SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Diazepam STADA 2 mg tabletten
Diazepam STADA 5 mg tabletten
Diazepam STADA 10 mg tabletten

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2 mg diazepam.
Each tablet contains 5 mg diazepam.
Each tablet contains 10 mg diazepam.

Excipient(s) with known effect
Each tablet contains 159.70 mg lactose.
Each tablet contains 156.85 mg lactose.
Each tablet contains 152.10 mg lactose.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

Tablet is white to almost white round, flat, 8.0 mm in diameter, with “2” on one side and break line on the other side.
Tablet is white to almost white round, flat, 8.0 mm in diameter, with “5” on one side and break line on the other side.
Tablet is white to almost white round, flat, 8.0 mm in diameter, with “10” on one side and break line on the other side.

The tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults
- symptomatic treatment of anxiety
  Benzodiazepines are only indicated when the disorder is severe, disabling or subjecting the individual to extreme distress.
- symptomatic treatment of Alcohol Withdrawal syndrome

Adults and children over 6 years old
- symptomatic treatment of skeletal muscle spasm (inflammation of muscles or joints, trauma), including spasticity caused by upper motor neuron disorders (such as cerebral palsy, paraplegia as well as athetosis and stiff-person syndrome)

4.2 Posology and method of administration

Posology

The dosage should be adapted to each particular condition. Treatment should begin at the lowest effective dose and then gradually increased until optimal effect is reached.

Adults

Anxiety
- Usual dose: 2 mg to 5 mg diazepam two to three times daily.
- Maximum dose: In severe cases the dose may be incrementally increased up to 30 mg diazepam daily in 2 to 4 divided doses. Adjusted on an individual basis.

- The lowest dose which can control symptoms should be used.
- Treatment should not be continued at the full dose beyond 4 weeks.
- Long-term chronic use is not recommended.
- Treatment should always be tapered off gradually. Patients who have taken benzodiazepines for a prolonged time may require a longer period during which doses are reduced.

Control of muscle spasm
- Muscle spasm: Up to 15 mg diazepam daily in 2 to 4 divided doses.
- Management of upper motor neuron spasticity (such as cerebral palsy) in selected cases: If necessary, the dose may be titrated up to a maximum of 60 mg diazepam daily in 3 to 4 divided doses.

Alcohol withdrawal symptoms
- 5 mg to 20 mg diazepam repeated once within 2 to 4 hours if necessary, or 10 mg diazepam three to four times on the first day. After the first day, the dose is usually lowered to 5 mg diazepam three to four times daily as needed.
- In severe cases, a loading-dose method may be used with initial administration of 10 mg diazepam every hour until patient is lightly sedated and asymptomatic, usually reaching up to 50–80 mg. Treatment should take place in a hospital setting and the patient should be appropriately monitored.

Special populations:
Individuals in the following patient groups should be checked regularly at the start of treatment. Monitoring during treatment is essential in order to minimise the dosage and/or the frequency of administration to prevent overdose due to accumulation, such as in children and adolescents, elderly patients and patients with impaired liver function.

Paediatric population

Children above 6 years of age and adolescents
The administration in children above 6 years of age and adolescents should only be for compelling medical reasons. The half-life may be extended in children. The dose level should be reduced and individual adjustments have to be performed.
- Usual dose: 0.1–0.3 mg/kg body weight per day in two to four divided doses. Treatment should be initiated with the lowest possible dose and increased gradually as necessary and tolerated.

Children below 6 years of age
<Product name> is not recommended for children below 6 years of age due to possible swallowing difficulties. More suitable pharmaceutical forms may be available for younger children.
However, should an administration in children under 6 years of age be considered, it should only be done after decision and under strict medical supervision of a specialist (paediatrician, neurologist, psychiatrist, anaesthesiologist, and intensivist) that will determine the dose.

Elderly
Treatment should be initiated with the lowest possible dose (2 to 2.5 mg, once or twice a day) and increased gradually as necessary and tolerated.
These patients should be checked regularly at the start of treatment in order to minimise the dosage and/or the frequency of administration to prevent overdose due to accumulation.

Renal impairment
Dose adjustment is usually not necessary. However, caution should be exercised when treating renal impaired patients with diazepam.
Benzodiazepines with active metabolites such as diazepam should be avoided in patients with end-stage renal disease.

Hepatic impairment
These patients should receive a reduced dose and be checked regularly at the start of treatment in order to adjust the dose and the frequency of administration to prevent overdose due to accumulation.
Patients with severe hepatic impairment must not be treated with diazepam due to risk of hepatic encephalopathy (see section 4.3).

Overweight patients
Various studies have shown that the kinetics are changed in overweight patients, compared to those of a normal weight. Overweight patients require significantly longer treatment times than patients of normal weight before the maximum effect of the drug occurs in long-term treatment. Similarly, the therapeutic effect and undesirable effects, including withdrawal symptoms, can occur for longer periods following the discontinuation of more long-term treatment of overweight patients (see section 5.2).

Duration of treatment
The duration of treatment of anxiety should be as short as possible (see section 4.4). The patient should be regularly re-evaluated in order to assess the need for continued treatment, especially in case the patient is symptom free. In general, treatment must not last longer than 8 to 12 weeks, including tapering off process.
In certain cases, extension beyond the maximum treatment period may be necessary; if so, it should not take place without re-evaluation of the patient‘s status with special expertise.
The effectiveness of long-term treatment (> 6 months) has not been assessed by systematic clinical studies.

Method of administration
Oral use.
This medicine is to be usually taken in the afternoon or evening.

Tapering off
Treatment should always be tapered off gradually. Patients who have taken benzodiazepines for a prolonged time may require a longer period during which doses are reduced.

4.3 Contraindications

Diazepam is contra-indicated for patients with
- hypersensitivity to diazepam or to any of the excipients listed in section 6.1
- myasthenia gravis
- severe respiratory insufficiency
- sleep apnoea syndrome
- severe hepatic insufficiency (risk of encephalopathy)

4.4 Special warnings and precautions for use

Benzodiazepines should not be used alone to treat depression or anxiety associated with depression (suicide may be precipitated in such patients).

Amnesia
Anterograde amnesia may occur (see also section 4.8) even if benzodiazepines are used within the normal dose range, though this is seen in particular at high dose levels. Amnestic effects may be associated with inappropriate behaviour.

Duration of treatment
The duration of treatment of anxiety should be as short as possible (see section 4.2) and must not last any longer than 8-12 weeks, including the 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 minimising anxiety over such symptoms should they occur while the medicinal product is being discontinued. When benzodiazepines with a long duration of action are being used it is important to warn against changing to a benzodiazepine with a short duration of action, as withdrawal symptoms may develop.

Psychiatric and 'paradoxical' reactions
Paradoxical reactions (such as restlessness, agitation, irritability, aggressiveness, delusion, rages, nightmares, hallucinations, psychoses, inappropriate behaviour and other adverse behavioural effects) have been reported from the use of benzodiazepines. Such reactions are possibly seen more often in the treatment of children and elderly patients and should result in the discontinuation of treatment.

Concomitant use of alcohol/CNS depressants
The concomitant use of diazepam with alcohol and/or CNS depressants should be avoided. Such concomitant use has the potential to increase the clinical effects of diazepam possibly including severe sedation, clinically relevant respiratory and/or cardio-vascular depression (see section 4.5 and 4.9).

Medical history of alcohol or drug abuse
Diazepam should be used with extreme caution in patients with a history of alcohol or drug abuse.
Diazepam should be avoided in patients with dependence on CNS depressants including alcohol, except for the treatment of acute withdrawal reactions.
Monitoring during treatment is essential in order to minimise the dosage and/or the frequency of administration to prevent overdose due to accumulation.
When benzodiazepines with a long duration of action are being used it is important to warn against changing to a benzodiazepine with a short duration of action, as withdrawal symptoms may develop.

Risk from concomitant use of opioids
Concomitant use of diazepam 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 diazepam with opioids should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe diazepam 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.

Paediatric population
Safety and effectiveness of diazepam in paediatric patients below the age of 6 months has not been established. Diazepam should be given to children with extreme caution and only when other therapeutic alternatives are not available.
Children have an increased sensitivity to the effects of benzodiazepines on the central nervous system. In this patient group, a non-complete metabolisation scheme could cancel or reduce the production of non-active metabolites. The duration of treatment in children must be as short as possible.

Specific patient groups
A lower dose is also recommended for patients with chronic respiratory insufficiency due to the risk of respiratory depression.
Elderly and debilitated patients should be given a reduced dose (see section 4.2).
In case of hepatic impairment, dose reduction is necessary. It is advised to control the blood counts and liver function during a long-term treatment.
Sudden discontinuation of treatment with diazepam in patients with epilepsy can result in epileptic status.
Diazepam should be used with caution in patients with a history of heart or respiratory failure.

Dependence
Treatment with benzodiazepines can result in mental or physical dependency (see section 4.8). The risk increases with dose and duration of treatment; it is also greater in patients with a history of alcohol or drug abuse or in patients with marked personality disorders.

Withdrawal
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, 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.

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.

Excipients
<Product name> 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
If diazepam is used with other centrally acting agents, careful consideration has to be given to the pharmacology of the agents employed, particularly with compounds that may potentiate or be potentiated by the action of diazepam, such as neuroleptics, anxiolytics/sedatives, hypnotics, antidepressants, anticonvulsants, sedating antihistamines, antipsychotics, anaesthetics for general anaesthesia and narcotic analgesics. Such concomitant use may increase sedative effects and cause depression of respiratory and cardiovascular functions.

Concomitant use not recommended

Alcohol

Alcohol should not be consumed while undergoing treatment with diazepam due to additive CNS inhibition and enhanced sedation (see section 4.4).

Combination with CNS depressants

Buprenorphine

The combination of buprenorphine with benzodiazepines may cause death due to respiratory depression. It should be avoided in case of misuse. If concomitant use is required, consider reducing dose of one or both agents.

Opioids

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

Mechanism: Pharmacodynamic synergism.

Effect: Severe hypotension, respiratory depression, unconsciousness and potentially fatal respiratory and/or cardiac arrest. Therefore, concomitant use is not recommended and should be avoided.

Narcotic analgesics

Concomitant use of narcotic analgesics may promote psychic dependency due to enhancement of euphorigenic effects.

Phenobarbital

Mechanism: Additive CNS inhibition.

Effect: Increased risk of sedation and respiratory depression.

Other centrally acting drugs such as opium alkaloids and derivatives used as cough suppressants, barbiturates, baclofen, thalidomide, pizotifen and centrally acting antihypertensives may potentiate or may be potentiated by the action of diazepam.

Special caution with concomitant use

Muscle relaxants (suxamethonium, tubocurarin)

Mechanism: Possible pharmacodynamic antagonism.

Effect: Modified intensity of neuromuscular blockage.

Theophylline

Mechanism: A proposed mechanism is competitive binding of theophylline to adenosine receptors in the brain.

Effect: Counteraction of the pharmacodynamic effects of diazepam, e.g. reduction of sedation and psychomotor effects.

Pharmacokinetic interactions

Diazepam is mainly metabolised to the pharmacologically active metabolites N - desmethyldiazepam, 3-hydroxydiazepam (temazepam) and oxazepam. The oxidative metabolism of diazepam is mediated by CYP2C19 and CYP3A isoenzymes. The results from *in vivo* studies in human volunteers have confirmed those observed *in vitro*.

Oxazepam and temazepam are further conjugated to glucuronic acid. Subtracts of CYP3A4 and/or CYP2C19 can potentially change the pharmacokinetics of diazepam. Drugs such as atazanavir, cimetidine, ketoconazole, fluvamine, fluoxetine, omeprazole, disulfiram, isoniazide, propranolol, ticlopidine and rifampicine inhibit CYP3A and CYP2C19 and may increase the action of diazepam increasing and prolonging sedation. Enzyme inducing drugs such as

rifampicin, hypericum perforatum and certain antiepileptics can result in substantially decreased plasma concentrations of diazepam.

Effects of other medicinal products on the pharmacokinetics of diazepam

Concomitant use not recommended

Inducers
Carbamazepine
Mechanism: Carbamazepine is a known inducer of CYP3A4 and increases hepatic metabolism of diazepam. This can result in up to three-fold greater plasma clearance and a shorter half-life of diazepam.
Effect: Reduced effect of diazepam.

Phenobarbital
Mechanism: Phenobarbital is a known inducer of CYP3A4 and increases hepatic metabolism of diazepam.
Effect: Reduced effect of diazepam.

Phenytoin
Mechanism – Phenytoin is a known inducer of CYP3A4 and increases hepatic metabolism of diazepam.
Effect: Reduced effect of diazepam.

Rifamycins (rifampicin)
Mechanism: Rifampicin is a potent inducer of CYP3A4 and substantially increases the hepatic metabolism and clearance of diazepam. In a study with healthy subjects administered 600 mg or 1.2 g rifampicin daily for 7 days, the clearance of diazepam was increased by about fourfold. Co-administration with rifampicin gives rise to substantially decreased concentrations of diazepam.
Effect: Reduced effect of diazepam. The concomitant use of rifampicin and diazepam should be avoided.

Inhibitors
Antiviral agents (atazanavir, ritonavir, delavirdine, efavirenz, indinavir, nelfinavir, saquinavir)
Mechanism: Antiviral agents may inhibit the CYP3A4 metabolic pathway for diazepam.
Effect: Increased risk of sedation and respiratory depression. Therefore, concomitant use should be avoided or the dose of diazepam reduced.

Azoles (fluconazole, ketoconazole, voriconazole)
Mechanism: Increased plasma concentration of benzodiazepines, due to inhibition of the CYP3A4 and/or CYP2C19 metabolic pathway.
Fluconazole: Co-administration with 400 mg fluconazole on the first day and 200 mg on the second day increased the AUC of a single 5 mg oral dose of diazepam 2.5-fold and prolonged the half-life from 31 hours to 73 hours.
Ketoconazole: Ketoconazole may increase the action of diazepam and increase the risk of drowsiness.
Voriconazole: A study with healthy subjects found that 400 mg voriconazole twice daily on the first day and 200 mg twice daily on the second day increased the AUC of a single 5 mg oral dose of diazepam 2.2-fold and prolonged the half-life from 31 hours to 61 hours.
Effect: Increased risk of undesired effects and toxicity of benzodiazepine. Concomitant use should be avoided or the dose of diazepam reduced.

Fluvoxamine
Mechanism: Fluvoxamine inhibits both CYP3A4 and CYP2C19, which leads to inhibition of the oxidative metabolism of diazepam. Co-administration with fluvoxamine results in an increased half-life and an approximately 190% increased plasma concentrations (AUC) of diazepam.

Effect: Drowsiness, reduced psychomotor performance and memory. Preferably, benzodiazepines that are metabolised via a non-oxidative pathway should be used instead.

Special caution with concomitant use

Inducers
Corticosteroids
Mechanism: Chronic use of corticosteroids may cause increased metabolism of diazepam due to induction of cytochrome P450 isoenzyme CYP3A4, or of enzymes responsible for glucuronidation.
Effect: Reduced effects of diazepam.

Inhibitors
Cimetidine
Mechanism: Cimetidine inhibits the hepatic metabolism of diazepam, reducing its clearance and prolonging its half-life. In one study where 300 mg cimetidine was administered four times daily for 2 weeks, the combined plasma level of diazepam and its active metabolite, desmethyldiazepam, was found to be increased by 57 %, but reaction times and other motor and intellectual tests remained unaffected.
Effects: Increased action of diazepam and increased risk of drowsiness. Reduction of the diazepam dose may be necessary.

Disulfiram
Mechanism: Reduced metabolism of diazepam leading to prolonged half -life and increased plasma concentration of diazepam. The elimination of the N-desmethyl metabolites of diazepam is slowed down which can give rise to marked sedative effects.
Effect: Increased risk of CNS inhibition such as sedation.

Esomeprazole
Mechanism: Esomeprazole inhibits the CYP2C19 metabolic pathway for diazepam. Co-administration with ezomeprazole results in an extended half-life and an increase in plasma concentrations (AUC) of diazepam by approximately 80 %.
Effect: Increased effect of diazepam. Reduction of the diazepam dose may be necessary.

Fluoxetine
Mechanism: Fluoxetine inhibits the metabolism of diazepam via CYP2C19 and other pathways, resulting in elevated plasma concentrations and decreased clearance of diazepam.
Effect: Increased effect of diazepam. Concomitant use should be monitored closely.

Grapefruit juice
Mechanism: Grapefruit juice is believed to inhibit CYP3A4 and increases the plasma concentration of diazepam. C_{max} is increased by 1.5 times and AUC by 3.2 times.
Effect: Possible increased effect of diazepam.

Isoniazid
Mechanism: Isoniazid inhibits the CYP2C19 and CYP3A4 metabolic pathway for diazepam.
Co-administration with 90 mg isoniazid twice daily for 3 days resulted in a prolonged elimination half- life of diazepam and in a 35 % increased plasma concentration (AUC) of diazepam.
Effect: Increased effect of diazepam.

Itraconazole
Mechanism: Increased plasma concentration of diazepam due to inhibition of the CYP3A4 metabolic pathway. In a study with healthy subject given 200 mg itraconazole daily for 4 days increased the AUC of a single 5 mg oral dose of diazepam by about 15 %, but there was no clinically significant interaction as determined by psychomotor performance tests.
Effect: Possible increased effect of diazepam.

Omeprazole
Mechanism: Omeprazole inhibits the CYP2C19 metabolic pathway for diazepam. Omeprazole prolongs the elimination half-life of diazepam and increases the plasma concentrations (AUC) of diazepam. The effect is seen in CYP2C19 extensive metabolisers but not in slow metabolisers, with a low clearance of diazepam.
Effects: Increased action of diazepam. Reduction of the diazepam dose may be necessary.

Oral contraceptives
Mechanism: Inhibition of oxidative metabolism of diazepam.
Effect: Increased effects of diazepam.

Other
Cisapride
Mechanism: Accelerated absorption of diazepam.
Effect: Temporary increase of the sedative effects of orally administered diazepam.

Ketamine
Mechanism: Due to similar oxidative processes, diazepam competitively inhibits ketamin metabolism.
Pre-medication with diazepam leads to prolonged half-life of ketamine with enhanced effect as a result. Effect: Increased sedation.

Levodopa
Mechanism: Unknown.
Effect: Concomitant use with diazepam resulted in reduced effects of levodopa in a small number of case reports.

Valproic acid
Mechanism: Valproate displaces diazepam from its plasma albumin binding sites and inhibits its metabolism.
Effect: Increased serum concentrations of diazepam.
Concomitant use of diazepam and valproic acid increases the risk of psychoses.

Effects of diazepam on the pharmacokinetics of other medicinal products

Phenytoin
Mechanism: The metabolism of phenytoin may be increased or decreased or remain unaltered by diazepam in an unpredictable way.
Effect: Increased or decreased serum concentration of phenytoin. Phenytoin concentrations should be monitored more closely when diazepam is added or discontinued.

Oral contraceptives
Mechanism – effect on oral contraceptives: Co-administration of diazepam and combined oral contraceptives has been known to cause breakthrough bleeding. The mechanism of this reaction is unknown.
Effect on oral contraceptives: Breakthrough bleeding, but no contraceptive failures have been reported.

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 2/1,000 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 apparition of withdrawal symptoms after birth depends on the half-life of the substance.

In addition, it should be taken in consideration that the enzyme system involved in the degradation of the drug is not yet fully developed in infants (especially in premature infants).

Please ask your doctor of pharmacist before taking this medicine.
Diazepam should not be used during pregnancy, unless under strict medical supervision.

Breast-feeding
Diazepam is excreted in breast milk. Diazepam should not be used during breast-feeding.

Fertility
There is no human data.

4.7 Effects on ability to drive and use machines

Sedation, amnesia and impaired motor skills may affect the ability to drive and to operate machines.
Periods of insufficient sleep can increase alertness impairment (see section 4.5).

4.8 Undesirable effects

The most frequent undesirable effects reported are fatigue, drowsiness and numbed emotions and muscle weakness. These adverse effects are usually related to the dose. They predominantly occur at the start of therapy but usually disappear with repeated administration.

The following side effects may also occur:

Blood and lymphatic system
Isolated cases of blood dyscrasia and agranulocytosis cases have been reported.

Psychiatric disorders
Confusion, emotional poverty, decreased alertness, depression, increased or decreased libido.
Psychiatric and paradoxical reactions such as restlessness, irritability, aggressiveness, delusion, rages, nightmares, hallucinations, psychoses, inappropriate behaviour and other adverse behavioural effects. Diazepam should be discontinued if such symptoms occur. They are more likely to occur in children and the elderly.
Chronic use (even at therapeutic doses) may lead to the development of physical dependence. Once physical dependence has developed, abrupt termination of treatment will be accompanied by withdrawal symptoms (see section 4.4). Psychic dependence may occur. Cases of abuse of benzodiazepines have been reported.

Nervous system disorders

Ataxia, dysarthria, headache, tremor, dizziness. Anterograde amnesia may occur using therapeutic dosages, the risk increasing at higher dosages. Amnestic effects may be associated with inappropriate behaviour.

Eye disorders
Diplopia, blurred vision.

Ear and labyrinth disorders
Vertigo.

Cardiac disorders
Heart failure including cardiac arrest.

Vascular disorders
Hypotension, circulatory depression.

Respiratory, thoracic and mediastinal disorders
Respiratory depression including respiratory arrest.

Gastrointestinal disorders
Nausea, dry mouth, excessive salivation, constipation and other gastrointestinal disorders.

Hepatobiliary disorders
Jaundice (very rare).

Skin and subcutaneous tissue disorders
The most common reactions are skin rash, hives, itching and rash erythematous.
In most cases of severe skin reactions (Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis and Erythema Multiforme) the concomitant medication and patients with impaired general condition have been considered to be important confounding factors.

Musculoskeletal and connective tissue disorders
Muscle weakness.

Renal and urinary disorders
Incontinence, urinary retention.

Investigations
Changing the pulse rate, elevated transaminases (very rare) and elevated alkaline phosphatase in the blood.

Injury, poisoning and procedural complications
There is an increased risk of falls and associated fractures in elderly patients using benzodiazepines.

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

In every case of overdose, it should be assessed whether multiple agents are involved, for example in an attempted suicide. Symptoms of overdose are more pronounced in the presence of alcohol or drugs causing a depression in central nervous system.

Symptoms
Benzodiazepines may cause drowsiness, ataxia, dysarthria, nystagmus. An overdose of diazepam is rarely life threatening if taken alone, but can lead to areflexia, apnoea, hypotension, cardiorespiratory depression and coma. If coma occurs, it usually lasts a few hours but can be extended and cyclical, particularly in elderly people. The respiratory depressant effect of benzodiazepines are more serious in patients with respiratory disease. Benzodiazepines increase the effects of other CNS depressants including alcohol.

Management
Monitoring of the vital signs of the patients and supporting measures should be performed in accordance with the clinical condition of the patient. Patients may require symptomatic treatment for cardiovascular, respiratory effects and effects in the central nervous system. Treatment with activated charcoal within 1-2 hours can be given to reduce absorption in the early stages of intoxication. Activated charcoal should be given with airway protected if the patient is unconscious. In case of mixed ingestion, gastric lavage should be considered although this is not routine measure.

The use of flumazenil, a specific benzodiazepine-receptor antagonist, can be considered if the depression in the central nervous system is severe. Flumazenil should only be administered under closely monitored conditions. Due to the short half-life of flumazenil (approximately 1 hour), therefore monitoring of the patient's clinical state remains essential. Flumazenil should be given with extreme caution in the case of mixed intoxication with agents that lower the threshold for seizures (e.g. tricyclic antidepressants).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anxiolytics, benzodiazepine derivatives, ATC code: N05BA01.

Benzodiazepines have anxiolytic, hypnosedatives, myorelaxants and anticonvulsants. Benzodiazepines enhance the neuronal inhibitory properties of the neurotransmitter gamma-aminobutyric acid (GABA).

5.2 Pharmacokinetic properties

Absorption
Diazepam is rapidly and completely absorbed from the gastrointestinal tract, peak plasma concentrations occurring within about 30-90 minutes after oral ingestion. Absorption is delayed and decreased when administered with a moderate fat meal. In the presence of food mean lag times are approximately 45 minutes as compared with 15 minutes when fasting. There is also an increase in the average time to achieve peak concentrations to about 2.5 hours in the presence of food as compared with 1.25 hours when fasting. This results in an average decrease in C_{max} of 20 % in addition to a 27 % decrease in AUC (range 15 % to 50 %) when administered with food.

Distribution
Following oral administration of 5 mg diazepam a maximum serum concentration of approx. 176 ng/ml is achieved after ½-1 hour. Further distribution entails an appreciable fall in plasma concentration lasting 2-4 hours. Diazepam and its metabolites are highly bound to plasma proteins (diazepam 98 %). Diazepam and its metabolites cross the blood-brain and placental barriers and are also found in breast milk in concentrations approximately one tenth of those in maternal plasma (see section 4.6). The volume of distribution at steady-state is 0.8-1.0 l/kg. The distribution half-life is reached in 3 hours.

Biotransformation

Diazepam is mainly metabolised to the pharmacologically active metabolites N - desmethyldiazepam, temazepam and oxazepam. The oxidative metabolism of diazepam is mediated by CYP3A 4 and CYP2C19 isoenzymes. Oxazepam and temazepam are further conjugated to glucuronic acid. The half-life for the metabolite N-desmethyldiazepam, which is biologically active, is 2-4 days.

Elimination
The decline in the plasma concentration-time profile after oral administration is biphasic, an initial rapid and extensive distribution phase being followed by a prolonged terminal elimination phase (half -life up to 48 hours). The terminal elimination half-life of the active metabolite N-desmethyldiazepam is up to 100 hours. Diazepam and its metabolites are excreted mainly in the urine, predominantly in their conjugated forms and approx. 10 % is excreted in the faeces. The clearance of diazepam is 20-30 ml/min.

Special populations
The elimination half-life may be prolonged in the newborn, in the elderly and in patients with liver disease. In renal failure, the half-life of diazepam is not clinically significantly changed.
Half-life: Elderly patients: 70-100 hours. Children: Premature 40-110 hours; full-term neonates approx. 30 hours; up to 1 year old approx. 10 hours; over 1 year old approx. 20 hours.

Overweight patients
Various studies have shown that the kinetics are changed in overweight patients, compared to those of a normal weight. In a study in which the test subjects were given 2 mg diazepam at night for 30 days, the accumulation was delayed and the half-life for the accumulated amount of diazepam in obese test subjects was extended compared to individuals of normal weight (7. 8 days as against 3.1 days). The accumulated amount of the active metabolite desmethyl-diazepam was similarly significantly extended. The plasma elimination half-life for diazepam was extended to 82 hours in overweight test subjects. The altered pharmacokinetics in the case of long-term treatment of overweight patients are due presumably to the distribution volume.
These data indicate that overweight patients require significantly longer treatment times than patients of normal weight before the maximum effect of the drug occurs in long-term treatment. Similarly, the therapeutic effect and undesirable effects, including withdrawal symptoms, can occur for longer periods following the discontinuation of more long-term treatment of overweight patients.

5.3 Preclinical safety data

Fertility studies performed in rats showed a decrease in the number of pregnancies and in the number of live offspring following oral administration of 100 mg/kg/day of diazepam.

Studies performed in rats and rabbits showed no teratogenic effects in the offspring following administration of 80-300 mg/kg/day and 20-50 mg/kg/day of diazepam, respectively. However, diazepam revealed to be teratogenic in mice at doses of 45-50 mg/kg, 100 mg/kg and 140 mg/kg/day and also in hamsters at doses of 280 mg/kg. Mutagenesis studies show contradictory results.

The carcinogenic potential of oral diazepam has been studied in several rodent species. An increase in the incidence of hepatocellular tumours occurred in male mice. No significant increase in the incidence of tumours was observed in female mice, rats, hamsters or gerbils.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate

Pregelatinised maize starch
Magnesium Stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years
5 years
5 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

<Product name> are packed in Al/PVC blisters. Blisters together with patient information leaflet are placed in a carton with imprinted label text.
<Product name> are packed in Al/PVC blisters or white HDPE bottles with PE screw cap. Blisters together with patient information leaflet are placed in a carton with imprinted label text. Bottles either have booklet label leaflet or together with patient information leaflet are placed in a carton with imprinted label text.
<Product name> are packed in Al/PVC blisters or white HDPE bottles with PE screw cap. Blisters together with patient information leaflet are placed in a carton with imprinted label text. Bottles either have booklet label leaflet or together with patient information leaflet are placed in a carton with imprinted label text.

Pack sizes: 20, 20x1, 25, 25x1, 30, 30x1, 50, 50x1, 60, 60x1, 90, 90x1, 100 and 100x1 tablets in blisters.
Pack sizes: 20, 20x1, 25, 25x1, 30, 30x1, 40, 40X1, 50, 50x1, 60, 60x1, 90, 90x1, 100and 100x1 tablets in blisters or 20 tablets in bottles.
Pack sizes: 20, 20x1, 25, 25x1, 30, 30x1, 50, 50x1, 60, 60x1, 90, 90x1, 100 and 100x1 tablets in blisters or 20 tablets in bottles.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

STADA Arzneimittel AG
Stadastrasse 2 – 18
61118 Bad Vilbel
Duitsland

8. MARKETING AUTHORISATION NUMBER(S)

Diazepam STADA 2 mg tabletten RVG 127016
Diazepam STADA 5 mg tabletten RVG 127017

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Datum van eerste verlening van de vergunning: 14 oktober 2021

10. DATE OF REVISION OF THE TEXT

Laatste gedeeltelijke wijziging betreft rubriek 6.5: 14 februari 2022