Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Alprazolam Krka 250 microgram tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 250 micrograms alprazolam.

Excipient with known effect
Each tablet contains 85.98 mg lactose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

White to almost white, round, biconvex tablets with bevelled edges. The tablet is scored on one side and engraved with mark 0.25 on the other, 7 mm in diameter. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Short-term symptomatic treatment of anxiety in adults when the disorder is severe, disabling or subjecting the individual to extreme distress.

4.2 Posology and method of administration

Posology
Duration of treatment
Alprazolam Krka 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).

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

Anxiety
Initial dose is 0.75 – 1.5 mg daily, divided in 3 equal doses. The maintenance dosage may be increased gradually if necessary up to 4 mg/day divided in several doses.

Elderly
For elderly patients and those sensitive to the sedative effects of the product, the initial and maintenance dose is 0.5 – 0.75 mg daily divided in 2 to 3 doses. Dosage may be increased gradually where necessary.

Hepatic impairment
Caution is advised when treating patients with hepatic impairment (see section 4.4.). The dose should be reduced. Alprazolam is contraindicated in severe hepatic impairment (see section 4.3).

Renal impairment
Caution is advised when treating patients with renal impairment (see section 4.4.). The dose should be reduced.

Paediatric population
Alprazolam Krka should not be used in children and adolescents under the age of 18 years. The efficacy and safety have not been established.

Discontinuation of treatment
The dose should be tapered gradually to avoid withdrawal symptoms (see section 4.4.).

Method of administration
For oral use.
The tablets can be taken with or without food and should be swallowed with a small amount of liquid.

4.3 Contraindications

-Hypersensitivity to the active substance, to other benzodiazepines or to any of the excipients listed in section 6.1.
-Myasthenia gravis.
-Severe respiratory insufficiency.
-Sleep apnoea syndrome.
-Severe hepatic insufficiency.
-Acute intoxication with alcohol or other CNS active substances (e.g. hypnotics, analgesics, antidepressants, antipsychotics).

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.

Specific patient groups
Paediatric population
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 these patients.

Renal and hepatic impairment
Caution is recommended when treating patients with impaired renal function or mild to moderate hepatic insufficiency. Alprazolam should not be used to treat patients with severe hepatic insufficiency, since benzodiazepines can promote the development of encephalopathy (see section 4.3).

Elderlyand debilitated patients
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 should be followed in elderly and/or debilitated patients (as poor general condition) to preclude the development of ataxia or over sedation.

Alprazolam can cause muscle weakness. Therefore, in patients with spinal or cerebellar ataxia special caution is required.

Chronic respiratory insufficiency
In patients with chronic respiratory insufficiency a lower dose should be used, given the possibility of respiratory depression.

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

Depression/suicidal behavior
Benzodiazepines and benzodiazepine-like agents should not be used alone to treat depression as they may precipitate or increase the risk of suicide. Therefore, Alprazolam Krka 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.

Previously unnoticed depressions may become apparent, in susceptible individuals, during benzodiazepine use.

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

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

Acute narrow angle glaucoma
Due to possible anticholinergic undesirable effects benzodiazepines should be used with great caution in patients with acute narrow angle glaucoma or in those patients that may be predisposed.

Risk 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 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).

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

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
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 physical dependence has developed, abrupt termination of treatment will be accompanied by withdrawal symptoms. These may consist of headaches, muscle pain, extreme anxiety, tension, sleep disorders, restlessness, confusion, irritability. 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, tremor or epileptic seizures. Withdrawal symptoms can appear several days after the end of treatment.

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, insomnia and restlessness. Since the risk of withdrawal phenomena/rebound phenomena is greater after rapid dose reduction or abrupt discontinuation of treatment, it is recommended that the dosage is decreased gradually.
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.

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.

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. Anterograde amnesia may occur using therapeutic dosages, the risk increasing at higher dosages. Amnesic effects may be associated with inappropriate behaviour (see section 4.8).

Special warnings about the excipients
Alprazolam Krka contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions
Psychotropic medicinal products
As enhancement of the central depressive effect may occur alprazolam should be used with caution when combined with other CNS depressants, such as antipsychotics (neuroleptics), hypnotics, anxiolytics/sedatives, some antidepressant agents, narcotic analgesics, anti-epileptic medicinal products, anaesthetics and sedative antihistamines. Enhancement of the euphoria may occur in case of concomitant use with narcotic analgesics, which may lead to increased psychic dependence.

Alcohol
Concomitant intake with alcohol should be avoided. Concomitant use with alcohol enhances sedative effect of alprazolam.

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

Clozapine
Concomitant use with clozapine can lead to increased risk of respiratory and/or cardiac arrest.

Muscle relaxants
It is necessary to inform the patients of enhanced activity of muscle relaxant (risk of falling) when concomitantly used with alprazolam, especially at the beginning of treatment.

Pharmacokinetic interactions
CYP3A4 inhibitors
Since alprazolam is metabolized by CYP3A4 liver enzyme, inhibitors of this enzyme may enhance alprazolam activity and increase its concentration. Alprazolam should be used with caution in patients taking CYP3A4 enzyme inhibitors such as fluoxetine, propoxyphene, oral contraceptives, sertraline or diltiazem and dosage reduction should be considered.

Data from clinical studies with alprazolam, in vitro studies and studies with medicinal products that are metabolised with the same enzymes proved different stages of interactions and possible interactions alprazolam has with many medicinal products.

Itraconazole, potent CYP3A4 inhibitor enhances bioavailability and prolongs alprazolam elimination half-life. Data from clinical study on healthy volunteers, who received 200 mg itraconazole per day with 0.8 mg alprazolam showed that bioavailability increased 2 to 3 times, with prolonged elimination half-time to about 40 hours. Changes in psychomotor functions caused by alprazolam have been noticed. Itraconazole can enhance alprazolam effect on CNS depression, so after discontinuation of itraconazole alprazolam effect can be decreased.

The co-administration of alprazolam with potent CYP3A4 inhibitors, such as itraconazole, ketoconazole, voriconazole, posaconazole and HIV protease inhibitors, is not recommended. If concomitant use of alprazolam and potent CYP3A4 inhibitor is necessary, dose of alprazolam should be decreased to one half or third.

Fluvoxamine prolongs alprazolam half-life for 20 to 34 hours and doubles the concentrations of alprazolam in the plasma. When used concomitantly with alprazolam, dose of alprazolam should be reduced to one half.

Fluoxetine has moderate effect on alprazolam metabolism, which results in increasing its concentrations in plasma. If used concomitantly with alprazolam, it enhances alprazolam psychomotor effects, which can lead to dose adjustment.

Erythromycin inhibits alprazolam metabolism and increases its concentrations in plasma for about 50%, which can lead to dose adjustment.

Other CYP3A4 inhibitors which can increase alprazolam concentrations in plasma are: clarithromycin, telithromycin, diltiazem and fluconazole. Dose adjustment could be necessary.

Cimetidine decreases alprazolam clearance, which can enhance its effect. Clinical significance of this interaction has not yet been determined.

CYP3A4 inductors
Since alprazolam is metabolized by CYP3A4, inducers of this enzyme may enhance the metabolism of alprazolam.

Interactions that include HIV protease inhibitor (ritonavir) and alprazolam are complex and time dependant. Low doses of ritonavir result in greater reduction of alprazolam clearance by prolongation of its elimination half-life and enhanced clinical effect, when ritonavir is used for a short time. However, after prolonged use of ritonavir, CYP3A induction balances that inhibition. That interaction may require dose adjustment or discontinuation of alprazolam treatment.

Patients that use alprazolam and theophylline concomitantly have significantly lower concentrations of alprazolam in plasma in contrast to the patients that take alprazolam as monotherapy, probably caused by induction of the metabolism. Clinical significance of this interaction has not yet been determined.

The data showed that carbamazepine induces alprazolam metabolism, which leads to its decreased effect. Clinical significance of this interaction has not yet been determined. Similar effects can occur when rifampicin or St. John ' s Wort is used.

Alprazolam effect on the pharmacokinetics of other medicinal products
Increased digoxin concentrations have been reported when 1 mg of 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 poisoning.

Medicinal product combinations that should be avoided
Dextropropoxyphene can inhibit metabolism or reduce clearance of alprazolam that leads to increase of alprazolam plasma concentrations, which can enhance its effect. Concomitant use with dextropropoxyphene should be avoided.

Medicinal product combinations that may require dose adjustment
At the beginning of alprazolam treatment, imipramine and its metabolite desmethylimipramine can reach 30% higher concentrations in plasma due to metabolism inhibition.

Nefazodone inhibits alprazolam oxidation by CYP3A4 system, which doubles its concentrations in plasma and enhances its effect. It should be considered to reduce the dose of alprazolam to one half.

Interactions to consider during dose adjustment
Contraceptives: Contraceptives can inhibit benzodiazepines metabolism and alprazolam oxidation, which leads to higher doses of alprazolam in plasma and enhances its effect.

Omeprazole can inhibit alprazolam metabolism, which increases alprazolam concentrations in plasma and its effect.

4.6 Fertility, pregnancy and lactation

Pregnancy
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 an increased risk of oral clefts. The data indicated that the risk of having an infant with an oral cleft after maternal benzodiazepine exposure is less than 2/1000 compared with an expected rate for such defects of approximately 1/1000 in the general population.
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 new-born may appear. Moreover, neonatal withdrawal symptoms with hyper excitability, 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.

Taking into account these data, the use of alprazolam during pregnancy may be considered, if therapeutic indications and posology are strictly respected.

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.

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

Fertility
Data on the effects of alprazolam on human fertility are not available. Alprazolam did not impair fertility in rats (see section 5.3).

4.7 Effects on ability to drive and use machines

Alprazolam Krka has major influence on the ability to drive and use machines.

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

Patients should be warned of this hazard and advised not to drive or operate machinery during treatment. These effects are potentiated by alcohol (see section 4.5).

4.8 Undesirable effects

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	Hyperprolactinemia*
Metabolism and nutrition disorders	Common	Decreased appetite
Psychiatric disorders	Very common	Depression
	Common	Confusion, disorientation, libido decreased, anxiety, insomnia, nervousness, libido increased*
	Uncommon	Mania*, hallucinations*, rage*, 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 disorder, concentration difficulties, hypersomnia, lethargy, tremor
	Uncommon	Amnesia
	Not known	Autonomic nervous system imbalance*, dystonia*
Eye disorders	Common	Blurred vision

Gastrointestinal disorders	Very common	Constipation, dry mouth
	Common	Nausea
	Uncommon	Vomiting
	Not known	Gastrointestinal disorder*
Hepatobiliary disorders	Not known	Hepatitis*, abnormal liver function *, jaundice*
Skin and subcutaneous tissue disorders	Common	Dermatitis*
	Not known	Angioedema*, photosensitive 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	Menstrual irregularities *
General disorders and administration site conditions	Very common	Fatigue, irritability
	Not known	Peripheral oedema*
Investigations	Common	Weight decreased, weight increased
	Not known	Intraocular pressure increased*

*undesirable effects registered in postmarketing period

Use (even at therapeutic doses) may lead to the development of physical dependence: discontinuation of the therapy may result in withdrawal or rebound phenomena. Psychic dependence may occur. Abuse of benzodiazepines has been reported (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 via HPRA Pharmacovigilance,
Website: www.hpra.ie.

4.9 Overdose

Symptoms
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.
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.

Management
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. Special attention should be paid to respiratory and cardiovascular functions in intensive care.
Flumazenil may be useful as an antidote.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: psycholeptics, benzodiazepine derivates, ATC code: N05BA12

Mechanism of action
Alprazolam, like other benzodiazepines, has a high affinity for the benzodiazepine binding site in the brain. Benzodiazepines facilitate the inhibitory neurotransmitter action of gamma-aminobutyric acid (GABA).

Pharmacodynamic effects

Like other benzodiazepines, in addition to its anxiolytic properties, alprazolam has also sedative, hypnotic, muscle-weakening and anticonvulsive properties.

5.2 Pharmacokinetic properties

Absorption
Alprazolam bioavailability is approximately 90%. Use of alprazolam with food postpones alprazolam absorption, without effect on absorbed concentration. Following oral administration peak concentration in the plasma occurs after 1-2 hours. Alprazolam plasma concentration is proportional to the dose administered.

Distribution
In vitro, 70% of alprazolam is bound to serum proteins. Clearance is approximately 1 mL/min/kg and distribution volume is around 1 l/kg.

Biotransformation
Alprazolam does not cause enzymes induction or can cause mild enzyme induction. Alprazolam is extensively metabolised in the liver, primarily to hydroxylated metabolites alpha-hydroxy-alprazolam and 4-hydroxy-alprazolam, which glucuronide before excretion in urine.

Elimination
Elimination half-life of alprazolam is approximately 12 hours. Alprazolam metabolites are biologically active. Their elimination half-lives are similar to that of alprazolam, but due to their low concentrations in plasma, they do not contribute to the pharmacological effect.

Elderly
In elderly, the mean elimination half-life can be prolonged (approximately 16 h).

Hepatic and renal impairment
The mean elimination half-life is increased with impaired liver and/or renal function.

5.3 Preclinical safety data

In rats 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. In dogs administered high oral alprazolam doses for 12 months convulsions were observed, some of which were lethal. The human relevance is unknown.

Alprazolam did not reveal a genotoxic potential *in vitro*. 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.

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).

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. In embryo-foetal development studies, high doses of alprazolam caused an increase in birth defects and foetal death in rats and rabbits. Prenatal exposure of mice and rats to benzodiazepines, including alprazolam, has been associated with behavioural changes in the offspring.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Maize starch
Crospovidone (type A)
Povidone K 25

Magnesium stearate (E470b)
Polysorbate 80

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25°C.
Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Blister (PVC/PE/PVDC//Alu foil): 10, 20, 30, 50, 100 tablets, in a box.
Perforated unit dose blister (PVC/PE/PVDC//Alu foil): 10x1, 20x1, 30x1, 50x1, 100x1 tablets, in a box.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7 MARKETING AUTHORISATION HOLDER

KRKA, d.d., Novo mesto
Šmarješka cesta 6
8501 Novo mesto
Slovenia

8 MARKETING AUTHORISATION NUMBER

PA1347/097/001

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