NEW ZEALAND DATA SHEET

1. PRODUCT NAME

Stesolid® Rectal Tubes

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tube contains 5 mg diazepam in 2.5 mL or 10 mg diazepam in 2.5 mL solution.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Stesolid® is a clear colourless-to-slightly-yellowish aqueous liquid, in a yellow polyethylene tube.

Stesolid® is available in a 5mg/2.5mL tube or 10mg/2.5mL tube, for rectal administration.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment of febrile and childhood convulsions, where rapid onset of anticonvulsant activity is imperative.

4.2 Dose and method of administration

Dose

AGE GROUP	Dosage in mg	Number of 5mg/2.5mL tubes		Number of 10mg/2.5mL tubes
Adults	10 to 20 mg	2 to 4	**OR**	1 to 2
Children (7-12 years)	10 mg	2		1
Children (1-6 years)	5 mg	1		Not applicable

If necessary, these doses may be repeated once only, after five minutes

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

Method of administration

For rectal administration only.

1. Position the patient with the buttocks raised. If a child, place the child across your knee.
2. Remove the tube cap and coat the opening of the nozzle with a little Vaseline.
3. Insert the **entire** length of the nozzle (about 5cm) into the anus.
   In children less than three years of age, insert the nozzle **halfway** only.
4. IMPORTANT: In order to empty the tube, the nozzle must point downwards.
5. When the tube feels empty, keep squeezing it, while simultaneously withdrawing the nozzle.
6. Keep the patient in the same position and press the buttocks together for a few minutes, to avoid seepage.

4.3 Contraindications

Hypersensitivity to diazepam or to benzodiazepines, or to any of the excipients listed in this data sheet (see Section 6.1 List of excipients).

Myasthenia gravis, severe respiratory insufficiency, sleep apnoea syndrome, severe hepatic insufficiency.

Not for IV, IM or oral administration.

4.4 Special warnings and precautions for use

Concomitant use of alcohol or other CNS depressants

The concomitant use of diazepam with alcohol and/or other 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 cardiovascular depression.

Risks from Concomitant Use with Opioids

Concomitant use of benzodiazepines, including Stesolid®, and opioids may result in profound sedation, respiratory depression, coma, and death. Because of these risks, reserve concomitant prescribing of benzodiazepines and opioids for use in patients for whom alternative treatment options are inadequate.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioids alone. If a decision is made to prescribe Stesolid® concomitantly with opioids, prescribe the lowest effective dosages and minimum durations of concomitant use, and follow patients closely for signs and symptoms of respiratory depression and sedation. Advise both patients and caregivers about the risks of respiratory depression and sedation when Stesolid® is used with opioids [see Section 4.5 Interactions with other medicines and other forms of interaction].

History of alcohol or drug abuse

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

Tolerance

After chronic use, tolerance will occur. For withdrawal of benzodiazepines, doses should be tapered off gradually, according to clinical response.

Dependence

Benzodiazepines can cause dependency, even in short-term use. Any course of treatment should be as brief as possible.

The risk of dependence developing is greater in patients with a history of alcohol or drug abuse or with marked personality disorders. Extreme caution should be exercised when prescribing benzodiazepines to these individuals. Regular monitoring is essential, routine repeat prescriptions should be avoided and treatment should be withdrawn gradually.

Withdrawal and rebound insomnia

Once physical dependence has developed, abrupt termination of treatment will be accompanied by withdrawal symptoms (see Section 4.8 Undesirable effects). 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 may also occur. This is a transient syndrome where the symptoms that led to treatment with a benzodiazepine recur in an enhanced form. This 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 minimise the risk of withdrawal symptoms or rebound insomnia.

Duration of treatment

The duration of treatment should be as short as possible 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 to 12 weeks, including the discontinuation process. Extension beyond these periods should not take place without re-evaluation of the patient's status.

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

Benzodiazepines can cause anterograde amnesia, even if they are used within the normal dose range (though this is seen in particular at high dose levels). The condition occurs most often several hours after ingesting the product and therefore to reduce the risk patients should ensure that they will be able to have an uninterrupted sleep of 7 to 8 hours. Amnestic effects may be associated with inappropriate behaviour.

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 during the use of benzodiazepines. These reactions are more likely to occur in children and elderly patients. Should these reactions occur, treatment with diazepam should be discontinued

Specific patient groups

The dose of diazepam should be reduced in elderly and debilitated patients. Due to the muscle relaxant 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 should not be used for the treatment of patients with severe hepatic impairment as they may precipitate encephalopathy. In patients with chronic hepatic disorders, dosage of this medicinal product may need to be reduced.

This medicinal product should be used with caution in patients with renal impairment. In general, a dose reduction is not necessary in these patients.

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.

Paediatric population

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

4.5 Interaction with other medicines and other forms of interaction

Other CNS depressant medicinal products

If diazepam is used concomitantly with other centrally acting agents, careful consideration is necessary before initiation of treatment. Some medicinal products may potentiate or be potentiated by the effects of diazepam, such as neuroleptics/antipsychotics, anxiolytics/sedatives, hypnotics, antidepressants, anticonvulsants, sedating antihistamines, anaesthetics for general anaesthesia, narcotic analgesics and alcohol.

Such concomitant use may increase sedative effects and cause respiratory depression and impairment of cardiovascular functions. Concomitant use of narcotic analgesics may promote psychic dependency due to enhancement of euphoria.

Alcohol

Alcohol should not be consumed while undergoing treatment with diazepam due to additive CNS inhibition and enhanced sedation.

Phenobarbital

Phenobarbital increases the risk of sedation and respiratory depression when co-administered with diazepam due to the additive CNS-depressant effects.

Also, phenobarbital is a known CYP3A4 inducer and increases the hepatic metabolism of diazepam, thus decreasing its effects.

Clozapine

When taken concomitantly with diazepam, treatment with clozapine may lead to severe hypotension, respiratory depression, unconsciousness and potentially fatal respiratory and/or cardiac arrest due to synergistic CNS depressant effects. Therefore, concomitant use of diazepam and clozapine is not recommended and should be avoided.

Opioids

The concomitant use of sedative medicines such as benzodiazepines or related drugs 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 “Special warnings and precautions for use”).

Benzodiazepines interact at $GABA_A$ sites, and opioids interact primarily at mu receptors. When benzodiazepines and opioids are combined, the potential for benzodiazepines to significantly worsen opioid-related respiratory depression exists. Limit dosage and duration of concomitant use of benzodiazepines and opioids and follow patients closely for respiratory depression and sedation.

Theophylline

When this medicinal product is concomitantly administered with theophylline, inhibition of the pharmacodynamic effects of diazepam may occur, e.g. reduction of sedation and psychomotor effects.

This possibly occurs due to competitive binding of theophylline to adenosine receptors in the brain.

Muscle relaxants (suxamethonium, tubocurarin)

Modified intensity of neuromuscular blockage may occur.

Hepatic metabolism

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 can result in substantially decreased plasma concentrations of diazepam.

CYP3A4 and CYP2C19 inducers

Medicinal products that are known inducers of CYP3A4 can substantially increase the hepatic metabolism and clearance of diazepam. Concomitant administration of CYP inducers and diazepam can lead to significantly decreased effects of diazepam. Therefore, concomitant use of diazepam is not recommended with rifampicin, carbamazepine, phenytoin, phenobarbital, etc.

When diazepam is co-administered with corticosteroids, it may lead to increased metabolism of diazepam due to induction of CYP3A4 enzyme, or enzymes responsible for glucuronidation of diazepam.

CYP3A4 and CYP2C19 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 may occur when these medicinal products are concomitantly used with diazepam. Therefore, concomitant use should be avoided.

Azoles (fluconazole, itraconazole, ketoconazole, voriconazole)

Co-administration of azole antifungals may lead to increased plasma concentration of benzodiazepines, due to inhibition of the CYP3A4 and/or CYP2C19 metabolic pathway.

When these medicinal products are concomitantly used, increased risk of undesired effects and toxicity of diazepam may occur. 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 of diazepam. When fluvoxamine is co-administered with diazepam, drowsiness, reduced psychomotor performance and memory may occur. Preferably, benzodiazepines that are metabolised via a non-oxidative pathway should be used instead.

Cimetidine

Cimetidine inhibits the hepatic metabolism of diazepam, reducing its clearance and prolonging its half-life. This interaction leads to increased effects of diazepam and increased risk of drowsiness. Reduction of the diazepam dose may be necessary.

Omeprazole, esomeprazole

Omeprazole and esomeprazole inhibit the CYP2C19 metabolic pathway for diazepam, resulting in an increased half-life and concentrations of diazepam. This leads to increased effects of diazepam. Reduction of the diazepam dose may be necessary.

Isoniazid

Isoniazid inhibits the CYP2C19 and CYP3A4 metabolic pathway for diazepam. This leads to increased effects of diazepam.

Fluoxetine

Fluoxetine inhibits the metabolism of diazepam via CYP2C19 and other pathways, resulting in elevated plasma concentrations and decreased clearance of diazepam. This can lead to 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.

Oral contraceptives

Effect on diazepam: Inhibition of oxidative metabolism of diazepam.

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.

Grapefruit juice

Grapefruit juice is believed to inhibit CYP3A4 and increases the plasma concentration of diazepam. This may lead to increased effects of diazepam.

Other

Levodopa

Concomitant use with diazepam may result in reduced effects of levodopa.

Valproic acid

Valproate displaces diazepam from its plasma albumin binding sites and inhibits its metabolism. This can lead to increased serum concentrations of diazepam.

Ketamine

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

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Data from observational studies suggest that there is an increased risk of miscarriage from benzodiazepine exposure during pregnancy. When treating women of childbearing potential, the benefits of treatment should be weighed against the risks and the patient should be informed of the increased risk of miscarriage.

Use in pregnancy
Category C

Diazepam should only be used in pregnant women on compelling indication.

Although there is no evidence that it induces teratogenic injury, diazepam, like other medicaments, should preferably not be used during pregnancy, especially during the first and last trimesters unless the benefit is considered to outweigh the potential risk. Data from observational studies suggest that there is an increased risk of miscarriage from benzodiazepine exposure during pregnancy.

If, for compelling medical reasons, diazepam is administered during the last trimester of pregnancy, or at high dose levels around the time of birth, effects can be expected in the neonate, such as hypothermia, hypotonia (“Floppy Infant Syndrome”), irregularities in the heart rate, poor suckling and moderate respiratory depression, due to the substance's pharmacological effect.

In addition, infants born to mothers who have taken benzodiazepines regularly during the last stage of pregnancy may develop a physical dependence and be at risk of developing withdrawal symptoms following the birth.

Data from animal experiments shows that the use of diazepam in the first trimester produces an increased risk of foetal abnormalities in the offspring.

Use in lactation
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

Diazepam has a significant influence on the ability to drive and to operate machines.

During treatment with diazepam, undesirable effects such as impaired motor skills, blurred vision/dizziness, tremor, somnolence, amnesia, impaired concentration and tiredness may occur (see section “Undesirable effects”).

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.

4.8 Undesirable effects

Summary of the safety profile

Drowsiness, numbed emotions, reduced alertness, confusion, fatigue, headache, dizziness, muscle weakness, ataxia or double vision predominantly occur at the start of therapy but usually disappear with repeated administration. Among elderly patients there may be confusion conditions at high dose levels.

There is an increased risk of falls and associated fractures in elderly patients using benzodiazepines.

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

Amnesia

Anterograde amnesia may occur using therapeutic dosages, the risk increasing at higher dosages. Amnestic effects may be associated with inappropriate behaviour.

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. Abuse of benzodiazepines has been reported.

List of adverse reactions

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).

Blood and lymphatic system disorders

Very rare:	Leukopenia

Immune system disorders

Not known:	Anaphylactic reaction

Metabolism and nutrition disorders

Rare:	Increased appetite

Psychiatric disorders

Rare:	Increased or decreased libido
Not known:	Confusional state, psychiatric and paradoxical reactions, numbed emotions, depression

Nervous system disorders

Common:	Ataxia
Uncommon:	Balance disorders
Rare:	Loss of consciousness, insomnia
Not known:	Tremor, somnolence, impaired motor ability, anterograde amnesia, disturbance in attention, dizziness, headache, dysarthria, depressed levels of consciousness

Eye disorders

Not known:	Vision blurred, diplopia, nystagmus

Cardiac disorders

Rare:	Bradycardia,
Not known:	Cardiac failure, cardiac arrest

Vascular disorders

Rare:	Hypotension, syncope

Respiratory, thoracic and mediastinal disorders

Not known:	Respiratory depression, respiratory arrest, increased bronchial secretion

Gastrointestinal disorders

Not known:	Salivary hypersecretion, nausea, vomiting, constipation, diarrhoea, dry mouth

Hepatobiliary disorders

Rare:	Jaundice

Skin and subcutaneous tissue disorders

Uncommon:	Pruritus, urticaria, rash

Musculoskeletal and connective tissue disorders

Not known:	Muscular weakness

Renal and urinary disorders

Rare:	Urinary retention,
Not known:	Urinary incontinence

Reproductive system and breast disorders

Rare:	Gynaecomastia, impotence

General disorders

Common:	Fatigue, withdrawal syndrome

Investigations

Not known:	Aspartate aminotransferase increased, alanine aminotransferase increased, blood alkaline phosphatase increased

Description of selected adverse reactions

Psychiatric and paradoxical reactions

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 are 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 "Special warnings and precautions for use").

Depression

Pre-existing depression may be unmasked during benzodiazepine use.

Anterograde amnesia

May occur using therapeutic dosages, the risk increasing at higher dosages. Amnestic effects may be associated with inappropriate behaviour (see section "Special warnings and precautions for use").

Withdrawal symptoms

Upon abrupt discontinuation of diazepam, withdrawal symptoms may occur (headaches, anxiety, panic, palpitations, sweating, tremor, gastrointestinal disorders, irritability, restlessness, aggression, disrupted sensory perception, muscle spasms, general malaise, loss of appetite, paranoid psychosis, and delirium.) The likelihood and degree of severity of withdrawal symptoms is dependent on the duration of treatment, dose level and degree of dependency. 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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/.

4.9 Overdose

Symptoms

In every case of overdose with diazepam, the presence of multiple drug intoxication must be considered.

In overdose with diazepam, symptoms such as confusion, somnolence, ataxia, dysarthria, hypotension and muscular weakness may occur. In case of severe overdose, central nervous system depression and respiratory depression can occur. This may lead to cyanosis, unconsciousness, coma and cardiac arrest. Therefore, patient must be placed under continuous monitoring.

In recovery phase from an overdose with diazepam, agitation has been reported.

Symptoms of overdose can be more pronounced under the concomitant influence of alcohol or other CNS depressant agents.

Treatment

In early stage of intoxication, gastrointestinal absorption should be reduced by administering activated charcoal.

A clear airway and adequate ventilation must be maintained, especially in unconscious patients.

Further treatment should be symptomatic and supportive. In intensive care unit, special attention should be given to monitoring of cardiovascular and respiratory functions. Patient's heart rate, blood pressure and body temperature should also be closely monitored.

Flumazenil, a benzodiazepine antagonist, may be administered for the reversal of central depressant effects of diazepam. Flumazenil may only be administered under close supervision.

Due to its high level of binding to plasma proteins, and its large volume of distribution, diazepam is poorly removed by forced diuresis or dialysis.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anxiolytics, benzodiazepine derivatives, ATC code: N05BA01

Diazepam has anxiolytic, sedative, amnestic, hypnotic, anticonvulsant and muscle-relaxing activity.

Diazepam acts centrally. As a benzodiazepine, it facilitates GABA-mediated synaptic inhibition. It is bound in the brain to specific benzodiazepine-receptors, which are found particularly in the limbic system, amygdaloid nucleus and the frontal cortex.

5.2 Pharmacokinetic properties

Absorption: diazepam is quickly absorbed from the rectal mucosa. The maximum serum concentration is reached within 17 minutes. Absorption by this route is 100%, and is therefore comparable in extent to an intravenous injection of diazepam formulated for IV injection.

Diazepam is distributed systemically. In the blood it is 96-98% bound to plasma protein. It quickly passes the blood-brain barrier. It crosses the placenta and passes into breast milk.

Diazepam is metabolised in the liver and its major metabolite, desmethyldiazepam, is pharmacologically active. The metabolites are excreted in the urine as glucuronide or sulphate. A very small amount is excreted via the bile.

The plasma half-life of diazepam varies from person to person, and increases with age. The mean is about 50 hours. The half-life of desmethyldiazepam is about 100 hours.

5.3 Preclinical safety data
None.

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
Store below 25°C. Protect from light.

6.5 Nature and contents of container
Yellow low density polyethylene tubes packed individually in aluminium foil pouch: Pack of 5 rectal tubes.

6.6 Special precautions for disposal
No special requirements for disposal.

7. MEDICINE SCHEDULE
Controlled Drug C5

8. SPONSOR
Teva Pharma (New Zealand) Limited
PO Box 128 244
Remuera
Auckland 1541
Telephone: 0800 800 097

9. DATE OF FIRST APPROVAL
11 August 1981

10. DATE OF REVISION OF THE TEXT
14 March 2025

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.6	Additional information added regarding the increased risk of miscarriage from benzodiazepine exposure during pregnancy.
4.4, 4.5, 4.6, 4.7, 4.8 & 4.9	Updated to align with Teva Company Core Safety Information (CCSI).

Stesolid® is a trademark of Actavis Group PTC ehf. (Iceland).