/day, which is 25 times the maximum recommended daily human dose of 10 mg/day.

Ocular Effects
When rats were treated orally with alprazolam at 3, 10, and 30 mg/kg/day (15 to 150 times the maximum recommended daily human dose of 10 mg/day) for 2 years, a tendency for a dose related increase in the number of cataracts (females) and corneal vascularization (males) was observed. These lesions did not appear until after 11 months of treatment.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose Monohydrate
Microcrystalline Cellulose
Colloidal Anhydrous Silica
Maize Starch
Magnesium Stearate
Docusate Sodium with Sodium Benzoate
Erythrosine Sodium Aluminium Lake (E127)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Blister pack: Do not store above 25°C. Keep blister in the outer carton.

6.5 Nature and contents of container

PVC/aluminium foil blister strips of 10 tablets, packed 10 strips (100 tablets) in a carton.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

7 MARKETING AUTHORISATION HOLDER

Viatris Healthcare Limited
Damastown Industrial Park
Mulhuddart
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8 MARKETING AUTHORISATION NUMBER

PA23355/058/003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 1st November 2007

10 DATE OF REVISION OF THE TEXT

April 2026