Diazepam Desitin® 10 mg Rectal solution

2. Qualitative and quantitative composition

Diazepam 10 mg in 2.5 ml

For a 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

For rectal administration only. Tubes are for single use only.

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 are provided in fixed, unit-doses of 5 and 10 mg, the dose is obtained by rounding upward to the next available dose.

Recommended doses:
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

two 10 mg tubes

Adults:
If no effect is seen after 10 minutes, the dose can be repeated in children or an additional 10mg tube 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.

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

Dosage reduction may also be required in patients with liver or kidney dysfunction.

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.

4.3 Contraindications
Known hypersensitivity to benzodiazepines or any of the excipients.

Myasthenia gravis.

Severe respiratory insufficiency sleep apnoea syndrome severe hepatic insufficiency As Diazepam Desitin contain benzyl alcohol, the products should not be used in premature babies.

4.4 Special warnings and precautions for use
Diazepam should be used with caution in patients with renal or hepatic dysfunction, chronic pulmonary insufficiency, closed angle glaucoma or organic brain changes, particularly arteriosclerosis.

Diazepam may enhance the effects of other CNS depressants, their concurrent use should be avoided.

In common with other Benzodiazepines the use of diazepam may be associated with anterograde amnesia and diazepam should not be used in cases of loss or bereavement as psychological adjustments may be inhibited.

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. Diazepam

should be used with extreme caution in patients with a history of alcohol or drug abuse.

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 self and others.

Diazepam should not be given to children without careful assessment of the need to do so; the duration of treatment must be kept to a minimum. Elderly should be given a reduced dose (see posology). A lower dose is also recommended for patients with chronic respiratory insufficiency due to the risk of respiratory depression. Diazepam is not indicated to treat patients with severe hepatic insufficiency as they may precipitate encephalopathy.

The dependence potential of diazepam is low when limited to short-term use. Withdrawal symptoms may occur with benzodiazepines following normal use of therapeutic doses for only short periods and may consist of headaches, muscle pain, extreme anxiety, tension, restlessness, confusion and irritability. In severe cases, the following symptoms may occur: derealization, depersonalization, hyperacusis, numbness and tingling of the extremities, hypersensitivity to light, voice 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.

Some loss of efficacy to the hypnotic effects of benzodiazepines may develop after repeated use for a few weeks.

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 (see also Undesirable Effects).

Psychiatric and paradoxical reactions

Reactions like restlessness, agitation, irritability, aggressiveness, delusion, rages, nightmares, hallucinations, psychoses, inappropriate behaviour and other adverse behavioural effects are known to occur when using benzodiazepines. Should this occur, use of the medicinal product should be discontinued.

They are more likely to occur in children and the elderly.

Diazepam Desitin contains more than 10 % alcohol.

4.5 Interaction with other medicinal products and other forms of interaction
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, antidepressants, hypnotics, narcotic analgesics, anaesthetics, antiepileptics, sedative antihistamines) or with agents that interfere with its metabolism by hepatic enzymes (e.g. isoniazid, disulfiram, cimetidine, omeprazole, oral contraceptives). In the case of narcotic analgesics enhancement of the euphoria may also occur leading to an increase in psychic dependence. 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.

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.

Diazepam metabolism is accelerated by theophylline and smoking.

Diazepam may interact with other hepatically metabolised drugs, causing inhibition (levodopa) or potentiation (phenytoin, muscle relaxants).

4.6 Pregnancy and lactation
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.

Women of childbearing potential should be warned to contact their physician if they intend to become or suspect that they are pregnant.

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 the product is administered during the late phase of pregnancy or during labour at high doses or repeated low doses hypothermia, hypotonia and moderate 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 for developing withdrawal symptoms in the postnatal period.

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

Diazepam Desitin contain benzyl alcohol. Benzyl alcohol may cross the placenta. The possible toxicity for premature babies should be taken into account after administration of Diazepam Desitin before or during labor.

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 should not drive or operate machines for at least 24 hours after administration of the last dose.

4.8 Undesirable effects

Elderly or debilitated patients are particularly susceptible to side effects and may require lower doses.

Cardiovascular disorders

Rare: Hypotension, bradycardia, chest pain.

Blood and the lymphatic system disorders

Rare: Blood dyscrasias including thrombocytopenia

Eye disorders

Common: Double vision.

Rare: Other visual disturbances

Musculoskeletal, connective tissue and bone disorders

Common: Muscle weakness.

Psychiatric disorders

Common: Reduced alertness, numbed emotions, confusion, anterograde amnesia, paradoxical reactions*.

In susceptible patients, an unnoticed depression may become evident.
Nervous system disorders Common: sedation, drowsiness, headaches, dizziness (with risk of falls in the elderly), ataxia, slurred speech, tremor, fatigue and a hangover effect.

Rare: Dry mouth.

Gastrointestinal disorders

Rare: Nausea, vomiting, epigastric pain, obstipation, diarrhoea.

Hepato-biliary disorders

Rare: Cholestatic jaundice, hepato-cellular jaundice.

Skin and subcutaneous tissue disorders

Allergic skin reactions, including urticaria and angioedema, are very rare.

Renal and urinary disorders

Rare: Urinary retention

Reproductive system and breast disorders

Rare: Changes in libido, menstrual disturbances.

Respiratory disorders

Rare: Laryngeal spasm, respiratory depression and apnoea.

General disorders

Rare: Increased appetite.

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 “Special warnings and special precautions for use”). Psychic dependence may occur. Abuse of benzodiazepines has been reported.

*Paradoxical reactions (restlessness, agitation, irritability, instability, aggressiveness, rages, delusions, nightmares, psychoses, hallucinations, inappropriate behaviour) are known to occur with benzodiazepines and are more likely in children and the elderly.

4.9 Overdose

a) Symptoms

Overdose is usually manifested by degrees of central nervous system depression ranging from drowsiness to coma. In mild cases, symptoms include drowsiness, mental confusion and lethargy, in more serious cases, symptoms may include ataxia, hypotonia, hypotension, respiratory depression, rarely coma and very rarely death.

b) Treatment

In the management of overdose with any medicinal product, it should be borne in mind that multiple agents may have been taken.

Following overdose by oral ingestion vomiting should be induced (within one hour) if the patient is conscious or gastric lavage undertaken with the airway protected if the patient is unconscious. If there is no advantage in emptying the stomach, activated charcoal should be given to reduce absorption. Treatment is symptomatic. Respiration, heart rate, blood pressure and body temperature should be monitored and supportive measures taken to maintain cardiovascular and respiratory function. Flumazenil is indicated to counteract the central depressive effect of benzodiazepines.

5. Pharmacological properties

Antiepileptic drug (N03AE),

Anxiolytic drug (N05BA)

5.1 Pharmacodynamic properties

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

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).

Diazepam is extensively protein bound (95-99%). The volume of distribution is between 0.95 and 2 l/kg 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.

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
None known.

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 and other handling
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 patients buttocks for a short time.