Date of Approval: February 8, 2019

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-297

ProZinc®

protamine zinc recombinant human insulin

Injectable suspension

Dogs

This supplement provides for the addition of the indication for the reduction of hyperglycemia and hyperglycemia-associated clinical signs in dogs with diabetes mellitus.

Sponsored by:

Boehringer Ingelheim Animal Health USA Inc.

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I. GENERAL INFORMATION

A. File Number

NADA 141-297

B. Sponsor

Boehringer Ingelheim Animal Health USA Inc.
3239 Satellite Boulevard
Duluth, GA 30096

Drug Labeler Code: 000010

C. Proprietary Name

ProZinc®

D. Product Established Name

Protamine zinc recombinant human insulin

E. Pharmacological Category

Hormone

F. Dosage Form

Injectable suspension

G. Amount of Active Ingredient

40 international units (IU) insulin/mL

H. How Supplied

10 mL multi-dose vials

I. Dispensing Status

Rx

J. Dosage Regimen

Starting dose: The recommended starting dose for ProZinc® is 0.2-0.5 IU insulin/pound of body weight (0.5-1.0 IU/kg) once daily. The recommended starting dose for naïve dogs is the lower end of the dose range. The recommended starting dose for dogs with poorly controlled diabetes mellitus and transitioning from another insulin product is the mid to higher end of the dose range based on the veterinarian's experience with the dog's medical history and previous insulin dose. When transitioning from another insulin, the dog's blood glucose and general condition should be closely monitored. When transitioning from another insulin, ProZinc® should be started once daily regardless of the frequency of prior insulin use.

The dose should be given concurrently with or right after a meal. The veterinarian should re-evaluate the dog at appropriate intervals and adjust the dose and frequency based on both clinical signs and laboratory test results (the blood glucose curve values and shape, nadir, and fructosamine) 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 125 mg/dL, the maximum blood glucose was ≤ 300 mg/dL, and clinical signs of hyperglycemia such as polyuria, polydipsia, or weight loss were improved.

Changing to twice daily dosing: Twice daily dosing should be considered if the duration of insulin action is determined to be inadequate with once daily dosing. Use caution when adjusting from once daily to twice daily dosing because ProZinc® may have prolonged duration of action in some dogs. The veterinarian should closely monitor the duration of action using blood glucose curves to avoid the increased risk of hypoglycemia. If twice daily dosing is initiated, the two doses should each be approximately 25% less than the once daily dose required to attain an acceptable glucose nadir. For example, if a dog receiving 10 units of ProZinc® once daily has an acceptable nadir but inadequate duration of activity, the dose should be changed to 7 units twice daily (round down to the nearest whole unit).

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

K. Route of Administration

Subcutaneous

L. Species/Class

Dogs

M. Indication

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

N. Effect of supplement

This supplement provides for the addition of the indication for the reduction of hyperglycemia and hyperglycemia-associated clinical signs in dogs with diabetes mellitus.

II. EFFECTIVENESS

A. Dosage Characterization

The starting dose for ProZinc®, 0.5-1.0 IU/kg (0.2-0.5 IU/lb), once daily was based on the results of a pharmacokinetic/pharmacodynamic study in healthy dogs and a pilot field study, summarized below:

In a pharmacokinetic and pharmacodynamic study (Study 2010062), ProZinc® was administered as a single dose subcutaneously to 10 healthy, fasted adult Beagles using an incomplete crossover design at doses of 0.5 IU/kg (5 dogs), 0.8 IU/kg at a single site (10 dogs), or 0.8 IU/kg divided into three separate sites (6 dogs). Insulin and glucose concentrations were measured over 24 hours. The shapes of insulin and glucose curves were variable among dogs; and the relationship between insulin dose, concentration, and glucose-lowering effect was nonlinear. There was a dose-related trend in reduction of glucose with increased insulin dose. There was a similar wide range in glucose concentration, onset of insulin action, time to glucose nadir, and duration of action for the 0.5 IU/kg and the two 0.8 IU/kg dosing protocols (Table II.1). Although this study was conducted in healthy, fasted dogs, it suggests that it is possible for absorption of insulin to occur over a 24-hour period.

Table II.1. Pharmacodynamics of three dosing groups

Dose group	Onset of Action	Time to nadir	Duration of Action
0.5 IU/kg at a single site	1 to 14 hours	6 to 16 hours	16 to > 24 hours
0.8 IU/kg at a single site	0.5 to 10 hours	5 to > 24 hours	16 to > 24 hours
0.8 IU/kg divided at three sites	1 to 10 hours	8 to 20 hours	18 to > 24 hours

A 60-day, pilot field study (Study 2010025) using ProZinc® was conducted in 17 client-owned dogs with diabetes mellitus. Six dogs were naïve to treatment and 11 dogs were receiving other insulin products. The median starting dosage of ProZinc® was 0.6 IU/kg (0.3 IU/lb) twice daily (BID), with a range of 0.2-0.8 IU/kg (0.1-0.4 IU/lb) BID. Doses were titrated to effect based on improvement of hyperglycemia and hyperglycemia-associated clinical signs.

The pharmacokinetic/pharmacodynamic study shows ProZinc® has a sufficiently long duration of action to investigate a once daily starting dose and both studies together support investigation of the starting dose range 0.5-1.0 IU/kg (0.2-0.5 IU/lb). The low end of the proposed starting dose range (0.5 IU/kg (0.2 IU/lb) once daily) is based on lack of adverse reactions seen at this dose in the pharmacokinetic/pharmacodynamic study. The high end of the proposed starting dose range (1.0 IU/kg (0.5 IU/lb) once daily) is based on the high end of the starting dose range (0.8 IU/kg (0.4 IU/lb) BID) in the pilot field study. Using a conversion factor described by Monroe et al[1] to convert from twice daily to once daily dosing, the dose 1.0 IU/kg was selected (0.8 IU/kg + 25% = 1.0 IU/kg). Therefore, the starting dose range selected for investigation in the pivotal field study was 0.5-1.0 IU/kg (0.2-0.5 IU/lb) once daily.

[1] Monroe WE et al Efficacy and safety of a purified porcine insulin zinc suspension for managing diabetes mellitus in dogs. *J Vet Intern Med* 2005 Sep;19(5): 675-82.

B. Substantial Evidence

The effectiveness of ProZinc® was demonstrated in an adequate and well-controlled six-month field study. ProZinc® was administered to 276 client-owned dogs, starting with a once daily dose and titrated to effect based on clinical signs and results of blood glucose curves. The most common adverse reactions were lethargy, anorexia, hypoglycemia, vomiting, seizures, shaking, diarrhea, and ataxia. Many of the adverse reactions, such as lethargy, seizures, shaking, and ataxia, are associated with hypoglycemia which is known to occur with insulin therapy in dogs. ProZinc® can have an extended duration of action in some dogs. Careful titration of the dose and dose frequency by the veterinarian and careful observation for signs of hypoglycemia by the owners is recommended during treatment. The field study demonstrated that ProZinc® was effective for the reduction of hyperglycemia and hyperglycemia-associated clinical signs in dogs with diabetes mellitus.

1. Field Study

   Title: A pivotal, clinical field study evaluating the effectiveness and safety of protamine zinc recombinant human insulin (PZIR) in dogs with diabetes mellitus (DM). (Study number 2012028)

   Study Dates: April 12, 2013 to December 28, 2017

   Study locations:

   Fountain Valley, California
   Riverside, California
   Rohnert Park, California
   Fort Collins, Colorado
   Atlanta, Georgia
   Chicago, Illinois
   Overland Park, Kansas
   Springfield, Missouri
   Wappingers Falls, New York
   Lantham, New York
   Greensboro, North Carolina
   Fairfax, Ohio
   Warrensville Heights, Ohio
   Worthington, Ohio
   Spring Hill, Tennessee
   Williston, Vermont

   Study Design: This was a multicenter, single arm, open label field study

   Objective: To investigate the effectiveness and safety of ProZinc® for the reduction of hyperglycemia and hyperglycemia-associated clinical signs in dogs with diabetes mellitus. This study was conducted in accordance with Good Clinical Practice (GCP).

Study Animals:
A total of 276 client-owned dogs with diabetes mellitus were enrolled and received at least one dose of ProZinc®. All 276 dogs were included in the evaluation of safety, and 224 dogs were evaluated for effectiveness. The dogs ranged in age from 2 to 16 years and in weight from 1.5 to 55.9 kg. The dogs represented both pure and mixed breeds. There were 128 neutered males, 8 intact males, 134 spayed females, and 6 intact females included in the evaluation of safety.

Treatment Groups:
All dogs received ProZinc® daily for up to 6 months. 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 dogs.

Inclusion Criteria: Dogs were enrolled in the study based on a diagnosis of diabetes mellitus according to the following criteria:
- Fasting blood glucose > 250 mg/dL in naïve diabetic dogs and > 250 mg/dL before insulin injection in fasted previously treated diabetic dogs
- Glucosuria
- At least one clinical sign consistent with diabetes mellitus (polyuria, polydipsia and/or body weight loss)

Exclusion Criteria:
Dogs with the following conditions or previous treatments were excluded:
- Female dogs in estrus or expected to be in estrus within 6 months
- A history of chronic pancreatitis or recurrent acute pancreatitis
- Clinical or laboratory signs of diabetic ketosis or ketoacidosis requiring hospitalization and treatment with regular insulin on Day -1 of the study
- Known or suspected concurrent diseases which might interfere with interpretation of study results (e.g. pancreatitis, hyperadrenocorticism, hypoadrenocorticism)
- Treated with oral steroids within 30 days, long-acting steroids within 60 days, or gestagens within 6 months prior to Day 0
- Pregnant, lactating dogs or dogs intended for breeding

Drug Administration:
Dosing started on Day 0. The starting dose was 0.2-0.5 IU/lb (0.5-1.0 IU/kg) given subcutaneously once daily and titrated to effect based on clinical signs and results of the blood glucose curve. Naïve dogs started at the lower end of the dose range while previously treated dogs were dosed at the middle to high end of the range. The dose frequency could be switched to twice daily, if necessary, based on duration of action.

Measurements and Observations:
Baseline (Day -1) demographics, physical examination, clinical signs, blood glucose curves, fructosamine, and laboratory panels (complete blood counts, chemistry, and urinalysis with culture and sensitivity) were obtained and compared to Day 84 to assess safety and effectiveness. After Day 84, dogs that had not improved were allowed to withdraw from the study.

Primary laboratory variables for effectiveness consisted of baseline fructosamine values and 9-hour blood glucose curves that determined the

mean and minimum blood glucose (nadir) values. Baseline clinical signs consisted of at least one clinical sign of diabetes: polyuria, polydipsia, or weight loss. Blood glucose curves, fructosamine and clinical signs were evaluated on Days 7, 14, 21, 28, 42, 63, and 84. Fructosamine was further evaluated on Days 112, 154, and 182. ProZinc® dose adjustments were based on laboratory findings and clinical signs at regularly scheduled and unscheduled visits.

Safety was evaluated throughout the study via physical examinations and laboratory or diagnostic testing. At regularly scheduled visits on Days 7, 14, 21, 28, 42, and 63, physical examinations, effectiveness laboratory variables, and abbreviated serum chemistry (albumin, globulin, total protein, blood urea nitrogen, and creatinine) were evaluated. Investigators had the option to run additional testing at regularly scheduled visits. Unscheduled visits were allowed at the discretion of the investigators throughout the study; and any necessary diagnostic or laboratory tests were allowed to aid in diagnosing and treating any changes in the dog's condition. Results from both scheduled and unscheduled visits were compared to those from baseline and to normal laboratory reference ranges. From Day 84 to Day 182, safety was assessed via physical examinations and laboratory or diagnostic testing, if deemed necessary.

Criteria for Success or Failure:
Effectiveness was based on the percentage of dogs that had treatment success at Day 84 compared to Day 0. Treatment success was a composite endpoint defined as improvement in at least one laboratory variable (blood glucose curve mean, blood glucose curve nadir, or fructosamine) and in at least one primary clinical sign (polyuria, polydipsia, or weight loss) when compared to baseline. Dogs removed for an adverse reaction related to ProZinc® through Day 84 or for perceived lack of effectiveness after Day 28 and before Day 84 were considered treatment failures.

Statistical Methods:
ProZinc® was considered effective if the lower bound of the 95% confidence interval for percentage of dogs achieving control of diabetes (treatment success) was ≥ 60%. The analysis utilized the GLIMMIX procedure in SAS with a binomial distribution and logit link. The model was an intercept model with site as a random effect. The percent of treatment successes and the lower 95% confidence limit was calculated by back transforming the logit estimates of the intercept and its lower 95% confidence limit based on two-sided test with alpha = 0.05.

The percentage of dogs demonstrating improvement in each laboratory variable and clinical sign was summarized as a mean and 95% confidence interval.

Results:

Of the 224 dogs included in the effectiveness analysis, 162 (72%) were considered treatment successes. The 95% confidence interval was 61.4 to 80.9%. The following table shows the percentage of dogs improving in each category.

Table II.2. Percentage of dogs achieving improvement in each category.

Variable	Number of Successful Cases	Total Cases*	Percentage (%)	Lower 95% Confidence Interval
Glucose Curve Mean	132	218	60.6	53.7
Glucose Curve Nadir	124	201	61.7	54.6
Fructosamine	119	180	66.1	58.7
Polyuria	184	205	89.8	84.8
Polydipsia	182	206	88.4	83.2
Weight loss	80	148	54.1	45.7

*The total number of cases for weight loss, polyuria, and polydipsia do not equal 224 because not all cases had those clinical signs present at enrollment. Likewise, some dogs entered the study with fructosamine, mean blood glucose, or minimum blood glucose in the "good" category and could not have improved in that category.

Adverse Reactions:
In the field study, 276 dogs received ProZinc® insulin daily for up to 6 months. The most common adverse reactions were lethargy, anorexia, hypoglycemia, vomiting, seizures, shaking, diarrhea, and ataxia.

The following table summarizes the adverse reactions reported in the study. Clinical signs of hypoglycemia varied and included seizure, collapse, ataxia, staggering, trembling, twitching, shaking, disorientation, lethargy, weakness, and vocalization. In Table II.3, the individual clinical signs that were observed during the episodes of hypoglycemia are captured as separate adverse reactions and a single dog may have experienced more than one clinical sign of hypoglycemia.

Table II.3. Adverse reactions seen in the safety population (276 dogs)

Adverse Reaction	Number and Percentage
Lethargy (lethargy, depression, listless, and tiredness)	45 (16.3%)
Anorexia (anorexia, decreased appetite, inappetence, and not eating)	28 (10.1%)
Hypoglycemia with clinical signs*	24 (8.9%)
Vomiting	21 (7.6%)
Seizures	16 (5.8%)
Shaking/trembling/twitching	13 (4.7%)
Ataxia (ataxia, balance problem, stumbling gait)	11 (4.0%)
Diarrhea (includes bloody diarrhea)	9 (3.3%)
Disorientation/confusion	9 (3.3%)
Weakness	8 (2.9%)
Restlessness/anxiety/agitation	6 (2.2%)
Cataract	6 (2.2%)
Panting (panting and tachypnea)	6 (2.2%)
Hematuria	4 (1.5%)

Clinical pathology: Mean cholesterol was elevated at Day 182 (432.6 mg/dL, normal range 131-345 mg/dL) compared to Day -1 (333.7 mg/dL). No other clinically significant, potentially drug-related changes were seen in laboratory testing.

Injection site reactions: Seven dogs had injection site reactions, including observations of thickened skin, swelling, bumps at the injection site, and redness. All injection site reactions resolved without cessation of ProZinc® therapy. Reaction to the injection, including vocalization, was observed in four dogs.

Hypoglycemia: There were 80 hypoglycemic episodes recorded during the study; 37 episodes were associated with clinical signs in 24 dogs, 40 were without clinical signs in 27 dogs, and 3 were with unknown signs in 2 dogs. Hypoglycemia without clinical signs was defined as two consecutive blood glucose curve values < 60 mg/dL unaccompanied by clinical signs. Although most dogs recovered after supportive care (ranging from hospitalization and intravenous dextrose to oral glucose supplementation), two dogs were euthanized when the hypoglycemia did not resolve with supportive care.

Diabetic ketoacidosis and pancreatitis: Diabetic ketoacidosis, a serious metabolic disorder, and pancreatitis, inflammation of the pancreas, can occur in dogs with diabetes mellitus. Eleven dogs were diagnosed with diabetic ketoacidosis. Four of these 11 dogs died or were euthanized, one after one dose of ProZinc®. Twenty-one dogs were diagnosed with pancreatitis. Seven of these 21 dogs died or were euthanized due to complications of pancreatitis. Four dogs had concurrent diabetic ketoacidosis and pancreatitis, three of which died or were euthanized. Not all the deaths were considered related to ProZinc®.

Deaths: Thirty-six (36) dogs died or were euthanized, six of which were possibly related to ProZinc®. One dog died from recurrent episodes of pancreatitis and one died after developing severe vomiting and diarrhea followed by a seizure. Four dogs were euthanized: one developed severe pancreatitis and azotemia, one had recurrent episodes of pancreatitis and diabetic ketoacidosis, and two for lack of effectiveness.

Conclusion:
Treatment with ProZinc® was safe and effective for the reduction of hyperglycemia and hyperglycemia-associated clinical signs in dogs with diabetes mellitus. The most common adverse reactions associated with ProZinc® are, lethargy, anorexia, hypoglycemia, vomiting, seizures, shaking, diarrhea, and ataxia.

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 dogs. 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.[2,3,4]

The safety of ProZinc® was confirmed in the field study, which included an extended use phase. The most common adverse reactions seen in the field study, in order of decreasing frequency, were: lethargy, anorexia, hypoglycemia, vomiting, seizures, shaking, diarrhea and ataxia.

IV. HUMAN FOOD SAFETY

This drug is intended for use in dogs. 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 dogs and 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 (FD&C Act) and 21 CFR part 514. The data demonstrate that ProZinc®, when used according to the label, is safe and effective for the reduction of hyperglycemia and hyperglycemia-associated clinical signs in dogs 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

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[2] Nelson, RW. Canine Diabetes Mellitus. In: Feldman EC, Nelson RW, Reusch CE, Scott-Moncrieff, JCR editors. *Canine and Feline Endocrinology*. 4th ed. St Louis: Saunders Elsevier 2015; 213-257.

[3] Monroe WE. Canine Diabetes Mellitus. In: Bonagura JD, Twedt DC, editors. *Kirk's Current Veterinary Therapy XIV*. 2009. p. 196-9.

[4] Reusch EC, Robben JH, Kooistra HS. Endocrine Pancreas. In: Rijnberk A, Kooistra HS, editors. *Clinical Endocrinology of Dogs and Cats*. Hannover: Schlütersche Verlagsgesellschaft GmbH & Co. KG; 2010. p. 155-85.

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.

B. Exclusivity

ProZinc®, as approved in our approval letter, does not qualify for marketing exclusivity under section 512(c)(2) of the FD&C Act.

The exclusivity provisions of section 512(c)(2)(F) of the FD&C Act do not apply to this drug because under section 106 of the Generic Animal Drug and Patent Term Restoration Act (Pub.L. 100-670), FDA cannot approve an abbreviated new animal drug application (ANADA) for a new animal drug that is primarily manufactured using recombinant DNA, recombinant RNA, hybridoma technology, or other processes involving site specific gene manipulation techniques. Therefore, a sponsor cannot submit an ANADA to market a generic version of this drug.

C. Patent Information

For current information on patents, see the Animal Drugs @ FDA database or the Green Book on the FDA CVM internet website.