Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Alprazolam Grindeks 500 microgram tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 500 microgram alprazolam.

Excipients with known effect:
Each tablet contains 92.2 mg lactose (as monohydrate) and 0.12 mg sodium benzoate (E 211).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.
Light pink to pink oval (10 mm x 5 mm) tablet with a score line on one side and debossed "0.5" on the other side. The tablet can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology

The dose and duration of use should be adjusted to the individual response, indication and severity of the disease.
Initial treatment
At the beginning of treatment, the dose is 0.25 to 0.5 mg alprazolam three times daily.

Maintenance therapy
If necessary, the total daily dose can be gradually increased to a maximum of 3 mg to 4 mg alprazolam, divided into individual doses throughout the day.

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

Discontinuation
The discontinuation of alprazolam should take place gradually and not exceed 0.5 mg every 3 days to avoid withdrawal symptoms. In some patients, an even slower dose reduction may be required.

Special populations
Elderly and sensitive patients or debilitated patients
Elderly and sensitive patients or debilitated patients should receive reduced doses.The recommended dose is 0.25 mg two to three times daily, which can be gradually increased if needed and tolerated.

Patients with renal and/or hepatic impairment
Caution should be exercised in patients with renal and mild or moderate hepatic impairment and the dose should be reduced, if necessary. For patients with severe hepatic impairment alprazolam is contraindicated (see section 4.3).

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

Paediatric population
The safety and efficacy of alprazolam in children and adolescents up to 18 years have not been established. Therefore, the use of alprazolam is not recommended in children and adolescents up to 18 years of age.

Method of administration
Alprazolam Grindeks is for oral use.

4.3 Contraindications

- Hypersensitivity to the active substance, other benzodiazepines or to any of the excipients listed in section 6.1,
- myasthenia gravis,
- severe respiratory insufficiency,
- sleep apnoea syndrome,
- severe hepatic impairment.

4.4 Special warnings and precautions for use

Note
Not all states of tension, agitation and anxiety require medicinal treatment. They are often signs of physical or mental illnesses and can be dealt with by other measures or treatment of the underlying condition.

Risks from concomitant use of opioids
Concomitant use of alprazolam 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 medicinal products such as alprazolam with opioids should be reserved for patients for whom alternative treatment options are not possible.
If a decision is made to prescribe Alprazolam Grindeks 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 regard, it is strongly recommended that patients and their caregivers (if applicable) be informed about these symptoms (see section 4.5).

Dependence/Abuse
The use of benzodiazepines can lead to the development of psychic and physical dependence. The risk of dependence increases with the dose and duration of treatment. In particular, this risk is increased in patients with a history of alcohol or drug dependence. This applies even to the therapeutic dosage range and regardless of whether a risk factor is present.
The risk of dependence is increased by the concomitant use of various benzodiazepines, regardless of whether these benzodiazepines have an anxiolytic or hypnotic effect.
Medicinal product abuse is a known risk with alprazolam and other benzodiazepines. Patients receiving alprazolam should be monitored accordingly. Diversion is possible with alprazolam. There have been reports of overdose fatalities when alprazolam was taken concomitantly with other CNS depressants, such as opioids, other benzodiazepines and alcohol. These risks should be taken into account when prescribing or dispensing. The smallest appropriate amount should be selected to minimise risk (see sections 4.2, 4.8 and 4.9).

Withdrawal symptoms
If dependence has developed, sudden discontinuation of treatment will be accompanied by withdrawal symptoms. These may manifest as headache, muscle pain, extreme anxiety, states of tension, inner restlessness, confusion and irritability. In severe cases, the following symptoms may also occur: derealisation, depersonalisation, hyperacusis, numbness and paraesthesia of the extremities, hypersensitivity to light, noise and physical contact, hallucinations or epileptic seizures (see sections 4.2 and 4.8).

Rebound phenomena
Similarly, if short-term treatment is suddenly discontinued, transient rebound phenomena may occur, with the symptoms leading to treatment with benzodiazepines possibly recurring in exaggerated form. Possible accompanying reactions are mood lability, states of anxiety or sleep disorders and restlessness. Rebound phenomena may also manifest as dangerous physical and psychic reactions, such as seizures and symptomatic psychosis (e.g., withdrawal delirium).

As the risk of withdrawal symptoms or rebound phenomena is higher after sudden termination of therapy, it is recommended that treatment be terminated by gradual dose reduction.

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 dose will be gradually decreased. There is evidence to suggest that withdrawal symptoms may occur within the dose 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.

Amnesia
Benzodiazepines can cause anterograde amnesia; in most cases, several hours post-dose. This means that, after taking their medicinal product, patients may perform actions that they cannot subsequently recollect.
This risk increases with the dose level and can be reduced by a sufficiently long duration of uninterrupted sleep (7 to 8 hours).

Psychiatric and "paradoxical" reactions
Particularly in elderly patients or children, psychiatric and "paradoxical" reactions may occur with the use of benzodiazepines, such as restlessness, excitability, irritability, aggression, delusions, anger, nightmares, hallucinations, psychoses, inappropriate behaviour and other behavioural disorders. In such cases, treatment with this medicinal product should be discontinued.

Tolerance
After repeated oral dosing with benzodiazepines over a few weeks, a loss of efficacy (tolerance) may occur.

Depression and suicidal ideation
Benzodiazepines and benzodiazepine-like substances should not be prescribed alone to treat depression as they may precipitate or increase the risk of suicide. 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.
Episodes of hypomania and mania have been reported in association with the use of alprazolam in patients with depression.

Psychoses
Benzodiazepines are not recommended for the primary treatment of psychoses.

Special populations
Elderly and debilitated patients
Benzodiazepines and related products should be used with caution in elderly patients, due to the risk of sedation and/or musculoskeletal weakness that can lead to 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.

Renal or hepatic impairment
If there are renal impairment or mild or moderate hepatic impairment, caution is advised, and the dose should be reduced as necessary. Patients with severe hepatic impairment must not be treated with benzodiazepines, as this increases the risk of encephalopathy.

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

History of alcohol and drug abuse
In patients with a history of alcohol or drug abuse, benzodiazepines should only be used with extreme caution (see section 4.5).

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

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

Sodium benzoate
This medicinal product contains 0.12 mg sodium benzoate in each tablet.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions
Alcohol
Benzodiazepines produce an additive effect when co-administered with alcohol. Therefore, concomitant intake with alcohol is not recommended. Combination with alcohol potentates the sedative effect of alprazolam.

Psychotropic medicinal products
Alprazolam should be used with caution when combined with other CNS depressants. Enhancement of the central depressive effect may occur, and benzodiazepines produce an additive effect when coadministered with other CNS depressants or psychotropic medicinal products, such as antipsychotics (neuroleptics), hypnotics, anxiolytics/sedatives, antidepressants, narcotic analgesics (e.g. opioids), antiepileptics, anaesthetics and sedative antihistamines.

However, when taking alprazolam in combination with narcotic analgesics, potentiation of euphoria can occur which may lead to an increased psychic dependence.

Clozapine
With clozapine there is an increased risk of respiratory and/or cardiac arrest.

Opioids
The concomitant use of sedatives such as benzodiazepines or related medicines such as alprazolam with opioids increases the risk of sedation, respiratory depression, coma and death because of an additive CNS depressant effect. The dose and duration of concomitant use should be limited (see section 4.4).

Particular caution should be exercised with medicinal products that trigger respiratory depression, such as opioids (analgesics, cough suppressants or drug replacement therapy). This is particularly important to consider for the elderly.
Pharmacokinetic interactions
CYP3A4 inhibitors
Pharmacokinetic interactions can occur when alprazolam is administered along with medicinal products that inhibit the hepatic enzyme CYP3A4 by increasing the plasma levels of alprazolam.
Alprazolam should therefore be used with caution in patients taking these medicinal products and a reduction of dose may be necessary when such medicinal products are concomitantly used.

Itraconazole, a potent CYP3A4-inhibitor, increases AUC and prolongs the elimination half-life for alprazolam. In a study where healthy volunteers were given itraconazole 200 mg/day and 0.8 mg alprazolam, the AUC was increased two-three-fold, and the elimination half-life was prolonged to about 40 hours. Alterations have also been seen on psychomotor function affected by alprazolam. Itraconazole may enhance the CNS-depressant effects of alprazolam and withdrawal of itraconazole may attenuate the therapeutic efficacy of alprazolam.

Concomitant use with potent CYP3A4 inhibitors such as itraconazole, ketoconazole, posaconazole, voriconazole, HIV protease inhibitors is not recommended. However, if concomitant use of alprazolam and a potent CYP3A4 inhibitor is considered necessary, the alprazolam dose should be reduced to one half or one third.

Fluvoxamine treatment extends the half-life for alprazolam from 20 hours to 34 hours and doubles the alprazolam concentration in plasma. When used in combination, half of the dose of alprazolam is recommended.

Fluoxetine has a moderate inhibitory effect on alprazolam-metabolism resulting in increased plasma concentrations. During concomitant use, the psychomotor effects of alprazolam are therefore intensified. Adjustment of the dose may be required.

Erythromycin inhibits the metabolism of alprazolam. The alprazolam concentration in plasma increases by about 50%. The combination may require adjustment of the dose.
Other CYP3A4 inhibitors that are expected to increase the plasma concentration of alprazolam are clarithromycin, telithromycin, diltiazem and fluconazole. A dose reduction may be needed.

Cimetidine reduces the clearance of alprazolam which may possibly intensify the effect. The clinical significance of the interaction has not yet been determined.

CYP3A4 inducers
Since alprazolam is metabolized by CYP3A4, inducers of this enzyme may increase 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 decrease 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.

Patients on concomitant treatment of alprazolam and theophylline get a significantly lower alprazolam concentration in plasma than patients only treated with alprazolam, possibly caused by induced metabolism. The clinical significance of this interaction has not yet been determined.

Carbamazepine seems to induce the alprazolam-metabolism resulting in a reduced effect. The clinical significance of this interaction has not yet been determined. Similar effects may be expected with concomitant administration of rifampicin or St. John's wort.

The effect of alprazolam on the pharmacokinetics of other medicinal products
Increase of digoxin plasma levels has been reported with concomitant use of 1 mg alprazolam daily, particularly in elderly (>65 years of age). Therefore, patients receiving alprazolam and digoxin concurrently should be closely monitored for signs and symptoms of digoxin toxicity.

The patient should be prepared for an increase of the muscle relaxing effect (risk of falls) when alprazolam is used during therapy with a muscle relaxant, especially during the beginning of treatment.
The plasma concentration of imipramine and its metabolite desmethylimipramine may increase by 30% when concomitantly administered with alprazolam due to inhibited metabolism.

Effect of other medicinal products on the pharmacokinetics of alprazolam
<u>The following combinations should be avoided:</u>
Dextropropoxyphene may inhibit the metabolism/reduce the clearance of alprazolam resulting in increased plasma concentration of alprazolam and thereby enhanced effect of alprazolam. Concomitant treatment with dextropropoxyphene should be avoided.

Nefazodone inhibits CYP3A4 mediated oxidation of alprazolam, which results in a doubling of the plasma concentration of alprazolam and risk of intensified CNS effects. In combination, it is therefore recommended to reduce the alprazolam dose to one half of the dose.

<u>Interactions that should be taken into account where dose adjustment may be needed:</u>
Contraceptives: contraceptive pills may inhibit the metabolism of benzodiazepines, including the oxidation of alprazolam, which may result in higher plasma concentrations and an enhancement of alprazolam's effect.

Omeprazole: may inhibit the metabolism of alprazolam resulting in higher plasma concentrations and an enhancement of alprazolam's effect.

4.6 Fertility, pregnancy and lactation

<u>Pregnancy</u>
No assessment is possible with regard to the risk of malformation and the effects on early childhood development and behaviour in humans, due to the low number of cases to date and insufficient documentation.

A large amount of data from cohort studies indicate that taking benzodiazepines in early pregnancy (1st trimester) is not associated with an increased risk of severe malformations. However, some epidemiological case-control studies have shown evidence of an increased risk of cleft palate.
The data indicate that, after maternal treatment with benzodiazepines, the risk of cleft palate for a child is less than 2 in 1,000, with the natural rate of such defects in the general population being approximately 1 in 1,000.

High-dose treatment with benzodiazepines during the 2nd and/or 3rd trimester leads to a decrease in foetal movements and fluctuations in foetal heart rhythm.

There are case reports of malformations and mental retardation in prenatally exposed children after benzodiazepine overdose and intoxication.

If, for compelling medical reasons, alprazolam is administered - even at small doses - during late pregnancy or during childbirth, effects on the newborn infant can be expected, such as axial hypotonia, decreased muscle tone and poor sucking reflex leading to lower weight gain (floppy infant syndrome). These effects are reversible and may last for 1 to 3 weeks in accordance with the elimination half-life.

At high doses, respiratory insufficiency or respiratory arrest and hypothermia may occur in newborn infants. Furthermore, withdrawal symptoms such as hyperexcitability, restlessness and tremor may be observed a few days after birth, even if no floppy infant syndrome is observed. The emergence of postnatal withdrawal symptoms 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 foetus. If treatment with Alprazolam Grindeks is necessary during last part of pregnancy, or during labour high doses should be avoided and possible withdrawal symptoms and/or floppy infant syndrome should be monitored in newborn.

Breast-feeding
Small amounts of alprazolam are excreted in human milk, where it accumulates. Alprazolam Grindeks should therefore not be used during breast-feeding. If repeated or high dosages of Alprazolam Grindeks are strictly indicated during breast-feeding, weaning is required.

Newborn infants metabolise benzodiazepines much more slowly than adults.

4.7 Effects on ability to drive and use machines

Alprazolam has major influence on the ability to drive and use machines.
Sedation, amnesia, reduced ability to concentrate and impaired muscle function can have an adverse effect on the ability to drive or use machines. This applies particularly at the start of therapy, after dose escalation, after an insufficient duration of sleep and in combination with alcohol or other CNS depressants (see section 4.5).

4.8 Undesirable effects

Depending on the patient's individual sensitivity and the dose taken, the following adverse reactions may occur, especially at the start of therapy:
emotional blunting, unsteady movement and gait (risk of falls, especially in elderly patients), visual disturbances, after-effects on the following day (light-headedness, reduced responsiveness, etc.), disturbances of the autonomic nervous system (bladder dysfunction).

As a rule, these symptoms diminish with repeated use.

Rarely, respiratory depression may occur, especially during the night.

The following categories are used for expressing the frequency of adverse reactions:

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)
Endocrine disorders					
					Hyperprolactinaemia*
Metabolism and nutrition disorders					
	Appetite				

	decreased				
Psychiatric disorders					
Depression	Confusion, disorientation, libido decreased, anxiety, insomnia, nervousness, libido increased*	Mania* (see section 4.4), hallucinations*, anger*, agitation*, drug dependence			Hypomania*, aggression*, hostility*, thought disorders*, psychomotor restlessness*, drug abuse*
Nervous system disorders					
Sedation, somnolence, ataxia, memory impairment, dysarthria, dizziness, headache	Coordination impaired, balance impaired, attention deficit, hypersomnia, lethargy, tremor	Amnesia			Autonomic nervous system disorders*, dystonia*
Eye disorders					
	Blurred vision				
Gastrointestinal disorders					
Constipation, dry mouth	Nausea	Vomiting			Gastrointestinal disorders*
Hepatobiliary disorders					
					Hepatitis*, impaired liver function* Jaundice*
Skin and subcutaneous tissue disorders					
	Dermatitis*				Angioedema*, photosensitivity reaction*
Musculoskeletal and connective tissue disorders					
		Muscle weakness			
Renal and urinary disorders					
		Urinary incontinence*			Urinary retention*
Reproductive system and breast disorders					
	Sexual dysfunction*	Menstrual disorders*			
General disorders and administration site conditions					
Fatigue, irritability		Drug withdrawal syndrome*			Peripheral oedema*

Investigations					
	Weight change				Intraocular pressure increased*

* ADR identified post-marketing

Dependence and withdrawal symptoms
The use of benzodiazepines (even at therapeutic doses) can lead to the development of physical and psychic dependence; withdrawal and/or rebound phenomena may occur upon termination of therapy (see section 4.4). Withdrawal symptoms can range from mild dysphoria and insomnia to a major syndrome, which may include abdominal and muscle cramps, vomiting, sweating, tremor and convulsions.

Benzodiazepine abuse has been reported (see section 4.4).

Amnesia
Benzodiazepines can cause anterograde amnesia (memory gaps for a period after ingestion) (see section 4.4).

Psychiatric and "paradoxical" reactions
Particularly in elderly patients or children, psychiatric and "paradoxical" reactions may occur with the use of benzodiazepines, such as restlessness, excitability, irritability, aggression, delusions, anger, nightmares, hallucinations, psychoses, inappropriate behaviour and other behavioural disorders. In such cases, treatment with this medicinal product should be discontinued.

Depression
Pre-existing depression can be unmasked during the use of benzodiazepines (see section 4.4).

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:
HPRA Pharmacovigilance
Website: www.hpra.ie

4.9 Overdose

Symptoms
Overdose of alprazolam should not present a threat to life unless combined with other CNS depressants, such as opioids, other benzodiazepines and alcohol.
In the management of overdose, it should always be taken into account that several substances have been taken at the same time (combined drug intoxication). Overdose of benzodiazepines, including alprazolam, 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 even death.

Toxicity
Alprazolam blood levels reported for human fatal intoxications are extremely variable. Toxic plasma concentrations of alprazolam range between 0.1 and 0.4 µg/ml, while some reports mentioned that postmortem blood concentration of alprazolam ranged from 2.1 to 2.3 µg/ml.

Management
The mainstay treatment for acute alprazolam overdose is supportive care, which may include maintaining an adequate airway, monitoring respiratory and circulatory functions. Intravenous (IV) access for fluids should be provided.
Patients with milder signs of intoxication who are still conscious should be allowed to sleep it off under medical observation. If the patient is conscious activated charcoal may be given within one hour of medicinal product ingestion to reduce absorption, but the benefit-risk ratio should be considered (due to risk of aspiration).
Forced diuresis or haemodialysis is of no value.

In severe cases flumazenil (a specific benzodiazepine antagonist) may be used as an adjunct to the management of respiratory functions associated with overdose. Flumazenil can increase the risk of convulsions.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Benzodiazepine derivatives, ATC code: N05BA12

Alprazolam is a psychotropic substance from the class of 1,4-triazolobenzodiazepines and binds with high affinity to specific benzodiazepine receptors in the CNS. Alprazolam enhances the inhibitory effect of GABAergic transmission on various neural assemblies. This results in properties that suppress tension, agitation and anxiety, as well as sedative and hypnotic effects. In addition, alprazolam demonstrates muscle relaxant and anticonvulsive properties.

5.2 Pharmacokinetic properties

Absorption
Alprazolam is rapidly and well absorbed after oral administration. Peak plasma levels are reached after 1 to 2 hours after single oral administration. The bioavailability of alprazolam is 80%.

Distribution
Plasma protein binding is 70 to 80%.
The mean volume of distribution is 1.0 to 1.2 L/kg and is significantly greater in obese patients.

Biotransformation
In addition, to unmetabolized alprazolam (approximately 20%), alpha-hydroxyalprazolam (approximately 17%) and a benzophenone derivative are excreted as the main metabolites. In addition, many other metabolites have been identified. The pharmacological activity of alphahydroxyalprazolam is approximately 50%, compared with alprazolam. The benzophenone derivative shows no pharmacological activity. Due to their low concentration, it is probable that the metabolites scarcely contribute to the therapeutic effect.

Alprazolam crosses the placental barrier and is secreted with breast milk.

Elimination
The elimination half-life after single administration is between 12 and 15 hours. The half-life of the two main metabolites is in the same range as that of alprazolam. About 20% of the dose is excreted unchanged via the kidneys.

Pharmacokinetics in Special populations
Elderly
The elimination halflife may be prolonged in elderly male patients.

Renalimpairment
As the kidney represents the main excretory organ, prolongation of the elimination half-life can be expected if renal function is impaired.

Hepaticimpairment
In cases of hepatic dysfunction, delayed metabolism of the active substance and prolongation of the elimination half-life are to be expected.

5.3 Preclinical safety data

Following alprazolam administration over 24 months, a tendency towards a dose-dependent increase in cataracts was shown in female rats and corneal vascularisations in male rats. In a chronic toxicity study (12 months) on dogs, seizures occurred at high oral doses, which proved fatal in some animals. The relevance for humans is unclear.

Studies on the mutagenicity of alprazolam were negative. Long-term studies in rats and mice showed no indications of a tumorigenic potential for alprazolam.

No impairment of male and female fertility was found in experimental animals, though placental passage of alprazolam was demonstrated in animal experiments. In studies on rats and rabbits, embryoletal effects and skeletal malformations have been observed after very high doses. No data on peri- and postnatal development after administration of alprazolam are available. However, there are indications of behavioural disorders in the offspring of rodents exposed to alprazolam.

Animal studies with alprazolam have shown reproductive toxicity.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Cellulose, microcrystalline (E460)
Maize starch, pregelatinised
Docusate sodium
Sodium benzoate (E211)
Magnesium stearate (E572)
Silica, colloidal anhydrous (E551)
Iron oxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 25 .

6.5 Nature and contents of container

OPA/Alu/PVC//Alu blisters containing 10, 20, 30, 50, 60 or 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

AS GRINDEKS
Krustpils iela 53
Riga
1057
Latvia

8 MARKETING AUTHORISATION NUMBER

PA22992/028/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 2nd August 2024

10 DATE OF REVISION OF THE TEXT