

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
NDA 20-648/S-002

Name: Diastat

Generic Name: (diazepam rectal gel)

Sponsor: Valeant Pharmaceuticals International

Approval Date: 04/11/2001

CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION NUMBER:
NDA 20-648/S-002**

CONTENTS

Reviews / Information Included in this Review

Approval Letter	X
Approvable Letter(s)	
Approved Labeling	X
Medical Review(s)	
Chemistry Review(s)	
EA/FONSI	
Pharmacology Review(s)	
Statistical Review(s)	
Microbiology Review(s)	
Clinical Pharmacology/Biopharmaceutics Review(s)	
Administrative and Correspondence Document(s)	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-648/S-002

APPROVAL LETTER



Food and Drug Administration
Rockville MD 20857

NDA 20-648/S-002

Elan Pharmaceuticals, Inc.
Attention: Louise C. Johnson
Director, Regulatory Affairs
800 Gateway Boulevard
South San Francisco, CA 94080

Dear Ms. Johnson:

Please refer to your supplemental new drug application dated April 14, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Diastat (diazepam rectal gel) Rectal Delivery System.

We acknowledge receipt of your amendment dated May 25, 1999.

Supplemental application S-002, submitted under "Changes Being Effected", provides for the modification of the commercially available container labels to consolidate the 10 mg adult and 10 mg pediatric container labels to a 10 mg universal container label. This change is also reflected in the package insert under the **HOW SUPPLIED** section.

We have completed the review of this supplemental application, S-002, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use. Accordingly, this supplemental application is approved effective on the date of this letter.

Labeling changes of the kind which you have proposed under the above supplemental application are permitted by section 314.70(c) of the regulations to be instituted prior to approval of the supplement. It is understood that the changes, described in the above NDA supplement, have been made.

We additionally request, at the next printing, that you replace the presently used storage recommendations under the **HOW SUPPLIED** section with the following statement:

"Store at 25°C (77°F); excursions permitted to 15 - 30°C (59 - 86°F) [see USP Controlled Room Temperature]"

This change may be reported in the next annual report.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Mr. Paul David, R.Ph., Senior Regulatory Project Manager, at (301) 594-5530.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

/s/

Russell Katz
4/11/01 08:47:33 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-648/S-002

APPROVED LABELING

Diastat®

(diazepam rectal gel)

Rectal Delivery System

APPROVED

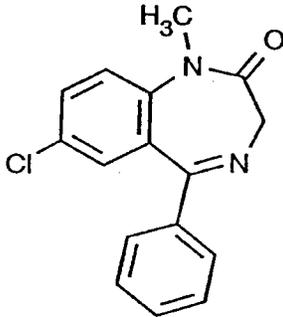


APR 11 2001

DESCRIPTION

DIASTAT® rectal delivery system is a non-sterile diazepam gel provided in a prefilled, unit-dose, rectal delivery system. 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.

Diazepam, the active ingredient of Diastat, is 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:



* Registered trademark of Athena Neurosciences, Inc.

CLINICAL PHARMACOLOGY

Mechanism of Action

Although the precise mechanism by which diazepam exerts its antiseizure 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.

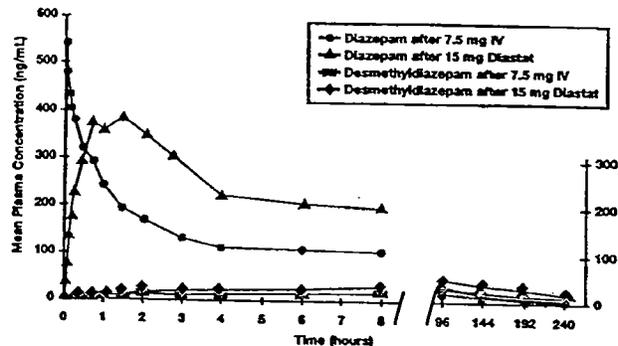
Pharmacokinetics

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.

Diastat is well absorbed following rectal administration, reaching peak plasma concentrations in 1.5 hours. The absolute bioavailability of Diastat relative to Valium® injectable is 90%. The volume of distribution of Diastat 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 Diastat was found to be about 46 hours (CV=43%) and 71 hours (CV=37%), respectively. Both diazepam and its major active metabolite desmethyldiazepam bind extensively to plasma proteins (95-98%).

Diastat® (diazepam rectal gel)

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



Metabolism and Elimination: 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.

Special Populations

Hepatic Impairment: No pharmacokinetic studies were conducted with Diastat in hepatically impaired subjects. Literature review indicates that following administration of 0.1 to 0.15 mg/kg of diazepam intravenously, the half-life of diazepam was prolonged by two to five-fold in subjects with alcoholic cirrhosis (n=24) compared to age-matched control subjects (n=37) with a corresponding decrease in clearance by half; however, the exact degree of hepatic impairment in these subjects was not characterized in this literature (see PRECAUTIONS section).

Renal Impairment: The pharmacokinetics of diazepam have not been studied in renally impaired subjects (see PRECAUTIONS section).

Pediatrics: No pharmacokinetic studies were conducted with Diastat in the pediatric population. However, literature review indicates that following IV administration (0.33 mg/kg), diazepam has a longer half-life in neonates (birth up to one month; approximately 50-95 hours) and infants (one month up to two years; about 40-50 hours), whereas it has a shorter half-life in children (two to 12 years; approximately 15-21 hours) and adolescents (12 to 16 years; about 18-20 hours) (see PRECAUTIONS section).

Elderly: A study of single dose IV administration of diazepam (0.1 mg/kg) indicates that the elimination half-life of diazepam increases linearly with age, ranging from about 15 hours at 18 years (healthy young adults) to about 100 hours at 95 years (healthy elderly) with a corresponding decrease in clearance of free diazepam (see PRECAUTIONS and DOSAGE AND ADMINISTRATION sections).

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

Diastat® (diazepam rectal gel)

diazepam. However, covariate analysis of a population of treated patients following administration of Diastat indicated that neither gender nor cigarette smoking had any effect on the pharmacokinetics of diazepam.

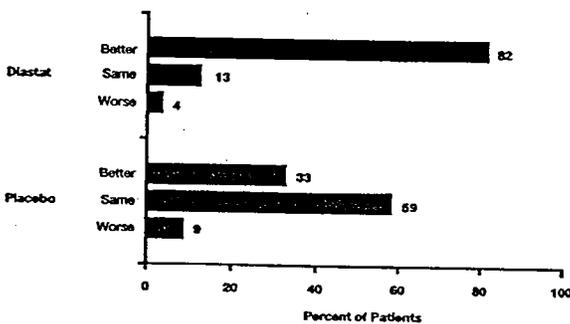
Clinical Studies

The effectiveness of Diastat has been established in two adequate and well-controlled clinical studies in children and adults exhibiting the seizure pattern described below under INDICATIONS.

A randomized, double-blind study compared sequential doses of Diastat 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 12 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.

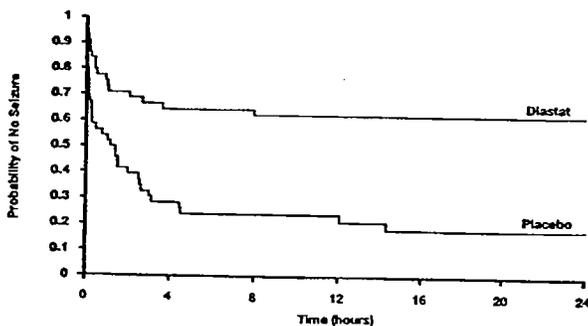
The median seizure frequency for the Diastat treated group was zero seizures per hour, compared to a median seizure frequency of 0.3 seizures per hour for the placebo group, a difference that was statistically significant ($p < 0.0001$). All three categories of the global assessment (seizure frequency,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

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



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

FIGURE 3: Kaplan-Meier Survival Analysis of Time-to-Next-Seizure - First Study



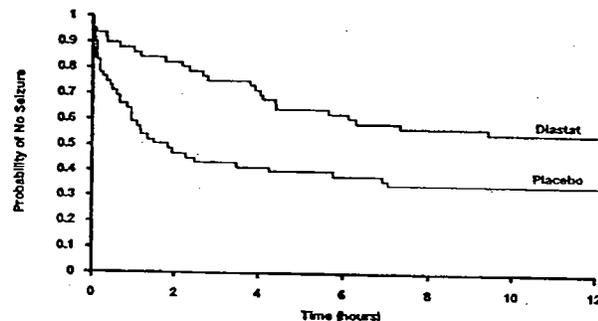
In addition, 62% of patients treated with Diastat were seizure-free during the observation period compared to 20% of placebo patients.

Diastat® (diazepam rectal gel)

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 Diastat 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 Diastat-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 Diastat experienced prolonged time-to-next-seizure compared to placebo ($p = 0.0072$) as shown in the following graph.

FIGURE 4: Kaplan-Meier Survival Analysis of Time-to-Next-Seizure - Second Study



In addition, 55% of patients treated with Diastat were seizure-free during the observation period compared to 34% of patients receiving placebo. Overall, caregivers judged Diastat 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 Diastat and judged Diastat 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

Diastat 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 bouts of increased seizure activity.

Evidence to support the use of Diastat 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 periodic episodes of markedly increased seizure activity, sometimes heralded by non-convulsive symptoms, that for the individual patient were characteristic and were deemed by the prescriber to be of a kind for which a benzodiazepine would ordinarily be administered acutely. Although these clusters or bouts of seizures differed among patients, for any individual patient the clusters of seizure activity were not only stereotypic but were judged by those conducting and participating in these studies to be distinguishable from other seizures suffered by that patient. The conclusion that a patient experienced such unique episodes of seizure activity was based on historical information.

Diastat* (diazepam rectal gel)

CONTRAINDICATIONS

Diastat is contraindicated in patients with a known hypersensitivity to diazepam. Diastat may be used in patients with open angle glaucoma who are receiving appropriate therapy but is contraindicated in acute narrow angle glaucoma.

WARNINGS

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.

CNS Depression

Because Diastat produces CNS depression, patients receiving this drug who are otherwise capable and qualified to do so should be cautioned against engaging in hazardous occupations requiring mental alertness, such as operating machinery, driving a motor vehicle, or riding a bicycle until they have completely returned to their level of baseline functioning.

Although Diastat is indicated for use solely on an intermittent basis, the potential 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.

Prolonged CNS depression has been observed in neonates treated with diazepam. Therefore, Diastat is not recommended for use in children under six months of age.

Pregnancy Risks

No clinical studies have been conducted with Diastat in pregnant women. Data from several sources raise concerns about the use of diazepam during pregnancy.

Animal Findings: Diazepam has been shown to be teratogenic in mice and hamsters when given orally at single doses of 100 mg/kg or greater (approximately eight times the maximum recommended human dose [MRHD=1 mg/kg/day] or greater on a mg/m² basis). Cleft palate and exencephaly are the most common and consistently reported malformations produced in these species by administration of high, maternally-toxic doses of diazepam during organogenesis. Rodent studies have indicated that prenatal exposure to diazepam doses similar to those used clinically can produce long-term changes in cellular immune responses, brain neurochemistry, and behavior.

General Concerns and Considerations About Anticonvulsants: Reports suggest an association between the use of anticonvulsant drugs by women with epilepsy and an elevated incidence of birth defects in children born to these women. Data are more extensive with respect to phenytoin and phenobarbital, but a smaller number of systematic or anecdotal reports suggest a possible similar association with the use of all known anticonvulsant drugs.

The reports suggesting an elevated incidence of birth defects in children of drug-treated epileptic women cannot be regarded as adequate to prove a definite cause and effect relationship. There are intrinsic methodologic problems in obtaining adequate data on drug teratogenicity in humans; the possibility also exists that other factors, e.g., genetic factors or the epileptic condition itself, may be more important than drug therapy in leading to birth defects. The great majority of mothers on anticonvulsant medication deliver normal infants. It is important to note that anticonvulsant drugs

Diastat* (diazepam rectal gel)

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.

General Concerns About Benzodiazepines: An increased risk of congenital malformations associated with the use of benzodiazepine drugs has been suggested in several studies.

There may also be non-teratogenic risks associated with the use of benzodiazepines during pregnancy. There have been reports of neonatal flaccidity, respiratory and feeding difficulties, and hypothermia in children born to mothers who have been receiving benzodiazepines late in pregnancy. In addition, 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.

Advice Regarding the Use of Diastat in Women of Childbearing Potential: In general, the use of Diastat in women of childbearing potential, 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, Diastat 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

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 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 Diastat 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,

Diastat® (diazepam rectal gel)

-hepatic Impairment). Therefore, Diastat should be used with caution in patients with liver disease.

Use in Pediatrics

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

Use in Patients with Compromised Respiratory Function

Diastat 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 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 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 Diastat to individuals in their care. Prescribers should routinely discuss the steps in the Patient/Caregiver Package Insert (see Patient/Caregiver Insert printed at the end of the product labeling and also included in the product carton). The successful and safe use of Diastat 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 Diastat 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 Diastat (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 Diastat, patients should be advised not to breast-feed for an appropriate period of time after receiving treatment with Diastat.

Concomitant Medication

Although Diastat is indicated for use solely on an intermittent basis, the potential 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 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.

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

Alproprate 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.

Diastat® (diazepam rectal gel)

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

The carcinogenic 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, Diastat 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 Diastat, patients should be advised not to breast-feed for an appropriate period of time after receiving treatment with Diastat.

ADVERSE REACTIONS

Diastat 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 Diastat died seven to 15 weeks following treatment; neither of these deaths was deemed related to Diastat.

The most frequent adverse event reported to be related to Diastat 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 Diastat in clinical trials of epilepsy discontinued treatment because of an adverse event. The adverse event most frequently associated with

Diastat* (diazepam rectal gel)

Discontinuation (occurring in three patients) was somnolence. Other adverse events most commonly associated with discontinuation and occurring in two patients were hypoventilation and rash. Adverse events occurring in one patient were asthenia, hyperkinesia, incoordination, vasodilatation and urticaria. These events were judged to be related to Diastat.

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 Diastat, versus 2% for the placebo group. In the Diastat 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 Diastat group. Adverse events were usually mild or moderate in intensity.

The prescriber should be aware that these figures, obtained when Diastat 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 studies. 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 Diastat Group

Body System	COSTART Term	Diastat N = 101 %	Placebo N = 104 %
Body As A Whole	Headache	5%	4%
Cardiovascular	Vasodilatation	2%	0%
Digestive	Diarrhea	4%	<1%
Nervous	Ataxia	3%	<1%
	Dizziness	3%	2%
	Euphoria	3%	0%
	Incoordination	3%	0%
	Somnolence	23%	8%
Respiratory	Asthma	2%	0%
Skin and Appendages	Rash	3%	0%

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 Diastat group were abdominal pain, pain, nervousness, and rhinitis. 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:

Diastat 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

Diastat* (diazepam rectal gel)

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 Diastat. 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.

BODY AS A WHOLE: Asthenia

CARDIOVASCULAR: Hypotension, vasodilatation

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

RESPIRATORY: Hiccup

The following infrequent adverse events 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.

DRUG ABUSE AND DEPENDENCE

Diazepam is a Schedule IV controlled substance and can produce drug dependence. 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 regular 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.

OVERDOSAGE

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

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.

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 instituted 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

Diastat* (diazepam rectal gel)

depression and other residual benzodiazepine effects for an appropriate period after treatment. The prescriber should be aware of a 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.

DOSAGE 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 Diastat 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 Diastat.

Second, because Diastat 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, make 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 Diastat dose should be individualized for maximum beneficial effect. The recommended dose of Diastat is 0.2-0.5 mg/kg depending on age. See the dosing table for specific recommendations.

Age (years)	Recommended 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 recommended 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

The rectal delivery system includes a plastic applicator with a flexible, molded tip available in two lengths, designated for convenience as Pediatric and Adult. The 2.5, 5.0, and 10.0 mg

Diastat* (diazepam rectal gel)

dosages are available with a 4.4 cm Pediatric tip. The 10.0, 15.0, and 20.0 mg dosages are available with a 6.0 cm Adult tip.

It is important to note that if a 15 mg dose is to be administered to a pediatric patient utilizing the plastic applicator with a pediatric tip, prescriptions must be written for 2 different twin packs, one for the 5 mg dosage and one for the 10 mg dosage (see HOW SUPPLIED section).

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 Diastat 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 six month intervals.

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 one of the four 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

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

Treatment Frequency

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

HOW SUPPLIED

Diastat (diazepam rectal 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 two lengths, designated for convenience as Pediatric and Adult. Diastat is available in the following six presentations:

Dosage Strength	Rectal Tip Size	NDC Number
2.5 mg Twin Pack	Pediatric (4.4 cm)	NDC 59075-650-20
5.0 mg Twin Pack	Pediatric	NDC 59075-651-20
10.0 mg Twin Pack	Pediatric Universal	NDC 59075-652-20
10.0 mg Twin Pack	Adult (6.0 cm)	NDC 59075-653-20
15.0 mg Twin Pack	Adult	NDC 59075-654-20
20.0 mg Twin Pack	Adult	NDC 59075-655-20

Each Twin Pack contains two Diastat rectal delivery systems, two packets of lubricating jelly, and Patient/Caregiver Package Insert. Store at controlled room temperature 15-30°C (59-86°F).

CAUTION: Federal law prohibits dispensing without prescription.

CAUTION: Federal law prohibits the transfer of this drug to any person other than the patient for whom it was prescribed.

Distributed by:

ATHENA NEUROSCIENCES, INC.
South San Francisco, California 94080

Manufactured by:

DPT Laboratories, Inc.
San Antonio, Texas 78215

Diastat[®] ADMINISTRATION INSTRUCTIONS

(diazepam rectal gel)



IMPORTANT

Read first before using

To the caregiver:

Please do not give DIASTAT[®] until:

1. you have thoroughly read these instructions,
2. reviewed administration steps with the doctor,
3. understand the directions.

Please do not administer DIASTAT until you feel comfortable with how to use DIASTAT. The doctor will tell you exactly when to use DIASTAT. When you use DIASTAT correctly and safely you will help bring seizures under control. Be sure to discuss every aspect of your role with the doctor. If you are not comfortable, then discuss your role with the doctor again.

To help the person with seizures:

- ✓ You must be able to tell the difference between a cluster and ordinary seizures.
- ✓ You must be comfortable and satisfied that you are able to give DIASTAT.
- ✓ You need to agree with the doctor on the exact conditions when to treat with DIASTAT.
- ✓ You must know how and for how long you should check the person after giving DIASTAT.

To know what responses to expect:

- ✓ You need to know how soon seizures should stop or decrease in frequency after giving DIASTAT.
- ✓ You need to know what you should do if the seizures do not stop or there is a change in the person's breathing, behavior or condition that alarms you.

If you have any questions or feel unsure about using the treatment, **CALL THE DOCTOR** before using DIASTAT.

When to treat. Based on the doctor's directions or prescription

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 _____

Check expiration date and always remove cap and seal pin before using.

TREATMENT 1

Important things to tell the doctor.

Date	Seizures Before DIASTAT			Seizures After DIASTAT		
	Time	Seizure Type	No. of Seizures	Time	Seizure Type	No. of Seizures
_____	_____	_____	_____	_____	_____	_____
_____	_____	_____	_____	_____	_____	_____

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 _____
- Confirm current weight is still the same as when DIASTAT was prescribed _____
- Possible side effects from treatment _____

TREATMENT 2

Important things to tell the doctor.

Date	Seizures Before DIASTAT			Seizures After DIASTAT		
	Time	Seizure Type	No. of Seizures	Time	Seizure Type	No. of Seizures
_____	_____	_____	_____	_____	_____	_____
_____	_____	_____	_____	_____	_____	_____

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 _____
- Confirm current weight is still the same as when DIASTAT was prescribed _____
- Possible side effects from treatment _____

Disposal

- Discard all used material in the garbage can.
- Do not reuse.
- Discard in a safe place away from children.



DIASTAT is a registered trademark of Athena Neurosciences, Inc.
Diastat and ASAP are trademarks of Athena Neurosciences, Inc.
© 1997 Athena Neurosciences, Inc.

Where can I find more information and support?

The two best places to go for information and support are:

ASAP[®] (Appropriate Seizure Action Program) sponsored by Athena Neurosciences, Inc. You can reach ASAP by calling 1-866-801-ASAP (7777).

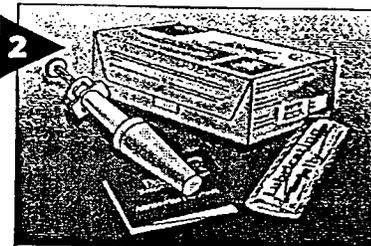
EFA (Epilepsy Foundation of America). You can reach EFA by calling 800-EFA-1000 or www.eafa.org.

HOW TO ADMINISTER *Diastat*[™] (diazepam rectal gel)

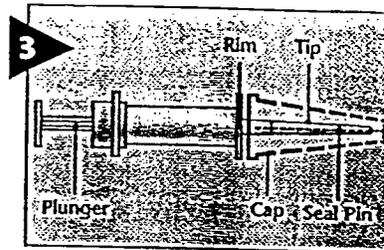
IV



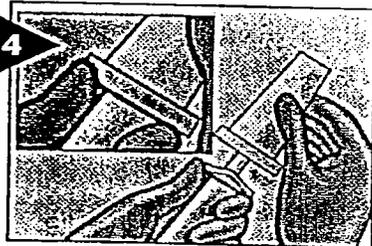
1 Put person on their side where they can't fall



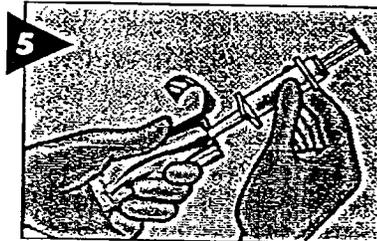
2 Get medicine



3 Get syringe



4 Push up with thumb and pull to remove protective cover from syringe



5 Lubricate rectal tip with lubricating jelly



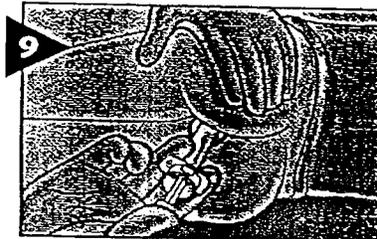
6 Turn person on side facing you



7 Bend upper leg forward to expose rectum

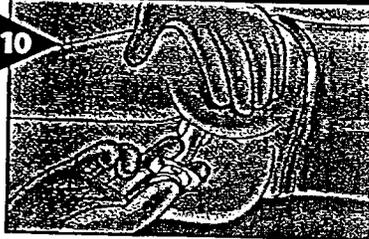


8 Separate buttocks to expose rectum

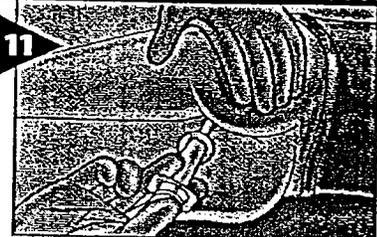


9 Gently insert syringe tip into rectum
Note: Rim should be snug against rectal opening.

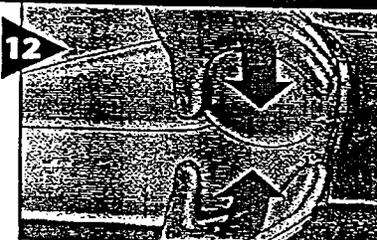
SLOWLY COUNT OUT LOUD TO THREE...1...2...3



10 Slowly count to 3 while gently pushing plunger in until it stops

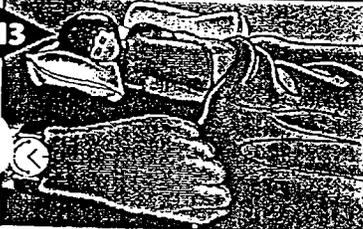


11 Slowly count to 3 before removing syringe from rectum



12 Slowly count to 3 while holding buttocks together to prevent leakage

ONCE DIASTAT[®] IS GIVEN



13 Keep person on side facing you, note time given and continue to observe



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: _____

Doctor's Number: _____

(Please be sure to note if your area has 911)

Information for Emergency Squad: Time DIASTAT given: _____

Dose: _____

There is no image file associated with this page.

Appears This Way
On Original

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 20-648/S-002

ADMINISTRATIVE and
CORRESPONDENCE DOCUMENTS

**REGULATORY PROJECT MANAGER
LABELING REVIEW**

Review Date: March 16, 2001
NDA: 20-648
Sponsor: Elan Pharmaceuticals
DRUG: Diastat (diazepam rectal gel) Rectal Delivery System
Supplements: SLR-002 dated 4-14-99, and amended on 5-25-99

Notes of interest:

- The last approved package insert and container labeling was the original NDA approval labeling. The approval letter was issued on 7-29-97.

REVIEW

20-649/SLR-002

Dated: 4-14-99, and amended on 5-25-99

CBE: Yes

Label Code: N/A, Container Labeling

Reviewed by Chemist: Yes, acceptable.

The supplement provides for the modification of the commercially available container labels to consolidate the 10 mg adult and 10 mg pediatric container labels to a 10 mg universal container label. This change is also reflected in the package inset under the **HOW SUPPLIED** section.

CONCLUSIONS

1. This supplement only provides for the revisions listed above.
2. The chemist concurs with the revisions provided for in the application.
3. I recommend that an approval letter issue for SLR-002.

Paul David, RPh
Regulatory Project Manager

John Purvis
Supervisory Consumer Safety Officer

/s/

Paul David
3/21/01 07:11:15 AM
CSO

Jack Purvis
3/23/01 03:31:50 PM
CSO