SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Diazepam RecTubes 2.5mg Rectal Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Diazepam 2.5mg in 1.25ml (2mg/ml)

Excipients with known effect:

Each 2.5mg tube contains:
Benzoic acid (E210) –1.25mg
Sodium benzoate (E211) – 61.25mg
Propylene glycol –500mg.
Benzyl alcohol – 18.75 mg

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Rectal solution

A clear, colourless or almost yellow solution

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Diazepam has anticonvulsant, sedative, and muscle relaxant properties. It is used in the treatment of severe anxiety and tension states, as a sedative and premedication, in the control of muscle spasm, and in the management of alcohol withdrawal symptoms.

Diazepam rectal tubes may be used in acute severe anxiety and agitation, epileptic and febrile convulsions, tetanus, as a sedative in minor surgical and dental procedures, or in 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 infants and children.

4.2 Posology and method of administration

Prior to starting treatment with diazepam, a discussion should be held with patients to put in place a strategy for ending treatment with diazepam in order to minimise the risk of dependence, addiction and drug withdrawal syndrome (see section 4.4).
Treatment should be given for the shortest possible duration. If this medicine is being used for the treatment of epilepsy this medicine should be used for as long as the prescriber considers it necessary.

Posology

Sensitivity to diazepam varies with age.

Adults:	*0.5 mg/kg body weight*
Elderly patients:	*0.25 mg/kg body weight*

A maximum dose of 30 mg diazepam is recommended, unless adequate medical supervision and monitoring are available.

Paediatric population:
Children above 1 year of age: *0.5 mg/kg body weight*

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

The dose can be repeated every 12 hours.

Method of administration

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 patient's 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

- Hypersensitivity to the active substance, benzodiazepines or to any of the excipients listed in section 6.1.
- Phobic or obsessional states; chronic psychosis, hyperkinesis (paradoxical reactions may occur)
- Acute pulmonary insufficiency; respiratory depression, acute or chronic severe respiratory insufficiency (ventilatory failure may be exacerbated)
- Myasthenia gravis (condition may be exacerbated)
- Sleep apnoea (condition may be exacerbated)
- Severe hepatic insufficiency (elimination half-life of diazepam may be prolonged)
- Acute porphyria
- Diazepam should not be used as monotherapy in patients with depression or those with anxiety and depression as suicide may be precipitated in such patients
- Planning a pregnancy (see section 4.6)
- Pregnancy (unless there are compelling reasons – see section 4.6).

4.4 Special warnings and precautions for use

Drug dependence, tolerance and potential for abuse

Drug addiction comprises behavioural, cognitive and physiological phenomena that may include a strong desire to take the drug, difficulties in controlling drug use and possible tolerance or physical dependence. Physical dependence is a state that develops as a result of physiological adaptation in response to repeated drug use, which manifests as withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug. Addiction and dependence are related but distinct presentations and in discussing these themes, terminology that apportion blame to the individual should be avoided.

For all patients, prolonged use of this product may lead to drug dependence and addiction but can occur with short-term use at recommended therapeutic doses. The risks are increased in individuals with current or past history of substance misuse disorder (including alcohol misuse) or mental health disorder (e.g., major depression).

Additional support and monitoring may be necessary when prescribing for patients at risk of drug misuse.

A comprehensive patient history should be taken to document concomitant medications, including over-the-counter medicines and medicines obtained on-line, and past and present medical and psychiatric conditions.

Patients may find that treatment is less effective with chronic use and express a need to increase the dose to obtain the same level of symptom control as initially experienced. Patients may also supplement their treatment with additional medications to achieve the same effect. These could be signs that the patient is

developing tolerance. The risks of developing tolerance should be explained to the patient.

Overuse or misuse may result in overdose and/or death. It is important that patients only use medicines that are prescribed for them at the dose they have been prescribed and do not give this medicine to anyone else.

Patients should be closely monitored for signs of misuse, abuse, or addiction.

The clinical need for treatment with <active> should be reviewed regularly, with frequent assessments of patients being undertaken during the course of their treatment.

Tolerance

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

Dependence

Use of benzodiazepines may lead to the development of physical and psychic dependence upon these products. The risk of dependence increases with dose and duration of treatment; it is also greater in patients with a history of alcohol or drug abuse or in patients with marked personality disorders. Regular monitoring in such patients is essential, routine repeat prescriptions should be avoided and treatment should be withdrawn gradually.

Withdrawal

Once physical dependence has developed, abrupt termination of treatment will be accompanied by withdrawal symptoms. These may consist of headaches, muscle pain, extreme anxiety, tension, restlessness, confusion and irritability. In severe cases the following symptoms may occur: derealisation, depersonalisation, hyperacusis, numbness and tingling of the extremities, hypersensitivity to light, noise and physical contact, hallucinations or epileptic seizures.

Sudden discontinuation of treatment with diazepam in patients with epilepsy or other patients who have had a history of seizures can result in convulsions or epileptic status. Convulsions can also be seen following sudden discontinuation in individuals with alcohol or drug abuse.

Discontinuation should be gradual in order to minimise the risk of withdrawal symptoms.

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.

Drug withdrawal syndrome

Prior to starting treatment with <active>, a discussion should be held with patients to explain the risk of dependence, addiction, and drug withdrawal syndrome. A withdrawal strategy for ending treatment with <active> should also be put in place with the patient before starting treatment (there may be exceptions to this in specific clinical situations such as symptom management in end of life palliative care, and for use in epilepsy).

Drug withdrawal syndrome may occur upon abrupt cessation of therapy or dose reduction. When a patient no longer requires therapy, it is advisable to taper the dose gradually to minimise symptoms of withdrawal. Tapering from a high dose may take in excess of weeks or months. Patients should be informed of this when the medication is first prescribed.

The reduction schedule for a patient should be tailored to the individual and should be modified to allow intolerable withdrawal symptoms to improve before making the next reduction. If using a published withdrawal schedule, apply it flexibly to accommodate the person's preferences, changes to their circumstances and the response to dose reductions.

Suggest a slow stepwise rate of reduction proportionate to the existing dose, so that decrements become smaller as the dose is lowered, unless clinical risk is such that rapid withdrawal is needed.

If a patient develops withdrawal reactions, consider pausing the taper or increasing the dosage to the previous tapered dosage level.

If women take this drug during pregnancy, there is a risk that their newborn infants will experience neonatal withdrawal syndrome.

Psychiatric and paradoxical reactions

Reactions like restlessness, agitation, irritability, aggressiveness, delusion, rages, nightmares, hallucinations, psychosis, 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.

Duration of treatment

The duration of treatment should be as short as possible (see section 4.2) depending on the indication. The patient must be evaluated after a period of no more than 4 weeks and then regularly thereafter in order to assess the need for continued treatment, especially if the patient is free of symptoms. 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.

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. Moreover 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. There are indications that, in the case of benzodiazepines with a short duration of action, withdrawal phenomena can become manifest within the dosage interval, especially when the dosage is high.

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

Diazepam may induce anterograde amnesia. The condition occurs most often several hours after administering 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. Anterograde amnesia may occur using therapeutic doses, the risk increases with higher doses.

Specific patient groups

Paediatric population

Benzodiazepines 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. Safety and effectiveness of diazepam in paediatric patients below the age of 6 months have not been established.

Elderly should be given a reduced dose (see posology). Due to the myorelaxant effect there is a risk of falls and consequently hip fractures in the elderly.

A lower dose is also recommended for patients with chronic respiratory insufficiency due to the risk of respiratory depression.

Benzodiazepines are not indicated to treat patients with severe hepatic insufficiency as they may precipitate encephalopathy. In patients with chronic hepatic disease dosage may need to be reduced.

The usual precautions in treating patients with impaired renal function should be observed. In renal failure, the half-life of diazepam is not clinically significantly changed, and dose adjustment is usually not necessary.

Benzodiazepines are not recommended for the primary treatment of psychotic illness.

Benzodiazepines should not be used alone to treat depression or anxiety associated with depression (suicide may be precipitated in such patients).

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

Diazepam rectal tubes should not be used in phobic or obsessional states, as there is insufficient evidence of efficacy and safety in such conditions.

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

Diazepam rectal tubes should not be used concomitantly with disulfiram due to its ethanol content. A reaction may occur as long as two weeks after cessation of disulfram.

Diazepam rectal tubes contains 15 mg/ml benzyl alcohol. Benzyl alcohol may cause toxic reactions and anaphylactoid reactions in infants and children up to 3 years old.

Diazepam rectal tubes, contains benzoic acid (E210) and sodium benzoate (E211) and it may be mildly irritating to the skin and mucous membranes.

Diazepam rectal tubes, contains propylene glycol and may cause skin irritation.
Potentially suicidal individuals should not have access to large amounts of diazepam due to the risk of overdosing.

Risk from concomitant use of opioids:

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).

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions

If diazepam is used with other centrally acting agents, careful consideration has to be given to the pharmacology of the agents employed, particularly with compounds that may potentiate or be potentiated by the action of diazepam, such as neuroleptics, anxiolytics/sedatives, hypnotics, antidepressants, anticonvulsants, sedating antihistamines, antipsychotics, anaesthetics for general anaesthesia and narcotic analgesics. Such concomitant use may increase sedative effects and cause depression of respiratory and cardiovascular functions. Concomitant use of narcotic analgesics may promote psychic dependency due to enhancement of euphorigenic effects.

Concomitant use not recommended

Alcohol

Alcohol should not be consumed while undergoing treatment with diazepam due to additive CNS inhibition and enhanced sedation (see section 4.4).

Phenobarbital

Additive CNS inhibition. Increased risk of sedation and respiratory depression.

Clozapine

Pharmacodynamic synergism. Severe hypotension, respiratory depression, unconsciousness and potentially fatal respiratory and/or cardiac arrest. Therefore, concomitant use is not recommended and should be avoided.

Sodium oxybate

Avoid concomitant use (enhanced effects of sodium oxybate).

Special caution with concomitant use

Theophylline

A proposed mechanism is competitive binding of theophylline to adenosine receptors in the brain. Counteraction of the pharmacodynamic effects of diazepam, e.g. reduction of sedation and psychomotor effects.

Muscle relaxants (suxamethonium, tubocurarin)

Possible pharmacodynamic antagonism. Modified intensity of neuromuscular blockage.
Other drugs enhancing the sedative effect of diazepam

Lofexidine and the muscle-relaxants - baclofen and tizanidine.

Antihypertensives, vasodilators& diuretics:

Enhanced hypotensive effect with ACE inhibitors, alpha-blockers, angiotensin–II receptor antagonists, calcium channel. blockers adrenergic neurone blockers, beta-blockers, moxonidine, nitrates, hydralazine, minoxidil, sodium nitroprusside and diuretics. Enhanced sedative effect with alpha-blockers or moxonidine.

Dopaminergics

Possible antagonism of the effect of levodopa.

Caffeine

Concurrent use may result in reduced sedative and anxiolytic effects of diazepam.

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. Oxazepam and temazepam are further conjugated to glucuronic acid. Inhibitors of CYP3A4 and/or CYP2C19 can give rise to increased concentrations of diazepam while enzyme inducing drugs such as rifampicin, hypericum perforatum and certain antiepileptics can result in substantially decreased plasma concentrations of diazepam.

Concomitant use not recommended

Inducers

Rifamycins (rifampicin)

Rifampicin is a potent inducer of CYP3A4 and substantially increases the hepatic metabolism and clearance of diazepam. In a study with healthy subjects administered 600 mg or 1.2 g rifampicin daily for 7 days, the clearance of diazepam was increased by about fourfold. Co-administration with rifampicin gives rise to substantially decreased concentrations of diazepam. Reduced effect of diazepam. The concomitant use of rifampicin and diazepam should be avoided.

Carbamazepine

Carbamazepine is a known inducer of CYP3A4 and increases hepatic metabolism of diazepam. This can result in up to three-fold greater plasma clearance and a shorter half-life of diazepam. Reduced effect of diazepam.

Phenytoin

Phenytoin is a known inducer of CYP3A4 and increases hepatic metabolism of diazepam. Reduced effect of diazepam.

The metabolism of phenytoin may be increased or decreased or remain unaltered by diazepam in an unpredictable way. Increased or decreased serum concentration of phenytoin. Phenytoin concentrations should be monitered more closely when diazepam is added or discontinued.

Phenobarbital

Phenobarbital is a known inducer of CYP3A4 and increases hepatic metabolism of diazepam. Reduced effect of diazepam.

Inhibitors

Antiviral agents (atazanavir, ritonavir, delavirdine, efavirenz, indinavir, nelfinavir, saquinavir)

Antiviral agents may inhibit the CYP3A4 metabolic pathway for diazepam. Increased risk of sedation and respiratory depression. Therefore, concomitant use should be avoided.

Azoles (fluconazole, itraconazole, ketoconazole, voriconazole)

Increased plasma concentration of benzodiazepines, due to inhibition of the CYP3A4 and/or CYP2C19 metabolic pathway.

Fluconazole: Co-administration with 400 mg fluconazole on the first day and 200 mg on the second day increased the AUC of a single 5 mg oral dose of diazepam 2.5-fold and prolonged the half-life from 31 hours to 73 hours.

Voriconazole: A study with healthy subjects found that 400 mg voriconazole twice daily on the first day and 200 mg twice daily on the second day increased the AUC of a single 5 mg oral dose of diazepam 2.2-fold and prolonged the half-life from 31 hours to 61 hours.

Increased risk of undesired effects and toxicity of benzodiazepine. Concomitant use should be avoided or the dose of diazepam reduced.

Fluvoxamine

Fluvoxamine inhibits both CYP3A4 and CYP2C19 which leads to inhibition of the oxidative metabolism of diazepam. Co-administration with fluvoxamine results in an increased half-life and an approximately 190% increased plasma concentrations (AUC) of diazepam. Drowsiness, reduced psychomotor performance and memory. Preferably, benzodiazepines that are metabolised via a non-oxidative pathway should be used instead.

Special caution with concomitant use

Inducers

Corticosteroids

Chronic use of corticosteroids may cause increased metabolism of diazepam due to induction of cytochrome P450 isoenzyme CYP3A4, or of enzymes responsible for glucuronidation. Reduced effects of diazepam.

Inhibitors

Cimetidine

Cimetidine inhibits the hepatic metabolism of diazepam, reducing its clearance and prolonging its half-life. In one study where 300 mg cimetidine was administered four times daily for 2 weeks, the combined plasma level of diazepam and its active metabolite, desmethyldiazepam was found to be increased by 57%, but reaction times and other motor and intellectual tests remained unaffected. Increased action of diazepam and increased risk of drowsiness. Reduction of the diazepam dose may be necessary.

Omeprazole

Omeprazole inhibits the CYP2C19 metabolic pathway for diazepam. Omeprazole prolongs the elimination half-life of diazepam and increases the plasma concentrations (AUC) of diazepam approximately between 30% - 120%. The effect is seen in CYP2C19 extensive metabolisers but not in slow metabolisers, with a low clearance of diazepam. Increased action of diazepam. Reduction of the diazepam dose may be necessary.

Esomeprazole

Esomeprazole inhibits the CYP2C19 metabolic pathway for diazepam. Co-administration with ezomeprazole results in an extended half-life and an increase in plasma concentrations (AUC) of diazepam by approximately 80%. Increased effect of diazepam. Reduction of the diazepam dose may be necessary.

Isoniazid

Isoniazid inhibits the CYP2C19 and CYP3A4 metabolic pathway for diazepam. Co-administration with 90 mg isoniazid twice daily for 3 days resulted in a prolonged elimination half-life of diazepam and in a 35% increased plasma concentration (AUC) of diazepam. Increased effect of diazepam.

Itraconazole

Increased plasma concentration of diazepam due to inhibition of the CYP3A4 metabolic pathway. In a study with healthy subject given 200 mg itraconazole daily for 4 days increased the AUC of a single 5 mg oral dose of diazepam by about 15%, but there was no clinically significant interaction as determined by psychomotor performance tests. Possible increased effect of diazepam.

Fluoxetine

Fluoxetine inhibits the metabolism of diazepam via CYP2C19 and other pathways, resulting in elevated plasma concentrations and decreased clearance of diazepam. Increased effect of diazepam. Concomitant use should be monitored closely.

Disulfiram

Reduced metabolism of diazepam leading to prolonged half-life and increased plasma concentration of diazepam. The elimination of the N-desmethyl metabolites of diazepam is slowed down which can give rise to marked sedative effects. Increased risk of CNS inhibition such as sedation.

Oral contraceptives

Inhibition of oxidative metabolism of diazepam. Increased effects of diazepam Co-administration of diazepam and combined oral contraceptives has been known to cause breakthrough bleeding. The mechanism of this reaction is unknown. Breakthrough bleeding, but no contraceptive failures have been reported.

Grapefruit juice

Grapefruit juice is believed to inhibit CYP3A4 and increases the plasma concentration of diazepam. Cmax is increased by 1.5 times and AUC by 3.2 times. Possible increased effect of diazepam.

Other

Levodopa

Concomitant use with diazepam resulted in reduced effects of levodopa in a small number of case reports.

Valproic acid

Valproate displaces diazepam from its plasma albumin binding sites and inhibits its metabolism. Increased serum concentrations of diazepam.

Ketamine

Due to similar oxidative processes, diazepam competitively inhibits ketamin metabolism. Pre-medication with diazepam leads to prolonged half-life of ketamine with enhanced effect as a result. Increased sedation.

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).

4.6 Fertility, pregnancy and lactation

In animal studies administration of benzodiazepines during gestation has lead to cleft palate, CNS malformation and permanent functional disturbances in the offspring.

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

In labour, high single doses or repeated low doses have been reported to produce hypotonia, poor sucking, and hypothermia in the neonate, and irregularities in the foetal heart.

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

If, for compelling medical reasons, the product is administered during the late phase of pregnancy, or during labour at high doses, effects on neonate, such as hypothermia, hypotonia and moderate respiratory depression, can be expected, due to the pharmacological action of the compound.

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

Breast-feeding
Since benzodiazepines are found in breast milk, benzodiazepines should not be given to

breast feeding mothers.

Fertility
Studies in animals have shown a decrease in pregnancy rate and reduced number of surviving offspring in rats at high doses. There are no human data.

4.7 Effects on ability to drive and use machines

Sedation, amnesia, impaired muscular function may adversely effect the ability to drive or use machines. If insufficient sleep occurs, the likelihood of impaired alertness may be increased (see also Interactions). Patients should be warned that effects on the central nervous system may persist into the day after administration even after a single dose.

This medicine can impair cognitive function and can affect a patient's ability to drive safely. This class of medicine is in the list of drugs included in regulations under 5a of the Road of Traffic Act 1988. When prescribing this medicine, patients should be told:

- The medicine is likely to affect your ability to drive
- Do not drive until you know how the medicine affects you
- It is an offence to drive while under the influence of this medicine.
- However, you would not be committing an offence (called 'statutory defence') if:
    - The medicine has been prescribed to treat a medical or dental problem and
    - You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and
    - It was not affecting your ability to drive safely

4.8 Undesirable effects

During the first week of administration or when high doses are used they may have a sedative effect and cause some degree of drowsiness. In such cases there is an advantage in administering half the total daily intake at night, the remainder being given in divided doses during the day.

The elderly and debilitated are particularly sensitive to the effects of central depressant drugs and may experience confusion, especially if organic brain changes are present; the dosage of diazepam should not exceed one-half that recommended for other adults.

Increased salivary and bronchial secretion has been reported, in particular in children.

Amnesia
Anterograde amnesia may occur using therapeutic dosages, the risk increasing at higher dosages. Amnestic effects may be associated with inappropriate behaviour (see section 4.4).

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

The frequencies of adverse events are ranked according to the following:
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).

System organ class	***Frequency***	***Undesirable effects***
Blood and lymphatic system disorders	Very rare	Leukopenia
	Rare	Blood dyscrasias
Immune system disorders	Very rare	Anaphylaxis.
Psychiatric disorders	Common	Confusion.
	Rare	Psychiatric and paradoxical reactions such as excitation, restlessness, agitation, irritability, aggressiveness, delusion, rages, hallucinations, psychoses, memory loss, nightmares, inappropriate behaviour and other adverse behavioural effects.[a] Emotional poverty, decreased alertness and depression.[b]
	Not known	the uncovering of depression with suicidal tendencies and dependence (see section 4.4). Abuse of benzodiazepines
Nervous system disorders	Very common	Drowsiness.
	Common	Sedation, unsteadiness, ataxia (these effects are doserelated and may persist into the following day even after a single dose), impaired motor ability, tremor.
	Uncommon	Anterograde amnesia.[c,] Concentration difficulties, balance disorders, dizziness, headache, slurred speech.
	Rare	Unconsciousness, insomnia, dysarthria, light headedness, vertigo, dystonic effects

Eye disorders	Not known	Reversible disorders of vision: blurred vision, diplopia, nystagmus.
Cardiac disorders	Rare	Bradycardia, heart failure including cardiac arrest.
Vascular disorders	Rare	Hypotension, syncope.
Respiratory, thoracic and mediastinal disorders	Uncommon	Respiratory depression.
	Rare	Respiratory arrest, increased bronchial secretion.
	Not known	Apnoea
Gastrointestinal disorders	Uncommon	Gastrointestinal disorders (nausea, vomiting, constipation, diarrhoea), increased salivary secretion.
	Rare	Dry mouth, increased appetite.
Hepatobiliary disorders	Rare	Jaundice, changes of hepatic parameters (elevation of ALT, AST, alkaline phosphatase).
Skin and subcutaneous tissue disorders	Uncommon	Allergic skin reactions (itching, erythema, rash).
Musculoskeletal and connective tissue disorders	Uncommon	Myasthenia.
Renal and urinary disorders	Rare	Urinary retention, incontinence.
Reproductive system and breast disorders	Rare	Gynaecomastia, impotence, increased or reduced libido or libido fluctuations.
General disorders and administration site conditions	Common	Fatigue**,** withdrawal symptoms (anxiety, panic, palpitations, sweating, tremor, gastrointestinal disorders, irritability, aggression, disrupted sensory perception, muscle spasms, general malaise, loss of appetite, paranoid psychosis, delirium and epileptic attacks).[d]
Investigations	Very rare	Elevation of transaminases

a Known to occur when using benzodiazepines or benzodiazepine-like agents. These reactions may be quite severe. They are more likely to occur in children and the elderly. Diazepam should be discontinued if such symptoms occur (see section 4.4).

b Pre-existing depression may be unmasked during benzodiazepine use.

c May occur using therapeutic dosages, the risk increasing at higher dosages. Amnestic effects may be associated with inappropriate behaviour (see section 4.4).

d The likelihood and degree of severity of withdrawal symptoms is dependent on the duration of treatment, dose level and degree of dependency.

Psychiatric disorders:

Drug dependence (see section 4.4)

General disorders and administration site conditions:
Drug withdrawal symptoms (see 4.4 Special warnings and precautions). Symptoms reported following discontinuation of benzodiazepines include headaches, muscle pain, anxiety, tension, depression, insomnia, restlessness, confusion, irritability, sweating, and the occurrence of “rebound” phenomena whereby the symptoms that led to treatment with benzodiazepines recur in an enhanced form. These symptoms may be difficult to distinguish from the original symptoms for which the drug was prescribed.

In severe cases the following symptoms may occur: derealisation; depersonalisation; hyperacusis; tinnitus; numbness and tingling of the extremities; hypersensitivity to light, noise, and physical contact; involuntary movements; hyperreflexia, tremor, nausea, vomiting; diarrhoea, abdominal cramps, loss of appetite, agitation, palpitations, tachycardia, panic attacks, vertigo, short-term memory loss, hallucinations/delirium; catatonia; hyperthermia, convulsions. Convulsions may be more common in patients with pre-existing seizure disorders or who are taking other drugs that lower the convulsive threshold such as antidepressants.

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 Yellow Card Scheme;
website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Features

The symptoms of diazepam overdose are mainly an intensification of the therapeutic effects (ataxia, drowsiness, dysarthria, sedation, muscle weakness, profound sleep, hypotension, bradycardia, nystagmus) or paradoxical excitation. In most cases only observation of vital functions is required.

Extreme overdosage may lead to coma, areflexia, cardiorespiratory depression and apnoea, requiring appropriate countermeasures (ventilation, cardiovascular support). Benzodiazepine respiratory depressant effects are more serious in patients with severe chronic obstructive airways disease. Severe effects in overdose also include rhabdomyolysis and hypothermia.

Patients should be informed of the signs and symptoms of overdose and to ensure that family and friends are also aware of these signs and to seek immediate medical help if they occur.

Management

Maintain a clear airway and adequate ventilation.

Monitoring level of consciousness, respiratory rate, pulse oximetry and blood pressure in symptomatic patients.

Consider arterial blood gas analysis in patients who have a reduced level of consciousness (GCS < 8; AVPU scale P or U) or have reduced oxygen saturations on pulse oximetry.

Correct hypotension by raising the foot of the bed and by giving an appropriate fluid challenge. Where hypotension is thought mainly due to decreased systemic vascular resistance, drugs with alpha-adrenergic activity such as noradrenaline or high dose dopamine (10-30 micrograms/kg/min) may be beneficial. The dose of inotrope should be titrated against blood pressure.

If severe hypotension persists despite the above measures, then central venous pressure monitoring should be considered.

Supportive measures are indicated depending on the patient's clinical state.

Benzodiazepines are not significantly removed from the body by dialysis.

Flumazenil, a benzodiazepine antagonist, is not advised as a routine diagnostic test in patients with reduced conscious level. It may sometimes be used as an alternative to ventilation in children who are naive to benzodiazepines, or in patients with COPD to avoid the need for ventilation. It is not necessary or appropriate in cases of poisoning to fully reverse the benzodiazepine effect. Flumazenil has a short half-life (about an hour) and in this situation an infusion may therefore be required. Flumazenil is contraindicated when patients have ingested multiple medicines, especially after co-ingestion of a benzodiazepine and a tricyclic antidepressant or any other drug that causes seizures. This is because the benzodiazepine may be suppressing seizures induced by the second drug; its antagonism by flumazenil can reveal severe status epilepticus that is very difficult to control.

Contraindications to the use of flumazenil include features suggestive of a tricyclic antidepressant ingestion including a wide QRS, or large pupils. Use in patients postcardiac arrest is also contraindicated.

It should be used with caution in patients with a history of seizures, head injury, or chronic benzodiazepine use.

Occasionally a respirator may be required but generally few problems are encountered, although behavioural changes are likely in children.

If excitation occurs, barbiturates should not be used.

Effects of overdose are more severe when taken with centrally-acting drugs, especially alcohol, and in the absence of supportive measures, may prove fatal.

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Diazepam, ATC code: N05BA01

Diazepam has anticonvulsant, sedative and muscle relaxant 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.

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 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
Sodium benzoate
Purified Water

6.2 Incompatibilities

None known.

6.3 Shelf life

Three years

Once foil is opened, use immediately

6.4 Special precautions for storage

Do not store above 25^{o}C.

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

6.5 Nature and contents of container

Packs of 2 or 5 rectal tubes each containing 1.25ml of 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

For single use only

7 MARKETING AUTHORISATION HOLDER

Wockhardt UK Ltd
Ash Road North
Wrexham
LL13 9UF
UK

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PL 29831/0067

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