SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Diazepam Desitin 10 mg Rectal solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Diazepam 10 mg in 2.5 ml
Excipients with known effect: 37,5 mg benzyl alcohol, 2,5 mg benzoic acid (E210), 122,5 mg sodium benzoate (E211), 12 vol % ethanol, 1 g propylene glycol (E1520) per 2.5 ml

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Rectal solution
Clear, colourless or slightly yellowish solution in rectal tubes

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Epileptic and febrile convulsions
- to relieve muscle spasm caused by tetanus
- as a sedative in minor surgical and dental procedures
- initial use in anxiety and agitation, when the disorder is severe, disabling or subjecting the individual to extreme distress

Diazepam Desitin may be used in these indications when a rapid effect is required but where intravenous injection is impracticable or undesirable.
Diazepam Desitin may be of particular value for the immediate treatment of convulsions in children.

4.2 Posology and method of administration

<u>Posology</u>
The usual dose is 0.25 - 0.5 mg / kg. Dosage depends on age, weight and individual response. Diazepam Desitin is also available in unit-doses of 5 mg. For doses of 5 mg Diazepam Desitin 5 mg Rectal solution is recommended. Because Diazepam Desitin is provided in fixed unit-doses of 5 and 10 mg the dose is obtained by rounding upward to the next available dose.

Recommended doses:

Paediatric population
Children: Under 10 kg (under 1 year): not recommended.
10 to 15 kg (1 to 3 years): one 5 mg tube of Diazepam Desitin 5 mg Rectal solution should be used.
Insert tube half way to mark on nozzle.
Over 15 kg (over 3 years): one 10 mg tube
If no effect is seen after 10 minutes, the dose can be repeated in children. The dose can be repeated every 12 hours. In case of repeated administration respiration should be monitored.

Adults

Adults: two 10 mg tubes
If no effect is seen after 10 minutes, an additional 10 mg tube can be given to adults. The dose can be repeated every 12 hours. In case of initially higher doses or repeated administration respiration should be monitored.

If convulsions are still not controlled other anticonvulsive measures should be instituted.

Treatment should be as short as possible. The lowest dose that can control the symptoms should be used.
The patient should be reassessed regularly and the need for continued treatment should be evaluated, especially in case the patient is symptom free.

Elderly and debilitated patients
Elderly and debilitated patients should be given not more than one half the usual adult dose.

Patients with liver or kidney dysfunction
Dosage reduction may also be required in patients with liver or kidney dysfunction.
Patients with chronic respiratory insufficiency
A lower dose is recommended for patients with chronic respiratory insufficiency due to the risk of respiratory depression.

Method of administration
For rectal administration only. Tubes are for single use only.
The foil should be removed only before use.

The solution is administered rectally. Adults should be in the lateral position; children should be in the prone or lateral position.

a) Tear open the foil pack. Unscrew the cap and remove.
b) Insert the tube nozzle completely into the rectum. For children under 15kg, insert only half way. Hold the tube with the spout downwards. The contents of the tube should be completely emptied by using firm pressure with the index finger and thumb.
c) To avoid suction, maintain pressure on the tube until it is withdrawn from the rectum. Press together the patient's buttocks for a short time.

The medicinal product is particularly suitable for acute clinical intervention.

When longer-term treatment with diazepam 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

- Hypersensitivity to the active substance, other benzodiazepines or to any of the excipients listed in section 6.1
- Myasthenia gravis
- Severe respiratory insufficiency
- Sleep apnoea syndrome
- Severe hepatic insufficiency

4.4 Special warnings and precautions for use

Diazepam should only be used with particular caution in patients with:
- renal or hepatic dysfunction
- chronic pulmonary insufficiency
- organic brain changes, particularly arteriosclerosis

Diazepam should not be used in cases of loss or bereavement as psychological adjustments may be inhibited.

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.

Diazepam should not be used concurrently with alcohol, the sedative effect may be enhanced. Patients should therefore be advised against the concomitant use in order to avoid the risk of profound sedation that may have other serious consequences for the patient (see section 4.5). Drugs with a central nervous system depressant effect: Concurrent use of Diazepam with other CNS depressants may enhance the CNS depressive effects which may possibly lead to profound sedation and clinically relevant cardiovascular and/or respiratory depression (see section 4.5).

Concomitant use of opioids
Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death (see section 4.5). Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate and limit dosages and durations to the minimum required. Follow patients for signs and symptoms of respiratory depression and sedation.

Paediatric population
Diazepam should not be given to children and adolescents without careful assessment of the need to do so; the duration of treatment must be kept to a minimum.

Specific patient groups
Elderly patients (≥ 65 years)
Caution is advised in elderly patients due to the risk of falling and consequently fractures, particularly when getting up at night. Elderly should be given a reduced dose (see section 4.2).

High-risk patients
Diazepam is not recommended for the primary treatment of psychotic illness.
Diazepam should not be used in phobic or obsessional states, nor be used alone in the treatment of depression or anxiety associated with depression due to the risk of suicide being precipitated in this patient group (see section 4.8).

As with other benzodiazepines extreme caution should be used if prescribing diazepam for patients with personality disorders. The disinhibiting effects of benzodiazepines may be manifested as the precipitation of suicide in patients who are depressed or show aggressive behaviour towards themselves and others.

Diazepam is not indicated to treat patients with severe hepatic insufficiency as it may precipitate encephalopathy (see section 4.3).
Diazepam should be used with extreme caution in patients with a history of alcohol or drug abuse.
Patients in shock may be treated with Diazepam only if measures are concurrently undertaken to correct the volume deficiency to avoid additional negative effects on circulation. Kinetics of diazepam may be affected by hypovolaemia since diazepam has a high distribution volume and lipophilic properties.

Development of tolerance
Loss of efficacy (tolerance) can occur following long-term and repeated benzodiazepine intake over a period of 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 or medicinal products or drug abuse.

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. The patient must be evaluated after a period of no more than 4 weeks. In general, treatment 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.
If physical dependence has developed, abrupt withdrawal of treatment is accompanied by withdrawal symptoms (see below).

Drug discontinuation effects/Withdrawal symptoms
Withdrawal symptoms may occur with benzodiazepines following normal use of therapeutic doses for only short periods and may consist of sleep disturbances, increased dreaming, headaches, muscle pain, extreme anxiety, tension, restlessness, sweating, trembling, mood changes, confusion and irritability. In severe cases, the following symptoms may occur: confusional state, derealization, depersonalization, hyperacusis, numbness and tingling of the extremities, hypersensitivity to light, noise and physical contact, hallucinations or epileptic seizures. This should be considered when treating patients for more than a few days.

Rebound insomnia and anxiety: a transient syndrome whereby the symptoms that led to treatment with a benzodiazepine recur in an enhanced form, may occur on withdrawal of treatment. 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.

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 is 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.

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.

Amnesia
Benzodiazepines may induce anterograde amnesia. The condition occurs most often several hours after ingesting the product and therefore to reduce the risk patients should ensure that they will be able to have an uninterrupted sleep of 7-8 hours (see section 4.8).

Psychiatric and paradoxical reactions
Reactions like restlessness, agitation, irritability, aggressiveness, delusion, rages, nightmares, hallucinations, psychoses, inappropriate behaviour and other behavioural disorders 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.

Outpatient administration
Following outpatient administration (e.g. for minor surgical or dental procedures), the patient should only be allowed home if accompanied (see section 4.7).

Information on excipients:
Propylene glycol may cause skin irritation.
Benzoic acid and sodium benzoate may cause local irritation.
Benzyl alcohol may cause allergic reactions or mild local irritation.

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, 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

CYP3A4, whereas both isoenzymes, CYP3A4 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 inhibitors or inducers of CYP3A4 and/or CYP2C19 can therefore alter the pharmacokinetics of diazepam. Thus, known CYP3A4 or CYP2C19 inhibitors, such as isoniazid, cimetidine, omeprazole, disulfiram, fluvoxamine, fluoxetine, oral contraceptives and HIV protease inhibitors, can lead to profound and prolonged sedation. Enzyme inducing medicinal products such as rifampicin, St. John's wort (Hypericum perforatum) and certain antiepileptics can cause reduced plasms concentrations of diazepam.

Itraconazole, ketoconazole, and to a lesser extent fluconazole and voriconazole are potent inhibitors of the cytochrome P450 isoenzyme CYP3A4 and may increase plasma levels of benzodiapines. The effects of benzodiapines may be increased and prolonged by concomitant use. A dose reduction of the benzodiazepine may be required.

Cimetidine and omeprazole have been shown to reduce the clearance of benzodiazepines and may potentiate their action whilst known inducers of hepatic enzymes for e.g. Rifampicin may increase the clearance of benzodiazepines.

Phenobarbital and phenytoin may accelerate the metabolism of diazepam.

Phenytoin concentrations may either be increased, decreased or remain unaltered by co-administration of diazepam.

Diazepam metabolism is accelerated by theophylline and smoking.

Pharmacodynamic interactions
A mutual potentiation and effects such as enhanced sedation or respiratory and cardiovascular depression may occur if diazepam is given with other drugs that have CNS depressant properties, e.g.:
- antipsychotics
- anxiolytics
- sedatives, hypnotics, narcotic analgesics (opioids), anaesthetics
- antiepileptics
- sedative antihistamines
- antidepressants

In the case of narcotic analgesics enhancement of the euphoria may also occur leading to an increase in psychic dependence.
Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma and death (see section 4.4).
The sedative effect may be enhanced when the product is used in combination with alcohol. This affects the ability to drive or use machines. Concomitant intake with alcohol is not recommended (see section 4.4, 4.7 and 4.9).

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

Given the possibility of increasing the risk of respiratory depression, the concomitant use of benzodiazepines and sodium oxybate should be avoided.
Diazepam can inhibit the therapeutic effects of levodopa.

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

Other information
Due to the slow elimination of diazepam, possible interactions must be anticipated even after discontinuation of treatment with diazepam.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential
Women of childbearing potential should be advised to contact their physician regarding discontinuation of the product if they intend to become or suspect that they are pregnant.

Pregnancy
There is no evidence regarding the safety of diazepam in pregnancy. It should not be used especially in the first and third trimesters, unless the benefit is considered to outweigh the risk.

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 of congenital abnormalities, mental retardation and neonatal nystagmus in prenatally exposed children following overdosage and intoxication with benzodiazepines.

If, for compelling reasons, diazepam is administered during the late phase of pregnancy or during labour at high doses or repeated low doses hypothermia, hypotonia and respiratory depression, irregularities in the foetal heart and poor suckling (floppy infant syndrome) in the neonate can be expected, due to the pharmacological action of the compound.

Moreover, infants born to mothers who took benzodiazepines chronically during the latter stages of pregnancy may have developed physical dependence and may be at some risk of developing withdrawal symptoms (e.g. hyperactivity, irritability) in the postnatal period.

Breast-feeding
Diazepam is excreted in the breast milk and therefore its use during lactation should be avoided. 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.

Fertility
No clinical data on fertility are available.

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. Patients treated with Diazepam Desitin must not drive or operate machines for at least 24 hours after administration of the last dose.

4.8 Undesirable effects

Drowsiness, numbed emotions, reduced alertness, confusion, fatigue, headache, dizziness, muscle weakness, ataxia or double vision. These phenomena occur predominantly at the start of therapy and usually disappear with repeated administration. Other adverse reactions like gastrointestinal disturbances, changes in libido or skin reactions have been reported occasionally. Elderly or debilitated patients are particularly susceptible to side effects and may require lower doses.

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)

Blood and lymphatic system disorders
Rare: Blood dyscrasias including thrombocytopenia

Metabolism and nutrition disorders
Rare: Increased appetite

Psychiatric disorders
Common: Reduced alertness, numbed emotions, confusion, anterograde amnesia which can be associated with inappropriate behaviour, paradoxical reactions*
Uncommon: Impaired concentration
Rare: Loss of libido, increased libido

In susceptible patients, an unnoticed depression may become evident.

Nervous system disorders
Common: Undesirable heavy sedation, drowsiness, headaches, dizziness (with risk of falls in the elderly), ataxia, dysarthria including slurred speech, tremor

Eye disorders
Common: Double vision
Rare: Other visual disturbances including blurred vision and nystagmus

Ear and labyrinth disorders
Not known: Vertigo

Cardiac disorders
Rare: Bradycardia, heart failure, including cardiac arrest

Vascular disorders
Rare: Hypotension

Respiratory, thoracic and mediastinal disorders
Rare: Laryngeal spasm, respiratory depression including apnoea and respiratory arrest

Gastrointestinal disorders
Rare: Nausea, vomiting, epigastric pain, obstipation, diarrhoea, dry mouth
Not known: Increased salivation

Hepatobiliary disorders
Rare: Cholestatic jaundice, hepato-cellular jaundice

Skin and subcutaneous tissue disorders
Very rare: Allergic skin reactions, including pruritus, urticaria and angioedema

Musculoskeletal and connective tissue disorders
Common: Increased muscle spasm, myasthenia

Renal and urinary disorders
Rare: Urinary retention, incontinence

Reproductive system and breast disorders
Rare: Menstrual disturbances

General disorders and administration site conditions

Common: Fatigue
Rare: Chest pain, hang-over effects**
Not known: Risk of falls

Investigations
Rare: changes of hepatic parameters (elevation of ALT, AST, alkaline phosphatase)

Dependence
Use (even at therapeutic doses) may lead to the development of physical dependence: discontinuation of the therapy may result in withdrawal or rebound phenomena (see section 4.4). Psychic dependence may occur. Abuse of benzodiazepines has been reported.

*Paradoxical reactions (acute excitation, suicidal tendencies, restlessness, agitation, irritability, instability, anxiety, aggressiveness, rages, tension, delusions, nightmares, insomnia, psychoses, hallucinations, hostility, inappropriate behaviour) are known to occur with benzodiazepines and are more likely in children and the elderly. If these undesirable effects occur, the medicinal product should be discontinued.

**In the morning after evening administration, hang-over effects (disturbance of concentration and residual tiredness) and daytime sedation can impair reaction capacity.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows 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

Effects of overdose are more severe when taken with centrally-acting drugs, especially alcohol.

Symptoms of overdose
Overdose is usually manifested by degrees of central nervous system depression ranging from drowsiness to coma. In mild cases, symptoms include drowsiness, somnolence, dysarthria, mental confusion, nystagmus and lethargy, in more serious cases, symptoms may include ataxia, areflexia, apnoea, hypotonia, hypotension, cardiorespiratory depression, rarely coma and very rarely death.
The respiratory depressant effect of benzodiazepines enhances pre-existing respiratory disturbances in patients with respiratory disease. In case of severe intoxication, depression of vital functions can occur, particularly of the respiratory centre (cyanosis, respiratory arrest, cardiac arrest; monitoring in an intensive care unit is required!).
As drug levels fall severe agitation, insomnia and, possibly, major convulsions may develop.

Management of overdose
In the management of overdose with any medicinal product, it should be borne in mind that multiple agents may have been taken.
Treatment is symptomatic. Respiration, heart rate, blood pressure and body temperature should be monitored and supportive measures taken to maintain cardiovascular and respiratory function. 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.

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 rarely 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

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anxiolytic drug , 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 demonstrates muscle relaxant and anticonvulsive properties. It is used in the short-term treatment of anxiety and tension states, as a sedative and premedicant, in the control of muscle spasm and in the management of alcohol withdrawal symptoms.

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

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. The rapidity of the rise in the serum level following rectal administration corresponds approximately to that following an intravenous dose but peak plasma concentrations are lower after rectal tubes than after intravenous administration. In adults maximal plasma concentrations following the administration of 10 mg diazepam in rectal solution are reached after about 10 - 30 minutes (ca. 150 - 400 ng/ml).

Distribution
Diazepam is extensively protein bound (95-99%). The volume of distribution is between 0.95 and 2 l/kg body weight depending on age. Diazepam is lipophilic and rapidly enters the cerebrospinal fluid. Diazepam and its main metabolite, N-desmethyldiazepam, cross the placenta and are secreted in breast milk.

Biotransformation, elimination
Diazepam is metabolised predominantly in the liver. Its metabolites, N-desmethyldiazepam (nordiazepam), 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.

Diazepam has a biphasic half life with an initial rapid distribution phase followed by a prolonged terminal elimination phase of 1-2 days. For the active metabolites N-desmethyldiazepam, temazepam and oxazepam, the half lives are 30-100 hours, 10-20 hours and 5-15 hours, respectively.

Excretion is mainly renal and also partly biliary. It is dependent on age as well as hepatic and renal function.

Metabolism and elimination 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 (liver cirrhosis, hepatitis), elimination is prolonged by a factor of 2.

5.3 Preclinical safety data

Chronic toxicity studies in animals have demonstrated no evidence of drug-induced changes. There are no long-term animal studies to investigate the carcinogenic potential of diazepam. Several investigations pointed to a weakly mutagenic potential at doses far above the human therapeutic dose.

Local tolerability has been studied following single and repeat dose applications into the conjunctival sac of rabbits and the rectum of dogs. Only minimal irritation was observed. There were no systemic changes.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzyl alcohol
Ethanol (96%)
Propylene glycol
Benzoic acid
Sodium benzoate
Purified Water

6.2 Incompatibilities

Not applicable**.**

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 25 °C.
Short-term exposure to higher temperatures (e.g. in emergencies), is of no consequence.

6.5 Nature and contents of container

Pack of 5 rectal tubes. Each tube contains 2.5 ml solution.
The tubes are made of low density polyethylene.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

to be completed nationally

8. MARKETING AUTHORISATION NUMBER(S)

to be completed nationally

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

to be completed nationally

10. DATE OF REVISION OF THE TEXT

2019-03-11