SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Diazepam Desitin rectal tube 5 mg, rectal solution
Diazepam Desitin rectal tube 10 mg, rectal solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Diazepam Desitin rectal tube 5 mg
2.5 ml rectal solution (1 rectal tube) contain 5 mg diazepam.

Diazepam Desitin rectal tube 10 mg
2.5 ml rectal solution (1 rectal tube) contain 10 mg diazepam.

Excipients with known effect: 37.5 mg benzyl alcohol, 12 vol % alcohol, 2.5 mg benzoic acid (E210), 122.5 mg sodium benzoate (E211) and 1 g propylene glycol per 2.5 ml

For the full list of excipients, see section 6.1.

This medicinal product contains 12 vol % ethanol (alcohol), i.e. up to 250 mg per dose.

3. PHARMACEUTICAL FORM

Rectal solution
Clear, colourless or slightly yellowish solution

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- status epilepticus
- for acute clinical intervention in states of anxiety, tension and agitation
- for premedication before surgery or diagnostic procedures and for post-operative medication
- conditions with increased muscle tone
- tetanus and febrile convulsions

4.2 Posology and method of administration

Posology

The dosage depends on individual response, age and body weight of the patient as well as type and severity of the disease. The basic principle is to keep the dose as low as possible. Rectal administration is appropriate in all cases in which intravenous administration or oral use is difficult or not indicated.

Depending on the rectally applicable quantity of diazepam in mg, the smallest number of rectal tubes should be used. For optimal individual treatment, rectal tubes are available in two strengths (5 and 10 mg diazepam).

The following dosage guidelines apply for single doses:

Treatment of status epilepticus

Adults receive initially 5 – 10 mg diazepam rectally (not more than 1 rectal tube containing 10 mg). If required, the dose may be repeated after 10 – 15 minutes up to a maximum of 30 mg diazepam.

Children receive depending on age and body weight 5 – 10 mg diazepam rectally (the maximum dose is 20 mg); up to 15 kg body weight: 5 mg diazepam, over 15 kg body weight: 10 mg diazepam; if required, the dose may be repeated (up to 10 mg). The maximum effect occurs after 11 – 23 minutes. The treatment may be repeated in adults and children after 2 – 4 hours if required.

Treatment of acute states of anxiety, tension and agitation as well as tetanus and febrile convulsions

Adults receive 5 – 10 mg diazepam rectally. If the desired effect is not achieved with this dosage, the dose may be repeated after 3 – 4 hours.

Children (up to 3 years) with a body weight of 10 – 15 kg: 5 mg diazepam rectally.
Children (over 3 years) with a body weight of over 15 kg: 2 x 5 mg or 1 x 10 mg diazepam rectally.
This dose can be repeated every 12 hours up to a maximum of 4 doses.

Premedication before surgical interventions in anaesthesiology and surgery and diagnostic procedures / post-operative medication

On the evening before the operation: 10 – 20 mg diazepam. 1 hour before the anaesthetic: 5 – 10 mg diazepam rectally. Post-operatively: 5 – 10 mg diazepam. If required, the dose may be repeated.

Treatment of conditions with increased muscle tone (muscle tension)

As initial treatment, a total of 10 – 20 mg diazepam daily is administered rectally in several divided doses or as a single evening rectal dose of 5 – 10 mg. As further treatment, if continuation of treatment by the oral route is not possible, a total of 5 – 10 mg diazepam (not more than two 5 mg rectal tubes) should be administered rectally in two single doses throughout the day. Children usually receive lower doses.

Special dosage instructions for all indications

Adolescents with a body weight of over 50 kg may be given the adult dose.

Elderly or weakened patients as well as patients with organic brain changes, circulatory or respiratory insufficiency and impaired hepatic or renal function should receive lower doses: initially not more than 5 mg diazepam once daily rectally. If further increases in dosage are necessary, these should be incremental and should be adjusted to the desired therapeutic effect. A single rectal dose of 5 mg (1 rectal tube containing 5 mg diazepam) should not be exceeded. This also applies to patients who are concomitantly receiving treatment with other centrally acting drugs.

Method of administration
The rectal solution is administered rectally. If possible, children should be in the prone or lateral position, adults should be in the lateral position. The contents of one rectal tube should be emptied completely for one application.

1. Tear open the foil pack. Open the tube by twisting off the cap.

2. Insert the whole length of the nozzle into the anus (in newborns or babies: only half of the length). Hold the rectal tube with the tip down. The contents of the rectal tube should be completely emptied by using firm pressure with the index finger and thumb.

3. Remove the rectal tube while continuing to squeeze it in order to avoid the rectal solution being sucked back. Press together the patient's buttocks for a short time. The duration of administration is determined by the doctor.

The medicinal product is particularly suitable for acute clinical intervention and is less suitable for chronic therapy. The duration of administration should be limited to single doses or to a few days in cases of acute illness.
When longer-term treatment with diazepam (lasting more than 1 week) is to be discontinued, the dose should be reduced gradually. In this case, temporary development of withdrawal effects should be considered (see section 4.4 and 4.8).

4.3 Contraindications

Diazepam must not be used in the case of
- hypersensitivity to the active substance other benzodiazepines or to any of the excipients listed in section 6.1
- addictive disorders (alcohol, prescription medications, illegal drugs)
- acute intoxication with alcohol, hypnotics, analgesics or psychopharmaceuticals (neuroleptics, antidepressants and lithium)
- *myasthenia gravis*
- severe respiratory insufficiency
- sleep apnoea syndrome
- severe hepatic insufficiency
- neonates and babies under six months of age

4.4 Special warnings and precautions for use

Diazepam should only be used with particular caution in:

- cerebellar and spinal ataxia

Diazepam may be administered to treat children and adolescents only if there is a compelling indication.

Diazepam should not be used in pregnancy and lactation (see section 4.6).

Not all states of tension, agitation or anxiety require drug treatment. They are often a manifestation of physical or mental disorders and can be managed by alternative means or by treatment of the underlying disease.

At the beginning of therapy, individual patient response to the medicinal product should be monitored, in order to ensure prompt recognition of any relative overdose due to accumulation. This particularly applies to elderly and debilitated patients, children and adolescents as well as patients with organic brain changes, circulatory or respiratory insufficiency and impaired renal or hepatic function. Furthermore, the patient should be given specific instructions with reference to his/her daily routine according to particular circumstances (e.g. occupation).

Diazepam should not be used concurrently with alcohol and/or drugs with a central depressant effect. Concurrent intake can enhance the effects of diazepam and possibly lead to profound sedation and clinically relevant cardiovascular and/or respiratory depression (see section 4.5).

<u>Risk from concomitant use of opioids</u>
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).

In long-term therapy, monitoring of the blood count and hepatic function is recommended.

Specific patient groups
Elderly patients (≥ 65 years)
Caution is advised in elderly patients due to the risk of falling, particularly when getting up at night.

High-risk patients
Benzodiazepines are not recommended in the primary treatment of psychoses.

Benzodiazepines should not be used alone to treat depression or anxiety states accompanied by depression. Under certain circumstances, the symptoms of depression may be enhanced if the underlying disease is not treated appropriately with antidepressants (risk of suicide) (see section 4.8).

The usual caution is required in elderly and weakened patients and in those with hepatic and renal impairment and a dose reduction should be made if appropriate (see section 4.2).

A lower dose is also recommended in patients with chronic respiratory insufficiency, due to the risk of respiratory depression (see section 4.2).

Patients with severely impaired hepatic function may not be treated with benzodiazepines, as they are at risk of encephalopathy (see section 4.3).

Patients in shock may be treated with Diazepam Desitin rectal tube only if measures are concurrently undertaken to correct the volume deficiency.

Development of tolerance
Loss of efficacy (tolerance) can occur following long-term and repeated benzodiazepine intake over a period of a few weeks.

Development of dependence
Benzodiazepine use can lead to the development of psychological and physical dependence. This applies not only to abuse of particularly high doses but also within the therapeutic dose range. The risk of drug dependence increases with the dose and duration of treatment. This risk is also increased in patients with a history of dependence on alcohol, medicinal products or illegal drugs.

If physical dependence has developed, abrupt withdrawal of treatment is accompanied by withdrawal symptoms (see below).

Drug discontinuation effects/Withdrawal symptoms
Withdrawal symptoms can occur, particularly if long-term treatment is ended. These could be manifested as sleep disturbances, increased dreaming, headache, myalgia, anxiety, tension, inner restlessness, sweating, trembling, mood swings, confusion and irritability. Additionally, in severe cases, the following symptoms can occur: confusional state, depersonalisation, derealisation, hypersensitivity to light, noise and physical contact, numbness and paraesthesia in the extremities, hallucinations or epileptic seizures.

Sudden discontinuation of short-term treatment can also lead to temporary drug discontinuation effects (rebound phenomena), whereby the symptoms which led to treatment with Diazepam Desitin rectal tube may recur in enhanced form. Possible concurrent reactions are mood swings, anxiety and agitation.

As the risk of withdrawal and discontinuation effects is higher following abrupt discontinuation of therapy, gradual dose reductions are recommended when treatment is ended.

The patient should be informed at the beginning of treatment about the limited duration of treatment and the gradual dose reduction should be precisely explained. It is also important that the patient be made aware of the risk of rebound phenomena, in order to reduce anxiety about such symptoms should they occur during withdrawal of the medicinal product.

Amnesia
Benzodiazepines can cause anterograde amnesia. This means that (usually several hours) after administration of medicinal product, the patient may perform actions of which he/she subsequently has no recollection.

This risk increases dose-dependently and can be reduced by a sufficiently long, uninterrupted period of sleep (7–8 hours).

Psychological and paradoxical reactions
Following benzodiazepine administration, particularly in the elderly or children, psychological and paradoxical reactions can occur (see section 4.8). In such cases, treatment with this medicinal product should be discontinued.

During treatment with the medicinal product and for 24 hours after the last rectal administration, the patient must not drive a vehicle or operate machines with which he/she could endanger himself/herself or others. Following out-patient application, the patient should only be allowed home after one hour and if accompanied (see section 4.7).

Long-term administration should be avoided unless there is a compelling indication and the therapeutic benefit has been carefully weighed up against the risk of tolerance and dependence. In all cases, the duration of treatment should not exceed 4 weeks.

Information on excipients:
This medicinal product contains 12% ethanol (alcohol), i.e. up to 250 mg per dose. Harmful for those suffering from alcoholism. To be taken into account in pregnant or breast-feeding women, children and high-risk groups such as patients with liver disease, or epilepsy.
Due to the content of benzyl alcohol, use for more than a week in young children (less than 3 years old) is not recommended. High doses should be used with caution and only if necessary, especially in patients with liver or kidney impairment because of the risk of accumulation and toxicity (metabolic acidosis).
Due to the content of propylene glycol, special care is required in children below 5 years of age, in particular if diazepam is co-administered with other medicinal products that contain propylene glycol or alcohol. Medical monitoring is required in patients with impaired renal or hepatic functions because various adverse events attributed to propylene glycol have been reported such as renal dysfunction (acute tubular necrosis), acute renal failure and liver dysfunction. Benzoic acid and sodium benzoate may cause local irritation.

This medicinal product contains less than 1 mmol sodium (23 mg) per 2.5 ml rectal solution, i.e. essentially "sodium-free".

4.5 Interaction with other medicinal products and other forms of interaction

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 CYP3A4 and CYP2C19 isoenzymes. In-vitro studies have shown that hydroxylation is mainly mediated by CYP3A, whereas both isoenzymes, CYP3A and CYP2C19, are involved in N-demethylation. These in-vitro observations were confirmed by findings from in-vivo studies with probands.

Concurrently administered medicinal products with active substances that are also substrates of CYP3A and/or CYP2C19 can therefore alter the pharmacokinetics of diazepam. Thus, known CYP3A or CYP2C19 inhibitors, such as cimetidine, omeprazole, disulfiram, ketoconazole, fluvoxamine, fluoxetine and HIV protease inhibitors, can lead to profound and prolonged sedation.

Phenobarbital and phenytoin may accelerate the metabolism of diazepam.

In smokers, diazepam elimination can be accelerated.

In rare cases, diazepam may inhibit the metabolism of phenytoin thus potentiating its effect.

Pharmacodynamic interactions
Concurrent administration of diazepam and the following drugs may cause a mutual potentiation:
- sedatives, hypnotics, narcotic analgesics (opioids), anaesthetics
- neuroleptics
- antiepileptics
- anxiolytics
- sedating antihistamines
- analgesics
- antidepressants, lithium

This applies particularly to concomitant consumption of alcohol which may alter or potentiate the effects in an unpredictable manner. Alcohol should therefore be avoided during diazepam treatment (see section 4.4 and 4.9).

Concurrent administration of buprenorphine (a potent analgesic) can lead to respiratory arrest and circulatory collapse.

Concurrent administration of diazepam and 4-hydroxybutyric acid (sodium oxybate) can potentiate the effect of sodium oxybate.

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).

Furthermore, concomitant use of narcotic analgesics may promote psychic dependency due to enhancement of euphorigenic effects.

Concurrent administration of muscle relaxants can potentiate the muscle-relaxant effect, particularly in elderly patients and at higher dosage (risk of falls!).

Theophylline in small doses reverses diazepam-induced sedation.

Diazepam can inhibit the effect of levodopa.

Due to the slow elimination of diazepam, possible interactions must be anticipated even after discontinuation of treatment with diazepam. In patients under long-term treatment with other medicines, e.g. centrally acting antihypertensive agents, beta-blockers, anticoagulants and cardiac glycosides, the type and extent of interactions cannot be predicted with certainty. Before administration of diazepam, the treating doctor should check whether there is any relevant chronic drug treatment. If this is the case, particular caution is necessary with the use of the medicinal product, especially at the start of treatment.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential
If Diazepam Desitin rectal tube is prescribed to a woman of childbearing potential, she should be advised to contact her physician immediately if she wishes to become pregnant or suspects she is pregnant.

Pregnancy
No clinical data on exposed pregnant women are available for diazepam. Animal studies have shown reproductive toxicity (see section 5.3).

In pregnancy, diazepam should only be prescribed in exceptional cases with a compelling indication - not in high doses or for a long period of time.
In humans, it would appear that the risk of congenital abnormalities from the ingestion of therapeutic doses of benzodiazepines is slight, although a few epidemiological studies have pointed to an increased risk of cleft palate (see section 5.3).

There are case reports concerning congenital abnormalities and mental retardation in prenatally exposed children following overdose and intoxication with benzodiazepines (see section 5.3).

If diazepam is used in later pregnancy over a longer period or in high doses, withdrawal phenomena (hyperactivity, irritability) may be observed postnatally in the neonate due to tolerance and physical dependence.

Use near the end of pregnancy, before and during birth can lead to development of hypothermia, respiratory insufficiency, reduced muscle tension, hypotension, respiratory depression and poor suckling (floppy infant syndrome) in the neonate. In the neonate, the possibility of respiratory disturbance requiring artificial ventilation should be anticipated. The treating doctor should therefore ask patients to report pregnancy occurring during treatment with diazepam immediately in order to decide, in that particular case, between continuation and termination of treatment.

Breast-feeding
Diazepam should not be used during lactation because it passes into breast milk. The milk/plasma ratio shows a large individual variation in this respect. Diazepam is metabolised significantly more slowly in the neonate than in children or adults. For this reason, if diazepam therapy is essential, breast-feeding should be terminated in order to avoid undesirable effects in the breastfed infant.

Diazepam Desitin rectal tube contains benzyl alcohol. High volumes can accumulate in the body and cause adverse effects ("metabolic acidosis").

Fertility
No clinical data on fertility are available. In mice, anomalies of the heads of spermatozoa were observed after treatment for one to six weeks (see section 5.3).

4.7 Effects on ability to drive and use machines

Even when used as directed, this medicinal product can affect the reaction capacity to such an extent (e.g. by means of sedation, amnesia, reduced concentration and impaired muscle function) as to impair the ability to drive or to use machines. This applies particularly when alcohol is taken at the same time or after insufficient period of sleep. During treatment with diazepam and for 24 hours following the last rectal dose, the patient should not drive a motor vehicle or use machines with which he/she could endanger himself/herself or others. If the medicinal product was used for diagnostic purposes, the patient may only proceed home if accompanied. Consumption of alcohol with concomitant administration of diazepam, even 10 hours after the last dose, causes increased impairment of motor functions and skills. This may significantly increase the risk of industrial and road traffic accidents. For this reason, driving motor vehicles, using machines and other dangerous activities should be avoided completely .

4.8 Undesirable effects

Undesirable effects are presented below by MedDRA System Organ Class, using the following frequency 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)

Undesirable effects are generally reversible on reduction of the dose and can usually be avoided by individual tailoring of the daily dose. Tolerance may develop with chronic or repeated use of diazepam. Diazepam has a primary dependence potential. Daily intake even over a period of a few weeks entails the risk of development of dependence. This applies not only to the abuse of particularly high doses but also within the therapeutic dose range (see section 4.4). Discontinuation of the therapy may result in discontinuation effects (e.g. rebound phenomena) or withdrawal symptoms (see section 4.4). In benzodiazepine treatment, it must generally be borne in mind that withdrawal symptoms can develop if the patient is switched to a benzodiazepine with a markedly shorter elimination half-life (see section 5.2).

Metabolism and nutrition disorders	
Rare	Increased appetite
Psychiatric disorders	
Common	Confusion
Rare	Loss of libido
Not known	Emotional poverty, impaired concentration, reduced alertness, increased libido, hallucinations[3], paradoxical reactions[3] such as acute excitation [3,4], suicidal tendencies[3], anxiety[3,4], tension[4], insomnia[3], fits of rages[3], depressed mood, sleep disturbances, increased dream activity or vivid dreams, inner restlessness[4], agitation, irritability, aggressive behaviour, nervousness, hostility, nightmares. Previously unrecognised depression may be unmasked during diazepam use (see section 4.4).
Nervous system disorders	
Common	Undesirable heavy sedation, sleepiness, drowsiness, dizziness, headache, ataxia, anterograde amnesia, which can be associated with inappropriate behaviour
Not known	Articulation disturbances[2] (retarded or unclear speech), motor and gait disturbances[2], tremor

Eye disorders	
Not known	Visual disturbances, such as diplopia, blurred vision, nystagmus[2]
Ear and labyrinth disorders	
Not known	Vertigo
Cardiac disorders	
Rare	Bradycardia
Not known	Arrhythmia, heart failure, including cardiac arrest
Vascular disorders	
Rare	Hypotension
Not known	Circulatory depression
Respiratory, thoracic and mediastinal disorders	
Rare	Laryngeal spasms, respiratory depression[1] including respiratory arrest
Gastrointestinal disorders	
Rare	Nausea, vomiting, epigastric complaints, constipation, diarrhoea, dryness of the mouth
Not known	Increased salivation and, after administration for several days in very high dosage, e.g. in the treatment of tetanus, colicky abdominal pain and diarrhoea may develop.
Hepatobiliary disorders	
Rare	Jaundice
Skin and subcutaneous tissue disorders	
Rare	Allergic skin changes such as pruritus, urticaria, flushes
Musculoskeletal and connective tissue disorders	
Not known	Increased muscle spasms[3], muscular weakness
Renal and urinary disorders	
Rare	Urinary retention
Not known	Incontinence
Reproductive system and breast disorders	
Rare	In women menstrual cycle disturbances
General disorders and administration site disorders	
Common	Tiredness, lassitude, prolonged reaction time
Rare	Chest pain
Not known	Risk of falls, fractures and in the morning after evening administration hang-over effects (disturbance of concentration and residual tiredness) and daytime sedation can impair reaction capacity
Investigations	
Not known	Increased transaminase and alkaline phosphatase values

[1] The depressive effect on respiration may be more evident in the case of airway obstruction and in patients with brain damage. This should be particularly taken into account in combination with other centrally acting agents (especially those with a respiratory depressant effect) (see section 4.4 and 4.5).
[2] In high dosage and with longer-term use of the medicinal product - which is more unlikely with this particular formulation – these reversible disturbances may occurred.[3] If these undesirable effects occur, the medicinal product should be discontinued.[4] These undesirable effects can occur approximately 2–4 days after sudden discontinuation of the medicinal product, particularly after longer-term daily use. Symptoms may include tremor and sweating which may intensify and lead to development of dangerous physical and mental reactions e.g. convulsions and symptomatic psychoses (e.g. withdrawal delirium). For this reason, withdrawal of treatment should be gradual.

Benzoic acid and sodium benzoate may cause local irritation.
Benzyl alcohol may cause allergic reactions or mild local irritation. Benzyl alcohol has been linked with the risk of severe side effects including breathing problems (i.e. gasping syndrome) in young children.
Propylene glycol may cause skin irritation.

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[1].

4.9 Overdose

The symptoms of overdose are increased under the influence of alcohol and other central depressants.

Symptoms of overdose
Symptoms of mild intoxication may include e.g. confusion, somnolence, ataxia, dysarthria, hypotension, muscular weakness, drowsiness and nystagmus. Overdose with diazepam alone is not generally life-threatening but can lead to areflexia, apnoea, hypotension, circulatory and respiratory depression and, in rare cases, coma. If coma occurs, this only lasts for a few hours; it can, however, be prolonged and periodic, particularly in elderly patients. The respiratory depressant effect of benzodiazepines enhances pre-existing respiratory disturbances in patients with respiratory disease. In the case of severe intoxication, depression of vital functions may occur, particularly of the respiratory centre (cyanosis, respiratory and cardiac arrest; intensive monitoring is required!). A fatal outcome is very rare. In the phase of subsidence of intoxication, severe agitation may occur.

Management of overdose
Apart from monitoring of vital parameters, respiration, pulse rate, blood pressure and body temperature, intravenous fluid replacement, supportive measures and anticipation of emergency measures in case of respiratory obstruction are normally indicated, depending on the clinical picture. Symptomatic treatment of cardiorespiratory and central nervous system effects may be particularly necessary. Hypotension can be treated with sympathomimetics. If respiratory insufficiency occurs, which can also be the result of reduced peripheral muscle tone, assisted respiration is necessary. Morphine antagonists are contraindicated. Note: To date, neither haemodialysis nor peritoneal dialysis has been described in the scientific literature. Following overdose with diazepam alone, forced diuresis and dialysis measures are unlikely to be very effective, due to diazepam's high plasma protein binding and large volume of distribution.
In order to cancel out the CNS-depressant effects of benzodiazepines it may be necessary to use the specific benzodiazepine antagonist flumazenil. The patient must be closely monitored, as flumazenil not only antagonises the sedative effect, but also the anticonvulsive and anxiolytic effects, for example. Due to the short half-life of approximately 1 hour, patients must be kept under continuous monitoring after the effect of flumazenil has worn off. Flumazenil is contraindicated if there is concurrent administration of drugs that lower the seizure threshold (e.g. tricyclic antidepressants). For further information on correct administration, please see the Summary of Product Characteristics for flumazenil.

5. PHARMACOLOGICAL PROPERTIES

[1] Implementation of the adverse reaction reporting paragraph is a legal requirement in the EU. Appendix V lists the national contact addresses for reporting in the EU. Please check your local reporting requirements and insert your national reporting address, if applicable.

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: anxiolytics, ATC code: N05BA01

Diazepam is a psychotropic substance from the class of 1,4-benzodiazepines with marked properties of suppression of tension, agitation and anxiety as well as sedative and hypnotic effects. In addition, diazepam exhibits muscle relaxant and anticonvulsive properties in higher doses.

Diazepam binds to specific receptors in the central nervous system and particular peripheral organs. The benzodiazepine receptors in the CNS have a close functional connection with receptors of the GABA-ergic transmitter system. After binding to the benzodiazepine receptor, diazepam augments the inhibitory effect of GABA-ergic transmission.

5.2 Pharmacokinetic properties

The pharmacokinetic parameters of diazepam show wide interindividual variation.

Absorption
After rectal administration of the solution, diazepam is absorbed rapidly and almost completely from the rectum. The onset of the therapeutic effect occurs within a few minutes of rectal administration and is more rapid than with suppositories (the rapidity of the rise in the serum level following rectal administration corresponds approximately to that following an intravenous dose). Peak plasma and serum concentrations following administration of 10 mg diazepam in rectal solution (about 369 ng/ml) are reached after approximately 10 -20 minutes, of suppositories (about 272 ng/ml) after approximately 30 - 120 minutes (depending on galenic composition).

Distribution
The plasma protein binding of diazepam is between 95 - 99 %; in liver and kidney patients, lower levels of binding are present. The volume of distribution is between 0.95 - 2 l/kg body weight depending on age.

Biotransformation, elimination
Metabolic breakdown of diazepam occurs mainly in the liver. Its metabolites, N-desmethyldiazepam (nordazepam), temazepam, and oxazepam, which appear in the urine as glucuronides, are also pharmacologically active substances. Only 20 % of the metabolites are detected in the urine in the first 72 hours. The active metabolites have the following plasma half-lives: N-desmethyldiazepam 30 - 100 hours, temazepam 10 - 20 hours, oxazepam 5 - 15 hours. Following repeated administration of diazepam, the portion of N-desmethyldiazepam predominates, with interindividual differences being large. This main metabolite shows a longer terminal half-life than the mother substance. In the case of chronic diazepam treatment, elimination is further prolonged due to cumulation and the therapeutically relevant plasma concentrations of the main metabolite are elevated. Diazepam and its main metabolite are eliminated from the blood plasma only very slowly. The first elimination phase has a half-life of 1 hour, for the second elimination phase half-lives between 20 and 100 hours (depending on age and state of the liver function) have been reported. Excretion is mainly renal and also partly biliary. It is dependent on age as well as hepatic and renal function. Metabolism and elimination of diazepam in the neonate are markedly slower than in children and adults. In the elderly, elimination is prolonged by a factor of 2 to 4. In patients with impaired renal function, elimination is also prolonged. In patients with hepatic disorders (e.g. liver cirrhosis, hepatitis), elimination is prolonged by a factor of 2.

Penetration into the cerebrospinal fluid:

Diazepam is lipophilic and penetrates quickly into the cerebrospinal fluid together with its main active metabolite.

- Transplacental passage and lactation:

Diazepam and its main metabolite, N-desmethyldiazepam, cross the placental barrier and are secreted into breast milk. Diazepam accumulates in the foetal compartment and can reach a level in the neonate of three times the maternal serum concentration. In premature babies, elimination is considerably prolonged due to immature hepatic and renal function and this can be as long as ten days. If diazepam is administered before or during birth or if the mother was given multiple large doses, Apgar values are significantly reduced both in premature and term neonates, the incidence of hyperbilirubinaemia is significantly increased and extensive oedema and muscular hypotonia may be observed for up to four days postpartum.

- Bioavailability

Compared with intravenous administration, systemic availability of diazepam from a rectally administered solution - dependent on the galenic composition - approximates to as much as 100 %.

5.3 Preclinical safety data

Acute toxicity:
see section 4.9

Chronic toxicity:
Experiments in several animal species have demonstrated no evidence of drug-induced changes.

Carcinogenic and mutagenic potential:
There are no long-term animal studies to investigate the carcinogenic potential of diazepam. Several investigations pointed weakly to a mutagenic potential in high dosages, which however were far above the human therapeutic dose.

Reproductive toxicity:
In humans, it would appear that the risk of congenital abnormalities from the ingestion of therapeutic doses of benzodiazepines is slight, although a few epidemiological studies have pointed to an increased risk of cleft palate. There are case reports concerning congenital abnormalities and mental retardation in prenatally exposed children following overdose and intoxication with benzodiazepines (see also section 4.6).

Results of animal studies:
In the mouse, cleft palate occurred after prenatal exposure to diazepam. In the hamster, in addition to cleft palate, exencephaly and limb deformities were seen after very high prenatal diazepam doses. In rats and primates, diazepam was not teratogenic. Animal studies have given indications of behavioural disturbances in the offspring of chronically exposed mother animals. In mice, anomalies of the heads of spermatozoa were observed after treatment for one to six weeks.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Each rectal tube with 5 or 10 mg contains
benzyl alcohol
propylene glycol
Ethanol 96%
benzoic acid (E210
sodium benzoate (E211)

purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Diazepam Desitin rectal tube 5 mg
2 years
Diazepam Desitin rectal tube 10 mg
2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Rectal tube of low-density PE in a tubular sachet of PET-Al PE foil.
Diazepam Desitin rectal tube 5 mg/10 mg pack with 5 rectal tubes, separately packed, containing 2.5 ml rectal solution each
Hospital packs containing 50 rectal tubes each

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

DESITIN ARZNEIMITTEL GMBH
Weg beim Jäger 214
22335 Hamburg
Telephone: (0 40) 5 91 01-525
Fax: (0 40) 5 91 01-377

8. MARKETING AUTHORISATION NUMBER(S)

Diazepam Desitin rectal tube 5 mg
15919.00.00
Diazepam Desitin rectal tube 10 mg
15919.01.00

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 July 1990
Date of latest renewal: 06 September 2000

10. DATE OF REVISION OF THE TEXT

September 2024

11. DOSIMETRY

Medicinal product subject to medical prescription.

Recommendations of the Committee of Experts of the German Government for the Doctor on the Appropriate Use of Medicines Containing Benzodiazepines

Benzodiazepines are drugs which are mainly used for the temporary treatment of severe anxiety states and sleep disorders, as well as for the treatment of muscle tension and epilepsy. According to current knowledge, benzodiazepines are prescribed too often and over too long a period, which can lead to the development of addiction. This risk increases with the level of the dose and the length of use. Besides their dependence potential, benzodiazepines cause other adverse drug reactions such as an impaired ability to react, increased recurrence of the original symptoms after discontinuation of the medication (rebound insomnia, rebound anxiety, delirious syndromes, seizures), memory disturbances and neuropsychiatric side effects. They can also influence the pharmacokinetic properties of other drugs. Besides the development of dependence, the abuse of benzodiazepines has been a cause of worry for a considerable time.

For this reason doctors prescribing benzodiazepines must comply with the following guidelines, which have been drawn up taking into account publications of the Drug Commission of the German Medical Association and the German Association for Neuropsychopharmacology and Pharmacopsychiatry:

- Careful indication!
- Particular caution is required in the case of patients with a history of dependence. As a rule benzodiazepines should not be prescribed.
- Prescribe the smallest packaging unit as a rule.
- Prescribe in the lowest possible dosage that is still sufficient. Reduce the dose at the earliest possible stage or increase the dosing interval depending on the duration of effect.
- Agree the length of the therapy with the patient before the start of treatment and verify that treatment is still required at short intervals. A treatment period of more than two months is only possible in substantiated exceptional cases due to the increased risk of developing dependence associated with the length of time for which benzodiazepines are taken. There is a possibility of dependence without any increase in the dose, as well as the so-called "low-dose dependence"!
- Reduce the dose step-by-step as early as possible during the treatment period (tapering) or increase the dosing interval in order to prevent withdrawal symptoms such as restlessness, anxiety, sleep disturbances, delirious syndromes or seizures.
- Explain to the patient that under no circumstances must benzodiazepines be given to others.
- Prescriptions for benzodiazepines should always be made out in the doctor's own hand and should always be handed over to the patient personally.
- Note the summary of product characteristics and package leaflet, as well as the relevant scientific publications.
- Bring all cases of dependence to the attention of the Federal Institute for Drugs and Medical Devices (BfArM) through the respective Drug Commissions of the Chambers of Health Professionals.