

# 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	OR	Number of 10mg/2.5mL tubes
Adults	10 to 20 mg	2 to 4		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**

##### **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].

##### **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).

Rebound insomnia and anxiety may also occur, especially after abrupt discontinuation of treatment. They may be accompanied by other reactions including mood changes or sleep disturbances and restlessness. Abrupt discontinuation may also result in convulsions and therefore particular care should be taken in patients with epilepsy, a history of seizures or a history of alcohol or drug abuse.

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

Diazepam should not be used together with alcohol as this can enhance the sedative effect of diazepam.

##### **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.

#### Paradoxical reactions

Paradoxical reactions have been reported from the use of benzodiazepines (see Section 4.8 Undesirable effects).

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.

### **4.5 Interaction with other medicines and other forms of interaction**

#### Pharmacodynamic interactions

Diazepam, as a benzodiazepine, enhances the central depressive effects of other CNS-active agents, for example: alcohol, narcotic analgesics, anaesthetics (eg. ketamine), anti-epilepsy compounds (eg. phenobarbital), hypnotics, anxiolytics/sedatives, antidepressant agents, antipsychotics (eg. clozapine) and sedative antihistamines. Narcotic analgesics may also promote psychic dependency due to enhancement of euphorogenic effects.

The concomitant use of benzodiazepines and opioids increases the risk of respiratory depression because of actions at different receptor sites in the CNS that control respiration. Benzodiazepines interact at GABA<sub>A</sub> 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.

Concomitant use is not recommended with alcohol, phenobarbital or clozapine.

Special caution is recommended for concomitant use with muscle relaxants such as suxamethonium or tubocurarin (where diazepam can enhance or reduce the intensity of the neuromuscular block) and for theophylline (competitive binding of theophylline to adenosine receptors may reduce the effect of diazepam).

#### Pharmacokinetic interactions

The effect of diazepam can be enhanced by agents that block or reduce its metabolism.

Compounds that inhibit certain hepatic enzymes (particularly cytochrome P450, 2C19 and P3A4) can increase the effects of diazepam.

Concomitant use is not recommended for antiviral agents (eg. atazanavir, ritonavir), azoles (eg. fluconazole, ketoconazole, itraconazole) and fluvoxamine.

Special caution is recommended for concomitant use with disulfiram, omeprazole, esomeprazole, cimetidine, isoniazid, fluoxetine, oral contraceptives and grapefruit juice.

Other compounds can induce hepatic enzyme activity and therefore decrease the effects of diazepam. Concomitant use is not recommended for rifamycins (eg. rifampicin), carbamazepine, phenytoin, phenobarbital. Special caution is recommended for concomitant use with corticosteroids.

Special caution is also recommended in the use of cispride (which accelerates diazepam absorption) and valproic acid (which inhibits metabolism of diazepam).

Agents on which diazepam exerts an effect include levodopa (diazepam causes a reduced effect of levodopa), and ketamine (diazepam blocks ketamine metabolism resulting in increased sedation).

## **4.6 Fertility, pregnancy and lactation**

### **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 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.

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

Benzodiazepines can cause blurred vision/dizziness and impair concentration. They can therefore affect ability to drive and to operate machinery.

## **4.8 Undesirable effects**

The adverse effects of diazepam are usually mild and infrequent.

### **Common ( $\geq 1/100$ )**

Drowsiness, dizziness balance disorders , ataxia, tremor, fatigue, confusion, impaired motor ability.

Withdrawal symptoms are also considered a commonly occurring adverse effect after discontinuation of therapy. The likelihood and severity depends on the duration of treatment, dose level, and degree of dependency. Withdrawal symptoms include 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.

### **Uncommon ( $> 1/1000$ to $< 1/100$ )**

Anterograde amnesia, concentration impairment, headache, slurred speech, respiratory depression, gastrointestinal disorders, increased salivation, allergic skin reactions, myasthenia.

### **Rare ( $\geq 1/10000$ to $< 1/1000$ )**

Unconsciousness, insomnia, respiratory arrest, increased bronchial secretion, bradycardia, heart failure including cardiac arrest, hypotension, syncope, dry mouth, increased appetite, jaundice, changes of hepatic parameters (elevation of ALT, AST, alkaline phosphatase), urinary retention, incontinence, gynaecomastia, impotence, changes in libido, dysarthria, emotional poverty, decreased alertness and depression (pre-existing depression may be unmasked with benzodiazepine use).Psychiatric and paradoxical reactions to benzodiazepines (provoking excitement instead of sedation) have been reported rarely. Reactions include restlessness, agitation, irritability, aggressiveness, delusion, rages, hallucinations, psychoses, memory loss, nightmares and inappropriate behaviour.

In very rare cases anaphylaxis, leukopenia or elevation of transaminases may occur.

## **Post-marketing experience**

Reversible vision disorders (blurred vision, diplopia and nystagmus) have also been reported during the post-marketing period.

### **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://nzphvc.otago.ac.nz/reporting/>).

### **4.9 Overdose**

Overdose of benzodiazepines usually presents as some degree of central nervous system depression, ranging from drowsiness to coma. In mild cases, symptoms include drowsiness, mental confusion and lethargy; in more severe cases, symptoms may include ataxia, hypotonia, hypotension, respiratory depression, hypothermia, bradycardia, dysarthria, rarely coma and very rarely death.

Overdose of diazepam should not present a threat to life unless administered to a recipient affected by CNS depressants, including alcohol.

Emergency management of overdose: Gastric lavage and adequate airway maintenance may be necessary. Otherwise, management is symptomatic.

Intravenous fluids may be administered and flumazenil may be useful as an antidote.

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**

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## **9. DATE OF FIRST APPROVAL**

11 August 1981

## **10. DATE OF REVISION OF THE TEXT**

29 May 2017

## **SUMMARY TABLE OF CHANGES**

<b>Section changed</b>	<b>Summary of new information</b>
	Update to the SPC-style format
4.4 & 4.5	Warning regarding the combined use of opioids and benzodiazepines and potential interaction as per MARC recommendation.

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