# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. NAME OF THE MEDICINAL PRODUCT

Alprazolam Stada 0.5 mg tablets
Alprazolam Stada 1 mg tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Alprazolam Stada 0.5 mg tablet: 1 tablet contains 0.5 mg alprazolam
Excipient with known effect: Each tablet contains 92.15 mg lactose, 0.12 mg sodium benzoate.

Alprazolam Stada 1 mg tablet: 1 tablet contains 1 mg alprazolam
Excipient with known effect: Each tablet contains 91.71 mg lactose, 0.12 mg sodium benzoate.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Tablet

Alprazolam Stada 0.5 mg: pink, oblong, scored tablets
Alprazolam Stada 1 mg: light blue, oblong, scored tablets

The tablet can be divided into equal doses.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

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

### 4.2 Posology and method of administration

The treatment should be started, followed up and completed by the same physician, if possible.

Dosage

*Anxiety*
Drug treatment of anxiety should always be an adjuvant. Initial dosage: 0.25 to 0.5 mg three times daily. The dose should be individualized. As a maintenance dose, 0.5 to 3 mg daily is given in divided doses. In elderly and sensitive patients, 0.25 mg is initially given 2-3 times daily (see section 4.4). The dosage can be gradually increased as needed.

In the elderly, states of confusion can occur with high doses.

*Duration of the treatment*
Alprazolam Stada should be used in the lowest possible effective dose, for the shortest possible treatment time and for a maximum of 2-4 weeks. The need for continued treatment

must be reconsidered frequently. Long-term treatment is not recommended. The risk of addiction may increase with dose and duration of treatment (see section 4.4).

The duration of the treatment should be agreed with the patient, and the patient should be made aware of the potential initial undesirable effects.

*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.

*Discontinuation of treatment*
The dose should be reduced gradually in order to avoid the discontinuation phenomenon.
Abrupt cessation of benzodiazepines can lead to paraesthesia, changes in perception and depersonalisation during one or a couple of weeks. Withdrawal symptoms in the form of mild dysphoria and insomnia have also been reported, as well as stomach and muscle cramps, vomiting, sweating and tremor. In some cases, convulsions have been reported (see section 4.8).

Method of administration
For oral use.
The tablets should be taken together with some fluid and may be taken with or without food.

**4.3 Contraindications**

- Hypersensitivity to the active substance, other benzodiazepines or to any of the excipients listed in section 6.1
- Sleep apnoea syndrome
- Myasthenia gravis
- Severe respiratory insufficiency
- Severe hepatic insufficiency
- Acute intoxication brought about by alcohol or other CNS active agents

**4.4 Special warnings and precautions for use**

Duration of treatment
The duration of the treatment should be as short as possible and no longer than 2-4 weeks (see section 4.2). Any extension of treatment beyond these periods should not take place without re-evaluation of the situation.

It may be useful to inform the patient when treatment is started that it will be of limited duration and to explain precisely how the dosage will be progressively decreased. There is evidence that withdrawal symptoms may occur within the dose range of short-acting benzodiazepines, particularly at high doses. When long-acting benzodiazepines are used, it is important to inform the patient not to switch to a short-acting benzodiazepine, as withdrawal symptoms may then develop.

Risk from concomitant use of opioids
Concomitant use of alprazolam and opioids may result in sedation, respiratory depression, coma and death. 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. Because of these risks, concomitant prescribing of sedative medicines such as benzodiazepines with opioids should be reserved for patients for whom alternative treatment options are not possible. The patients should be followed closely for signs and symptoms of respiratory depression and sedation (see section 4.5).

Tolerance

The sedative effect may diminish after several weeks of repeated use.

Dependence
Use of benzodiazepines may lead to the development of physical and psychic dependence. The risk of dependence increases with dose and duration of treatment and with the combination of different benzodiazepines. There is also an increased risk in patients with a history of alcohol or drug abuse. Addiction may also occur at therapeutic doses and / or in patients without individual risk factors.

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, difficulty sleeping, 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. When discontinuing alprazolam treatment, the dose should be reduced gradually.

Abuse
Drug abuse is a known risk for alprazolam and other benzodiazepines, and patients should be closely monitored for signs and symptoms during treatment with alprazolam. Alprazolam may be subject to diversion. There have been reports of overdose-related deaths when alprazolam was used in combination with opioids, other benzodiazepines, alcohol or with other central nervous system (CNS) depressants. These risks should be considered when prescribing or dispensing alprazolam.

To reduce these risks the lowest possible effective dose and duration of treatment 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 be used with extreme caution in patients with a history of alcohol, drug or medicinal product abuse (see section 4.5).

*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 with alprazolam. It may be accompanied by other reactions including mood changes, anxiety or sleep disturbances and restlessness. Since the risk of withdrawal phenomena/rebound phenomena is greater after abrupt discontinuation of treatment, it is recommended that the dosage is decreased gradually (tapering off) (see section 4.2).

In order to avoid as much as possible, the feeling of discomfort for the patient, it is important to inform the patient about the possibility of rebound phenomena at the end of the treatment. With abrupt discontinuation of benzodiazepines, paraesthesias, perceptual changes and feelings of unreality may occur for one or more weeks. In some cases, seizures have been reported.

Amnesia
Like other benzodiazepines, alprazolam may induce anterograde amnesia. The condition occurs most often several hours after ingesting the product.

*Psychiatric and “paradoxical” reactions*
During treatment with benzodiazepines, psychiatric and "paradoxical" reactions may occur. If reactions like restlessness, agitation, irritability, aggressiveness, nightmares, aggravated insomnia, hallucinations, psychoses, inappropriate behaviour, delirium and other adverse behavioural effects occur, use of the medicinal product should be discontinued. These reactions are more

likely to occur in children and elderly. Extreme caution should be used in prescribing benzodiazepines in patients with borderline or antisocial personality disorders.

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

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

Benzodiazepines are not indicated for the treatment of patients with severe liver disorders, since benzodiazepines can promote the development of encephalopathy.

Psychoses
Benzodiazepines should not be used for the primary treatment of psychoses.

Depression and suicidal ideation
Benzodiazepines and benzodiazepine-like agents should not be used 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.

Elderly 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 be followed in elderly and/or debilitated patients to preclude the development of ataxia or oversedation (see section 4.2).

Dextropropoxyphene
Concomitant treatment with dextropropoxyphene should be avoided due to the risk of respiratory depression.

Excipients
Lactose: Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.
Sodium: This medicinal product 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**

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 Pharmaceuticals*
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 co-administered with other CNS depressants or psychotropic medicinal products, such as antipsychotics (neuroleptics), hypnotics, anxiolytics/sedatives, antidepressant agents, narcotic analgesics (e.g. opioids), antiepileptics, anaesthetics and sedative antihistamines (see section 4.4).

However, when taking the tablets 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 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).

Particular caution should be exercised with drugs 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 drugs that inhibit the hepatic enzyme CYP3A4 by increasing the plasma levels of alprazolam. Alprazolam should therefore be used with caution in patients taking these medicines and a reduction of dosage may be necessary when such pharmaceuticals 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 dosage 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 alprazolam, 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.

*The 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 (see section 4.4).

<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>
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 2/1,000 compared with an expected rate for such defects of approximately 1/1,000 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 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 occurrence of withdrawal symptoms after birth depends on the half-life of the substance.

Use during pregnancy is only allowed on strict indication if absolutely necessary.

Physicians prescribing alprazolam to women of childbearing age should encourage their patients to contact their physician for possible discontinuation of treatment if the patient believes she is pregnant or planning to become pregnant. Based on the pharmacological mechanism of action, effects (hypothermia, hypotension and moderate respiratory depression) on the newborn infant are to be expected. Consequently, use during labour is permitted only if absolutely necessary. In addition, the children of mothers who have regularly used benzodiazepines during late pregnancy may experience withdrawal symptoms after birth.

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 human milk in small amounts. Therefore, alprazolam is not recommended during breast-feeding.

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

**4.7 Effects on ability to drive and use machines**

Alprazolam has major influence on the ability to drive and use machines.
Alprazolam may cause sedation, amnesia, impaired concentration and impaired muscular function which may adversely affect the ability to drive or use machines.

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).

If insufficient sleep duration occurs, the likelihood of impaired alertness may be increased.

**4.8 Undesirable effects**

Adverse reactions have been ranked under headings of frequency using the following convention:
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).

| System Organ Class | Very common (≥ 1/10) | Common (≥ 1/100 to < 1/10) | Uncommon (≥ 1/1,000 to < 1/100) | Not known (cannot be estimated from the available data) |
|---|---|---|---|---|
| ***Endocrine disorders*** | | | | Hyperprolactinaemia*. |
| ***Metabolism and nutrition disorders*** | | Decreased appetite, anorexia, | | |

| System Organ Class | Very common (≥ 1/10) | Common (≥ 1/100 to < 1/10) | Uncommon (≥ 1/1,000 to < 1/100) | Not known (cannot be estimated from the available data) |
|---|---|---|---|---|
| | | increased appetite. | | |
| ***Psychiatric disorders*** | Depression. | Confusional state,<br>disorientation,<br>libido decreased,<br>anxiety,<br>insomnia,<br>nervousness,<br>libido increased*. | Mania* (see section 4.4),<br>hallucination*,<br>anger*,<br>agitation*,<br>drug dependence. | Hypomania*,<br>aggression*,<br>hostility*,<br>delusions*,<br>psychomotor hyperactivity*,<br>drug abuse*. |
| ***Nervous system disorders*** | Sedation,<br>somnolence,<br>ataxia,<br>memory impairment,<br>dysarthria,<br>dizziness,<br>headache. | Balance disorder,<br>coordination abnormal,<br>hypersomnia,<br>lethargy,<br>tremor,<br>disturbance in attention. | Amnesia,<br>feeling of intoxication. | Autonomic nervous system imbalance*,<br>dystonia*,<br>impaired reactivity,<br>speech difficulties,<br>hypotonia. |
| ***Eye disorders*** | | Vision blurred. | | |
| ***Gastrointestinal disorders*** | Constipation,<br>dry mouth. | Nausea,<br>vomiting. | | Gastrointestinal disorder*,<br>dysphagia. |
| ***Hepatobiliary disorders*** | | | | Hepatitis*,<br>hepatic function abnormal*,<br>jaundice*. |
| ***Skin and subcutaneous tissue disorders*** | | Dermatitis*. | | Angioedema*,<br>photosensitivity reaction*. |
| ***Musculoskeletal and connective tissue disorders*** | | | Muscular weakness. | |
| ***Renal and urinary disorders*** | | | Incontinence*. | Urinary retention*. |
| ***Reproductive system and breast disorders*** | | Sexual dysfunction*. | Menstruation irregular*. | |
| ***General disorders and administration site conditions*** | Fatigue,<br>irritability. | | Drug withdrawal syndrome*. | Oedema peripheral*. |
| ***Investigations*** | | Weight increased,<br>weight decreased. | | Intraocular pressure increased*. |

* ADR identified post-marketing

*Depression*
Previously unnoticed depression may become apparent during benzodiazepine use (see also section 4.4).

*Psychiatric and "paradoxical" reactions*

Reactions such as restlessness, agitation, irritability, aggression, delusions, fits of rage, nightmares, hallucinations, psychoses, inappropriate behaviour and other behavioural disorders can occur; they are more likely in 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. Psychic dependence may occur. Abuse of benzodiazepines has been reported (see section 4.4).

*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).

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**

*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.

Likewise dizziness, dysarthria and unconsciousness, but also some paradox reactions as agitation, aggressiveness, and hallucinations have been reported.

Agitation and hallucinosis are more common with alprazolam than for other benzodiazepines. Mydriasis and miosis may occur.

Convulsions, arrhythmia and AV-block may also occur as well as tachycardia, hypothermia, nausea and vomiting.

*Toxicity:*
A dose of 25 – 50 mg in combination with alcohol (2 per mille in blood), given to adults, showed lethal intoxication. After a dose of 0.3 mg/kg was given to an eight years old child, the intoxication was moderate to serious. A dose of 10 mg to a thirteen year old showed a moderate intoxication. A serious intoxication was seen after administering 15 mg (in combination with alcohol) in an adult, whereas 20-40 mg only showed moderate intoxication. Overdose in combination with other CNS depressants and substances (including alcohol) result in mortality risk. 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.

*Treatment:*
Patients with slight signs of intoxication should sleep it off under medical observation.

In severe cases, gastric lavage should be performed while ensuring an unobstructed airway by intubation if the patient is unconscious. If the patient is conscious, vomiting should be induced. If there is no advantage in emptying the stomach, the use of activated charcoal is generally indicated to reduce absorption. Special attention should be paid to respiratory and cardiovascular functions in intensive care.

Treatment with benzodiazepine antagonists (i.e. flumazenil) should be considered in severe

cases, but due to the longer effect of benzodiazepines, a continuous infusion is recommended (see the SmPC for flumazenil products for dosage instructions). Flumazenil can increase the risk of convulsions. Forced diuresis or haemodialysis is of no value.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anxiolytics, benzodiazepine derivatives.
ATC-code: N05BA12

Alprazolam is a benzodiazepine with a triazolo-ring added to the structure. Alprazolam binds to the benzodiazepine-receptors and thereby gives potentiation of the GABA-system. The medicinal product has a rapid onset on the common anxiety symptoms such as agitation, restlessness, and tension. Drowsiness is not unusual at therapeutic doses initially, but usually passes with continued treatment. In anxiolytic doses, alprazolam gives no or slight muscular weakness.

Alprazolam gives a dose-dependent reduction of the REM sleep and a prolongation of REM latency.

There is a risk for development of tolerance.

### 5.2 Pharmacokinetic properties

The bioavailability of alprazolam is approx. 90 %. Food ingestion at the same time delays the absorption of alprazolam, but has not influence on the absorbed quantity. The time taken for peak concentration in plasma after ingestion is 1-2 hours and the plasma concentration is proportional to the ingested dose. The protein-binding level for alprazolam is approx. 70 % whereas the clearance is approx.

1 ml/min/kg body weight and the volume of distribution approx. 1 litre/kg. Alprazolam gives no or only slight enzyme induction.

Alprazolam undergoes considerable metabolism in the liver, mainly by hydroxylation to alpha-hydroxy-alprazolam and 4-hydroxyalprazolam. These metabolites are glucuronised before elimination in the urine. Several studies indicate that the enzyme CYP3A4 catalyses the metabolism of alprazolam. The elimination half-life for alprazolam is approx. 12 hours. The main metabolites are biologically active. Their half-lives are comparable with alprazolam and they occur in low concentrations so that they hardly contribute to the pharmacological effect.

In elderly men there can be a prolonged elimination half-life (approx. 19 h).

The half-life is increased with impaired liver function.

### 5.3 Preclinical safety data

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.

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.

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.

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 man is not clear.

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

Prenatal exposure to benzodiazepines, including alprazolam, has in animal studies been associated with cleft palate and 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

Docusate sodium
Sodium benzoate (E211)
Starch, pregelatinised
Cellulose, microcrystalline
Lactose monohydrate
Magnesium stearate
Silica, colloidal anhydrous.

Alprazolam Stada 0.5 mg tablet: additionally contains erythrosine aluminium lake* (E127) (*consists of erythrosine and aluminium hydroxide).
Alprazolam Stada 1 mg tablet: additionally contains indigo carmine aluminium lake (E132) (*consists of indigotin and aluminium hydroxide).

### 6.2 Incompatibilities

Not applicable

### 6.3 Shelf life

Alprazolam Stada 0,5 mg tablets – 2 years
Alprazolam Stada 1 mg tablets - 3 years

### 6.4 Special precautions for storage

Do not store above 30 °C.

### 6.5 Nature and contents of container

Aluminium/PVC blister.
/0,5 mg:
Packs containing 7, 10, 14, 20, 21, 28, 30, 40, 50, 60, 70, 80, 84, 90, 100, 200, 250, 500 and 1000 tablets.
1 mg:
Packs containing 10, 14, 20, 21, 28, 30, 40, 50, 60, 70, 80, 84, 90, 100, 200, 250, 500 and

1000 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: 15 December 2000
Date of last renewal: 15 December 2010

## 10. DATE OF REVISION OF THE TEXT

2024-03-18