When to treat. Based on the doctor’s directions or prescription. Your doctor may prescribe a second dose of Diazepam rectal gel. If a second dose is needed, give it 4 hours to 12 hours after the first dose.

Special considerations.

DIASTAT should be used with caution:

- In people with respiratory (breathing) difficulties (e.g., asthma or pneumonia)
- In the elderly
- In women of child bearing potential, pregnancy and nursing mothers

Discuss beforehand with the doctor any additional steps you may need to take if there is leakage of DIASTAT or a bowel movement.

Patient’s DIASTAT dosage is: _____mg

Patient’s resting breathing rate ________  Patient’s current weight ________

Confirm current weight is still the same as when DIASTAT was prescribed _____________________

Check expiration date and always remove cap before using. Be sure seal pin is removed with the cap.

Important things to tell the doctor.

Seizures Before DIASTAT

<table>
<thead>
<tr>
<th>Date</th>
<th>Time</th>
<th>Type</th>
<th>No. of Seizures</th>
</tr>
</thead>
<tbody>
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Seizures After DIASTAT

<table>
<thead>
<tr>
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<th>No. of Seizures</th>
</tr>
</thead>
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</table>

Things to do after treatment with DIASTAT.

Stay with the person for 4 hours and make notes on the following:

- Changes in resting breathing rate
- Changes in color
- Possible side effects from treatment
- Your doctor may prescribe a second dose of Diazepam rectal gel. If a second dose is needed, give it 4 hours to 12 hours after the first dose.

Important things to tell the doctor.

Seizures Before DIASTAT

<table>
<thead>
<tr>
<th>Date</th>
<th>Time</th>
<th>Type</th>
<th>No. of Seizures</th>
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</table>

Seizures After DIASTAT

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<th>Date</th>
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<td></td>
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</tr>
</tbody>
</table>

Things to do after treatment with DIASTAT.

Stay with the person for 4 hours and make notes on the following:

- Changes in resting breathing rate
- Changes in color
- Possible side effects from treatment
HOW TO ADMINISTER AND DISPOSAL

1. Put person on their side where they can't fall.
2. Get medicine.
3. Get syringe. Note: Seal Pin is attached to the cap.
4. Push up with thumb and pull to remove cap from syringe. Be sure Seal Pin is removed with the cap.
5. Lubricate rectal tip with lubricating jelly.
6. Turn person on side facing you.
7. Bend upper leg forward to expose rectum.
8. Separate buttocks to expose rectum.
9. Gently insert syringe tip into rectum. Note: Rim should be snug against rectal opening.
10. Slowly count to 3 while gently pushing plunger in until it stops.
11. Slowly count to 3 before removing syringe from rectum.
12. Slowly count to 3 while holding buttocks together to prevent leakage.
13. Keep person on side facing you, note time given and continue to observe.

SLOWLY COUNT OUT LOUD TO THREE...1...2...3

ONCE DIASTAT® IS GIVEN

14a. Pull on plunger until it is completely removed from the syringe body. Point tip over sink or toilet.
14b. At the completion of step 13:
   • Discard all used materials in the garbage can.
   • Do not reuse.
   • Discard in a safe place away from children.

This step is for Diastat AcuDial™ users only
At the completion of step 14a:
• Discard all used materials in the garbage can.
• Do not reuse.
• Discard in a safe place away from children.

CALL FOR HELP IF ANY OF THE FOLLOWING OCCUR

• Seizure(s) continues 15 minutes after giving DIASTAT or per the doctor's instructions.
• Seizure behavior is different from other episodes.
• You are alarmed by the frequency or severity of the seizure(s).
• You are alarmed by the color or breathing of the person.
• The person is having unusual or serious problems.

Local Emergency Number: ____________________________
(please be sure to note if your area has 911)

Doctor's Number: ____________________________

Information for Emergency Squad:

Time DIASTAT given: ____________________________
Dose: ____________________________

Please see Important Safety Information attached.
DIASTAT® (diazepam rectal gel) is a gel formulation of diazepam intended for rectal administration for certain patients with epilepsy who are already taking antiepileptic medications, and who require occasional use of diazepam to control bouts of increased seizure activity.

**INDICATION**

**IMPORTANT SAFETY INFORMATION**

- Do not use DIASTAT if you are allergic to diazepam.

- Do not use DIASTAT if you have an eye condition known as acute narrow angle glaucoma

- If you are a caregiver administering DIASTAT ensure that you have read and understand the accompanying Administration and Disposal Instructions. Ensure that (1) you can identify the difference between cluster of seizures (and/or the events that precipitate the onset of seizures) from ordinary seizure activity, (2) a doctor confirms that you are able to use the product as instructed, (3) you understand which seizures may or may not be treated with diazepam rectal gel, and (4) you monitor the effect of diazepam rectal gel and know when to seek professional medical help.

- Do not operate machinery, drive a motor vehicle, or ride a bike until you no longer feel the effects of DIASTAT.

- Do not use DIASTAT with alcohol or in combination with other Central Nervous System (CNS) medications or products that cause respiratory (breathing) or CNS effects. Talk to your doctor if you have any questions about medications or products that you should not use in combination with DIASTAT.

- DIASTAT should not be used in children under 6 months of age.

- Pregnancy Category D - No clinical studies have been conducted with diazepam rectal gel in pregnant women. Data from several sources raise concerns about the use of diazepam during pregnancy. Talk to your doctor before using DIASTAT if you are nursing, pregnant, or of childbearing potential.

- Use with caution if you have breathing difficulties (such as asthma or pneumonia), kidney or liver disease, or are elderly. Talk to your doctor if any of these conditions apply to you, or if you are not sure if any of these conditions apply to you.

- Diazepam rectal gel can cause drug addiction. Use no more than every five days and no more than five times per month.

- The most frequent side effect reported for DIASTAT in clinical trials was somnolence (sleepiness or drowsiness). Other side effects include dizziness, headache, pain, abdominal pain, nervousness, vasodilation (increase in diameter of blood vessel), diarrhea, ataxia/incoordination (lack of coordination), euphoria (feeling of great happiness or well-being), asthma, rhinitis (irritation of the nose similar to an allergy or a cold) and rash.

**Please see accompanying full Prescribing Information.**

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088. You may also contact Valeant Customer Service at 1-800-556-1937.
**Diazepam**: A benzodiazepine anticonvulsant with the chemical name 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one. The structural formula is as follows:

![Structural formula of Diazepam](image)

**Mechanism of Action**

Although the precise mechanism by which diazepam exerts its antiepileptic effects is unknown, animal and in vitro studies suggest that diazepam acts to suppress seizures through an interaction with γ-aminobutyric acid (GABA) receptors of the A-type (GABA_A). GABA, the major inhibitory neurotransmitter in the central nervous system, 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. It is believed that diazepam enhances the actions of GABA by causing GABA to bind more tightly to the GABA_A receptor.

**Pharmacokinetics**

Pharmacokinetic information of diazepam following rectal administration was obtained from studies conducted in healthy adult subjects. No pharmacokinetic studies were conducted in pediatric patients. Therefore, information from the literature is used to define pharmacokinetic labeling in the pediatric population.

Diazepam rectal gel is well absorbed following rectal administration, reaching peak plasma concentrations in 1.5 hours. The absolute bioavailability of Diazepam rectal gel relative to Valium® injectable is 90%. The volume of distribution of Diazepam rectal gel is calculated to be approximately 1 L/kg. The mean elimination half-life of diazepam and desmethyldiazepam following administration of a 15 mg dose of Diazepam rectal gel was found to be about 46 hours (CV=33%) and 71 hours (CV=37%), respectively.

Both diazepam and its major active metabolite desmethyldiazepam bind extensively to plasma proteins (95-98%).

**Effect of Gender, Race, and Cigarette Smoking**

No targeted pharmacokinetic studies have been conducted to evaluate the effect of gender, race, and cigarette smoking on the pharmacokinetics of diazepam. However, covariate analysis of a population of treated patients following administration of diazepam rectal gel, indicated that neither gender nor cigarette smoking had any effect on the pharmacokinetics of diazepam.

**Clinical Studies**

The effectiveness of diazepam rectal gel has been established in two adequate and well controlled clinical studies in children and adults exhibiting the seizure profile described below. A randomized, double-blind study compared sequential doses of diazepam rectal gel and placebo in 91 patients (47 children, 44 adults) exhibiting the appropriate seizure profile. The first dose was given at the onset of an identified episode. Children were dosed again four hours after the first dose and were observed for a total of 24 hours. Adults were dosed at four and 12 hours after the first dose and were observed for a total of 24 hours. Primary outcomes for this study were seizure frequency during the period of observation and a global assessment that took into account the severity and nature of the seizures as well as their frequency.

The median seizure frequency for the diazepam rectal gel treated group was zero seizures per hour, compared to a median seizure frequency of 0.3 seizures per hour for the placebo group, a difference that was statistically significant (p < 0.0001). All three categories of the global assessment (seizure frequency, seizure severity, and “overall”) were also found to be statistically significant in favor of Diazepam rectal gel (p < 0.0001). The following histogram displays the results for the “overall” category of the global assessment.

**Patients treated with Diazepam rectal gel experienced prolonged time-to-next-seizure compared to placebo (p = 0.0002) as shown in the following graph.**

**FIGURE 1: Plasma Concentrations of Diazepam and Desmethyldiazepam Following Diastal or IV Diazepam**

**FIGURE 2: Caregiver Overall Global Assessment of the Efficacy of Diastat**

Patients treated with Diazepam rectal gel experienced prolonged time-to-next-seizure compared to placebo (p = 0.0002) as shown in the following graph.
in addition, 62% of patients treated with diazepam rectal gel were seizure-free during the observation period compared to 20% of placebo patients. Analysis of response by gender and age revealed no substantial differences between treatment in either of these subgroups. Analysis of response by race was considered unreliable, due to the small percentage of non-Caucasians. A second double-blind study compared single doses of diazepam rectal gel and placebo in 114 patients (53 children, 61 adults). The dose was given at the onset of the identified episode and patients were observed for a total of 12 hours. The primary outcome in this study was seizure frequency. The median seizure frequency for the diazepam rectal gel-treated group was zero seizures per 12 hours, compared to a median seizure frequency of 2.0 seizures per 12 hours for the placebo group, a difference that was statistically significant (p < 0.03). Patients treated with diazepam rectal gel experienced prolonged time-to-next-seizure compared to placebo (p = 0.0072) as shown in the following graph.

In addition, 55% of patients treated with diazepam rectal gel were seizure-free during the observation period compared to 34% of patients receiving placebo. Overall, caregivers judged diazepam rectal gel to be more effective than placebo (p = 0.018), based on a 10 centimeter visual analog scale. In addition, investigators also evaluated the effectiveness of diazepam rectal gel and judged diazepam rectal gel to be more effective than placebo (p < 0.001).

An analysis of response by gender revealed a statistically significant difference between treatments in females but not in males in this study, and the difference between the 2 genders in response to the treatments reached borderline statistical significance. Analysis of response by race was considered unreliable, due to the small percentage of non-Caucasians.

INDICATIONS AND USAGE
Diazepam rectal gel is a gel formulation of diazepam intended for rectal administration in the management of selected, refractory, patients with epilepsy, on stable regimens of AEDs, who require intermittent use of diazepam to control outbreaks of increased seizure activity.

Evidence to support the use of diazepam rectal gel was adduced in two controlled trials (see CLINICAL PHARMACOLOGY, CLINICAL STUDIES subsection) that enrolled patients with partial onset or generalized convulsive seizures who were identified jointly by their caregivers and physicians as suffering intermittent and enrolleed patients with partial onset or generalized convulsive seizures who were identified jointly by their caregivers and physicians as suffering intermittent and more specifically during known pregnancy, should be considered only when the clinical situation warrants the risk to the fetus. The specific considerations addressed above regarding the use of anticonvulsants in epileptic women of childbearing potential should be weighed in treating or counseling these women.
Because of experience with other members of the benzodiazepine class, Diazepam rectal gel is assumed to be capable of causing an increased risk of congenital abnormalities when administered to a pregnant woman during the first trimester. The possibility that a woman of childbearing potential may be pregnant at the time of institution of therapy should be considered. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Patients should also be advised that if they become pregnant during therapy or intend to become pregnant they should communicate with their physician about the desirability of discontinuing the drug.

Withdrawal Symptoms
Withdrawal symptoms of the barbiturate type have occurred after the discontinuation of regular use of benzodiazepines (see DRUG ABUSE AND DEPENDENCE section).

Chronic Use
Diazepam rectal gel 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 tonic clonic 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.

Use in Patients with Petit Mal Status
Tonic status epilepticus has been precipitated in patients treated with IV diazepam for petit mal status or petit mal variant status.

PRECAUTIONS

Caution in Renally Impaired Patients
Metabolites of Diazepam rectal gel are excreted by the kidneys; to avoid their excess accumulation, caution should be exercised in the administration of the drug to patients with impaired renal function.

Caution in Hepatically Impaired Patients
Concomitant liver disease is known to decrease the clearance of diazepam (see CLINICAL PHARMACOLOGY, Special Populations, Hepatic Impairment). Therefore, Diazepam rectal gel should be used with caution in patients with liver disease.

Use in Pediatrics
The controlled trials demonstrating the effectiveness of Diazepam rectal gel included children two years of age and older. Clinical studies have not been conducted to establish the efficacy and safety of Diazepam rectal gel in children under two years of age.

Use in Patients with Compromised Respiratory Function
Diazepam rectal gel should be used with caution in patients with compromised respiratory function related to a concurrent disease process (e.g., asthma, pneumonia) or neurologic damage.

Use in Elderly
In elderly patients Diazepam rectal gel should be used with caution due to an increase in halflife with a corresponding decrease in the clearance of free diazepam. It is also recommended that the dosage be decreased to reduce the likelihood of ataxia or oversedation.

Information to be Communicated by the Prescriber to the Caregiver
Prescribers are strongly advised to take all reasonable steps to ensure that caregivers fully understand their role and obligations vis a vis the administration of Diazepam rectal gel to individuals in their care. Prescribers should routinely discuss the steps in the Patient/Caregiver Package Insert (see Patient/Caregiver Insert printed as the product labeling and also included in the product carton). The successful and safe use of Diazepam rectal gel depends in large measure on the competence and performance of the caregiver. Prescribers should advise caregivers that they expect to be informed immediately if a patient develops any new findings which are not typical of the patient’s characteristic seizure episode.

Interference With Cognitive and Motor Performance:
Because benzodiazepines have the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that Diazepam rectal gel therapy does not affect them adversely.

Pregnancy: Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy with Diazepam rectal gel (see WARNINGS section).

Nursing: Because diazepam and its metabolites may be present in human breast milk for prolonged periods of time after acute use of Diazepam rectal gel, patients should not breast-feed for an appropriate period of time after receiving treatment with Diazepam rectal gel.

Concomitant Medication
Although Diazepam rectal gel is indicated for use solely on an intermittent basis, the potential exists for a synergistic CNS-depressant effect when used simultaneously with alcohol or other CNS-depressants must be considered by the prescribing physician, and appropriate recommendations made to the patient and/or caregiver. Drug Interactions If Diazepam rectal gel is to be combined with other psychotropics 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. The clearance of diazepam and certain other benzodiazepines can be delayed in association with cimetidine administration. The clinical significance of this is unclear. Valproate may potentiate the CNS-depressant effects of diazepam. There have been no clinical studies or reports in 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. Effect of Other Drugs on Diazepam Metabolism: 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 interactions may occur when diazepam is given concurrently with agents that affect CYP2C19 and CYP3A4 activity. Potential inhibitors of CYP2C19 (e.g., cimetidine, quinidine, and tranylcypromine) and CYP3A4 (e.g., ketoconazole, troleandomycin, and clotrimazole) could decrease the rate of diazepam elimination, while inducers of CYP2C19 (e.g., rifampin) and CYP3A4 (e.g., carbamazepine, phenytoin, dexamethasone and phenobarbital) could increase the rate of elimination of diazepam.

Effect 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 warfarin) leading to a potential drug-drug interaction.

Carcinogenesis, Mutagenesis, Impairment of Fertility
No oncogenic potential of rectal diazepam has not been evaluated. In studies in which mice and rats were administered diazepam in the diet at a dose of 75 mg/kg/day (approximately six and 12 times, respectively, the maximum recommended human dose [MRHD=1 mg/kg/day] on a mg/m2 basis) 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 decreases in the number of pregnancies and in the number of surviving offspring following administration of an oral dose of 100 mg/kg/day (approximately 16 times the MRHD on a mg/m2 basis) prior to and during mating and throughout gestation and lactation. No adverse effects on fertility or offspring viability were noted at a dose of 80 mg/kg/day (approximately 13 times the MRHD on a mg/m2 basis).

Pregnancy - Category D (see WARNINGS section)

Labor and Delivery
In humans, measurable amounts of diazepam have been found in maternal and cord blood, indicating placental transfer of the drug. Until additional information is available, Diazepam rectal gel is not recommended for obstetrical use.

Nursing Mothers
Because diazepam and its metabolites may be present in human breast milk for prolonged periods of time after acute use of Diazepam rectal gel, patients should not breast-feed for an appropriate period of time after receiving treatment with Diazepam rectal gel.

ADVERSE REACTIONS
Diazepam rectal gel adverse event data were collected from double-blind, placebo-controlled studies and open-label studies. The majority of adverse events were mild to moderate in severity and transient in nature. Two patients who received Diazepam rectal gel died seven to 15 weeks following treatment; neither of these deaths was deemed related to Diazepam rectal gel. The most frequent adverse event reported to be related to Diazepam rectal gel in the two double-blind, placebo-controlled studies was somnolence (23%). Less frequent adverse events were dizziness, headache, pain, abdominal pain, nervousness, vasodilatation, diarrhea, ataxia, euphoria, incoordination, asthma, rhinitis, and rash, which occurred in approximately 2-5% of patients. Approximately 1.4% of the 573 patients who received Diazepam rectal gel in clinical trials of epilepsy discontinued treatment because of an adverse event. The adverse event most frequently associated with discontinuation (occurring in three patients) was somnolence. Other adverse events most commonly associated with discontinuation and occurring in two patients were headache and rash. Adverse events occurring in one patient were asthenia, hyperkinesia, incoordination, vasodilatation and urticaria. These events were judged to be related to diazepam rectal gel. In the two domestic double-blind, placebo-controlled, parallel-group studies, the proportion of patients who discontinued treatment because of adverse events was 2% for the group treated with Diazepam rectal gel, versus 2% for the placebo group. In the Diazepam rectal gel group, the adverse events considered
the primary reason for discontinuation were different in the two patients who discontinued treatment; one discontinued due to rash and one discontinued due to lethargy. The primary reason for discontinuation in the patients treated with placebo was lack of effect.

Adverse Event Incidence in Controlled Clinical Trials

Table 1 lists treatment-emergent signs and symptoms that occurred in > 1% of patients enrolled in parallel-group, placebo-controlled trials and were numerically more common in the Diazepam rectal gel group. Adverse events were usually mild or moderate in intensity.

The prescriber should be aware that these figures, obtained when Diazepam rectal gel was added to concurrent antiepileptic drug therapy, cannot be used to predict the frequency of adverse events in the course of usual medical practice when patient characteristics and other factors may differ from those prevailing during clinical trials. Similarly, the cited frequencies cannot be directly compared with figures obtained from other clinical investigations involving different treatments, uses, or investigators. An inspection of these frequencies, however, does provide the prescribing physician with one basis to estimate the relative contribution of drug and non-drug factors to the adverse event incidences in the population studied.

**TABLE 1: Treatment-Emergent Signs And Symptoms That Occurred In > 1% Of Patients Enrolled In Parallel-Group, Placebo-Controlled Trials And Were Numerically More Common In The Diazepam rectal gel Group**

<table>
<thead>
<tr>
<th>Body System</th>
<th>COSTART Term</th>
<th>Diastat N = 101 %</th>
<th>Placebo N = 104 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body As A Whole</td>
<td>Headache</td>
<td>5%</td>
<td>4%</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Vomodilation</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>Digestive</td>
<td>Diarrhea</td>
<td>4%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Nervous</td>
<td>Ataxia</td>
<td>3%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Digestive</td>
<td>Dizziness</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>Nervous</td>
<td>Euphoria</td>
<td>3%</td>
<td>0%</td>
</tr>
<tr>
<td>Nervous</td>
<td>Incoordination</td>
<td>3%</td>
<td>0%</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Asthma</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>Skin and Appendages</td>
<td>Rash</td>
<td>3%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Other events reported by 1% or more of patients treated in controlled trials but equally or more frequent in the placebo group than in the Diazepam rectal gel group were abdominal pain, pain, nervousness, and rhiitis. Other events reported by fewer than 1% of patients were infection, anorexia, vomiting, anemia, lymphadenopathy, grand mal convulsion, hyperkinesia, cough increased, pruritus, sweating, mydriasis, and urinary tract infection.

The pattern of adverse events was similar for different age, race and gender groups.

Other Adverse Events Observed During All Clinical Trials:

Diazepam rectal gel has been administered to 573 patients with epilepsy during all clinical trials, only some of which were placebo-controlled. During these trials, all adverse events were recorded by the clinical investigators using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals having adverse events, similar types of events were grouped into a smaller number of standardized categories using modified COSTART dictionary terminology. These categories are used in the listing below. All of the events listed below occurred in at least 1% of the 573 individuals exposed to Diazepam rectal gel.

All reported events are included except those already listed above, events unlikely to be drug-related, and those too general to be informative. Events are included without regard to determination of a causal relationship to diazepam.

**BODIES AS A WHOLE:** Asthenia

**CARDIOVASCULAR:** Hypotension, vasodilatation

**NERVOUS:** Agitation, confusion, convulsion, dysarthria, emotional lability, speech disorder, thinking abnormal, vertigo

**RESPRITORY:** Hiccup

The following infrequent adverse events were not seen with Diazepam rectal gel but have been reported previously with diazepam use: depression, slurred speech, syncope, constipation, changes in libido, urinary retention, bradycardia, cardiovascular collapse, myasthenia, urticaria, neuropenia and jaundice. Paradoxical reactions such as anxiety, hyperactivity, states of confusion, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances and stimulation have been reported with diazepam; should these occur, use of Diazepam rectal gel should be discontinued.

**DRUG ABUSE AND DEPENDENCE**

Diazepam is a Schedule IV controlled substance and can produce drug dependence. It is recommended that patients be treated with Diazepam rectal gel 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 no more frequent than every five days and no more than five times per month. Diazepam is a Schedule IV controlled substance and can produce drug dependence. It is recommended that patients be treated with Diazepam rectal gel no more frequently than every five days and no more than five times per month.

**OVERDOSAGE**

Two patients in the clinical studies received more than twice the target dose; no adverse events were reported.

Previous reports of diazepam overdose have shown that manifestations of diazepam overdose include somnolence, confusion, coma, and diminished reflexes. Respiration, pulse and blood pressure should be monitored, as in all cases of drug overdose, 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.

Flumazenil, a specific benzodiazepine-receptor antagonist, is indicated for the complete or partial reversal of the sedative effects of benzodiazepines and may be used in situations when an overdose with a benzodiazepine is known or suspected. Prior to the administration of flumazenil, necessary measures should be taken to secure airway, ventilation and intravenous access. Flumazenil is intended as an adjunct to, not as a substitute for, proper management of benzodiazepine overdose. Patients treated with flumazenil should be monitored for resedation, respiratory depression and other residual benzodiazepine effects for an appropriate period after treatment. The prescriber should be aware of the risk of seizure in association with flumazenil treatment, particularly in long-term benzodiazepine users and in cyclic antidepressant overdose. The complete flumazenil package insert, including CONTRAINDICATIONS, WARNINGS and PRECAUTIONS, should be consulted prior to use.

**DOSEAGE AND ADMINISTRATION (see also Patient/Caregiver Package Insert)**

This section is intended primarily for the prescriber; however, the prescriber should also be aware of the dosing information and directions for use provided in the patient package insert.

A decision to prescribe Diazepam rectal gel involves more than the diagnosis and the selection of the correct dose for the patient.

First, the prescriber must be convinced from historical reports and/or personal observations that the patient exhibits the characteristic identifiable seizure cluster that can be distinguished from the patient’s usual seizure activity by the caregiver who will be responsible for administering Diazepam rectal gel.

Second, because Diazepam rectal gel is only intended for adjunctive use, the prescriber must ensure that the patient is receiving an optimal regimen of standard anti-epileptic drug treatment and is, nevertheless, continuing to experience these characteristic episodes.

Third, because a non-health professional will be obliged to identify episodes suitable for treatment, the decision to administer treatment upon that identification, administer the drug, monitor the patient, and assess the adequacy of the response to treatment, a major component of the prescribing process involves the necessary instruction of this individual.

Fourth, the prescriber and caregiver must have a common understanding of what is and is not an episode of seizures that is appropriate for treatment, the timing of administration in relation to the onset of the episode, the mechanics of administering the drug, how and what to observe following administration, and what would constitute an outcome requiring immediate and direct medical attention.

**Calculating Prescribed Dose**

The Diazepam rectal gel dose should be individualized for maximum beneficial effect. The recommended dose of Diazepam rectal gel is 0.2-0.5 mg/kg depending on age. See the dosing table for specific recommendations.

**Age (years)**

<table>
<thead>
<tr>
<th>Age</th>
<th>Recommended Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 - 5</td>
<td>0.5 mg/kg</td>
</tr>
<tr>
<td>6 - 11</td>
<td>0.3 mg/kg</td>
</tr>
<tr>
<td>12+</td>
<td>0.2 mg/kg</td>
</tr>
</tbody>
</table>

Because Diazepam rectal gel is provided as unit doses of 2.5, 5, 7.5, 10, 12.5, 15, 17.5, 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 recommended dose. The safety of this strategy has been established in clinical trials.

<table>
<thead>
<tr>
<th>Weight (mg)</th>
<th>Dose (mg)</th>
<th>Weight (mg)</th>
<th>Dose (mg)</th>
<th>Weight (mg)</th>
<th>Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 to 10</td>
<td>5</td>
<td>10 to 16</td>
<td>5</td>
<td>14 to 25</td>
<td>5</td>
</tr>
<tr>
<td>11 to 15</td>
<td>7.5</td>
<td>17 to 25</td>
<td>7.5</td>
<td>26 to 37</td>
<td>7.5</td>
</tr>
<tr>
<td>16 to 20</td>
<td>10</td>
<td>26 to 33</td>
<td>10</td>
<td>38 to 50</td>
<td>10</td>
</tr>
<tr>
<td>21 to 25</td>
<td>12.5</td>
<td>34 to 41</td>
<td>12.5</td>
<td>51 to 62</td>
<td>12.5</td>
</tr>
<tr>
<td>26 to 30</td>
<td>15</td>
<td>42 to 50</td>
<td>15</td>
<td>63 to 75</td>
<td>15</td>
</tr>
</tbody>
</table>
The rectal delivery system includes a plastic applicator with a flexible, molded tip available in two lengths. The Diastat® AcuDial™ 10-mg syringe is available with a 4.4 cm tip and the Diastat® AcuDial™ 20 mg syringe is available with a 6.0 cm tip. Diastat® 2.5 mg is also available with a 4.4 cm tip.

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 Diazepam rectal gel should be adjusted by the physician periodically to reflect changes in the patient’s age or weight. The Diastat® 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

The prescriber may wish to prescribe a second dose of Diazepam rectal gel. A second dose, when required, may be given 4-12 hours after the first dose.

Treatment Frequency

It is recommended that Diazepam rectal gel be used to treat no more than five episodes per month and no more than one episode every five days.

HOW SUPPLIED

Diazepam rectal gel rectal delivery system is a non-sterile, prefilled, unit dose, rectal delivery system. The rectal delivery system includes a plastic applicator with a flexible, molded tip available in two lengths, designated for convenience as 10 mg Delivery System and 20 mg Delivery System. The available doses from 20 mg delivery system are 12.5 mg, 15 mg, 17.5 mg and 20 mg. The available doses from 10 mg delivery system are 5 mg, 7.5 mg and 10 mg. The Diazepam rectal gel delivery system is available in the following three presentations: