Date of Approval: October 28, 2009

# FREEDOM OF INFORMATION SUMMARY

## ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-297

PROZINC

Protamine zinc recombinant human insulin
Injectable aqueous suspension
Cats

PROZINC (protamine zinc recombinant human insulin) is indicated for the reduction of hyperglycemia and hyperglycemia-associated clinical signs in cats with diabetes mellitus.

Sponsored by:

Boehringer Ingelheim Vetmedica, Inc.

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## I. GENERAL INFORMATION:

**A. File Number:** NADA 141-297

**B. Sponsor:** Boehringer Ingelheim Vetmedica, Inc.
2621 North Belt Highway
St. Joseph, MO 64506-2002

Drug Labeler Code: 000010

**C. Proprietary Name(s):** PROZINC

**D. Established Name(s):** Protamine zinc recombinant human insulin

**E. Pharmacological Category:** Hormone

**F. Dosage Form(s):** Injectable aqueous suspension

**G. Amount of Active Ingredient(s):** 40 international units (IU) insulin/mL

**H. How Supplied:** 10 mL multidose vials

**I. How Dispensed:** Rx

**J. Dosage(s):** The initial recommended PROZINC dose is 0.1 - 0.3 IU insulin/pound of body weight (0.2 - 0.7 IU/kg) every 12 hours. The dose should be given concurrently with or right after a meal. The veterinarian should re-evaluate the cat at appropriate intervals and adjust the dose based on both clinical signs and glucose nadirs until adequate glycemic control has been attained. In the effectiveness field study, glycemic control was considered adequate if the glucose nadir from a 9-hour blood glucose curve was between 80 and 150 mg/dL and clinical signs of hyperglycemia such as polyuria, polydipsia, and weight loss were improved.

Further adjustments in the dosage may be necessary with changes in the cat's diet, body weight, or concomitant medication, or if the cat develops concurrent infection, inflammation, neoplasia, or an additional endocrine or other

medical disorder.

**K. Route(s) of Administration:** PROZINC should be administered subcutaneously along the back of the neck or on the side of the cat using a U-40 insulin syringe.

**L. Species/Class(es):** Cats

**M. Indication(s):** PROZINC (protamine zinc recombinant human insulin) is indicated for the reduction of hyperglycemia and hyperglycemia-associated clinical signs in cats with diabetes mellitus.

## II. EFFECTIVENESS:

### A. Dosage Characterization:

The starting dose for insulin is dependent on many factors including body weight, stress, diet, level of exercise and concurrent disease. The starting dose must be enough to initiate a decrease in blood glucose levels without producing significant hypoglycemia. The dose is then adjusted based on individual response. The starting dose for PROZINC (0.1-0.3 IU/lb [0.2-0.7 IU/kg] every 12 hours) was based on experience using another protamine zinc insulin formulation and is supported by doses found in literature.[1,2,3]

### B. Substantial Evidence:

### 1. Field Study

Study Title and Number: Field trial to evaluate the safety and efficacy of PZIR (protamine zinc recombinant insulin) for the reduction of hyperglycemia and hyperglycemia-associated clinical signs in cats with diabetes mellitus. Study Number IPI-PZI-0106

Type of Study: Field effectiveness and safety study

Study dates: July 2006 to March 2007

[1]Nelson RW. Diabetes Mellitus. In: Ettinger SJ and Feldman EC, eds. *Textbook of Veterinary Internal Medicine: Diseases of the Dog and Cat*. 6th Edition, St. Louis, MO, Elsevier Saunders; 2005; 1576-1577.
[2]Feldman EC and Nelson RW. Feline Diabetes Mellitus. In: Feldman EC and Nelson RW, eds *Canine and Feline Endocrinology and Reproduction*. 3rd Edition, St. Louis, MO, Elsevier Saunders; 2004; 550-551.
[3]Fleeman LM and Rand JS. Options for Monitoring Diabetic Cats. In: August JR, ed. *Consultations in Feline Internal Medicine*. Vol. 5, St. Louis, MO, Elsevier Saunders; 2006; 185.

Investigators/Locations:

| Name | City | State |
|---|---|---|
| Kevin Barcus, DVM | Mounds View | Minnesota |
| Noemi Benitah, DVM | Tinton Falls | New Jersey |
| Marc Bercovitch, DVM | Cleveland | Ohio |
| Adrianne Brode, DVM | Spring | Texas |
| Cheryl Burke, DVM | Catonsville | Maryland |
| Bonnie Cate, DVM | Houston | Texas |
| Marcia Chastain, DVM | Kansas City | Kansas |
| Jeff Dennis, DVM | Overland Park | Kansas |
| Gary Edlin, DVM | St. Matthews | Kentucky |
| Deborah Edwards, DVM | Largo | Florida |
| Scott Linick, DVM | South Plainfield | New Jersey |
| Harrison Monk, DVM | Annapolis | Maryland |
| Richard Nelson, DVM | Davis | California |
| Jean Pitcarin, DVM | North Dartmouth | Massachusetts |
| James Prueter, DVM | Shaker Heights | Ohio |
| Michelle Purnell, DVM | Greensboro | North Carolina |
| Michael Radcliffe, DVM | Lafayette | California |
| Roger Sifferman, DVM | Springfield | Missouri |
| Jennifer Usiak, DVM | Lynn | Massachusetts |

Purpose of study: To evaluate the safety and effectiveness of PROZINC for the reduction of hyperglycemia and hyperglycemia-associated clinical signs in cats with diabetes mellitus, when administered under conditions of clinical use, over a 45 day period.

Description of Test Animals: A total of 187 client-owned cats with diabetes mellitus were enrolled, with 176 receiving PROZINC treatment. All 176 treated cats were included in the evaluation of safety, and 151 cats were included in the evaluation of effectiveness. The cats ranged in age from 3 to 19 years and in weight from 4.6 to 20.8 pounds (2.1 to 9.4 kg). The cats represented both pure and mixed breeds. There were 101 castrated males, 49 spayed females, and one intact female included in the evaluation of effectiveness.

Control and Treatment Groups: All cats received PROZINC. In accordance with 21CFR 514.117(b)(4)(iv), the effects of PROZINC were compared with experience historically derived from the predictable history of diabetes mellitus in cats.

Inclusion criteria: Cats were enrolled in the study based on a diagnosis of diabetes mellitus according to the following criteria:

- Blood glucose > 250 mg/dL
- Glycosuria
- Clinical signs of polyuria, polydipsia, and/or weight loss

In addition to treatment naïve cats, cats that were poorly regulated on another insulin product were allowed to enroll as long as they met the inclusion criteria. Cats enrolled as poorly regulated had a 9-hour blood glucose curve generated on Day 0, the nadir of which had to be > 250 mg/dL.

Dosage Form: 40 IU/mL protamine zinc recombinant human insulin aqueous suspension

Drug Administration: Twice daily injection at approximately 12 hour intervals

Route of Administration: Subcutaneous injection

Dosage Used: The starting dose of PROZINC was 0.1 – 0.3 IU/lb (0.2 – 0.7 IU/kg) every 12 hours with a maximum starting dose of 3 IU every 12 hours. The dose was adjusted based on clinical signs (polyuria, polydipsia, and body weight) and blood glucose nadirs obtained from a 9-hour blood glucose curve on Days 7, 14, 30, and 45. Glycemic control was considered adequate if the glucose nadir from a 9-hour blood glucose curve was between 80 and 150 mg/dL and clinical signs of hyperglycemia (polyuria, polydipsia, and weight loss) were improved.

Study Duration: 45 days

Variables Measured: On study Days 0, 7, 14, 30, and 45, investigators performed a physical examination with body weight and took an owner history to assess clinical signs and changes in polyuria and polydipsia. A 9-hour blood glucose curve was performed on Day 0 for cats enrolled as poorly regulated and on Days 7, 14, 30, and 45 for all cats. The blood glucose curve was used to determine the glucose mean and glucose nadir. Serum fructosamine was evaluated on Days 0, 14, 30, and 45. Urinalysis, complete blood count, and serum chemistry were evaluated on Days 0 and 45.

Criteria for Success or Failure: Effectiveness was based on the percentage of cats that had treatment success at Day 45 compared to Day 0. Treatment success was defined as improvement in at least one blood glucose variable (glucose curve mean, nadir, or fructosamine) and in at least one clinical sign (polyuria, polydipsia, body weight). For evaluation of safety, a complete blood count, serum chemistry, and urinalysis were performed on Days 0 and 45. Results from Day 45 were compared to those from Day 0 and to normal laboratory reference ranges.

Statistical Methodology: Based on a study conducted by the sponsor with another insulin product, CVM and the sponsor agreed that PROZINC would be considered effective if the lower bound of the 90% confidence interval for percentage of cats achieving control of diabetes (treatment success) was > 66%. Descriptive statistics were reported for blood glucose curve mean and nadir, fructosamine, and body weight. The percentage of cats achieving success in each of the individual parameters was summarized as a mean and 90% confidence interval. Serum chemistry and hematology values for all treated cats were compared against normal laboratory reference ranges for safety assessment.

Results: Of the 151 cats included in the effectiveness analysis, 115 (76.2%) were considered treatment successes. The 90% confidence interval was 70.5% to 81.9%. Six cats were transiently diabetic and did not require insulin at the end of the study. The following table summarizes the objective numerical variables measured during the study in the 151 cats included in the effectiveness analysis:

**Table 1: Mean values of blood variables and body weights**

| Day | Glucose Mean (mg/dL) | Glucose Nadir (mg/dL) | Fructosamine (µmol/L) | Weight (lbs) |
|---|---|---|---|---|
| 0 | 415.3* | 407.9* | 505.9 | 12.2 |
| 7 | 338.6 | 271.9 | n/a | 12.4 |
| 14 | 288.9 | 221.5 | 456.1 | 12.4 |
| 30 | 232.4 | 163.8 | 408.4 | 12.8 |
| 45 | 203.2 | 142.4 | 380.7 | 13.1 |

*The Day 0 glucose values for treatment naïve cats were single values, so were not true means or nadirs.

The following table shows the percentage of cats achieving improvement in each variable by Day 45:

**Table 2: Percentage of cats achieving improvement in each category.**

| Variable | Successes | Total Cases* | Percentage (%) | Lower 90 % Confidence Interval |
|---|---|---|---|---|
| Body weight | 118 | 151 | 78.2 | 72.6 |
| Blood glucose mean | 105 | 151 | 69.5 | 63.4 |
| Blood glucose nadir | 101 | 151 | 66.9 | 60.6 |
| Fructosamine | 90 | 144 | 62.5 | 55.9 |
| Consumption of water | 111 | 146 | 76.0 | 70.2 |
| Frequency of urination | 107 | 144 | 74.3 | 68.3 |

*The total number of cases for consumption of water and frequency of urination do not equal 151 because not all cases had those clinical signs present at enrollment. Likewise, some cats entered the study with fructosamine in the "good" category so could not have improved in that category.

The following table shows a summary of effectiveness variables on Days 0 and 45:

**Table 3: Summary statistics for effectiveness variables**

| Variable | Day | Mean | Std Dev | Range | |
|---|---|---|---|---|---|
| | | | | min | max |
| Body weight (lbs) | 0 | 12.2 | 3.2 | 4.6 | 20.8 |
| | 45 | 13.1 | 3.0 | 5.9 | 20.3 |
| Blood glucose nadir (mg/dL) | 0 | 407.9 | 85.3 | 224.0 | 601.0 |
| | 45 | 142.4 | 112.7 | 19.0 | 431.0 |
| Blood glucose mean (mg/dL) | 0 | 415.3 | 81.6 | 259.0 | 601.0 |
| | 45 | 203.2 | 116.4 | 28.8 | 462.8 |
| Fructosamine (µmol/L) | 0 | 505.9 | 97.2 | 182.0 | 923.0 |
| | 45 | 380.7 | 117.5 | 185.0 | 661.0 |

The dose of insulin was adjusted for each cat based on clinical signs and results of a 9-hour blood glucose curve. The following table shows the mean doses used in this study:

**Table 4: Mean insulin dose given twice daily**

| Day | Number of cases* | Dose (IU) | |
|---|---|---|---|
| | | Mean | Range (min, max) |
| 0 | 151 | 1.8 | (0.5, 3.0) |
| 7 | 150 | 2.6 | (1.0, 5.0) |
| 14 | 150 | 3.3 | (1.0, 7.0) |
| 30 | 150 | 3.6 | (0.0, 9.0) |
| 45 | 143 | 3.7 | (0.5, 10) |

*The number of cases decreased as some cats left the study.

Adverse Reactions: In the field study, 176 cats received PROZINC insulin. The most common adverse reactions were hypoglycemia, vomiting, lethargy, and diarrhea. Seventy-one cats experienced hypoglycemia (defined as a blood glucose value of < 50 mg/dL on the blood glucose curve). Most of these cases were not reported as adverse reactions by the investigators, because there were no clinical signs of hypoglycemia associated with the low blood value or the investigator had an alternate explanation for the low values. Clinical signs of hypoglycemia were generally mild in nature (described as lethargic, sluggish, weak, trembling, uncoordinated, groggy, glassy-eyed, or dazed). In 17 cases, the investigator provided oral glucose supplementation or food as treatment. One cat had a serious hypoglycemic event associated with stupor, lateral recumbency, hypothermia and seizures. The cat fully recovered after supportive therapy and finished the study. All cases of hypoglycemia with clinical signs resolved with appropriate therapy and if needed, a dose reduction.

Diabetic ketoacidosis: Four cats were diagnosed with diabetic ketoacidosis during the study. Two of these were euthanized.

Deaths: Seven cats were euthanized during the study. One was euthanized by the referring veterinarian for hypoglycemia. Two had ketoacidosis. Four cats were euthanized after receiving PROZINC for less than 1 week due to worsening of concurrent medical conditions.

Diabetic neuropathy: Three cats entered the study with plantigrade stance, one of which resolved by Day 45. Four cats developed diabetic neuropathy during the study.

Injection site reactions: Three cats had injection site reactions. One developed small, punctate, red lesions. Another cat developed painful lesions around the injection site near a pre-existing skin lesion. The owner tried to change injection site, but the cat experienced pain when injected in the hindquarters. The third cat developed a non-painful subcutaneous thickening at the injection site. All injection site reactions resolved without cessation of PROZINC therapy.

There were other abnormal signs reported during the study. The following table summarizes adverse reactions:

**Table 5: Adverse reactions**

| Adverse reaction | No. of cases |
|---|---|
| Vomiting | 23 |
| Lethargy | 22 |
| Diarrhea, loose stool | 10 |
| Cystitis, hematuria | 6 |
| Upper respiratory infection | 3 |
| Abnormal vocalization | 1 |
| Black stool | 1 |
| Dry coat | 1 |
| Hair loss | 1 |
| Ocular discharge | 1 |
| Rapid breathing | 1 |

Serum chemistry and hematology results from blood samples collected on Day 0 were compared to those from Day 45. No unusual changes were seen.

Conclusions: PROZINC is effective for the reduction of hyperglycemia and hyperglycemia-associated clinical signs in cats with diabetes mellitus. The most common adverse reactions associated with PROZINC are hypoglycemia, vomiting, lethargy, and diarrhea.

**2. Field Study - Extended use**

Study Title and Number: Field Trial to Evaluate the Extended Safety of PZIR (Protamine Zinc Recombinant Insulin) for the Reduction of Hyperglycemia and Hyperglycemia-Associated Clinical Signs in Cats with Diabetes Mellitus. Study Number IPI-PZI-0206

Type of Study: Field safety and effectiveness study

Study Dates: September 2006 to August 2007

Investigators/Locations: Investigators who conducted the effectiveness study (Study IPI-PZI-0106) also conducted the extended use study. The exceptions were that Drs. Brode and Burke did not enroll any cases into this study.

Purpose of Study: To evaluate the safety and effectiveness of extended use of PROZINC for the reduction of hyperglycemia and hyperglycemia-associated clinical signs in cats with diabetes mellitus.

Description of Test Animals: A total of 145 cats were enrolled into the extended use study. Of these, 113 completed the study. Three cats were withdrawn within a few days of enrollment because they did not meet inclusion criteria; 14 cats died or were euthanized; 12 cats were transiently diabetic; one cat dropped out to undergo treatment for a pituitary tumor; and two cats were lost to follow-up.

Control and Treatment Groups: All cats received PROZINC. In accordance with 21CFR 514.117(b)(4)(iv), the effects of PROZINC were compared with experience historically derived from the predictable history of diabetes mellitus in cats.

Inclusion Criteria: Cats that completed the 45-day field study were eligible for enrollment in the extended use study if their diabetes was considered controlled at the end of the 45-day field study.

Dosage Form: 40 IU/mL protamine zinc recombinant human insulin

Drug Administration: Twice daily injection at approximately 12 hour intervals

Route of Administration: Subcutaneous injection

Dosage Used: The dose of insulin was adjusted based on individual investigator preference, including assessment of fructosamine, clinical signs, and in some cases, blood glucose curves. The following table shows the mean doses used in this study:

**Table 6: Mean insulin dose given twice daily**

| Day | Number of Cases | Dose (IU) | |
|---|---|---|---|
| | | Mean | Range (min, max) |
| 45 | 137 | 3.7 | (0.5, 10.0) |
| 68 | 120 | 3.7 | (1.0, 12.0) |
| 102* | 113 | 3.8 | (0.5, 12.0) |

*The dose was not recorded on the last day of the study.

Study Duration: 136 days

Variables Measured: On study Days 0, 34, 68, 102, and 136, investigators performed a physical examination including body weight. Cat owners kept a dosing diary, which included weekly assessment of appetite, attitude, polyuria, and polydipsia. Serum fructosamine was evaluated on Days 0, 68, and 136. Urinalysis, complete blood count, and serum chemistry were evaluated on Days 0 and 136.

Statistical Methodology: Summary statistics were calculated for all urinalysis, complete blood count, and serum chemistry variables for Day 0 and Day 136. All values were compared to normal laboratory reference ranges. In addition, these variables were analyzed by mixed model repeated measures analysis of variance. Descriptive statistics were reported for fructosamine and body weight for study days 0, 68, and 136.

Results: The mean fructosamine values and body weights continued to improve with prolonged use of PROZINC as shown in Table 7 below.

**Table 7: Summary statistics for effectiveness variables**

| Variable | Day | Number of Cases | Mean | Range | |
|---|---|---|---|---|---|
| | | | | min | max |
| Fructosamine (µmol/L) | 0 | 137 | 383.5 | 185 | 661 |
| | 68 | 120 | 344.0 | 166 | 590 |
| | 136 | 110 | 342.0 | 171 | 591 |
| Body weight (lbs) | 0 | 137 | 13.1 | 5.9 | 20.3 |
| | 68 | 120 | 14.3 | 7.0 | 23.8 |
| | 136 | 113 | 14.7 | 6.7 | 25.3 |

Twelve cats' diabetic states went into remission during the extended use study. Evaluation of urinalysis, complete blood count, and serum chemistry showed no unusual trends when comparing values from Day 0 to Day 136 or to laboratory reference range.

Adverse Reactions:
The adverse reactions seen in the extended use study were similar to those reported during the 45-day field study (see Table 5 Adverse reactions under "Field Study").

The most common adverse reactions seen in the extended use study, in order of decreasing frequency, were: vomiting, hypoglycemia, anorexia/poor appetite, diarrhea, lethargy, cystitis/hematuria, and weakness.

Twenty cats had signs consistent with hypoglycemia described as: sluggish, lethargic, unsteady, wobbly, seizures, trembling, or dazed. Most of these were treated by the owners or investigators with oral glucose supplementation or food, but some received intravenous glucose. One cat had a serious hypoglycemic event associated with seizures and blindness. The cat fully recovered after supportive therapy and finished the study. All cases of hypoglycemia resolved with appropriate therapy and if needed, a dose reduction.

Fourteen cats died or were euthanized during the extended use study. In two cases, continued use of insulin despite anorexia and signs of hypoglycemia contributed to the deaths. In one case, the owner decided not to pursue continued therapy after a presumed episode of hypoglycemia. The others were due to concurrent medical conditions or worsening diabetes mellitus.

Diabetic neuropathy: Five cats entered the extended use study with plantigrade stance, one of which resolved by Day 102. The other four did not resolve, but were otherwise considered well controlled by PROZINC. One cat developed a plantigrade stance during the extended use study, but improved by the end of the study.

Conclusions: Long-term treatment with PROZINC was safe and effective for the reduction of hyperglycemia and hyperglycemia-associated clinical signs in cats with diabetes mellitus.

## III. TARGET ANIMAL SAFETY:

The physiologic effect of both endogenous insulin and of all exogenous insulins is to lower blood glucose concentrations. The amount of insulin required to regulate blood glucose levels within a normal range varies considerably over time both within and between individuals with diabetes mellitus. An overdose of insulin results in hypoglycemia. Hypoglycemia can occur with changes in insulin dosage, an overlap of insulin activity, or with a well-established dose in an individual with changes in physiologic status. Hypoglycemia may be associated with clinical signs that range from mild (e.g. lethargy, weakness, or ataxia) to severe (e.g. seizures, coma, or death), and is a common adverse reaction of insulin administration in cats. There is extensive literature

documenting the physiologic effects of insulin, the general safety of insulin, as well as the common adverse reactions associated with insulin therapy.[4,5,6]

The safety of protamine zinc recombinant human insulin was confirmed in the field study and the extended use field study. The most common adverse reactions seen in the extended use study, in order of decreasing frequency, were: vomiting, hypoglycemia, anorexia/poor appetite, diarrhea, lethargy, cystitis/hematuria, and weakness.

## IV. HUMAN FOOD SAFETY:

This drug is intended for use in cats, which are non-food animals. Because this new animal drug is not intended for use in food producing animals, CVM did not require data pertaining to drug residues in food (i.e., human food safety) for approval of this NADA.

## V. USER SAFETY:

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to PROZINC:

> Warnings: User Safety: For use in cats only. Keep out of the reach of children. Avoid contact with eyes. In case of contact, immediately flush eyes with running water for at least 15 minutes. Accidental injection may cause hypoglycemia. In case of accidental injection, seek medical attention immediately. Exposure to product may induce local or systemic allergic reaction in sensitized individuals.

## VI. AGENCY CONCLUSIONS:

The data submitted in support of this NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act and 21 CFR part 514. The data demonstrate that PROZINC, when used according to the label, is safe and effective for reduction of hyperglycemia and hyperglycemia-associated clinical signs in cats with diabetes mellitus.

### A. Marketing Status:

This product may be dispensed only by or on the lawful order of a licensed veterinarian (Rx marketing status). Adequate directions for lay use cannot be written because professional expertise is needed to properly diagnose diabetes mellitus and to monitor the safe use of the product, including treatment of any adverse reactions.

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[4] Davis SN and Cranner DK. Insulin, Oral Hypoglycemic Agents, and the Pharmacology of the Endocrine Pancreas. In: Hardman JG, Limbird LE, eds. *Goodman & Gilman's: The Pharmacological Basis of Therapeutics*. 10th Edition, McGraw-Hill. 2001;1692-1699.

[5] Nelson RW and Feldman EC. Feline Diabetes Mellitus. In: Nelson RW and Feldman EC, eds. *Canine and Feline Endocrinology and Reproduction.* 3rd Edition, St. Louis, MO: WB Saunders, 2004;486-579.

[6] Whitley NT, Drobatz KJ and Panciera DL. Insulin overdose in dogs and cats: 28 cases (1986-1993). *JAVMA* 1997;211(3):326-330.

**B. Exclusivity:**

Under section 106 of the Generic Animal Drug and Patent Term Restoration Act (Public Law 100-670), PROZINC (protamine zinc recombinant human insulin) is not eligible for generic copying because it is a drug primarily manufactured using biotechnology.

**C. Patent Information:**

The sponsor did not submit any patent information with this application.

## VII. ATTACHMENTS:

Facsimile Labeling:
Package Insert and Cat Owner Information
Vial label
Carton label
Case label