SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Alprazolam-ratiopharm 0,5 mg, tabletten

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 0.5 mg alprazolam.

Excipient with known effect:
Each tablet contains 97.0 mg lactose monohydrate.
Each tablet contains 0.12 mg sodium benzoate.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Tablets

Pink, oblong scored tablets, length approx. 10 mm.
The tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Symptomatic treatment of anxiety.
Only use alprazolam if the disorder is severe or is causing invalidity, or if the patient is experiencing inordinate suffering as a result of the disorder.

4.2 Posology and method of administration

The treatment period should be as short as possible. The necessity of treatment with alprazolam and the appropriate dosage should be reassessed periodically for each patient. The total length of treatment should not exceed 8-12 weeks, including the period of gradual dosage reduction. Prolonged treatment may be necessary in certain circumstances, but this should not be done until the patient's condition has been reassessed.
The optimal dose of alprazolam should be individually determined in accordance with the severity of the symptoms and the patient's response.
In most patients, the symptoms of anxiety can generally be effectively treated with a dose of between 0.5 mg per day and 3 mg per day, divided up into separately administered measures. Under no circumstances should the maximum dose of 3 mg per day be exceeded. Patients who are chronic alcoholics and those who have never previously taken psychotropic medications generally require lower doses than patients who have already been treated with tranquilisers, antidepressants or hypnotic drugs. In order to avoid ataxia and over-sedation it is recommended that the lowest effective dose be used.

If side effects occur, the dose should be reduced.
If required the evening dose should be increased before the daytime dose.

Adults
Initial dosage: 0.25 mg to 0.5 mg, three times a day.
If necessary, increase in intervals of 3-4 days to:
Maintenance dosage: 0.5 mg to maximal 3 mg per day in divided doses.

Elderly, weakened patients, or patients with kidney or liver function disorders
There is reduced clearance of the drug and, as with other benzodiazepines, an increased sensitivity to the drug in the elderly patients.
Initial dosage: 0.25 mg, twice or three times a day.
If necessary, and if the disease permits increase in intervals of 3-4 days to:
Maintenance dosage: maximal 1.5 mg per day in divided doses.
For physically frail elderly patients, or weakend patients with kidney or liver function disorders a reduced dose (0.75 mg per day) is recommended.

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
Tablets for oral use.
The tablets should be taken with a sufficient amount of liquid.

Discontinuation of treatment
The dose should be gradually reduced. It is recommended that the daily dose of alprazolam be reduced at a rate not exceeding 0.5 mg per three days. In some patients, it may indeed be necessary to reduce the dose even more gradually.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

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.

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

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).

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

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

Benzodiazepines are not effective for the primary treatment of psychoses.
In a few cases manic episodes were reported in patients with latent depression.

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

In patients presenting with major depression or anxiety associated with 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.

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. Cases of abuse have also been reported.

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 and 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 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.

Duration of treatment
The duration of the treatment should be as short as possible (see section 4.2), but should not exceed 8 to 12 weeks, including tapering off process. Extension 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.
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. There are indications that, in the case of benzodiazepines with short duration of action, withdrawal phenomena can become manifest within the dosage interval, especially when the dosage is high. When benzodiazepines with long duration of action are being used, it is important to warn against changing in benzodiazepines with short duration of action, as withdrawal symptoms may develop.

Amnesia
Benzodiazepines may induce anterograde amnesia. The condition occurs most often several hours after ingesting the product (see section 4.8).

Psychiatric and paradoxical reactions
Reactions like restlessness, agitation, irritability, aggressiveness, delusion, rages, nightmares, aggravated insomnia, hallucinations, psychoses, inappropriate behaviour, oneiroid delirium 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.

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 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).

Excipients
Lactose
The tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Sodium benzoate
This medicine contains 0,12 mg sodium benzoate in each tablet. Sodium benzoate may increase jaundice (yellowing of the skin and eyes) in newborn babies (up to 4 weeks old).

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

4.5 Interaction with other medicinal products and other forms of interaction

Benzodiazepines produce an additive effect when co-administered with alcohol or other CNS depressants.

Concomitant intake with alcohol is not recommended.

Special care should be made with drugs depressing respiratory function such as opioids (analgesics, antitussives, substitutive treatments), notably in the elderly people.

Opioids: The concomitant use of sedative medicines such as benzodiazepines 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).

Alprazolam should be used with caution when combined with other CNS depressants. Enhancement of the central depressive effect may occur in case of concomitant use with antipsychotics (neuroleptics), hypnotics, anxiolytics/sedatives, some antidepressant agents, opioids, anticonvulsants, anasthetics and sedative H1-antihistamines. However, when taking the tablets in combination with opioids, potentiation of euphoria can occur which may lead to increased psychic dependence.

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

The co-administration of alprazolam with strong CYP3A4 inhibitors like azole antifungals (ketoconazole, itraconazole, posaconazole, voriconazole), protease inhibitors, nefazodon, fluvoxamine, fluoxetine, dextropropoxyphene, cimetidine, oral contraceptives, sertralin, diltiazem or some macrolides (erythromycin, clarithromycin, telithromycin and troleandomycin) should be made with caution and a substantial dose reduction considered.

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.

Carbamazepine: In view of pharmacokinetic interactions a reduced effect of alprazolam might occur in patients taking carbamazepine (CYP3A4 inducer). The plasma alprazolam concentrations in the elimination phase are dependent on certain hepatic enzymes (in particular CYP3A4) for the metabolism and are reduced by pharmaceuticals that induce these enzymes.

Muscle relaxants: one should be prepared for an increase of the muscle relaxing effect when alprazolam is used during therapy with a muscle relaxant, especially during the beginning of treatment with alprazolam.

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

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.

Warfarin: it could not be determined whether there was any effect on prothrombin times and warfarin plasma levels.

St. John’s wort: Long-term use of St John’s wort may diminish clinical efficacy of alprazolam. When St John’s wort therapy is suddenly stopped, overdose symptoms of alprazolam may occur.

No interaction was found with propranolol and disulfiram. Substances, which may induce CYP3A4 (e.g. rifampicin, phenytoin), can reduce the effect of Alprazolam.

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 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.

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

4.7 Effects on ability to drive and use machines

Sedation, amnesia, impaired concentration and impaired muscular function may adversely affect the ability to drive 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 also 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).

Symptoms marked by an asterisk (*) occur particularly at the start of treatment or higher doses and usually disappear following continued use.

Endocrine disorders
Uncommon: hyperprolactinaemia

Metabolism and nutrition disorders
Common: decreased appetite
Not known: stimulation of appetite

Psychiatric disorders
Common: confusion*, depression
Uncommon: hallucinations, rage, aggressive behaviour, hostile behaviour, anxiety, agitation, changes in libido, insomnia, thinking abnormal, nervousness; stimulation

Nervous system disorders
Very common: sedation, drowsiness*
Common: ataxia*, coordination disorders, memory impairment, slurred speech, concentration difficulties, dizziness*, headache*, light-headedness
Uncommon: amnesia, dystonia*, tremor
Not known: autonomic manifestations, numbness of feeling*, reduced alertness*

Eye disorders
Common: blurred vision*
Not known: double vision*

Cardiac disorders
Not known: tachycardia

Vascular disorders
Not known: hypotension

Respiratory, thoracic and mediastinal disorders
Not known: nasal congestion

Gastrointestinal disorders
Common: constipation, nausea
Uncommon: vomiting
Not known: diarrhoea, dry mouth, increased salivation, dysphagia

Hepatobiliary disorders
Uncommon: abnormal liver function, jaundice
Not known: hepatitis

Skin and subcutaneous tissue disorders
Uncommon: dermatitis
Not known: angioedema, skin reactions

Musculoskeletal and connective tissue disorders
Uncommon: musculoskeletal weakness*

Renal and urinary disorders
Uncommon: incontinence, urinary retention

Reproductive system and breast disorders
Uncommon: sexual dysfunction, menstrual irregularities

General disorders and administration site conditions
Common: asthenia, irritability
Not known: peripheral oedema, fatigue*

Investigations
Uncommon: change in weight, increased intraocular pressure

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 such as restlessness, agitation, irritability, aggressiveness, delusions, rages, nightmares, hallucinations, psychoses, inappropriate behaviour and other adverse behavioural effects. Such paradoxical reactions are more likely to occur in elderly patients. In case of paradoxical reactions treatment should be stopped.

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).

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.

Forced diuresis or haemodialysis is of no value.

Flumazenil may be useful as an antidote.

For individuals in coma, treatment is largely symptomatic. Measures should be taken to avoid possible complications such as asphyxia due to patients swallowing their tongue or aspiration of the stomach contents. The intravenous administration of liquids can be useful in preventing dehydration.
Especially when combined with other sedatives, supporting the vital functions, in particular respiration, is important.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Anxiolytics, Benzodiazepine derivatives
ATC code: N05BA12
Alprazolam is an effective anxiolytic medication. Like other benzodiazepines, in addition to its anxiolytic properties, alprazolam has sedative, hypnotic, muscle relaxant and anticonvulsive properties.

5.2 Pharmacokinetic properties

Absorption
Alprazolam is rapidly absorbed following oral administration. After oral administration, bioavailability is 80% or more. Maximum plasma levels are reached one to two hours after oral administration.

Distribution
Following a single administration, the plasma levels are directly proportional to the administered dose. The maximum plasma levels observed following a dose of 0.5 mg to 3 mg are 8 to 37 ng/ml. Following several administrations of 1.5 mg to 10 mg/day, the average steady-state level was 18.3 to 100 ng/ml.
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 a benzophenone derivative. The major metabolites in plasma are alpha-hydroxy-alprazolam and 4-hydroxy-alprazolam.

The benzophenone 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 of 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. In elderly patients the elimination half-life is significantly increased. Alprazolam and its metabolites are mainly excreted via the urine.

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 and mice.
Alprazolam has no adverse effects on fertility in either male or female rats but, when administered to pregnant animals at relatively high doses, may cause some delay in foetal development.
Prenatal exposure of mice and rats to benzodiazepines, including alprazolam, has been associated with behavioural changes in later life. The possible significance of these changes to the human situation is unclear.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Docusate sodium
Sodium benzoate
Pregelatinized starch
Microcrystalline cellulose
Lactose monohydrate
Magnesium stearate
Silica, colloidal anhydrous
Erythrosine (E127)

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

PVC/Aluminium blisters

10, 10x1, 20, 20x1, 30, 40x1, 50, 50x1, 60, 60x1, 100, 100x1 tablets
Not all pack sizes may be marketed.

6.6 Special precautions for disposal <and other handling>

No special requirements.

7. MARKETING AUTHORISATION HOLDER

ratiopharm GmbH
Graf-Arco-Str. 3
89079 Ulm
Duitsland

8. MARKETING AUTHORISATION NUMBER(S)

RVG 26305

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Datum van eerste verlening van de vergunning: 12 februari 2001
Datum van laatste verlenging: 30 juli 2007

10. DATE OF REVISION OF THE TEXT

Laatste gedeeltelijke wijziging betreft de rubrieken 4.4 en 4.5: 18 oktober 2018.