Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Diazepam RecTube 5 mg Rectal Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Diazepam 5mg in 2.5 ml (2mg/ml).

Excipients: each 2.5ml dose contains Benzoic acid (E210) 2.5mg, Sodium benzoate (E211) 122.5mg and Propylene glycol 1000mg.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Rectal solution
A clear, colourless to slightly 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 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(c) To avoid suction, maintain pressure on the tube until it is withdrawn from the rectum.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.

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.

Benzodiazepines should be avoided in patients with head injuries, as there is a risk of irreversible neurological damage.

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, muscle weakness, myasthenia gravis, coma, organic brain changes, particularly arteriosclerosis and in patients with hypoalbuminaemia who may be predisposed to an increased incidence of sedative side effects associated with diazepam.

Benzodiazepines may produce paradoxical exacerbation of seizures in patients with epilepsy.

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). Benzodiazepines should be used with caution in the elderly as long term use may be associated with an increase risk of developing dementia.

<u>Dependence and withdrawal symptoms</u>
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 the 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 excipients benzoic acid and sodium benzoate may be mildly irritant to skin, eyes, and mucous membranes. Propylene glycol may cause skin irritation.

4.5 Interaction with other medicinal products and other forms of interaction

Alcohol: Enhanced sedation or respiratory or CNS depression with concomitant administration of diazepam. Concomitant use should be avoided.

General 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. isoniazid) may reduce the clearance of diazepam and potentiate its action. Known inducers of hepatic enzymes, for example, rifampicin, may increase the clearance of diazepam.

Antidepressants: Enhanced sedation or respiratory or CNS depression with concomitant administration of mirtazapine or tricyclic antidepressants. Diazepam plasma levels increased by concomitant fluvoxamine or fluoxetine.

Antiepileptics: Enhanced sedation or respiratory and cardiovascular depression. Known inducers of hepatic enzymes, for example, carbamazepine, phenobarbital and phenytoin, may increase the clearance of benzodiazepines-, however, despite enzyme stimulation, the net effect of adding these antiepileptics can be augmentation of benzodiazepine-induced sedation. 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 with concomitant administration of ACE inhibitors or beta-blockers or calcium-channel blockers or vasodilator antihypertensives e.g. hydralazine. Enhanced sedative effect 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, ritonavir and saquinavir have been shown to reduce the clearance of diazepam and may potentiate its 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.

Diuretics: Enhanced hypotensive effect when benzodiazepines and diuretics are used concomitantly.

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.

Nitrates: Enhanced hypotensive effect when benzodiazepines and nitrates are used concomitantly.

Oral contraceptives: May reduce the clearance of diazepam and potentiate its actions.

Sedatives: Enhanced sedation or respiratory and cardiovascular depression.

Sodium oxybate: Enhanced CNS depressant effects of sodium oxybate with concomitant benzodiazepines.

Ulcer-healing drugs: Cimetidine, omeprazole and esomeprazole have been shown to reduce the clearance of diazepam and may potentiate its actions.

Xanthines: Diazepam metabolism is accelerated by theophylline. Sedative effects of diazepam reduced by caffeine. Sedative effects of diazepam reversed with concomitant administration of aminophylline.

4.6 Fertility, pregnancy and lactation

There is no evidence regarding the safety of diazepam in pregnancy, however, diazepam and its metabolite desmethyldiazepam freely cross the placenta and accumulate in the fetal circulation. 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 malformation, 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 hyperbilirubinaemia, hypothermia, hypotonia, 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

*Blood and lymphatic system disorders***:** Blood dyscrasias including thrombocytopenia and agranulocytosis have been reported with diazepam.

Immunological: Hypersensitivity reactions, including anaphylaxis, are rare.

Psychiatric disorders: Numbed emotions. In susceptible patients, an unnoticed depression may become evident. Paradoxical reactions (including aggression, rage, hostility, hallucinations, nightmares, disinhibition, euphoria, excitation, irritability, restlessness, increased anxiety, agitation, inappropriate behaviour and insomnia) are known to occur with benzodiazepines and may be quite severe with diazepam. They are more likely to occur in children and the elderly.

Nervous system disorders: Headaches, confusion, slurred speech, tremor, reduced alertness and drowsiness with diazepam. 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. Extrapyramidal effects and convulsions have occurred rarely with diazepam.

Eye disorders: Visual disturbances.

Ear and labyrinth disorders: Rarely, vertigo with diazepam

Cardiac disorders: bradycardia, chest pain.

Vascular disorders: Hypotension, particularly with high dosage

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

Gastrointestinal disorders: Rarely, salivation changes, including dry mouth or excessive salivation and; gastrointestinal disturbances including nausea with diazepam.

Hepatobiliary disorders: Raised liver enzymes, jaundice and cholestasis with diazepam.

Skin and subcutaneous tissue disorders: Skin reactions such as Steven-Johnson syndrome is known to occur with benzodiazepines, and urticaria, rash which are known to occur with diazepam.

Musculoskeletal and connective tissue disorders: Muscle weakness.

Renal and urinary disorders: Urinary retention, incontinence

Reproductive, puerperium and perinatal conditions: Inhibition of female orgasm, changes in libido, gynaecomastia and rarely, increased prolactin levels causing galactorrhoea with benzodiazepines. Plasma testosterone concentrations may be increased in men taking diazepam. Impotence has also been noted in men taking diazepam.

General disorders and administration site conditions: Fatigue and a hangover effect. Application site reactions, characterised by local irritation (e.g. pain/or burning) may occur with rectal administration of diazepam. Hypothermia has also been observed with diazepam.

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 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, muscle aches/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.

Drug class effects of benzodiazepines

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). Long term use of benzodiazepines in the elderly may be associated with an increased risk of dementia.

There have been rare reports of cutaneous reactions to benzodiazepines, including Stevens-Johnson syndrome.

Galactorrhoea, with and without hyperprolactinaemia, has been associated with benzodiazepine use. Female orgasm is inhibited by some central depressant and psychotropic drugs, including benzodiazepines.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Healthcare professionals are asked to report any suspected adverse reactions via the online reporting option (preferred method) accessible from the IMB homepage (http://www.imb.ie/). A downloadable report form is also accessible from the IMB website, which may be completed manually and submitted to the IMB via ‘freepost’ (see details below). Alternatively, the traditional post-paid ‘yellow card’ option may also be used.

FREEPOST
Pharmacovigilance Section
Irish Medicines Board
Kevin O'Malley House
Earlsfort Centre
Earlsfort Terrace
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Tel: +353 1 6764971
Fax: +353 1 6762517
Website: http://www.imb.ie/
e-mail: imbpharmacovigilance@imb.ie

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, nystagmus, 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. Coma usually lasts for only a few hours but in elderly people it may be more protracted and cyclical. Benzodiazepine respiratory depressant effects are more serious in patients with severe chronic respiratory disease.

As drug levels fall severe agitation, insomnia and, possibly, major convulsions may develop.

Benzodiazepines potentiate the effects of other central nervous system depressants, including alcohol.

b) Treatment

Treatment is symptomatic. Respiration, heart rate, blood pressure and body temperature should be monitored in intensive care and supportive measures taken to maintain cardiovascular and respiratory function.
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). Use of flumazenil can be hazardous in benzodiazepine-dependent patients. Flumazenil should not be used in mixed overdoses or as a diagnostic test. Flumazenil is contraindicated in the presence of drugs that reduce seizure threshold (e.g. tricyclic antidepressants).

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.

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 the 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 0.9 and 2 1/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 overdosage and intoxication with benzodiazepines.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzyl alcohol
Ethanol 96%
Propylene glycol
Benzoic acid (E210)
Sodium benzoate (E211)
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

Once foil is opened, use immediately.

6.4 Special precautions for storage

Do not store above 25°C.

Store in the original package in order to protect from light.

6.5 Nature and contents of container

Pack of 2 or 5 rectal tubes. Each tube contains 2.5 ml solution.

The tubes are made of low density polyethylene. The tubes have a nozzle attached for application. Each tube is individually presented in a foil wrap and placed in an outer carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

For single use only.

7 MARKETING AUTHORISATION HOLDER

Wockhardt UK Ltd
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Wrexham
LL13 9UF
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8 MARKETING AUTHORISATION NUMBER

PA 1339/6/4

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Date of first authorisation: 09 May 1996

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