

## **SUMMARY OF PRODUCT CHARACTERISTICS**

### **1 NAME OF THE MEDICINAL PRODUCT**

Diazepam RecTubes 20mg

### **2 QUALITATIVE AND QUANTITATIVE COMPOSITION**

Diazepam 20mg in 5.0ml (4mg/ml)

For excipients, see 6.1

### **3 PHARMACEUTICAL FORM**

Rectal solution

A clear, colourless or almost yellow solution

### **4 CLINICAL PARTICULARS**

#### **4.1 Therapeutic indications**

Diazepam rectal tubes may be used in severe or disabling anxiety and agitation; epileptic and febrile convulsions; to relieve muscle spasm caused by tetanus; as a sedative in minor surgical and dental procedures, or other circumstances in which a rapid effect is required but where intravenous injection is impracticable or undesirable.

Diazepam rectal tubes may be of particular value for the immediate treatment of convulsions in children.

#### **4.2 Posology and method of administration**

Dosage depends on age and weight.

*Children:* 0.5mg/kg

(not recommended for use in children less than one year old)

*Adults:* 0.5mg/kg

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

The dose can be repeated every 12 hours.

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

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

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. Remove the cap.
- b) Insert the tube nozzle completely into the rectum. For children under 15kg, insert only halfway. 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- c) To avoid suction, maintain pressure on the tube until it is withdrawn from the rectum.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.

In anxiety, the duration of treatment should be as short as possible and generally not more than 8-12 weeks, including a tapering off process (see 4.4 Special Warnings and Special Precautions for Use).

Patients requiring chronic dosing should be checked regularly at the start of treatment in order to decrease, if necessary, the dose or frequency of administration, to prevent overdose due to accumulation.

### **4.3 Contraindications**

Known hypersensitivity to benzodiazepines or any of the ingredients.  
Severe or acute respiratory insufficiency/depression.  
Sleep apnoea syndrome

Severe hepatic insufficiency

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 not be used for the primary treatment of psychotic illness. In common with other benzodiazepines the use of diazepam may be associated with amnesia and diazepam should not be used in cases of loss or bereavement as psychological adjustments may be inhibited.

#### **4.4 Special warnings and precautions for use**

Diazepam should be used with caution in patients with renal or hepatic dysfunction (see 4.2 Posology and Method of Administration), chronic pulmonary insufficiency, porphyria, myasthenia gravis, coma, organic brain changes, particularly arteriosclerosis.

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

Elderly and debilitated patients are more prone to the CNS effects of benzodiazepines and, therefore, lower doses are required (see section 4.2 Posology and Method of Administration).

##### Dependence and withdrawal symptoms

Use of benzodiazepines may lead to the development of physical and psychological dependence upon these products. This should be considered when treating patients for more than a few days. The dependence potential of diazepam is low when limited to short-term use but increases with the dose and duration of treatment; it is also greater in patients with a history of alcohol or drug abuse.

Once physical dependence has developed, abrupt termination of treatment will be accompanied by withdrawal symptoms (See Section 4.8 Withdrawal symptoms).

Since the risk of withdrawal phenomena/rebound phenomena is greater after abrupt discontinuation of treatment, it is recommended that dose is decreased gradually.

When benzodiazepines with a long duration of action, such as diazepam, are being used, it is important to warn against changing to a benzodiazepine with a short duration of action, as withdrawal symptoms may develop.

##### Treatment of anxiety (see 4.2 Posology and Method of Administration)

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. 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.

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 or sleep disturbances and restlessness. 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.

Benzodiazepines should not be given to children for anxiety without careful assessment of the need to do so.

#### Amnesia

Benzodiazepines may induce anterograde amnesia (see 4.8 Undesirable Effects). The condition occurs most often several hours after administration. To reduce the risk, where appropriate and possible, patients should be able to have an uninterrupted sleep of 7-8 hours after administration.

#### 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 (See 4.8 Undesirable Effects). Should they occur, use of diazepam should be discontinued.

#### Use in patients with concomitant mental illness or addiction

Benzodiazepines 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 show aggressive behaviour towards self and others.

The excipient benzoic acid may be mildly irritant to mucous membranes.

This medicinal product contains 1.70mmol sodium per dose. To be taken into consideration by patients on a controlled sodium diet.

### **4.5 Interaction with other medicinal products and other forms of interaction**

Alcohol: Concomitant intake of alcohol is not recommended. The sedative effect of diazepam may be enhanced. This affects the ability to drive or use machines (see 4.7 Effects on ability to drive and use machines).

Anaesthetics and narcotic analgesics: Enhanced sedation or respiratory and cardiovascular depression. In the case of narcotic analgesics, enhancement of euphoria may also occur leading to an increase in psychological dependence.

Antibacterials: Agents that interfere with metabolism by hepatic enzymes (e.g. erythromycin and isoniazid) may reduce the clearance of benzodiazepines and potentiate their actions. Known inducers of hepatic enzymes, for example, rifampicin, may increase the clearance of benzodiazepines.

Antidepressants: Enhanced sedation or respiratory and cardiovascular depression. Diazepam plasma levels increased by concomitant fluvoxamine.

Antiepileptics: Enhanced sedation or respiratory and cardiovascular depression. Known inducers of hepatic enzymes, for example, carbamazepine and phenytoin, may increase the clearance of benzodiazepines. Serum phenytoin levels may rise, fall or remain unaltered. In addition, phenytoin may cause diazepam serum levels to fall. Concomitant sodium valproate may increase serum levels of diazepam, with associated drowsiness.

Antihistamines: Enhanced sedation or respiratory and cardiovascular depression with sedative antihistamines.

Antihypertensives: Enhanced hypotensive effect, enhanced sedative with alpha-blockers and possibly moxonidine.

Antipsychotics: Enhanced sedation or respiratory and cardiovascular depression. Increased plasma concentrations of zotepine. Severe hypotension, collapse, respiratory depression, potentially fatal respiratory arrest and unconsciousness have been reported in a few patients on benzodiazepines and clozapine. Caution is advised when initiating clozapine therapy in patients taking benzodiazepines.

Antivirals: Amprenavir and ritonavir have been shown to reduce the clearance of benzodiazepines and may potentiate their actions, with risk of extreme sedation and respiratory depression – avoid concomitant use.

Anxiolytics: Enhanced sedation or respiratory and cardiovascular depression with other anxiolytics.

Digoxin: Reduced clearance of digoxin.

Disulfiram: Has been shown to reduce clearance and may potentiate actions of benzodiazepines.

Dopaminergic agents: Diazepam may cause inhibition of levodopa.

Hypnotics: Enhanced sedation or respiratory and cardiovascular depression.

Lofexidine: Enhanced sedation or respiratory and cardiovascular depression.

Muscle relaxants: Increased CNS depressant effects with baclofen and tizanidine.

Nabilone: Enhanced sedation or respiratory and cardiovascular depression.

Nicotine: Diazepam metabolism is accelerated by smoking.

Oral contraceptives: Reduce the clearance of benzodiazepines and may potentiate their actions.

Sedatives: Enhanced sedation or respiratory and cardiovascular depression.

Theophylline: Diazepam metabolism is accelerated by theophylline.

Ulcer-healing drugs: Cimetidine and omeprazole may reduce the clearance of benzodiazepines and potentiate their actions.

#### **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.

If diazepam is prescribed to a woman of childbearing potential, she should be warned to contact her physician regarding discontinuation of the product if she intends to become, or suspects that she is, pregnant.

There may be a small increase in the risk of congenital malformations, particularly oral cleft, with the use of benzodiazepines in the first trimester. In labour, high single doses or repeated low doses have been reported to produce effects on the neonate, such as hypothermia, hypotonia, moderate respiratory depression and poor suckling (floppy infant syndrome) and irregularities in the foetal heart.

Infants born to mothers who take benzodiazepines chronically during the latter stages of pregnancy may develop physical dependence and may be at some risk for developing withdrawal symptoms in the postnatal period.

A small number of children exposed in utero to benzodiazepines have shown slow development in the early years but by four years of age have developed normally.

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

#### **4.7 Effects on ability to drive and use machines**

Patients treated with Diazepam Rectal Tubes should not drive or operate machines as sedation, amnesia, impaired concentration and impaired muscular function may adversely affect their ability. If insufficient sleep duration occurs, the likelihood of impaired alertness may be increased.

#### **4.8 Undesirable effects**

Elderly or debilitated patients are particularly susceptible to the CNS effects of benzodiazepines. It is recommended that dosage be limited to the smallest effective dose and increased gradually, if necessary, to decrease the possibility of development of ataxia, dizziness, and oversedation, which may lead to falls and other accidents (see 4.2 Posology and method of administration).

Cardiovascular: Hypotension, particularly with high dosage, bradycardia, chest pain.

Disorders of the eye: Visual disturbances.

Gastrointestinal: Dry mouth, gastrointestinal disturbances.

General: Fatigue and a hangover effect.

Haematological: Blood dyscrasias.

Hepatic: Raised liver enzymes, jaundice.

Immunological: Hypersensitivity reactions, including anaphylaxis, are rare.

Musculoskeletal: Muscle weakness.

Neurological: Headaches, confusion, slurred speech, tremor, reduced alertness. Anterograde amnesia may occur using therapeutic doses, the risk increasing at higher doses (see 4.4 Special Warnings and Special Precautions for Use). Amnestic effects may be associated with inappropriate behaviour.

Psychiatric disorders: Numbed emotions. In susceptible patients, an unnoticed depression may become evident. Paradoxical reactions (including aggressive behaviour, hostility, disinhibition, euphoria, excitation, irritability, increased anxiety and insomnia) are known to occur with benzodiazepines and may be quite severe with diazepam (see 4.4 Special Warnings and Special Precautions for Use). They are more likely to occur in children and the elderly.

Reproductive disorders: Changes in libido, gynaecomastia.

Respiratory disorders: Rarely, respiratory depression and apnoea, particularly with high dosage.

Skin: Skin reactions.

Urinary: Urinary retention, incontinence.

Withdrawal symptoms: Development of dependence is common after regular use, even in therapeutic doses for short periods, particularly in patients with a history of drug or alcohol abuse or marked personality disorders. Discontinuation of the therapy may result in withdrawal or rebound phenomena (see 4.4 Special Warnings and Special Precautions for Use). Symptoms of benzodiazepine withdrawal include anxiety, depression, impaired concentration, insomnia, headache, dizziness, tinnitus, loss of appetite, tremor, perspiration, irritability, perceptual disturbances such as hypersensitivity to physical, visual, and auditory stimuli and abnormal taste, nausea, vomiting, abdominal cramps, palpitations, mild systolic hypertension, tachycardia, and orthostatic hypotension.

Rare and more serious symptoms include muscle twitching, confusional or paranoid psychosis, convulsions, hallucinations, and a state resembling delirium tremens. Broken sleep with vivid dreams and increased REM sleep may persist for some weeks after withdrawal of benzodiazepines.

## **4.9 Overdose**

### **a) Symptoms**

The symptoms of mild overdose may include confusion, impairment of consciousness with somnolence or a sleep-like state, little or no respiratory depression, ataxia, dysarthria, hypotension, and muscular weakness. Cardiac rate and rhythm remain normal in the absence of anoxia or severe hypotension.

In severe overdose, deep coma or other manifestations of severe depression of brainstem vital functions, particularly the respiratory centre, may occur. As drug levels fall severe agitation, insomnia and, possibly, major convulsions may develop.

### **b) Treatment**

Treatment is symptomatic. Respiration, heart rate, blood pressure and body temperature should be monitored in intensive and supportive measures taken to maintain cardiovascular and respiratory function. Activated charcoal may be administered to increase clearance as well

as decrease absorption of diazepam. Flumazenil may be indicated to counteract the central depressive effect of benzodiazepines but expert advice is essential since adverse effects may occur (e.g. convulsions in patients dependent on benzodiazepines).

## **5 PHARMACOLOGICAL PROPERTIES**

### **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.

### **5.2 Pharmacokinetic properties**

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.

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 21/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. The time to reach steady state plasma levels is therefore 4-10 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.

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 and mental retardation in prenatally exposed children following overdose and intoxication with benzodiazepines.

## **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**

Three years.

**6.4 Special precautions for storage**

Do not store above 25°C.

**6.5 Nature and contents of container**

Packs of 2 or 5 rectal tubes each containing 5ml of solution.

The tubes are made of low density polyethylene.

**6.6 Special precautions for disposal**

No special requirements.

**7 MARKETING AUTHORISATION HOLDER**

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Ash Road North  
Wrexham  
LL13 9UF  
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