PRODUCT MONOGRAPH

DIASTAT®

diazepam gel

Rectal Delivery System

5 mg/mL

Benzodiazepine Anticonvulsant

Valeant Pharmaceuticals North America LLC
400 Somerset Corporate Boulevard
Bridgewater, New Jersey USA
08807

Canadian Importer/Distributor:
Valeant Canada LP
Laval (Quebec), Canada H7L 4A8

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Control # 098579

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Table of Contents

DIASTAT® Rectal Delivery System

diazepam gel

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
rectal	gel 5 mg/mL	Ethyl alcohol (10%) *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

DIASTAT® (diazepam gel) is indicated for the management of selected, refractory, patients with epilepsy, on stable regimens of AEDs, who require intermittent use of diazepam to control bouts of increased seizure activity.

These bouts are defined as a form of severe seizures variously referred to as recurrent, serial, cluster or crescendo seizures. These clusters are a predictable component of the patient's seizure disorder that are historically distinct from the patient's other seizures in either type, frequency, severity or duration and have an onset that is easily recognized by the family and physician. The clusters have a consistent component, such as an aura, prodrome or characteristic single or multiple seizures, that is predictably and temporally linked to subsequent seizures. Patients typically demonstrate recovery between these seizures. As is the case with all seizure classifications, there is a common pattern of seizure presentation and there are clearly different features for every individual.

DIASTAT® is intended for use by caregivers to treat patients in the home setting, as well as in hospitals, emergency and urgent care units and residential institutions.

Geriatrics (> 60 years of age):
Evidence from clinical studies and experience suggests that use in the geriatric population may be associated with differences in safety or effectiveness**.** A brief discussion can be found in the appropriate sections **(DOSAGE AND ADMINISTRATION, ACTION AND CLINICAL PHARMACOLOGY, WARNINGS AND PRECAUTIONS).**

Pediatrics (< 2 years of age):
Evidence from clinical experience suggests that use in the infant pediatric population is associated with differences in safety. A brief discussion can be found in the appropriate sections **(CLINICAL TRIALS, DOSAGE AND ADMINISTRATION, ACTION AND CLINICAL PHARMACOLOGY, WARNINGS AND PRECAUTIONS)**.

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the Product Monograph.
- DIASTAT® is contraindicated in patients with a known hypersensitivity to diazepam. DIASTAT® (diazepam gel) may be used in patients with open angle glaucoma who are receiving appropriate therapy but is contraindicated in acute narrow angle glaucoma.

WARNINGS AND PRECAUTIONS

General
DIASTAT® should only be administered by caregivers who in the opinion of the prescribing physician: 1) are able to distinguish the distinct cluster of seizures (and/or the events presumed to herald their onset) from the patient's ordinary seizure activity, 2) have been instructed and judged to be competent to administer the treatment rectally, 3) understand explicitly which seizure manifestations may or may not be treated with DIASTAT®, and 4) are able to monitor the clinical response and recognize when that response is such that immediate professional medical evaluation is required.

Carcinogenesis and Mutagenesis
Only animal data are available (see **TOXICOLOGY** section)

The data currently available are inadequate to determine the mutagenic potential of diazepam.

Dependence/Tolerance
Although diazepam can produce drug dependence, it is expected that DIASTAT® has minimal potential for abuse. It is recommended that patients be treated with DIASTAT® no more frequently than every five days and no more than five times per month.

Addiction-prone individuals (such as drug addicts or alcoholics) should be under careful surveillance when receiving diazepam or other psychotropic agents because of the predisposition of such patients to habituation and dependence.

Abrupt discontinuation of diazepam following chronic daily use has resulted in withdrawal symptoms, similar in character to those noted with barbiturates and alcohol (convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). The more severe withdrawal symptoms have usually been limited to those patients who had received excessive doses over an extended

period of time. Generally milder withdrawal symptoms (e.g., dysphoria and insomnia) have been reported following abrupt discontinuation of benzodiazepines taken continuously at therapeutic levels for several months.

DIASTAT® is not recommended for chronic, daily use as an anticonvulsant because of the potential for development of tolerance to diazepam. Chronic daily use of diazepam may increase the frequency and/or severity of grand mal seizures, requiring an increase in the dosage of standard anticonvulsant medication. In such cases, abrupt withdrawal of chronic diazepam may also be associated with a temporary increase in the frequency and/or severity of seizures.

Hepatic/Biliary/Pancreatic

Precautions in treating patients with impaired hepatic function should be observed because patients with severely impaired hepatic function may be unable to biotransform diazepam to inactive metabolites.

Neurologic

CNS Depression

Occupational Hazards: As is true of most preparations containing central nervous system (CNS)-acting drugs, patients should be cautioned against engaging in hazardous occupations requiring complete mental alertness, such as operating machinery, driving a motor vehicle or riding a bicycle following use of DIASTAT® (diazepam gel).

Concomitant Use of Other CNS Depressants: Since diazepam has a CNS-depressant effect, patients should be advised against the simultaneous use of alcohol or other CNS-depressants during DIASTAT® therapy.

Use in Patients with Petit Mal Status

Tonic status epilepticus has been precipitated in patients treated with intravenous diazepam for petit mal status or petit mal variant status.

Use in Patients with Neurologic Damage

DIASTAT® should be used with caution in patients with neurologic damage.

Renal

Metabolites of diazepam are excreted by the kidney; to avoid their excess accumulation, caution should be exercised in the administration to patients with compromised kidney function.

Respiratory

DIASTAT® should be used with caution in patients with compromised respiratory function related to a concurrent disease process (e.g., asthma, pneumonia).

Special Populations

Pregnant Women: In humans, measurable amounts of diazepam have been found in maternal and cord blood, indicating placental transfer of the drug. Diazepam has been shown to be teratogenic in mice and hamsters when given orally in doses that are more than 140 times the highest DIASTAT® treatment dose. Cleft palates and resorptions are the most common and consistently reported form of developmental toxicity produced in laboratory animals by high doses (>100 mg/kg) of diazepam during gestation. There are no adequate and well-controlled studies of diazepam in pregnant women. However, benzodiazepines have been associated with an increased risk of congenital malformations after first trimester exposure. Hypotonia, lethargy, hypothermia, respiratory and suckling difficulties have been reported in infants whose mothers received benzodiazepines during labor. Children born to mothers receiving benzodiazepines on a regular basis late in pregnancy may be at some risk of experiencing withdrawal symptoms during the postnatal period. DIASTAT® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

It is important to note that anticonvulsant drugs should not be discontinued in patients in whom the drug is administered to prevent seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that the removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even mild seizures do not pose some hazards to the developing embryo or fetus.

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy with DIASTAT®.

Nursing Women: Diazepam is excreted in human milk; therefore, DIASTAT® should not be administered to nursing women.

Pediatrics (< 2 years of age): Clinical studies have not been conducted to establish the efficacy and safety of DIASTAT® in children under 2 years of age. Prolonged CNS depression has been observed in neonates treated with diazepam, apparently due to an inability to biotransform diazepam into inactive metabolites. Therefore, DIASTAT® is not recommended for use in children under 6 months of age.

Geriatrics (> 60 years of age): The effects of DIASTAT® in patients over 60 years of age have not been well characterized. In elderly patients, DIASTAT® should be used with caution due to an increase in half-life with a corresponding decrease in the clearance of free diazepam. It is also recommended that the dosage be adjusted downward to reduce the likelihood of ataxia or oversedation.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The most frequent adverse event (AE) reported to be related to DIASTAT® (diazepam gel) in the 2 double-blind, placebo-controlled studies was somnolence (23%). Less frequent AEs were dizziness, headache, pain, diarrhea, euphoria, incoordination and nervousness, which occurred in approximately 2-5% of patients. In addition, ataxia (8%), asthenia (4%), hiccup (2%) and vertigo (2%) were reported in open-label studies. There were no differences in the pattern of AEs in children and adults.

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates*.

DIASTAT® AE data were collected from double-blind, placebo-controlled studies and open-label studies. The majority of AEs were mild to moderate in severity and transient in nature.

Table 1- Number and Percent of Patients with Adverse Events for Combined Data from the Controlled Studies (AN094-001, AN094-003) (Adverse events with a frequency of ≥ 1%)
Intent-to-Treat Population

	DIASTAT® n= 101		Placebo n= 104	
	All	**Related***	**All**	**Related***
	n (%)	**n (%)**	**n (%)**	**n (%)**
Body as a whole	**12 (12)**	**7 (7)**	**14 (13)**	**9 (9)**
Abdominal Pain	2 (2)	1 (<1)	2 (2)	1 (<1)
Fever	0 (0)	0 (0)	4 (4)	2 (2)
Headache	5 (5)	2 (2)	4 (4)	3 (3)
Pain+	3 (3)	3 (3)	4 (4)	3 (3)
Cardiovascular	**2 (2)**	**2 (2)**	**1 (<1)**	**1 (<1)**
Vasodilatation	2 (2)	2 (2)	0 (0)	0 (0)
Digestive	**6 (6)**	**4 (4)**	**8 (8)**	**6 (6)**
Anorexia	1 (<1)	1 (<1)	2 (2)	2 (2)
Diarrhea	4 (4)	2 (2)	1 (<1)	0 (0)
Vomitting	1 (<1)	1 (<1)	2 (2)	2 (2)
Hemic and Lymphatic†	**2 (2)**	**0 (0)**	**3 (3)**	**1 (<1)**
Metabolic and Nutritional†	**0 (0)**	**0 (0)**	**3 (3)**	**1 (<1)**
Nervous	**32 (32)**	**29 (29)**	**16 (15)**	**13 (13)**
Ataxia	3 (3)	1 (<1)	1 (<1)	1 (<1)
Convulsion	1 (<1)	1 (<1)	3 (3)	0 (0)
Dizziness	3 (3)	3 (3)	2 (2)	2 (2)
Euphoria	3 (3)	3 (3)	0 (0)	0 (0)
Incoordination	3 (3)	3 (3)	0 (0)	0 (0)
Nervousness	2 (2)	2 (2)	2 (2)	2 (2)
Somnolence	23 (23)	23 (23)	8 (8)	8 (8)
Other Body System	**1 (<1)**	**1 (<1)**	**2 (2)**	**2 (2)**
Other	1 (<1)	1 (<1)	2 (2)	2 (2)
Respiratory	**4 (4)**	**0 (0)**	**3 (3)**	**2 (2)**
Asthma	2 (2)	0 (0)	0 (0)	0 (0)
Rhinitis	**2 (2)**	**0 (0)**	**2 (2)**	**2 (2)**
Skin and Appendages	**5 (5)**	**3 (3)**	**1 (<1)**	**0 (0)**
Rash	3 (3)	2 (2)	0 (0)	0 (0)
Special Senses	**1 (<1)**	**1 (<1)**	**2 (2)**	**0 (0)**
Otitis Media	0 (0)	0 (0)	2 (2)	0 (0)
Urogenital†	**1 (<1)**	**0 (0)**	**2 (2)**	**0 (0)**

* Related means the adverse event was definitely, probably, or possibly related to the study drug.
\+ Pain includes rectal symptoms such as rectal burning, discomfort, that code to "pain".
† Individual adverse events in these categories were less than 1% and therefore are not included in this table.

The following infrequent AEs were not seen with DIASTAT® but have been reported previously with diazepam use: depression, slurred speech, syncope, constipation, changes in libido, urinary retention, bradycardia, cardiovascular collapse, nystagmus, urticaria, neutropenia and jaundice.

Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances and stimulation have been reported with diazepam; should these occur, use of DIASTAT® should be discontinued.

Less Common Clinical Trial Adverse Drug Events (<1%)

Body as a whole: Asthenia, infection.
Cardiovascular: Palpitation.
Digestive: Dyspepsia, dysphagia, fecal incontinence, nausea.
Hemic and Lymphatic: Anemia, cyanosis, ecchymosis, lymphadenopathy, thromboplastin decreased.
Metabolic and Nutritional: Acidosis, dehydration, peripheral edema.
Nervous: Agitation, grand mal convulsion, hyperkinesia, increased salivation, stupor, tremor, twitching.
Respiratory: Cough increased, pneumonia, sinusitis.
Skin and Appendages: Pruritus, skin discoloration, sweating.
Special senses: Mydriasis.
Urogenital: Kidney failure, urinary incontinence, urinary tract infection.

Other AEs occurring less frequently (<2%) and reported to be related to DIASTAT® in clinical studies

Body as a whole: Abdominal pain, accidental injury, accidental overdose, back pain, chills, fever, infection.
Cardiovascular: Hypotension, pallor, postural hypotension, vasodilation.
Digestive: Abnormal stools, anorexia, diarrhea, dysphagia, increased salivation, nausea, nausea and vomiting, rectal disorder, rectal hemorrhage, tenesmus, thirst, vomiting.
Hemic and Lymphatic: Prothrombin time increased.
Musculoskeletal: Myasthenia.
Nervous: Agitation, amnesia, confusion, convulsion, dysarthria, emotional lability, euphoria, hyperkinesia, hypokinesia, hypotonia, incoordination, increased salivation, insomnia, movement disorder, nervousness, speech disorder, stupor, thinking abnormal, tremor, twitching.
Respiratory: Cough increased, hypoventilation, hypoxia.
Skin and Appendages: Pruritis, rash.
Special senses: Abnormal vision, amblyopia, diplopia, mydriasis, taste perversion.
Urogenital: Urinary incontinence.

DRUG INTERACTIONS

Overview

Effects of Other Drugs on the Metabolism of Diazepam:

There have been no clinical studies or reports in the literature to evaluate the interaction of rectally administered diazepam with other drugs. As with all drugs, the potential for interaction by a variety of mechanisms is a possibility.

In vitro studies using human liver preparations suggest that CYP2C19 and CYP3A4 are the principal isozymes involved in the initial oxidative metabolism of diazepam. Therefore, potential drug-drug interactions may occur when diazepam is given concurrently with agents that affect CYP2C19 (e.g., cimetidine, quinidine, tranylcypromine, rifampicin) or CYP3A4 (e.g., ketoconazole, clotrimazole, carbamazepine, phenytoin, dexamethasone and phenobarbital) activity.

The clearance of diazepam and certain other benzodiazepines can be delayed in association with cimetidine administration. The clinical significance of this is unclear.

If DIASTAT® is to be combined with other psychotropic agents or other CNS depressants, careful consideration should be given to the pharmacology of the agents to be employed - particularly with known compounds which may potentiate the action of diazepam, such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants.

When diazepam is used simultaneously with alcohol or other CNS depressants, the potential for a synergistic CNS-depressant effect must be considered. Valproate is known to potentiate the CNS-depressant effects of diazepam; therefore, DIASTAT® should be used with caution in patients expected to have high plasma concentrations of valproic acid.

Effects of Diazepam on the Metabolism of Other Drugs:

There are no reports as to which isozymes could be inhibited or induced by diazepam. But, based on the fact that diazepam is a substrate for CYP2C19 and CYP3A4, it is possible that diazepam may interfere with the metabolism of drugs which are substrates for CYP2C19, (e.g. omeprazole, propranolol, and imipramine) and CYP3A4 (e.g. cyclosporine, paclitaxel, terfenadine, theophylline and warfarine) leading to a potential drug-drug interaction.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

- In elderly and debilitated patients, it is recommended that the dosage be adjusted downward to reduce the likelihood of ataxia or oversedation.
- The prescribed dose of study medication should be adjusted by the physician periodically to reflect changes in the patient's age or weight. It is recommended that dosage be reviewed at 6 month intervals.

Recommended Dose and Dosage Adjustment

Calculating Prescribed Dose

The DIASTAT® (diazepam gel) dose should be individualized for maximum beneficial effect. The target dose of DIASTAT® is 0.2 - 0.5 mg/kg depending on age. See the dosing table for specific recommendations.

Age (years)	Target Dose
2 through 5	0.5 mg/kg
6 through 11	0.3 mg/kg
12 and older	0.2 mg/kg

Because DIASTAT® is provided in fixed, unit-doses of 5, 10, 15, and 20 mg, the prescribed dose is obtained by rounding upward to the next available dose. The following table provides acceptable weight ranges for each dose and age category, such that patients will receive between 90% and 180% of the calculated target dose. The safety of this strategy has been established in clinical trials.

2-5 Years 0.5 mg/kg		6-11 Years 0.3 mg/kg		12+ Years 0.2 mg/kg	
Weight (kg)	Dose (mg)	Weight (kg)	Dose (mg)	Weight (kg)	Dose (mg)
6 to 11	5	10 to 18	5	14 to 27	5
12 to 22	10	19 to 37	10	28 to 50	10
23 to 33	15	38 to 55	15	51 to 75	15
34 to 44	20	56 to 74	20	76 to 111	20

A 2.5 mg dose is available for use as a supplemental dose. This dose may be prescribed at the discretion of the physician for patients who require more precise dose titration than is achieved using on of the 4 standard doses provided. The 2.5 mg dose may also be used as a partial replacement dose for patients who may expel a portion of the first dose.

Additional Dose

If a single dose does not adequately treat the episode, the physician may wish to prescribe 2 doses of DIASTAT®. The second dose may be given 4-12 hours after the first dose if seizures persist, are known to reoccur, or if the patient is known to have especially refractory seizures.

Treatment Frequency
It is recommended that patients be treated with DIASTAT® no more frequently than every five days and no more than five times per month. If a patient requires more frequent administration of DIASTAT® for seizure control, the patient's treatment regimen may require reevaluation by the physician.

Administration
See **WARNINGS AND PRECAUTIONS** section for general considerations.

OVERDOSAGE

In the DIASTAT® (diazepam gel) clinical trials, the practice was to dose patients up to twice the target dose (see **DOSAGE AND ADMINISTRATION**). Two patients received more than twice the target dose and reported no AEs.

Previous reports of diazepam overdosage have shown that manifestations of diazepam overdosage include somnolence, confusion, coma, and diminished reflexes. Respiration, pulse and blood pressure should be monitored, as in all cases of drug overdosage, although, in general, these effects have been minimal. General supportive measures should be employed, along with intravenous fluids, and an adequate airway maintained. Hypotension may be combated by the use of levarterenol or metaraminol. Dialysis is of limited value.

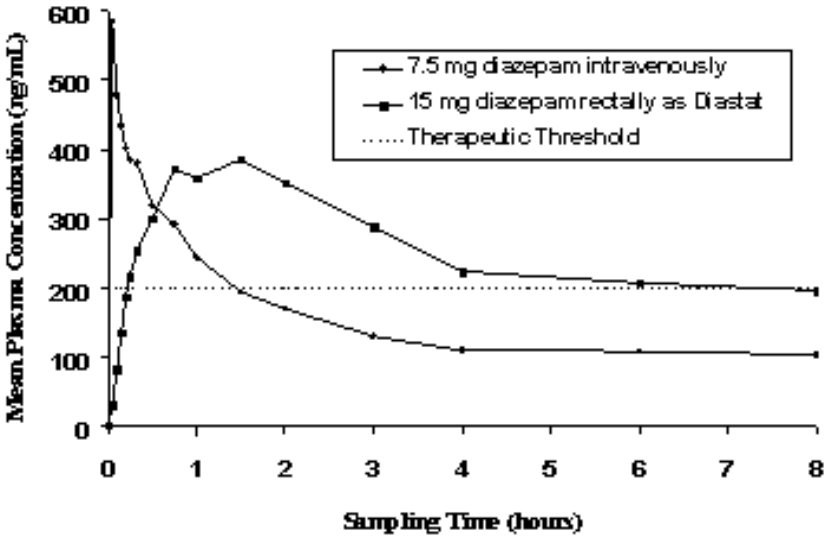
ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action
Animal and in vitro studies indicate that diazepam acts to suppress seizures through an allosteric influence on the γ-aminobutyric acid (GABA) receptors of the A-type ($GABA_A$). GABA acts at this receptor to open the membrane channel allowing chloride ions to flow into neurons. Entry of chloride ions causes an inhibitory potential that reduces the ability of neurons to depolarize to the threshold potential necessary to produce action potentials. Excessive depolarization of neurons is implicated in the generation and spread of seizures.

The benzodiazepine binding site is associated with the $GABA_A$ receptor. Diazepam binds to this site and enhances the actions of GABA by causing GABA to bind more tightly to the $GABA_A$ receptor, increasing the opening of the chloride channel and increasing the chloride ion influx into the neuron. At doses in the lower therapeutic range, diazepam decreases the spread of seizures from the active site or focus by increasing inhibition in the surrounding neurons. At high therapeutic doses, diazepam may suppress seizures originating at the active focus as well.

Pharmacokinetics

Absorption and Distribution: The absorption, distribution, metabolism and excretion of diazepam are well characterized. Protein binding is high, ranging from 96.8%-98.6%. After DIASTAT® (diazepam gel) administration, the absorption of diazepam from the rectum is rapid with an absolute bioavailability of 90.4% relative to an intravenous dose. The following figure shows diazepam plasma levels following rectal administration of 15 mg diazepam as DIASTAT® and intravenous administration of 7.5 mg diazepam. Following rectal dosing, diazepam plasma levels reach 200 ng/mL within 15 minutes, reaching peak plasma concentrations within 1.5 hours. Intravenous dosing results in a quicker rise in plasma levels followed quickly by a fall as diazepam is sequestered in muscle and fat. Following rectal dosing, absorptive and redistribution phases overlap and therapeutic levels of diazepam are maintained for at least 4 hours without having the high peak concentrations of intravenous diazepam, which are often associated with adverse events. The time to maximum plasma concentration (T_{max}) following rectal administration is not different in children and adults given doses normalized to body weight.



Metabolism: It has been reported in the literature that diazepam is extensively metabolized to one major active metabolite (desmethyldiazepam) and two minor active metabolites, 3-hydroxydiazepam (temazepam) and 3-hydroxy-N-diazepam (oxazepam) in plasma. At therapeutic doses, desmethyldiazepam is found in plasma at concentrations equivalent to those of diazepam while oxazepam and temazepam are not usually detectable. The metabolism of diazepam is primarily hepatic and involves demethylation (involving primarily CYP2C19 and CYP3A4) and 3-hydroxylation (involving primarily CYP3A4), followed by glucuronidation. The marked inter-individual variability in the clearance of diazepam reported in the literature is probably attributable to variability of CYP2C19 (which is known to exhibit genetic polymorphism; about 3-5% of Caucasians have little or no activity and are "poor metabolizers") and CYP3A4. No inhibition was demonstrated in the presence of inhibitors selective for CYP2A6, CYP2C9, CYP2D6, CYP2E1, or CYP1A2, indicating that these enzymes are not significantly involved in metabolism of diazepam.

The primary metabolite of diazepam following a single dose is desmethyldiazepam in both children and adults.

Excretion: The elimination kinetics of diazepam are similar following rectal and intravenous administration.

Special Populations and Conditions

Pediatrics: Clinical studies have not been conducted to establish the efficacy and safety of DIASTAT® in children under 2 years of age. Prolonged CNS depression has been observed in neonates treated with diazepam, apparently due to an inability to biotransform diazepam into inactive metabolites. Therefore, DIASTAT® is not recommended for use in children under 6 months of age.

Geriatrics: The effects of DIASTAT® (diazepam gel) in patients over 60 years of age have not been well characterized. In elderly patients, DIASTAT® should be used with caution due to an increase in half-life with a corresponding decrease in the clearance of free diazepam.

Hepatic Insufficiency: Precautions in treating patients with impaired hepatic function should be observed because patients with severely impaired hepatic function may be unable to biotransform diazepam to inactive metabolites.

Renal Insufficiency: Metabolites of diazepam are excreted by the kidney; to avoid their excess accumulation, caution should be exercised in the administration to patients with compromised kidney function.

STORAGE AND STABILITY

Store at controlled room temperature 15 - 30ºC (59 - 86ºF).

DOSAGE FORMS, COMPOSITION AND PACKAGING

DIASTAT® (diazepam gel) rectal delivery system is a non-sterile diazepam gel provided in a prefilled, unit-dose, rectal delivery system. The rectal delivery system includes a plastic applicator with a flexible, molded tip available in 2 lengths, designated for convenience as Pediatric, Universal or Adult. DIASTAT® is available in the following 5 presentations:

Dose of Diazepam (mg)	Rectal Tip Size	DIN Number
2.5	Pediatric (4.4 cm)	02238162
5.0	Pediatric (4.4 cm)	02238162
10.0	Universal (4.4 cm)	02238162
15.0	Adult (6.0 cm)	02238162
20.0	Adult (6.0 cm)	02238162

Each package contains 2 DIASTAT® rectal delivery systems, 2 packets of lubricating jelly, and Instructions for Use.

DIASTAT® contains 5 mg/mL diazepam, propylene glycol, ethyl alcohol (10%), hydroxypropyl methylcellulose, sodium benzoate, benzyl alcohol (1.5%), benzoic acid, and water. DIASTAT®® is clear to slightly yellow and has a pH between 6.5 – 7.2.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

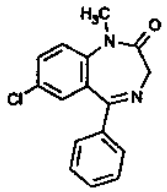
Drug Substance

Proper name: diazepam

Chemical name: 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one

Molecular formula and molecular mass: The molecular weight is 284.75

Structural formula:



Physicochemical properties: Diazepam is a crystalline powder, freely soluble in chloroform, soluble in ethanol and propylene glycol, and practically insoluble in water. Diazepam has a pKa of 3.4, a partition coefficient of 382 (octanol:phosphate) and a melting range of 131-135ºC.

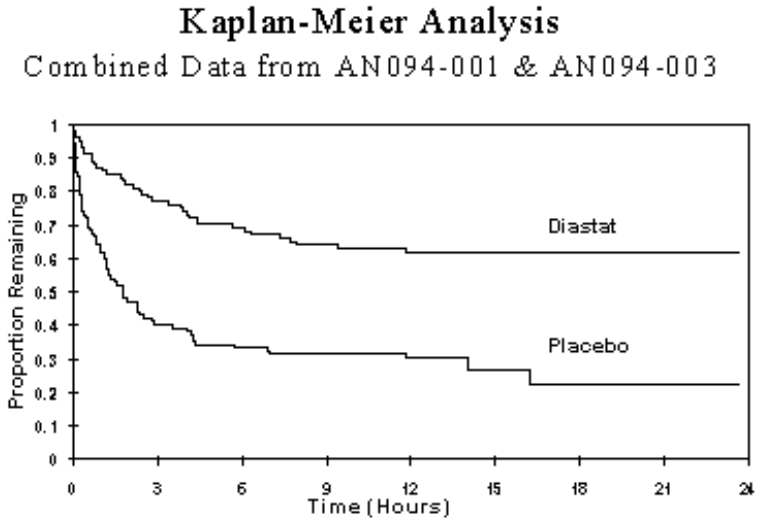
CLINICAL TRIALS

The usefulness of DIASTAT® (diazepam gel) as an adjunct in treatment of bouts of increase seizure activity has been established in 2 adequate and well-controlled clinical studies in children and adults. These studies confirmed the efficacy of rectal diazepam as treatment for acute seizures as established in numerous scientific reports. The first double-blind study compared sequential doses of DIASTAT® and placebo in 91 patients (47 children, 44 adults). The first dose was given at the onset of the defined episode. Children could be dosed again 4 hours after the first dose and were observed for 12 hours. Adults could be dosed again 4 and 12 hours after the first dose and were observed for 24 hours. DIASTAT® significantly reduced seizure frequency ($p < 0.0001$) and increased the time to the next seizure ($p = 0.0002$). In addition, 62% of patients treated with DIASTAT® were seizure-free during the observation period compared to 20% of placebo patients. Overall, caregivers judged DIASTAT® to be much more effective than placebo ($p < 0.0001$).

A second double-blind study compared single doses of DIASTAT® and placebo in 114 patients (53 children, 61 adults). The dose was given at the onset of the defined episode and patients were observed for 12 hours. DIASTAT® significantly reduced seizure counts ($p = 0.029$) and increased the time to the next seizure ($p=0.0072$). In addition, 55% of patients treated with DIASTAT® were seizure-free during the observation period compared to 34% of placebo

patients. Overall, caregivers judged DIASTAT® to be more effective than placebo (p=0.018). In addition, investigators also evaluated the effectiveness of DIASTAT® and judged DIASTAT® to be more effective than placebo ($p < 0.001$).

The following figure shows the proportion of patients remaining seizure-free following treatment of an episode with DIASTAT®. This analysis of the combined data from both double-blind, placebo-controlled studies, confirms that the anti-seizure effect of DIASTAT® is maintained throughout the observation period.



Long-term experience has been evaluated in 2 open-label studies following the double-blind studies. Patients in these studies were prescribed DIASTAT® for treatment of bouts of increased seizure activity. Patients' episodes could be treated with DIASTAT® no more frequently than every 5 days and no more than 5 times per month. There was no evidence for development of tolerance to the effect of DIASTAT® over time.

DETAILED PHARMACOLOGY

Refer to the **ACTION AND CLINICAL PHARMACOLOGY** section for details on the mechanism of action.

Studies in animals have provided information that is relevant to the pharmacology of diazepam in humans. Diazepam, unlike chlorpromazine and reserpine, has no demonstrable peripheral autonomic blocking action, nor does it produce extrapyramidal side effects; however, animals treated with diazepam do have a transient ataxia at higher doses. Diazepam was found to have transient cardiovascular depressor effects in dogs. Long-term experiments in rats revealed no disturbances of endocrine function. It is expected that rectal administration of diazepam will not alter the pharmacologic or toxic effects previously observed with other formulations of diazepam. No irritation was observed following repeated rectal administration of DIASTAT® to rabbits.

TOXICOLOGY

Carcinogenesis, mutagenesis, impairment of fertility

The carcinogenic potential of rectal diazepam has not been evaluated. In studies in which mice and rats were administered diazepam in the diet (orally) at a dose of 75 mg/kg/day (approximately 6 and 12 times, respectively, the maximum recommended human dose) for 80 and 104 weeks, respectively, an increased incidence of liver tumors was observed in males of both species.

The data currently available are inadequate to determine the mutagenic potential of diazepam.

Reproduction studies in rats showed a decrease in the number of pregnancies and surviving offspring at an oral dose of 100 mg/kg [approximately 100 times the highest DIASTAT® (diazepam gel) treatment dose]. These effects may be secondary to prolonged sedation. Normal neonatal survival rates were observed at doses lower than 100 mg/kg.

REFERENCES

1. Agurell S, Berlin A, Ferngren H, Hellstrom B. Plasma levels of diazepam after parenteral and rectal administration in children. Epilepsia 1975;16:277-283.

2. Burdette D.E., Browne T.R. Benzodiazepines. In: Dam M. and Gram L. eds. Comprehensive Epileptology. New York Raven Press 1991;547-61.

3. Camfield C.S., Camfield P.R., Smith E., Dooley J.M. Home use of rectal diazepam to prevent status epilepticus in children with convulsive disorders. J Child Neurol 1989;4:125-6.

4. Consensus Statement of Expert Panel to Discuss Classification of Acute Repetitive Seizures and Safety of Rectally Administered Diazepam.

5. Daugbjerg P, Brems M, Mai J et al. Intermittent prophylaxis in febrile convulsions: Diazepam or valproic acid? Acta Neurol Scand, 1990;82:17-20.

6. Franzoni E, Carboni C, Lambertini A. Rectal diazepam: A clinical and EEG study after a single dose in children. Epilepsia 1983;24:35-41.

7. Garofalo E.A., Hirschorn K.A, Komarynski M.A. Improved control of seizure clusters with rectal diazepam and lorazepam. Clevel Clin J Med. 1989;56(Suppl. Part2):S-277.

8. Gonzalez RC. Emergency care of convulsions and the prevention of the epileptic status with rectal diazepam administered by parents. Bol Med Hosp Infant Mex 1991;48:469-473. (Spanish)

9. Harvey S. Hypnotics and sedatives. In: Gilman A., Goodman L., Rall T., et al. eds.

Goodman and Gilman's The Pharmacological Basis of Therapeutics, Seventh Edition. 7th ed. New York Macmillan Publishing Company 1985;339-71.

10. Hauser W.A., Hesdorffer D.C. Pregnancy and Teratogenesis. In: Epilepsy: Frequency, Causes and Consequences. Epilepsy Foundation of America 1990;147-96.

11. Hoppu K., Santavuori P. Diazepam rectal solution for home treatment of acute seizures in children. Acta Paediatr Scand 1981; 70:369-72.

12. Kalra A, Chaturvedi N, Vashishtha VM et al. Per rectal diazepam therapy in convulsive disorders. Indian Pediatr 1992;29:975-978.

13. Kamayachi S, Hashimoto K, Fujino O, et al. Serum levels of diazepam following rectal administration of suppositories and solutions. Brain Develop 1982;4:160.

14. Knudsen F.U. Plasma-diazepam in infants after rectal administration in solution and by suppository. Acta Paediatr Scand 1977;66:563-7.

15. Knudsen F.U. Rectal administration of diazepam in solution in the acute treatment of convulsions in infants and children. anticonvulsant effect and side effects. Arch Dis Child 1979;54:855-7.

16. Knudsen FU. Effective short-term diazepam prophylaxis in febrile convulsions. J Pediatr, 1985, 106: 487-490.

17. Kriel R.L., Cloyd J.C., Hadsall R.S., Carlson A.M., Floren K.L., Jones-Saete C.M. Home use of rectal diazepam for cluster and prolonged seizures: efficacy, adverse reactions, quality of life, and cost analysis. Pediatr Neurol 1991;7:13-7.

18. Krumholz A., Grufferman S., Orr S., Stern B.J. Seizures and seizure care in an emergency department. Epilepsia 1989;30(2):175-81.

19. Langslet A, Meberg A, Bredesen JE, Lunde PKM. Plasma concentrations of diazepam and N-desmethyldiazepam in newborn infants after intravenous, intramuscular, rectal, and oral administration. Acta Paediatr Scand 1978;67:699-704.

20. Lombroso C.T. Intermittent home treatment of status and clusters of seizures. Epilepsia 1989;30(Suppl 2):S11-4.

21. Macdonald R.L., Kelly K.M. Antiepileptic drug mechanisms of action. Epilepsia 1993;34(Suppl 5):S1-8.

22. Milligan N., Dhillon S., Richens A., Oxley J. Rectal diazepam in the treatment of absence status: a pharmacodynamic study. J Neurol Neurosurg Psychiatry 1981;44:914-7.

23. Minagawa K, Miura H, Kaneko T, Sudo Y. Plasma concentrations of diazepam and N-desmethyldiazepam in infants with febrile convulsion after single rectal administrations of diazepam suppositories or solutions. Brain and Development (JPN) 1982;14:11-19.

24. Minagawa K, Miura H, Mizuno S, Shirai H. Pharmacokinetics of rectal diazepam in the prevention of recurrent febrile seizures. Brain Dev 1986;8:53-59.

25. Olsen R.W. Antiepileptic actions of benzodiazepines. In: Faingold C.L. and Fromm G.H. eds. Drugs for control of epilepsy: Actions on neuronal networks involved in seizure disorders. Boca Raton, FL CRC Press 1992;464-76.

26. Rall T.W., Schleifer L.S. Drugs Effective in the Therapy of the Epilepsies. In: Gilman A.G., Goodman L.S., Rall T.W., et al. eds. The Pharmacological Basis of Therapeutics. Seventh ed. New York MacMillan Publishing Company 1985;464-7.

27. Remy C, Jourdil N, Villemain D et al. Intrarectal diazepam in epileptic adults. Epilepsia 1992,33:353-358.

28. Schmidt D. Benzodiazepines. Diazepam. In: Levy R., Mattson R., Meldrum B., et al. eds. Antiepileptic Drugs. Third ed. New York Raven Press, Ltd. 1989;735-64.

29. Seigler R.S. The administration of rectal diazepam for acute management of seizures. J Emerg Med 1990;8:155-9.

30. Treiman D.M. Current treatment strategies in selected situations in epilepsy. Epilepsia 1993;34(Suppl. 5):S17-23.

31. Watson HR. A diazepam rectal solution for home or institutional treatment of status epilepticus in children and adults. Aust J Hosp Pharm 1988;18:333-339.

32. Woods JH, Katz JL, and Winger G. Benzodiazepines: Use, abuse, and consequences. Pharmacol Rev 1992;44(2):151-347.

PART III: CONSUMER INFORMATION

DIASTAT® Rectal Delivery System
diazepam gel

This leaflet is part III of a three-part "Product Monograph" published when DIASTAT® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about DIASTAT®. Contact your doctor or pharmacist if you have any questions about the drug.

Please read this before you start taking DIASTAT®. It may answer some of the questions you have and help you to understand how to take DIASTAT® to obtain the best results. However, this leaflet does not contain all available information about DIASTAT® and does not take the place of your doctor's instructions. If you need more information or advice about DIASTAT®, talk to your doctor or pharmacist.

ABOUT THIS MEDICATION

What the medication is used for:
DIASTAT® (diazepam gel) is a gel formulation of diazepam intended for rectal administration in the management of selected, resistant to treatment, patients with epilepsy, on stable regimens of anti-epileptic drugs, who require occasional use of diazepam to control bouts of increased seizure activity.

What it does:
At lower doses, diazepam decreases the spread of seizures from the active site or focus to the surrounding neurons. At high therapeutic doses, diazepam may suppress seizures originating at the active focus as well.

DIASTAT® is intended for use by caregivers to treat patients in the home setting, as well as in hospitals, emergency and urgent care units and residential institutions.

When it should not be used:
DIASTAT® should not be used in patients with a known hypersensitivity to diazepam and other nonmedicinal ingredients (see What the nonmedicinal ingredients are). DIASTAT® may be used in patients with open angle glaucoma who are receiving appropriate therapy but is contraindicated in acute narrow angle glaucoma.

What the medicinal ingredient is:
diazepam

What the important nonmedicinal ingredients are:
Propylene glycol, ethyl alcohol (10%), hydroxypropyl methylcellulose, sodium benzoate, benzyl alcohol (1.5%), benzoic acid, and water.

What dosage forms it comes in:
DIASTAT® (diazepam gel) rectal delivery system is a non-sterile diazepam gel provided in prefilled, single dose, rectal delivery system. The rectal delivery system includes a plastic applicator with a flexible, molded tip available in 2 lengths, designated for convenience as Pediatrics, Universal or Adult. DIASTAT® is available in the following 5 presentations:

Dose of Diazepam (mg)	Rectal Tip Size
2.5	Pediatric (4.4 cm)
5.0	Pediatric (4.4 cm)
10.0	Universal (4.4 cm)
15.0	Adult (6.0 cm)
20.0	Adult (6.0 cm)

Each package contains 2 DIASTAT® rectal delivery systems, 2 packets of lubricating jelly, and Instructions for Use.

WARNINGS AND PRECAUTIONS

BEFORE you use DIASTAT®, talk to your doctor or pharmacist if:

- **You have acute narrow angle glaucoma.**
- **You are pregnant or of child-bearing age. DIASTAT® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.**
- **You are breast feeding.**
- **You have kidney problems, liver problems, or respiratory problems (asthma, pneumonia).**
- **You have a history of alcohol consumption or drug use (past or present).**
- **You are allergic to diazepam or any of the nonmedicinal ingredients.**

You should not engage in hazardous occupations requiring complete mental alertness, such as operating machinery, driving a motor vehicle or riding a bicycle following use of DIASTAT®.

INTERACTIONS WITH THIS MEDICATION

Tell your doctor or pharmacist about any medication that you are taking, including non-prescription medications and natural health products.

A drug interaction may occur between diazepam and the following drugs: cimetidine, quinidine, tranylcypromine, rifampicin, ketoconazole, clotrimazole, carbamazepine, phenytoin, dexamethasone, phenobarbital, omeprazole, propranolol, imipramine, cyclosporine, paclitaxel, terfenadine, theophylline, warfarine, cimetidine, phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants and valproate.

PROPER USE OF THIS MEDICATION

Usual dose:

The usual dose of DIASTAT® is as directed by your doctor.

Overdose: Possible symptoms of an overdose of diazepam could include sleepiness, confusion, unconsciousness, and slow reactions. In case of an overdose, please contact your doctor or go to the nearest hospital or emergency room.

Missed Dose: Not applicable.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

During clinical studies, the most frequent side effect was sleepiness. Less frequent side effects were dizziness, headache, pain, diarrhea, sense of well-being or euphoria, clumsiness and nervousness. In addition, movement disorder, weakness, hiccup and dizziness were reported.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common	None			
Uncommon	Increased acid levels of the blood and body tissues		T	
	Convulsion		T	
	Difficulty breathing		T	
	Not enough oxygen being supplied to body tissues		T	
	Kidney failure		T	
	Pneumonia		T	
	Stupor (Unconsciousness)		T	

This is not a complete list of side effects. For any unexpected effects while taking DIASTAT®, contact your doctor or pharmacist.

HOW TO STORE IT

Store at controlled room temperature 15 - 30ºC (59 - 86ºF).

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

toll-free telephone: 866-234-2345
toll-free fax 866-678-6789
By email: cadrmp@hc-sc.gc.ca

By regular mail:
National AR Centre
Marketed Health Products Safety and Effectiveness Information Division
Marketed Health Products Directorate
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:
http:/webprod.hc-sc.gc.ca/dpd-bdpp/index-eng.jsp
or by contacting:
Valeant Canada LP
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