Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Stesolid rectal solution 10mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Diazepam 4 mg/ml

Each tube contains 10 mg of diazepam
Excipients with known effect: Benzoic acid 1 mg/ml and Propylene Glycol 400 mg/ml

For the full list of excipients, see Section 6.1

3 PHARMACEUTICAL FORM

Rectal solution
Clear, colourless to yellowish 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.

Stesolid rectal tubes 10mg 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.

4.2 Posology and method of administration

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 30mg 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

4.3 Contraindications

Stesolid is contraindicated for patients with:

- Hypersensitivity to benzodiazepines or to one or more of the excipients (see section 6.1)
- Phobic or obsessional states; chronic psychosis, hyperkinesis (paradoxical reactions may occur)
- Myasthenia gravis (condition may be exacerbated)
- Sleep apnoea syndrome (condition may be exacerbated)
- Acute pulmonary insufficiency; respiratory depression, acute or chronic severe respiratory insufficiency (ventilator failure 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

Concomitant use of alcohol/CNS depressants
The concomitant use of diazepam with alcohol and/or CNS depressants should be avoided. Such concomitant use has the potential to increase the clinical effects of diazepam possibly including severe sedation, clinically relevant respiratory and/or cardio-vascular depression (see section 4.5)

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).

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

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

Dependence
Treatment with diazepam can result in mental or physical dependency. 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.

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.

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 minimize the risk of withdrawal symptoms.

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 (see also section 4.8). Anterograde amnesia may occur using therapeutic doses, the risk increases with higher doses.

Psychiatric and 'paradoxical' reactions
Paradoxical reactions (such as restlessness, agitation, irritability, aggressiveness, delusion, rages, nightmares, hallucinations, psychoses, inappropriate behaviour and other adverse behavioural effects) have been reported from the use of benzodiazepines. Such reactions are possibly seen more often in the treatment of children and elderly patients and should result in the discontinuation of treatment.

Specific patient groups
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 patients should be given a reduced dose (see section 4.2). Due to the myorelaxant effect of benzodiazepines there is a risk of falls and consequently of 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).

Potentially suicidal individuals should not have access to large amounts of diazepam due to the risk of overdosing.

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.

Stesolid 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. Stesolid 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

Excipients
Benzoic acid and sodium benzoate are mild irritants to the skin, eyes and mucous membranes.

Propylene glycol may cause skin irritation.

4.5 Interaction with other medicinal products and other forms of interactions

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

Mechanism: Additive CNS inhibition.
Effect: Increased risk of sedation and respiratory depression.

Clozapine

Mechanism: Pharmacodynamic synergism.
Effect: 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

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

Muscle relaxants (suxamethonium, tubocurarin)

Mechanism: Possible pharmacodynamic antagonism.
Effect: Modified intensity of neuromuscular blockage.

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).

Other drugs enhancing the sedative effect of diazepam

Lofexidine and the muscle-relaxants - baclofen and tizanidine.

Antihypertensives, vasodilators & diuretics:
Enhanced hypotensive effect with ACEinhibitors, 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)
Mechanism: 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.
Effect: Reduced effect of diazepam. The concomitant use of rifampicin and diazepam should be avoided.

Carbamazepine
Mechanism: 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.
Effect: Reduced effect of diazepam.

Phenytoin
Mechanism – effect on diazepam: Phenytoin is a known inducer of CYP3A4 and increases hepatic metabolism of diazepam.
Mechanism – effect on phenytoin: The metabolism of phenytoin may be increased or decreased or remain unaltered by diazepam in an unpredictable way.
Effect on diazepam: Reduced effect of diazepam.
Effect on phenytoin: Increased or decreased serum concentration of phenytoin. Phenytoin concentrations should be monitored more closely when diazepam is added or discontinued.

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

Inhibitors

Antiviral agents (atazanavir, ritonavir, delavirdine, efavirenz, indinavir, nelfinavir, saquinavir)
Mechanism: Antiviral agents may inhibit the CYP3A4 metabolic pathway for diazepam.
Effect: Increased risk of sedation and respiratory depression. Therefore, the concomitant use should be avoided.

Azoles (fluconazole, itraconazole, ketoconazole, voriconazole)
Mechanism: 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.
Effect: Increased risk of undesired effects and toxicity of benzodiazepine. Concomitant use should be avoided or the dose of diazepam reduced.

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

Inhibitors

Cimetidine
Mechanism: 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.
Effects: Increased action of diazepam and increased risk of drowsiness. Reduction of the diazepam dose may be necessary.

Omeprazole
Mechanism: 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.
Effects: Increased action of diazepam. Reduction of the diazepam dose may be necessary.

Esomeprazole
Mechanism: 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%.
Effect: Increased effect of diazepam. Reduction of the diazepam dose may be necessary.

Isoniazid
Mechanism: 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.
Effect: Increased effect of diazepam.

Itraconazole
Mechanism: 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.
Effect: Possible increased effect of diazepam.

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

Disulfiram
Mechanism: 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.
Effect: Increased risk of CNS inhibition such as sedation.

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

Grapefruit juice
Mechanism: Grapefruit juice is believed to inhibit CYP3A4 and increases the plasma concentration of diazepam. C_{max} is increased by 1.5 times and AUC by 3.2 times.
Effect: Possible increased effect of diazepam.

Other

Cisapride
Mechanism: Accelerated absorption of diazepam.
Effect: Temporary increase of the sedative effects of orally administered diazepam.

Levodopa
Mechanism: Unknown.
Effect: Concomitant use with diazepam resulted in reduced effects of levodopa in a small number of case reports.

Valproic acid
Mechanism: Valproate displaces diazepam from its plasma albumin binding sites and inhibits its metabolism.
Effect: Increased serum concentrations of diazepam.

Ketamine
Mechanism: 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.
Effect: Increased sedation.

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.

Women of childbearing potential
Any woman wishing to become or suspecting that she is pregnant should be urged to contact her doctor concerning stopping the treatment.

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 benzodiazepines 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 took 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:
Diazepam is excreted in breast-milk. Diazepam should not be used during breast-feeding.

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

Diazepam significantly affects the ability to drive and to operate machines.
This is usually due to impaired motor skills, tremor, somnolence, amnesia, impaired concentration and tiredness (see section 4.8).
The effect can be observed immediately after the start of treatment and it can last for several days following discontinuation due to the long half-life of diazepam.
If insufficient sleep duration occurs, the likelihood of impaired alertness may be increased.

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, rage, hallucinations, psychoses, memory loss, nightmares, inappropriate behavior 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 dose-related 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, lightheadedness, 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 dosage. 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.

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 HPRA Pharmacovigilance, Website: www.hpra.ie.

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.

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 inpatients 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 post cardiac 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 behavioral 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 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anxiolytic, belonging to the benzodiazepine group. ATC code: N05BA01

Mode of action: Diazepam is an agonist which binds to specific benzodiazepine receptors in the brain, thereby enhancing the normal transmission of the signal substance, GABA. GABA blocks the transmission of important signal substances, whereby neuronal inhibition is achieved. The muscle-relaxing effect is mediated by spinal synaptic reflexes.

Pharmacodynamic effects: Diazepam is an anxioltic, which acts by suppressing the symptoms of anxiety, agitation, restlessness, and tension. Further diazepam has anticonvulsant, sedative, and muscle relaxing properties.

5.2 Pharmacokinetic properties

Absorption: Diazepam is quickly absorbed from the rectal mucosa. The bioavailability is 100%.

Distribution: After rectal administration of diazepam 10mg a maximum serum concentration of about 300 ng/ml is reached after 10-15 minutes.
Further distribution brings about a perceptible fall in the plasma concentration lasting 2-4 hours. Protein binding: 96-98%. Diazepam is lipid soluble, penetrates tissue well, and passes the blood-brain barrier.

Metabolism: Diazepam is metabolised chiefly in the liver by hydroxylation and glucuronidation. The half-life of the metabolite, N-desmethyldiazepam, which is biologically active, is 2-4 days.

Elimination: Diazepam is eliminated mainly in the urine as metabolites, and about 10% is eliminated with the faeces. Half-life: Adults: 20-50 hours; elderly patients: 70-100 hours. Children: premature infants: 40-110 hours; new-born, full-term infants: about 30 hours; infants up to 1 year: about 10 hours; above 1 year: about 20 hours.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential.

Impairment of fertility
Reproductive studies in rats showed decreases in the number of pregnancies and in the number of surviving offspring following administration of diazepam prior to and during mating and throughout gestation and lactation.

Teratogenicity
Exposure to diazepam in the first trimester produces an increased risk of cleft palate (mice), CNS abnormalities and permanent functional disorder in the offspring (rats).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzoic acid
Ethanol

Propylene glycol
Sodium benzoate
Benzyl alcohol
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

30 months.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Box containing sealed low density polyethylene tubes, single packed in alufoil.

Package size: 5 x 2.5ml.

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

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Accord Healthcare Ireland Ltd.
Euro House
Euro Business Park
Little Island
Cork T45 K857
Ireland

8 MARKETING AUTHORISATION NUMBER

PA2315/137/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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