

SUMMARY OF PRODUCT CHARACTERISTICS

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1. NAME OF THE MEDICINAL PRODUCT

Alprazolam Krka 0.5 mg prolonged-release tablets

Alprazolam Krka 1 mg prolonged-release tablets

Alprazolam Krka 2 mg prolonged-release tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged-release tablet contains 0.5 mg alprazolam.

Each prolonged-release tablet contains 1 mg alprazolam.

Each prolonged-release tablet contains 2 mg alprazolam.

Excipient with known effect:

	0.5 mg tablets	1 tablets	2 mg tablets
Lactose	183.74 mg	183.69 mg	182.93 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Prolonged-release tablet.

0.5 mg: greenish-yellow, round, slightly biconvex.

1 mg: white, round, slightly biconvex.

2 mg: light blue, round, slightly biconvex.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Alprazolam is indicated for short-term symptomatic treatment of anxiety in adults.

Alprazolam is only indicated when the disorder is severe, disabling or subjecting the individual to extreme distress.

4.2 Posology and method of administration

Posology

If possible, treatment should be started, monitored and finished by the same doctor.

Symptomatic treatment of anxiety: Pharmacological therapy of anxiety should always be adjuvant. Initial dose 0.5 mg once daily, adjusted individually. Maintenance dosage is 0.5–3 mg/day in one or two divided doses.

For elderly patients, patients with impaired hepatic or renal function and those sensitive to the sedative effects of the product, the initial and maintenance dose is 0.5 - 1 mg daily. Dosage may be increased gradually where necessary. It is recommended that daily doses greater than 3 mg be taken in two divided doses.

In elderly patients, if too high doses are used, confusion can occur.

Duration of treatment: Alprazolam 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).

Discontinuation of treatment: The dose should be gradually reduced to avoid withdrawal symptoms. With abrupt discontinuation of benzodiazepines, paresthesias, perceptual disturbances and depersonalization may occur within one or two weeks. Withdrawal symptoms in the form of mild dysphoria and insomnia, as well as muscle and stomach cramps, vomiting, sweating and tremor have been reported in cases of abrupt cessation of benzodiazepine use. In some cases, seizures have also been reported (see section 4.8).

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

Alprazolam Krka has a prolonged absorption time (5-11 hours) due to its pharmaceutical form. Because of the pharmaceutical form, the tablets should be swallowed whole, not divided or crushed.

4.3 Contraindications

- Hypersensitivity to alprazolam, other benzodiazepines or to any of the excipients listed in section 6.1.
- *Myasthenia gravis*.
- Severe respiratory insufficiency.
- Severe sleep apnoea syndrome.
- 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.

Tolerance

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

Dependence

Use of benzodiazepines can lead to the development of physical and mental 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.

Misuse

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).

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

Withdrawal symptoms

Once physical dependence has developed, abrupt termination of treatment will be accompanied by withdrawal symptoms. These may consist of headache, muscle pain, extreme anxiety, tension, 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 or epileptic seizures. Withdrawal symptoms can appear several days after the end of treatment.

Rebound 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 swings, anxiety or sleep disturbances and restlessness. Since the risk of withdrawal phenomena/rebound phenomena is greater following rapid dose reduction or the abrupt discontinuation of treatment, it is recommended that the dose be reduced gradually (tapering off).

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 (see also section 4.8).

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 drugs 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).

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 use of alprazolam is not recommended.

Renal or hepatic impairment

Caution is recommended when treating patients with impaired renal function or mild to moderate hepatic insufficiency (see section 4.2). Benzodiazepines are contraindicated for the treatment of patients with severe hepatic disorders, since benzodiazepines can promote the development of encephalopathy.

Elderly population

It is recommended that the general principle of using the lowest effective dose be followed in elderly and/or debilitated patients to preclude the development of ataxia or oversedation (see section 4.2). Use alprazolam with caution in elderly patients as there is a risk of falls secondary to the myorelaxant effects of benzodiazepines.

Patients with major depression

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 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.

Respiratory insufficiency

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

Psychoses

Benzodiazepines are not effective for the primary treatment of psychoses.

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:

Caution should be exercised if other psychotropic medicinal products are concomitantly used. Increased depression of the activity of the central nervous system can occur when using the tablets concurrently with psychotropic medicinal products, such as anti-psychotics (neuroleptics), hypnotics, sedatives, some antidepressant agents, opioids, anti-epileptic drugs, sedative H1-antihistamines. Special care should be made with drugs depressing respiratory function such as opioids (analgesics, antitussives, substitutive treatments), notably in the elderly people. However, when taking the tablets in combination with opioids, potentiation of euphoria can occur which may lead to increased psychic dependence.

Opioids:

The concomitant use of sedative medicines such as benzodiazepines or related drugs 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).

Alcohol:

Combination with alcohol potentiates the sedative effect of alprazolam. This will affect patients' ability to drive and use machines. Intake of alcohol is not recommended during treatment with alprazolam.

Clozapine:

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

Muscle relaxants:

One should be prepared for increase of muscle relaxing effect (risk of falls) when alprazolam is used during therapy with a muscle relaxant, especially during the beginning of treatment with alprazolam.

Pharmacokinetic interactions

Pharmacokinetic interactions can occur when alprazolam is administered along with drugs that inhibit the hepatic enzyme CYP3A4 by increasing the plasma levels of alprazolam.

CYP3A4 inhibitors:

Anti-mycotics: Concurrent use of itraconazole, ketoconazole, posaconazole, voriconazole and other anti-fungal agents of the azole type (potent CYP3A4 inhibitors) is not recommended.

Particularly, appropriate caution should be exercised and a substantial dose reduction considered in the case of concurrent use of CYP3A4 inhibitors such as HIV protease inhibitors (e.g. ritonavir), fluoxetine, dextropropoxyphene, oral contraceptives, sertraline, diltiazem or macrolide antibiotics, such as erythromycin, clarithromycin, telithromycin and troleandomycin.

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.

Nefazodone, fluvoxamine and cimetidine: Caution is required when using these agents (CYP3A4 inhibitors) and alprazolam concurrently and a possible reduction of the dose of alprazolam should be considered.

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 dosage to one half of the dose.

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 dosage of alprazolam is recommended.

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:

A reduced effect of alprazolam might occur in patients taking CYP3A4 inducers like rifampicin, phenytoin, carbamazepine or St John's wort. The plasma alprazolam concentrations in the elimination phase are dependent on certain hepatic enzymes (in particular CYP3A4) for the metabolism and are reduced by medicinal products that induce these enzymes. When St. John's wort therapy or treatment with other CYP3A4 inducing agents is suddenly stopped, overdose symptoms of alprazolam may occur.

The effect of alprazolam on the pharmacokinetics of other medicinal products:

Digoxin:

Increase of digoxin plasma levels has been reported with concomitant use of 1 mg alprazolam daily, particularly in the elderly. Therefore, patients receiving alprazolam and digoxin concurrently should be closely monitored for signs and symptoms of digoxin toxicity.

Imipramine and desipramine:

It has been reported that concurrent administration of alprazolam (at doses of up to 4 mg/day) with imipramine and desipramine caused the steady state plasma levels of these substances to increase by 31 % and 20 % respectively. It is not yet known whether these changes are of clinical significance.

4.6 Fertility, pregnancy and lactation

Pregnancy

If Alprazolam Krka is prescribed to a woman of childbearing potential, she should be warned to contact her physician regarding discontinuance of the product if she intends to become or suspects that she is pregnant.

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 apnea 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.

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.

4.7 Effects on ability to drive and use machines

Alprazolam 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.

Patients should be warned of this hazard and advised not to drive or operate machinery during treatment. These effects are potentiated by alcohol. If insufficient sleep duration occurs, the likelihood of impaired alertness may be increased (see section 4.5).

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 most frequent adverse event is sedation and sleepiness, which occurs in more than 10% of those treated.

The frequency of undesirable effects is defined according to the following convention:

Very common ($\geq 1/10$)

Common ($\geq 1/100$, $< 1/10$)

Uncommon ($\geq 1/1,000$, $< 1/100$)

Rare ($\geq 1/10,000$, $< 1/1,000$)

Very rare ($< 1/10,000$)

Not known (cannot be estimated from the available data).

	Very common	Common	Uncommon		Not known
Endocrine disorders					Hyperprolactinemia*
Metabolism and nutrition disorders		Decreased appetite, increased appetite			
Psychiatric disorders	Depression	Confusion, disorientation, libido decreased, anxiety, insomnia, nervousness, libido increased*	Mania* (see section 4.4), hallucination*, rage*, agitation, drug dependence		Hypomania*, aggression*, hostility*, delusion*, psychomotor hyperactivity*, drug abuse*
Nervous system disorders	Sedation, somnolence, ataxia, memory impairment, dysarthria, dizziness, headache	Balance disorder, coordination disorder, concentration difficulties, hypersomnia, lethargy, tremor	Amnesia, intoxication		Autonomic nervous system imbalance*, reduced alertness, speech difficulties, dystonia*
Eye disorders		Blurred vision			
Gastrointestinal disorders	Constipation, dry mouth	Nausea, vomiting			Gastrointestinal disorder*, dysphagia
Hepatobiliary disorders					Hepatitis*, jaundice*, abnormal liver function*
Skin and subcutaneous tissue disorders		Dermatitis*			Angioedema*, photosensitive reaction*
Musculoskeletal and connective tissue disorders			Musculoskeletal weakness		
Renal and urinary disorders			Incontinence*		Urinary retention*
Reproductive system and breast disorders		Sexual dysfunction*	Menstrual irregularities*		
General disorders and administration site conditions	Fatigue, irritability				Peripheral oedema*
Investigations		Weight decreased, weight increased			Increased intra-ocular pressure*

*undesirable effects registered in postmarketing period

Amnesia:

Anterograde amnesia can occur even at therapeutic doses and the risk increases at higher doses.

Amnesia may be accompanied by inappropriate behaviour (see also section 4.4.).

Depression:

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

Psychiatric and “paradoxical” reactions

Reactions like restlessness, agitation, irritability, insensibility, delusion, rages, nightmares, hallucinations, psychoses, inappropriate behaviour and other behavioural effects are known to occur during benzodiazepine treatment, especially in elderly patients.

Dependence:

Use (event 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).

In many of the adverse events reported, patients had received other CNS medications concurrently with alprazolam and / or with underlying mental illness. Patients with borderline personality disorder, a history of violence or aggression or alcohol or drug abuse may be at risk of these side effects. Upon discontinuation of alprazolam treatment, cases of irritability, hostility and intrusive thoughts have been reported in patients suffering from post-traumatic stress disorder.

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 **the national reporting system listed in Appendix V.**

4.9 Overdose

General information about toxicity

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 born in mind that multiple agents may have been taken. Treatment should be adjusted accordingly.

Symptoms

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.

Therapy

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. A long time forced diuresis or haemodialysis is of no value.

Flumazenil can be useful as an antidote.

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).

Alprazolam is an anxiolytic medicinal product. Like other benzodiazepines, in addition to its anxiolytic properties, alprazolam has sedative, hypnotic, muscle-weakening and anticonvulsive properties.

5.2 Pharmacokinetic properties

Absorption

After oral administration, bioavailability is 80 % or more. Maximum plasma levels are reached 5 - 11 hours after oral administration of Alprazolam Krka prolonged-release tablets.

Distribution

Following a single administration, the plasma levels are directly proportional to the administered dose. In vitro, 70 % of alprazolam is bound to serum proteins.

Biotransformation

The most important metabolites of alprazolam present in urine are alpha-hydroxy-alprazolam and benzophenone derivative. The major metabolites in plasma are alpha-hydroxy-alprazolam and 4-hydroxy-alprazolam. Alprazolam is mainly metabolised by CYP3A4.

The benzodiazepine derivative is virtually inactive. The biological activity of alpha-hydroxy-alprazolam is comparable with that of alprazolam, while 4-hydroxy-alprazolam is about 10 x less active.

The plasma levels of these metabolites are low. Their half-lives appear to be the same order of magnitude as that of alprazolam. The metabolites therefore make only a limited contribution to the biological activity of alprazolam.

Elimination

The average half-life of alprazolam is between 12 and 15 hours. Alprazolam and its metabolites are mainly excreted via urine.

Elderly

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

Hepatic impairment

The mean elimination half-life is increased with impaired liver function (approximately 19 h)

5.3 Preclinical safety data

In rats administered alprazolam for 24 months a tendency for dose-related increase in number of cataracts and in corneal vascularisation was evident in females and males, respectively.

In a repeated dose toxicity study (12 months) with high dosages p.o. convulsions were observed in dogs, some of which were lethal. Relevance for men is not clear.

There was no evidence of carcinogenic potential as revealed by carcinogenicity studies conducted in rats at doses of up to 30 mg/kg/day (150 times the maximum daily human dose of 10 mg/day) and mice at doses of up to 10 mg/kg/day (50 times the maximum daily human dose).

Alprazolam administered to rats and rabbits at high doses caused an increase in birth defects and foetal death.

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

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

Prenatal exposure of mice and rats to benzodiazepines, including alprazolam, has been associated with behavioural changes in the offspring. The possible significance of these changes to the human situation is unclear.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Each prolonged-release tablet 0.5 mg contains:

Lactose monohydrate

Hypromellose

Magnesium stearate

Indigo carmine (E 132)

Quinoline yellow (E 104)

Each prolonged-release tablet 1 mg contains:

Lactose monohydrate

Hypromellose

Magnesium stearate

Each prolonged-release tablet 2 mg contains:

Lactose monohydrate

Hypromellose

Magnesium stearate

Indigo carmine (E 132)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Blister (Alu/Alu): 20, 30, 60, 100 and 100x1 prolonged-release tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

<To be completed nationally>

8. MARKETING AUTHORISATION NUMBER(S)

<To be completed nationally>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: <To be completed nationally>

Date of latest renewal: <To be completed nationally>

10. DATE OF REVISION OF THE TEXT

[To be completed nationally]

2022-06-17

Detailed information on this medicine is available on the website of { name of Member State Agency
(link) }

