Approval Date: December 17, 1992

FREEDOM OF INFORMATION SUMMARY

I. GENERAL INFORMATION

A. File Number

NADA 140-848

B. Sponsor

Hoffman-La Roche Inc.
Nutley, NJ 07110

C. Proprietary Name

Veteeze® Injection

D. Established Name

diazepam

E. Dosage Form

Veteeze® Injection 5 mg diazepam/mL, 10-mL multiple use vial.

F. Amount of Active Ingredient

5 mg diazepam/mL

G. How Supplied

10-mL multiple use vial

H. Dosage Regimen

A single intravenous dose of 0.2 mg diazepam/kg body weight, 3-5 minutes before inducing anesthesia with a short acting barbiturate.

I. Route of Administration

Intravenous injection

J. Indication

As a preanesthetic agent to reduce the amount barbiturate required for short duration anesthesia in dogs.

II. EFFECTIVENESS

This NADA provides for the use of Veteeze® (diazepam) as a preanesthetic agent to reduce the quantity of barbiturates required to induce anesthesia.

Effectiveness for the recommended indication has been established on the basis of a laboratory dose titration study and four well-controlled field trials validating *in vivo* activity under clinical conditions.

Dose Titration Study - Pivotal

Study Number: C-88-1

Investigator:

William W. Muir, III, DVM, PhD
Columbus, Ohio

A blinded titration study was conducted to determine the dose of Veteeze (diazepam) required as a preanesthetic drug to reduce the amount of barbiturate required to achieve anesthesia in dogs. The barbiturate, thiamylal sodium, was used to induce anesthesia, as indicated by achieving endotracheal intubation, in dogs. The parameter measured was the amount of thiamylal required to achieve intubation. Subsequent to intubation, the dogs were maintained on Halothane. Diazepam dosage was evaluated at 0 (placebo), 0.05, 0.1 and 0.2 mg/kg b.w., intravenously. Twentyfour (12 male, 12 female) mixed breed dogs weighing 15-25 kg were randomly assigned to six replicates of a 4 x 4 Latin square. Every animal received each dose, thus providing 24 dogs per treatment. Following a treatment cycle, all dogs were rested for 3 weeks before the next treatment cycle was started. The quantity of thiamylal required to achieve endotracheal intubation was measured. The dogs were monitored for drug effect on respiration rate, heart rate and body temperature, and any visible signs of drug effect, including depression, anger or vocalization. Time to achieve extubation, and sternal and standing recovery were noted.

Diazepam or placebo was injected 3-5 minutes prior to the anesthetic thiamylal sodium, which was administered until endotracheal intubation was possible. The dose used was blinded to the person administering the drug and making the observations.

Results:

0.2 mg group used 8.261 mg/kg thiamylal (22% reduction)

0.1 mg group used 9.097 mg/kg thiamylal (14% reduction)

0.05 mg group used 9.293 mg/kg thiamylal (12% reduction)

Control group used 10.6 mg/kg thiamylal

Statistical analyses of the data show that the intravenous administration of diazepam at 0.05, 0.1 and 0.2 mg/kg of body weight decreased ($P < .05$) the amount of thiamylal sodium required to achieve intubation. It was further shown that the 0.2 mg/kg intravenous dose of Veteeze reduced the amount of thiamylal required over that of the 0.05 and 0.1 mg/kg dose levels ($P < .05$).

No adverse reactions were observed. No treatment differences were noted for respiratory rate, heart rate, body temperature, demeanor or recovery time associated with the four treatment levels.

Four clinical field studies, comprising a placebo, 0.10 and 0.20 mg/kg bw groups, administered IV doses of diazepam, were conducted to confirm that the dose of 0.2 mg was consistently more effective than the 0.1 mg dose in reducing the amount of anesthetic required for endotracheal intubation. Note clinical studies C-88-23, C-89-10, C-89-13 and C-89-14.

It is concluded that the 0.2 mg/kg of body weight dose of Veteeze administered by the intravenous route is the appropriate dose to reduce the amount of a barbiturate required for endotracheal intubation in dogs.

Clinical Studies - Pivotal

A. Study Number: C-88-23

Investigator:

Dr. Robert McLain
Addison, Illinois

A blinded, well-controlled study was conducted in dogs to determine the amount of thiamylal required to induce anesthesia following the intravenous use of Veteeze (diazepam) as a preanesthetic agent. Ninety (90) dogs of various breeds, age and sex, which were surgical candidates from routine hospital admissions, were randomly assigned by a computer-generated schedule to treatments of 0.1, 0.2 mg/kg body weight of diazepam (as Veteeze Injection) or sterile water placebo. Veteeze or the placebo was given 3 to 5 minutes prior to administration of thiamylal which was administered intravenously until endotracheal intubation was possible. The amount of thiamylal required for satisfactory endotracheal intubation was measured. Animals were monitored for drug effect on heart rate, respiratory rate and levels of depression, anger and aggression.

Results were as follows:

Table 1. Thiamylal Reduction Following Diazepam Administration - 90 Dog Study

No. of Dogs	Diazepam (mg/kg b.w.)	Thiamylal (mg/kg b.w.)	% Reduction of Thiamylal vs. Control
30	0.2	7.77	28
30	0.1	8.8	18.6
30	0.0	10.81	-

No adverse reactions or behavioral changes were noted during the course of the study. It is concluded that Veteeze (diazepam) as a preanesthetic agent is effective at the dose of 0.2 mg/kg bw in reducing the amount of barbiturate required for endotracheal intubation.

B. Study Number: C-89-10

Investigator:

Dr. Michael Aronsohn
Boston, Massachusetts

A blinded, well-controlled study was conducted in 90 dogs following the same study protocol as described in the previous summary (C-88-23).

Results were as follows comparing controls to 0.1 and 0.2 mg/kg diazepam treated groups:

Table 2. Thiamylal Reduction Following Diazepam Administration - 90 Dog Study

No. of Dogs	Diazepam (mg/kg b.w.)	Thiamylal (mg/kg b.w.)	% Reduction of Thiamylal vs. Control
30	0.2	12.95	12.3
30	0.1	13.7	7.2
30	0.0	14.76	-

Adverse reactions were recorded for 7 dogs; three in each of the treatment groups and one in the placebo group. The reactions reported were not life-threatening and are generally expected reactions noted in dogs undergoing surgical procedures. Reactions reported varied from hyperexcitability, nausea, vomiting or retching and excessive salivation. These occurred post-operatively in all dogs. No adverse reactions were reported in the other three studies. It is concluded that Veteeze (diazepam) as a preanesthetic agent is effective at the dose of 0.2 mg/kg bw in reducing the amount of barbiturate required for endotracheal intubation.

C. Study Number: C-89-13

Investigator:

Dr. Robert Gordon
Oakland, New Jersey

A blinded, well-controlled study was conducted in 30 dogs following the same study protocol as described for studies C-89-23 and C-89-10.

Results were as follows:

Table 3. Thiamylal Reduction Following Diazepam Administration - 30 Dog Study

No. of Dogs	Diazepam (mg/kg b.w.)	Thiamylal (mg/kg b.w.)	% Reduction of Thiamylal vs. Control
10	0.2	8.16	24
10	0.1	9.95	7
10	0.0	10.70	-

No adverse reactions or behavioral changes were noted during the course of the study. It is concluded that Veteeze (diazepam) as a preanesthetic agent is effective as the dose

of 0.2 mg/kg bw in reducing the amount of barbiturate required for endotracheal intubation.

D. Study Number: C-89-14

Investigator:

Dr. Thomas Mulligan
San Diego, California

A blinded, well-controlled study was conducted in 28 dogs following the same study protocol as described for the previous studies, C-88-23, C-89-10, and C-89-13.

Results were as follows:

Table 4. Thiamylal Reduction Following Diazepam Administration - 28 Dog Study

No. of Dogs	Diazepam (mg/kg b.w.)	Thiamylal (mg/kg b.w.)	% Reduction of Thiamylal vs. Control
10	0.2	9.89	22
9	0.1	11.97	6
9	0.0	12.73	-

No adverse reactions or behavioral changes were noted during the course of the study. It is concluded that Veteeze (diazepam) as a preanesthetic agent is effective at the dose of 0.2 mg/kg bw in reducing the amount of barbiturate required for endotracheal intubation.

Statistical analyses of the pooled data from the four studies showed that the average 20% reduction in thiamylal use is significant ($P < .017$).

Table 5. Statistical analyses of the pooled data

Study	Placebo	0.1 mg/kg	0.2 mg/kg	Decrease from placebo
1	10.8	8.8	7.8	-3.0 (27.8%)
2	14.8	13.7	12.9	-1.9 (12.8%)
3	10.7	10.0	8.2	-2.5 (23.4%)
4	12.7	12.0	9.9	-2.8 (22%)
Pooled	12.3	11.0	9.7	-2.6 (21%)

A summary of the amount of thiamylal used within various age groups are presented in Table 6. The results consistently showed that there was no treatment effect on the

physiological variables, leading to the conclusion that Veteeze has no effect on body temperature, heart rate or respiratory rate. Only one significant difference (change in depression score to an increase in the 0.2 mg group) was observed and no treatment effect was observed on anger or vocalization. A summary of the distribution of ages, and of the procedures performed, by center, are presented in Tables 7 and 8, respectively.

Table 6. Four Center Summary Thiamylal Usage By Treatment (Veteeze vs Placebo) and by Age

SUMMARY BY AGE	VETEEZE - # DOGS	VETEEZE – THIAMYLAL	VETEEZE - % Reduction from amount of thiamylal used in Placebo Group	PLACEBO - # DOGS	PLACEBO – THIAMYLAL	PLACEBO - % Increase over amount of thiamylal used in Veteeze Group
All Dogs	80	10.0 mg/kg avg.	(-20.0)	80	12.5 mg/kg avg.	(+25.0)
2 years & under	37	11.2 mg/kg avg.	(-17.8)	33	13.3 mg/kg avg.	(+18.7)
3 to 6 years of age	17	10.0 mg/kg avg.	(-20.6)	17	12.6 mg/kg avg.	(+12.6)
Over 6 years of age	25	8.6 mg/kg avg.	(-23.7)	25	11.3 mg/kg avg.	(+31.4)
Under 6 years of age	54	10.8 mg/kg avg.	(-17.6)	50	13.1 mg/kg avg.	(+21.3)

Table 7. Summary - Age Distribution by Center

Age	New Jersey – V	New Jersey – P	Cali-fornia – V	Cali-fornia – P	Illi-nois – V	Illi-nois – P	Mass-achu-setts – V	Mass-achu-setts – P	TOTAL* - V	TOTAL * - P
Under 1	3	4			5	2	4		12	6
2	3	3	2	3	8	7	13	16	26	29
3	2		2	2	1	1	5	2	10	5
4		1	2	1	1	2	1	1	4	5
5	1					5	1		2	5

Age	New Jersey – V	New Jersey – P	Cali-fornia – V	Cali-fornia – P	Illi-nois – V	Illi-nois – P	Mass-achu-setts – V	Mass-achu-setts – P	TOTAL* - V	TOTAL * - P
6			1	2		4	1	1	2	7
7	1				3	2		1	4	3
8		2	1		3	2	1	2	5	6
9			2		1		3	4	6	4
10					4				4	0
11						2			0	2
12					1	1	1		2	1
13* older				1	2			1	2	2
TOTAL *	10	10	10	9	29	28	30	28	79	75

*May not total exact numbers used in study(s), information was missing from some case reports.

Table 8. Summary - Procedure Distribution by Center

	New Jersey – V	New Jersey – P	Cali-fornia – V	Cali-fornia – P	Illi-nois – V	Illi-nois – P	Mass-achu-setts – V	Mass-achu-setts – P	TOTAL * - V	TOTAL * - P
Spay	2	3	1	3	6	9	17	12	26	27
Dental	2		6	4	7	6	1	4	16	14
Cast-ration	3	4			5	5	8	4	16	13
Ortho-pedics					2	1	2	6	4	7
Tumor				2	5	4		2	5	8
X-Ray	1	2			2	3		1	3	6
Other	2	1	3		3	2	2	1	10	4
Total*	10	10	10	9	30	30	30	30	80	79

*May not total exact numbers used in study(s), information was missing from some case reports.

III. TARGET ANIMAL SAFETY

Four-week Intravenous Toxicity Study in Dogs with Diazepam Solutions

Investigator:

B. Schlappi
Hoffmann-La Roche Inc.
Toxicology Department
Basle, Switzerland

The purpose of the study was to compare the tolerance in dogs to commercial injectable diazepam that: (1) had been stored under optimal conditions; (2) had been heat stressed; or (3) contained added principal degradation products.

Four dogs (2 male, 2 female) were assigned to each treatment group and were injected intravenously with 1 mL Veteeze (5 mg diazepam)/kg daily for a period of 30 days.

Group 1: Control group (sterile saline)

Group 2: Injectable diazepam (fresh or optimally stored)

Group 3: Injectable diazepam (not optimally stored - heat stressed)

Group 4: Injectable diazepam (degradation products added)

Monitoring activities included daily weighing and observations, hematology, serum chemistries, urinalysis, ophthalmologic exams, ECG, autopsies and histology.

In all three groups treated with injectable diazepam, the same type and degree of findings were noted, principally:

A minimal increase in bilirubin (control mean 0.08, treated groups 0.11 mg/100 ml), cholesterol (control mean 126, treated groups 208 mg/100 ml) and ALT (SGPTcontrol 21, treated groups 28).

A moderate to marked increase of alkaline phosphatase. Dogs in control group levels were 111 and group 2 had increased levels up to 416 U/L.

Increased liver weights were observed in the treated groups. On an absolute basis the mean liver weight of the control dogs was 325 gms vs 434 for the medicated dogs. Adjusting for differences in average body weights of each group, the relative increase (i.e. gms liver/kg body weight) was approximately 15%.

Intracanalicular cholestatsis was observed more often in the treated groups.

Ataxic gait and sedation were observed for approximately three hours after injection, mainly during the first experimental week. An increase in appetite was also observed in treated animals. From day 16 of the study onward, subcutaneous injections were necessary in some of the dogs in groups 1, 2, and 3 because of hardening of the vessels from continuous intravenous injections. Hematology, urinalysis, ophthalmology and ECG findings were within normal limits.

This 30-day dosing at 25 times the approved level confirms the safety of the preanesthetic dose of 0.2 mg a.i./kg b.w. of injectable diazepam in the dog (a.i. means active ingredient).

Acute Toxicity Studies for Injectable Diazepam and the Diazepam Vehicle in Dogs

Investigator:

D. Hane
Hoffman-La Roche Inc.
Toxicology Department
Nutley, New Jersey

The purpose of the study was to evaluate and compare the acute toxicity of injectable diazepam and of the diazepam vehicle in dogs.

Sixteen beagle dogs, (two of each sex per test group), received four intravenous injections of diazepam (2 mg a.i./mL) or the vehicle given at 2-3 day intervals. All dogs survived the 0.15, 0.5, 1.5, and 5 mL/kg intravenous doses of injectable diazepam (2 mg a.i./mL), equivalent to 0.3, 1.0, 3.0, and 10 mg/kg of the active ingredient, or 0.15, 0.5, 1.5, and 5 mL/kg doses of the vehicle. Transient ataxia and general decrease in motor activity occurred following administration of diazepam. Emesis occurred in one dog each at 0.5, 1.5, and 5 mL/kg doses of diazepam and at the highest dose, 5 mL/kg, of the vehicle. A transient decrease in motor activity occurred in one dog receiving 5 mL/kg of the vehicle. Increases occurred in serum group) and alkaline phosphatase values (control/baseline of 67 IU/L to 334 IU/L in the 10 mg/kg group) of diazepam-treated animals compared to their own baseline values and compared to vehicle-treated controls. Other changes (urea nitrogen predose of 12 mg/dL to 16 mg/dL in the 10 mg/kg group) in serum clinical chemistry values of both diazepam- and vehicle-dosed dogs were not considered biologically significant. In the dogs receiving vehicle intravenously, salivation, licking, emesis and decreased motor activity occurred following the 1.5 and 5 ml/kg doses. An increase in glucose values was noted at 8 and 15 days after the final dose of vehicle (glucose from 110 mg/dL in the control to 124 mg/dL in the 10.0 mg/kg group and in the vehicle group).

The final administration of diazepam was 50 times (10 mg/kg body weight I.V.) the preanesthetic dosage of 0.2 mg/kg body weight I.V. All dogs survived the doses and the 15-day observation period following the four incremental administrations of injectable diazepam or vehicle, which affirms the safety of Veteeze in dogs.

Acute Toxicity of Diazepam Injectable in Dogs

Investigators:

W. Pool
D. Suckow
Hoffman-La Roche Inc.
Toxicology Department
Nutley, New Jersey

The purpose of the study was to determine the drug tolerance of diazepam administered intravenously to dogs. Three dogs each (weighing 8-11 kg) were injected with either 5, 10, or 20 mg diazepam/kg b.w. as a single dose.

Diazepam at 5 and 10 mg/kg I.V. produced ataxia and sedation, while 20 mg/kg I.V. produced hypnosis for 30-60 minutes. All dogs survived and were considered normal by 48 hours postdosing.

Three out of three dogs surviving a dose 100 times (i.e., 20 mg/kg b.w., I.V.) the preanesthetic dose of diazepam (0.2 mg/kg b.w., I.V.) reaffirms the safety of diazepam in dogs.

Toxicity of Diazepam in Dogs by Repeated Intravenous Doses

Investigator:

R. E. Bagdon
Hoffman-La Roche Inc.
Pharmacology Department
Nutley, New Jersey

The purpose of the study was to evaluate the tolerance of dogs to repeated injections of diazepam (5 mg a.i./mL) with doses of 10 mg diazepam intravenously 5 days/week for four weeks. A control group received 2 mL I.V. of the vehicle. Four dogs (2 male, 2 female) were assigned to each group. The average starting weight of the dogs was 8.36 kg (6.7-10.2 kg). The group given 10 mg diazepam I.V. received the equivalent of 1.1 mg of diazepam per kg of body weight.

Group 1, four dogs were administered 10 mg in 2 ml diazepam I.V. for five days for four weeks. Group 2 Controls, two dogs were administered 2 ml of vehicle I.V. for 5 days for four weeks.

In group 1, dogs given 10 mg of diazepam I.V., transient ataxia was observed, but they were normal within one hour after the drug was given. Sedation was not observed in these animals.

In the control group dogs given the vehicle, no toxic effects were observed.

The results of the hematology, serum chemistries and urinalyses carried out before treatment and during the 2nd and 4th experimental weeks were within the normal range.

In both the control and diazepam treated animals, the injection sites were firm, with local fibrosis and occasional foci of necrotic tissue and hemorrhage. Thickening of the veins used for I.V. administration and localized irritation of the tissues surrounding the injection sites occurred in both control and treated animals.

Following sacrifice of animals in both groups, the animals were observed for gross pathological changes and apart from localized irritation at the sites of injection, no evidence of gross pathology was seen in the animals. The localized irritation did not differ significantly between control and diazepam-treated animals, indicating that these localized effects were produced by the injection *per se*.

Administration of injectable diazepam to dogs did not result in toxic manifestations; no changes in blood counts, liver, kidney and pancreatic function were observed. No histopathological changes, other than irritation at the injection sites, were noted. These findings, after 20 intravenous doses of 5 times the single preanesthetic dose of 0.2 mg/kg b.w. during a four week period, confirm the safety of diazepam in the dog.

Toxicity of Diazepam in Dogs by Repeated Daily 10X Doses

Investigator:

R. E. Bagdon
Hoffman-La Roche Inc.
Pharmacology Department
Nutley, New Jersey

The tolerance of four dogs to 4 mL of either injectable diazepam (5 mg a.i./mL) administered as 10 intravenous or intramuscular injections over a period of two weeks was determined in this study. Based on an average body weight of 10.2 kg, each dog received 10 doses of 2 mg/kg b.w. each. Following intravenous administration, both animals displayed marked muscle relaxation, loss of righting reflex and ataxia, which disappeared approximately 30 minutes post-dosing.

Hematology and blood chemistry values before treatment and following the 10^{th} injection remained within normal ranges. Gross and histopathologic examination of organs and tissues in the I.V. group were within normal limits when compared to controls.

The results of this study in which the animals received 10 intravenous doses of 2 mg/kg b.w. during a period of two weeks, i.e., each dose equivalent to 10 times the preanesthetic dosage of 0.2 mg/kg b.w., confirms the safety of diazepam in the dog.

IV. HUMAN FOOD SAFETY

Data on human safety, pertaining to consumption of drug residues in food, were not required for approval of this NADA. The drug is to be labeled for use in dogs, which are non-food animals.

V. AGENCY CONCLUSIONS

The data submitted in support of this NADA comply with the requirements of section 512 of the Act and section 514.111 of the regulations. It demonstrates that Veteeze® (diazepam) Injection, when used under the labeled conditions of use, is safe and effective.

Section 512(c) (2) (F) (i) of the Federal Food, Drug and Cosmetic Act provides a five year period of exclusivity to this original new animal drug which has not been approved in any other application.

The Agency has carefully considered the potential environmental effects of this action and has concluded that the action will not have a significant impact on the human environment and that an environmental impact statement is not required. A Finding of No Significant Impact for this action has been prepared.

The drug is restricted to use by or on the order of a licensed veterinarian as knowledge of veterinary anesthesia is needed for the safe use, monitoring and detection of possible adverse reactions with this drug.

The format of this FOI Summary document has been modified from its original form to conform with Section 508 of the Rehabilitation Act (29 U.S.C. 794d). The content of this document has not changed.