

## WRITTEN REQUEST (ISSUED BY THE FDA)

To obtain needed pediatric information on lorazepam, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), that you submit information from the trials in pediatric patients described below.

### **USE OF LORAZAPAM FOR THE TREATMENT OF STATUS EPILEPTICUS**

#### ***Type of Study***

***Study 1:*** Pediatric Pharmacokinetic Study

This study must be completed prior to conducting the Pediatric Efficacy and Safety Study (Study 2 below).

***Study 2:*** Pediatric Efficacy and Safety Study; Randomized, double blind, active-control, parallel group inpatient study in pediatric patients with generalized tonic clonic status epilepticus.

Pediatric patients presenting to a participating emergency room, or as inpatients, with generalized tonic clonic status epilepticus must have an intravenous line started within 5 minutes of entry and then be randomized to one of two treatment arms:

- (1) Intravenous lorazepam (study drug) or
- (2) Intravenous diazepam (active control).

A single dose of either lorazepam or diazepam must be given at time zero. Ten minutes later, if needed, a second dose of either drug must be delivered. Ten minutes after that (twenty minutes from time zero), other pharmacologic interventions can be initiated as deemed necessary. Meanwhile, fifteen minutes from time zero (in responders to the first dose) or 25 minutes from time zero (in responders to the second dose) maintenance therapy can be initiated if deemed necessary.

Sparse samples should be obtained from patients in this clinical trial to obtain information on the plasma concentrations (total and unbound as described under *Study 1*, Study Endpoints, below) of lorazepam. This data should be used along with the data from *Study 1* to conduct a population analysis of pharmacokinetic data and to report pharmacokinetic parameters in different age groups and to evaluate the effect of covariates such as age, gender, concomitant medications etc.

#### ***Indication to be studied (i.e., objective of each study):***

***Study 1:*** To evaluate the single dose pharmacokinetics in pediatric patients ages 3 months to less than 18 years.

***Study 2:*** To establish the efficacy of lorazepam as initial therapy in the treatment of generalized tonic clonic status epilepticus in pediatric patients ages 3 months to less than

18 years and to develop other information, (e.g., pharmacokinetic, short-term safety) pertinent to using the drug in the pediatric population.

Although current practice (as reflected in the recent medical literature and current textbooks) uses lorazepam as a first-line agent for the initial treatment of status epilepticus in all pediatric patients beyond the neonatal period, there is no convincing evidence in the medical literature of its efficacy. Lorazepam is approved in current labeling for initial treatment of status epilepticus in adults over age 18 years.

Status epilepticus is a life-threatening medical emergency that may be followed by significant central nervous system morbidity. Generalized tonic clonic status epilepticus must be defined as:

- (1) 3 or more generalized tonic clonic seizures within one hour, or
- (2) 2 or more generalized tonic clonic seizures in rapid succession with no recovery of consciousness in between seizures, or
- (3) A single ongoing generalized tonic clonic seizure which has lasted at least 5 minutes

Status epilepticus occurs most commonly in infancy and childhood. In younger children, status epilepticus occurs primarily in those who are neurologically normal and who have no history of unprovoked seizures. In older children, status epilepticus occurs primarily in those who have had prior unprovoked seizures and who often also have neurological abnormalities.

In the pediatric population, most status epilepticus seizures are generalized tonic clonic seizures. Status epilepticus may occur as part of an acute illness, in patients with established epilepsy or as a first unprovoked seizure. The seizures may be idiopathic, remote symptomatic, febrile, acute symptomatic, or associated with a progressive encephalopathy.

Pediatric status epilepticus is phenomenologically similar to status epilepticus seen in adults (age 18 years and older). Thus, the study of status epilepticus in infants, children, and adolescents should be feasible and should yield useful information.

### ***Age Groups to be Studied***

***Studies 1 and 2:*** Pediatric patients ages 3 months to less than 18 years. An approximately uniform distribution over this age range is required.

In ***Study 1***, pediatric patients should be grouped as follows – 3 months up to less than 3 years, 3 years to less than 13 years, and 13 years to less than 18 years. Within these age groups, you must enroll a sufficient number of patients to adequately characterize pharmacokinetics of lorazepam after intravenous administration (with a minimum of 8 patients per age group for a total of at least 24 patients).

***Studies 1 and 2:*** A minimum of 110 patients per study, age 3 months to less than 18 years, exposed to lorazepam for one or two doses, must be monitored for adverse effects

for at least 48 hours. An approximately uniform distribution over this age range is required.

### ***Study Endpoints***

***Study 1:*** In this separate pharmacokinetic study in these age groups you could use either a frequent sampling approach (traditional design) or a sparse sampling approach. If a sparse sampling approach is followed (at least 2 to 3 samples per patient), the blood samples should be obtained within time brackets and not at fixed time points, to cover the entire pharmacokinetic profile. The samples must be analyzed to determine total lorazepam concentrations. Free (unbound) drug concentrations must be determined at randomly selected time points (to include approximately 20% of the total samples).

In these age groups, relevant lorazepam (total and unbound as appropriate) pharmacokinetic parameters such as C<sub>max</sub>, AUC, CL, terminal half-life etc. must be calculated and compared to those seen in adults. Effects of covariates such as age, body-weight, and body-surface area on lorazepam pharmacokinetic parameters must be studied. In addition, the effect of concomitant medications (including other concomitant anti-epileptic drugs) on lorazepam pharmacokinetic parameters should be studied as appropriate.

***Study 2:*** The primary efficacy endpoint is cessation of seizures within 10 minutes and sustained absence of seizures for at least 30 minutes.

The secondary endpoint is the response latency time, i.e. the interval from completion of the study drug injection to the end of the last convulsive episode following which the patient regained consciousness.

Sparse samples should be obtained from patients in this clinical trial to obtain information on the plasma concentrations (total and unbound as described under Study 1) of lorazepam. This data should be used along with the data from Study 1 to conduct a population analysis of pharmacokinetic data and to report pharmacokinetic parameters in different age groups and to evaluate the effect of covariates such as age, gender, concomitant medications etc.

### ***Drug Information***

#### ***Studies 1 and 2:***

***Dosage form:*** lorazepam injection

***Route of administration:*** intravenous

***Regimen:*** After Study 1 is completed; appropriate age-dependent dosing for Study 2 can be determined from the preliminary pharmacokinetic data accrued in Study 1.

#### ***Drug-Specific Safety Concerns:***

##### ***Studies 1 and 2:***

Routine safety assessments must be collected at baseline and appropriate follow-up times, i.e. vital signs (HR, RR, BP, pulse oximetry), clinical laboratory measures, ECGs, and

monitoring for adverse events (including apnea, respiratory depression, sedative effects, prolonged impairment of consciousness, and paradoxical excitation).

Safety concerns deserving special attention include paradoxical excitation and paradoxical seizure exacerbation. Tremors, agitation, euphoria, logorrhea, and brief episodes of visual hallucinations have characterized paradoxical excitation (reported particularly in patients less than 8 years of age). Paradoxical seizure exacerbation or myoclonus has been reported to occur rarely in pediatric and adult patients after benzodiazepine therapy particularly in the setting of atypical petit mal status epilepticus.

Pediatric patients could potentially exhibit sensitivity to benzyl alcohol, polyethylene glycol and propylene glycol, components of injectable lorazepam. The "gaspings syndrome," characterized by central nervous system depression, metabolic acidosis, gasping respirations, and high levels of benzyl alcohol and its metabolites found in the blood and urine, has been associated with benzyl alcohol dosages >99 mg/kg/day in neonates. Although normal therapeutic doses of injectable lorazepam contain very small amounts of these compounds, very young pediatric patients receiving high doses (or concomitant medications also containing benzyl alcohol, polyethylene glycol and/or propylene glycol) could be more susceptible to their effects.

The amounts of benzyl alcohol, polyethylene glycol, and propylene glycol administered, from lorazepam and from all other sources, will be projected and tracked. Total daily administration of benzyl alcohol will not approximate or exceed potentially toxic doses (approximately 99 mg/kg/day). Incidents in which administration of drugs, including lorazepam, are limited or curtailed due to toxicity or concerns of reaching potentially toxic levels of benzyl alcohol, polyethylene glycol or propylene glycol will be recorded. If it is projected that potential doses of benzyl alcohol, polyethylene glycol, or propylene glycol from all sources will limit the ability to deliver adequate and efficacious doses of lorazepam, a formulation of lorazepam that is free of the limiting solvent(s) and/or preservative may be developed for these trials.

Appropriate measures must be taken for early identification of potential toxicity due to benzyl alcohol, polyethylene glycol, and propylene glycol, including frequent screening of blood gases, electrolytes, calcium, lactate, hematology, hepatic enzymes, and renal function. In addition, blood levels of benzyl alcohol (or benzoic acid), propylene glycol, and if feasible, polyethylene glycol will be drawn on a regular schedule and also when toxicity from one of these inactive ingredients is suspected. Criteria for discontinuing the test drug due to potential toxicity from these excipients will be pre-specified in the protocol.

#### ***Statistical Information, Including Statistical Assessments***

***Study 1:*** Descriptive assessment of the effect of age on pharmacokinetic parameters and comparison to adults.

***Study 2:*** The study must be powered so that a sufficient number of pediatric epilepsy patients must be enrolled to detect with a power of 90% a difference between an expected

80% response rate after lorazepam and an expected 60% response rate after diazepam (as observed in the pivotal adult study leading to the indication for lorazepam in adult status epilepticus) with a significance level of 0.05, 2-tailed. An appropriate statistical test should be used analyze the significance of this difference.

Survival analysis may be used for the response-latency time efficacy outcome.

Safety data analysis is descriptive.

