Now approved for cats and dogs*

THE PROVEN WAY TO TREAT CANINE DIABETES ONCE-A-DAY

ProZinc®
(protamine zinc recombinant human insulin)

Boehringer Ingelheim

*PROZINC® (protamine zinc recombinant human insulin) is approved for twice-daily use in cats.[1]

ProZinc®
(protamine zinc recombinant human insulin)

FINALLY: ONCE-DAILY DOSING CAN BE A REALITY FOR DOGS

Now, in addition to being a SINGLE insulin you can stock for your canine and feline patients, you can trust PROZINC® (protamine zinc recombinant human insulin) to make treating canine diabetes more convenient than ever. ***A study employing continuous glucose monitoring (CGM) PROVES that once-daily dosing can be used to achieve diabetic control.[2]***

Extended Duration of Action

According to pharmacokinetic/pharmacodynamic data, protamine zinc recombinant human insulin demonstrates a duration of action, in both healthy[3] and diabetic dogs, of 18 to >24 hours [4]

Consistent Glycemic Control

Based on a study using CGM, the biphasic nature of PROZINC ensures well-controlled blood glucose levels following the dog's second feeding.[2]

Demonstrated Improvement in Clinical Signs

In a study, clinical signs began to resolve quickly, and then progressively[5]: 62% of dogs showed improvement by Day 14, and 87% of dogs showed improvement by Day 86

Rigorously Tested

Diabetic control with PROZINC was attained at similar rates in both naïve and previously insulin-treated populations[5]

Now available in two presentations!

10 mL - SKU 139527

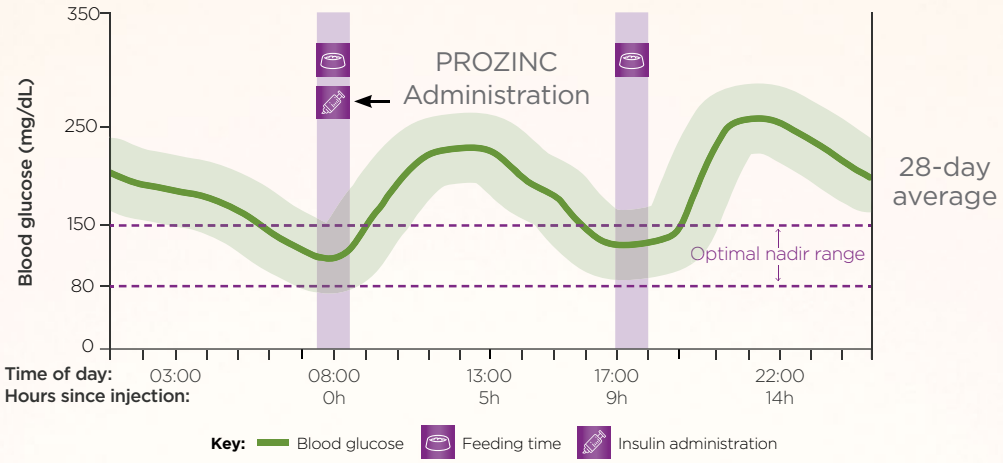
20 mL - SKU 153938

IMPORTANT SAFETY INFORMATION: PROZINC is for use in dogs and cats only. Keep out of the reach of children. Animals presenting with severe ketoacidosis, anorexia, lethargy, and/or vomiting should be stabilized with short-acting insulin and appropriate supportive therapy until their condition is stabilized. As with all insulin products, careful patient monitoring for hypoglycemia and hyperglycemia is essential to attain and maintain adequate glycemic control and to prevent associated complications. Overdose can result in profound hypoglycemia and death. The most common adverse reactions were lethargy, anorexia, hypoglycemia, vomiting, seizures, shaking (dogs only), diarrhea, and ataxia. Many of the adverse reactions, such as lethargy, seizures, shaking (dogs only), and ataxia, are associated with hypoglycemia. Glucocorticoid and progestogen use should be avoided. The safety and effectiveness of PROZINC in puppies, kittens, or breeding, pregnant, and lactating animals has not been evaluated. PROZINC is contraindicated during episodes of hypoglycemia and in animals sensitive to protamine zinc recombinant human insulin or any other ingredients in PROZINC. **For more information, please see full prescribing information.**

TRUE ONCE-DAILY DOSING *FOR CANINE DIABETICS*

24-Hour PROZINC® Blood Glucose Curve Example

(protamine zinc recombinant human insulin)



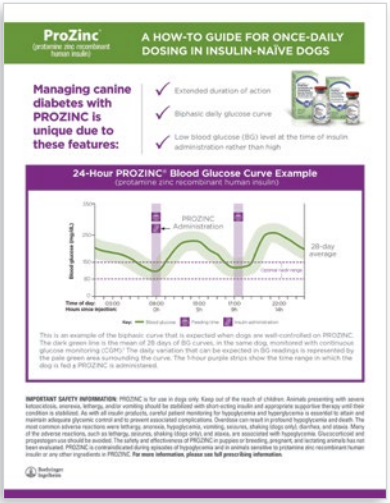
This is an example of the biphasic curve that is expected when dogs are well-controlled on PROZINC. The dark green line is the mean of 28 days of BG curves, in the same dog, monitored with continuous glucose monitoring (CGM).[2] The daily variation that can be expected in BG readings is represented by the pale green area surrounding the curve. The 1-hour purple strips show the time range in which the dog is fed + PROZINC is administered.

Managing canine diabetes with PROZINC is unique due to these features:

1. **Extended duration of action**
2. **Biphasic daily glucose curve**
3. **Low blood glucose (BG) level at the time of insulin administration rather than high**

With proper expectations and a little patience, your practice can successfully manage canine diabetes with PROZINC® (protamine zinc recombinant human insulin).

For comprehensive tips on how to treat canine patients with once-daily dosing of PROZINC, please refer to our SID Treatment Guide. For more information, ask your Boehringer Ingelheim Professional Services Veterinarian.


ProZinc (protamine zinc recombinant human insulin)

A HOW-TO GUIDE FOR ONCE-DAILY DOSING IN INSULIN-NAÏVE DOGS

Managing canine diabetes with PROZINC is unique due to these features:

- Extended duration of action
- Biphasic daily glucose curve
- Low blood glucose (BG) level at the time of insulin administration rather than high

24-Hour PROZINC® Blood Glucose Curve Example (protamine zinc recombinant human insulin)

Diabetes Care Kits for Pet Owners

Diabetes Care Kits are now available with two sizes of U-40 syringes - 0.33 cc or 1.0 cc - to match your patients' needs.

Each kit includes:

- 100 syringes
- A sharps disposal container

SKU for 0.33 cc kit:-155772

SKU for 1.0 cc kit:-155771

PROZINC® (protamine zinc recombinant human insulin) **is the game-changing treatment that diabetic dogs and their owners have been waiting for.**

UNSURPASSED EFFICACY IN CATS

The only AAHA-recommended and FDA-approved first-line treatment for feline diabetes

A recent comparative study found that PROZINC® (protamine zinc recombinant human insulin) and glargine[6]:

- ✓ Delivered comparable glycemic control
- ✓ Produced no detectable difference in remission rates

A systematic review determined that diabetic remission rate was independent of insulin formulation, and no single factor predicted remission.[7] However, cats that experienced remission were more likely to have achieved rapid glycemic control:

- ✓ In a field study, 76.2% of cats that received PROZINC achieved diabetic control in 45 days[2]
- ✓ PROZINC's rapid efficacy promotes conditions that favor remission[8]

PROZINC	GLARGINE
Specifically developed for veterinary use and FDA-approved for cats	Developed for treatment of diabetes in human patients and not FDA-approved for cats
Clinical results backed by the largest prospective study in diabetic cats to date[2] (151 subjects)	Small number of studies with usually fewer than 10 subjects
40 IU concentration and U-40 syringe to facilitate precise dosing	100 IU concentration and U-100 syringe
Backed by full technical support from Boehringer Ingelheim	Limited to absent technical support from the manufacturer due to off-label usage
Pet owner costs can be less than half that of glargine	Pet owner costs are rising and can be in excess of $300 per bottle*
Accessed through veterinarians, which keeps revenue and control of treatment in your clinic	Purchased at retail pharmacy unfamiliar with your patients and feline diabetes

*Data compiled from www.goodrx.com. Prices are current as of August 2020.

Twice-daily dosing of PROZINC delivers appropriate duration of action for cats[2]

Approximately half of the cats treated with PROZINC showed improvement in as soon as 7 days.

- 76% of cats saw an improvement in excessive thirst
- 74% of cats saw an improvement in excessive urination

IMPORTANT SAFETY INFORMATION: PROZINC is for use in dogs and cats only. Keep out of the reach of children. Animals presenting with severe ketoacidosis, anorexia, lethargy, and/or vomiting should be stabilized with short-acting insulin and appropriate supportive therapy until their condition is stabilized. As with all insulin products, careful patient monitoring for hypoglycemia and hyperglycemia is essential to attain and maintain adequate glycemic control and to prevent associated complications. Overdose can result in profound hypoglycemia and death. The most common adverse reactions were lethargy, anorexia, hypoglycemia, vomiting, seizures, shaking (dogs only), diarrhea, and ataxia. Many of the adverse reactions, such as lethargy, seizures, shaking (dogs only), and ataxia, are associated with hypoglycemia. Glucocorticoid and progestogen use should be avoided. The safety and effectiveness of PROZINC in puppies, kittens, or breeding, pregnant, and lactating animals has not been evaluated. PROZINC is contraindicated during episodes of hypoglycemia and in animals sensitive to protamine zinc recombinant human insulin or any other ingredients in PROZINC. **For more information, please see full prescribing information.**

TOGETHER WE'RE MORE THAN JUST TREATMENT

Boehringer Ingelheim is committed to helping you educate your clients and staff with free educational tools and resources, including:

Care Kits Increase convenience for clients by providing new syringes, and an easy way to properly dispose of used needles and syringes.

Educational Materials Help your healthcare team educate your clients with a variety of easy-to-use and easy-to-understand resources, including:

- Educational brochures for cat and dog owners
- *YOU CAN DO THIS* videos on **ProZinc.us** that help educate pet owners on how to use, store and administer insulin
- Take-home printed diary and reminder magnets available through Customer Care to help pet owners track their pet's progress

On-Call Technical Support Reach our knowledgeable, on-call support team at **1-888-637-4251**.

Now approved for use in cats and dogs!

For more information

Contact your Boehringer Ingelheim Sales Representative or Professional Services Veterinarian.

[1] ProZinc® (protamine zinc recombinant human insulin) [Freedom of Information Summary]. St. Joseph, MO: Boehringer Ingelheim Animal Health USA Inc.; 2009.
[2] Data on file at Boehringer Ingelheim.
[3] Clark et al, Pharmacokinetics and Pharmacodynamics of protamine zinc recombinant human insulin in healthy dogs, *J Vet Pharmacol Ther*. 2011.
[4] Maggiore AD, Nelson RW, Dennis J, et al. Efficacy of protamine zinc recombinant human insulin for controlling hyperglycemia in dogs with diabetes mellitus. *J Vet Intern Med*. 2012;26(1):109–15.
[5] ProZinc® (protamine zinc recombinant human insulin) [Freedom of Information Summary]. Duluth, GA: Boehringer Ingelheim Animal Health USA Inc.; 2019.
[6] Gostelow R, Scudder C, et al. One-year prospective randomized trial comparing efficacy of glargine and protamine zinc insulin in diabetic cats. Abstract format.
[7] Gostelow R, Forcada Y, Graves T, et al. Systematic review of feline diabetic remission: separating fact from opinion. *Vet J*. 2014;202(2):208-21.
[8] ProZinc Cat Prescribing Information.

Boehringer Ingelheim

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ProZinc®
(protamine zinc recombinant human insulin)

Package Insert for Cats

ProZinc®
(protamine zinc recombinant human insulin)

40 IU/mL

Caution: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

Description: PROZINC® is a sterile aqueous protamine zinc suspension of recombinant human insulin.

Each mL contains:

recombinant human insulin	40 International Units (IU)
protamine sulfate	0.466 mg
zinc oxide	0.088 mg
glycerin	16.00 mg
dibasic sodium phosphate, heptahydrate	3.78 mg
phenol (added as preservative)	2.50 mg
hydrochloric acid	1.63 mg
water for injection (maximum)	1005 mg

pH is adjusted with hydrochloric acid and/or sodium hydroxide.

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

Dosage and Administration: USE OF A SYRINGE OTHER THAN A U-40 SYRINGE WILL RESULT IN INCORRECT DOSING.

FOR SUBCUTANEOUS INJECTION ONLY.

DO NOT SHAKE OR AGITATE THE VIAL.

PROZINC should be mixed by gently rolling the vial prior to withdrawing each dose from the vial. Once mixed, PROZINC suspension has a white, cloudy appearance. Clumps or visible white particles can form in insulin suspensions: do not use the product if clumps or visible white particles persist after gently rolling the vial.

Using a U-40 insulin syringe, the injection should be administered subcutaneously on the back of the neck or on the side of the cat.

Always provide the Client Information Sheet with each prescription.

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.

Contraindications: PROZINC is contraindicated in cats sensitive to protamine zinc recombinant human insulin or any other ingredients in PROZINC. PROZINC is contraindicated during episodes of hypoglycemia.

Warnings: User Safety: For use in cats and dogs 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 a local or systemic allergic reaction in sensitized individuals.

Animal Safety: Owners should be advised to observe for signs of hypoglycemia (see Client Information Sheet). Use of this product, even at established doses, has been associated with hypoglycemia. A cat with signs of hypoglycemia should be treated immediately. Glucose should be given orally or intravenously as dictated by clinical signs. Insulin should be temporarily withheld and, if indicated, the dosage adjusted.

Any change in insulin should be made cautiously and only under a veterinarian's supervision. Changes in insulin strength, manufacturer, type, species (human, animal) or method of manufacture (rDNA versus animal-source insulin) may result in the need for a change in dosage.

Appropriate diagnostic tests should be performed to rule out other endocrinopathies in diabetic cats that are difficult to regulate.

Precautions: Cats presenting with severe ketoacidosis, anorexia, lethargy, and/or vomiting should be stabilized with short-acting insulin and appropriate supportive therapy until their condition is stabilized. As with all insulin products, careful patient monitoring for hypoglycemia and hyperglycemia is essential to attain and maintain adequate glycemic control and to prevent associated complications. Overdose can result in profound hypoglycemia and death.

Glucocorticoids, progestogens, and certain endocrinopathies can have an antagonistic effect on insulin activity. Glucocorticoid and progestogen use should be avoided.

The safety and effectiveness of PROZINC in breeding, pregnant, and lactating cats has not been evaluated.

The safety and effectiveness of PROZINC in kittens has not been evaluated.

Adverse Reactions: Effectiveness Field Study

In a 45-day effectiveness field study, 176 cats received PROZINC. Hypoglycemia (defined as a blood glucose value of < 50 mg/dL) occurred in 71 of the cats at various times throughout the study. 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 veterinarian provided oral glucose supplementation or food as treatment. Most cases were not associated with clinical signs and received no treatment. One cat had a serious hypoglycemic event associated with stupor, lateral recumbency, hypothermia and seizures. All cases of hypoglycemia resolved with appropriate therapy and if needed, a dose reduction.

Three cats had injection site reactions which were described as either small, punctate, red lesions; lesions on neck; or palpable subcutaneous thickening. All injection site reactions resolved without cessation of therapy.

Four cats developed diabetic neuropathy during the study as evidenced by plantigrade stance. Three cats entered the study with plantigrade stance, one of which resolved by Day 45. Four cats were diagnosed with diabetic ketoacidosis during the study. Two were euthanized due to poor response to treatment. Five other cats were euthanized during the study, one of which had hypoglycemia. Four cats had received PROZINC for less than a week and were euthanized due to worsening concurrent medical conditions.

The following additional clinical observations or diagnoses were reported in cats during the effectiveness field study: vomiting, lethargy, diarrhea, cystitis/hematuria, upper respiratory infection, dry coat, hair loss, ocular discharge, abnormal vocalization, black stool, and rapid breathing.

Extended Use Field Study

Cats that completed the effectiveness study were enrolled into an extended use field study. In this study, 145 cats received PROZINC for up to an additional 136 days. Adverse reactions were similar to those reported during the 45-day effectiveness study and are listed in order of decreasing frequency: 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 owner or veterinarian with oral glucose supplementation or food; others 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 continue therapy after a presumed episode of hypoglycemia. The rest were due to concurrent medical conditions or worsening of the diabetes mellitus.

To report suspected adverse drug events, for technical assistance or to obtain a copy of the Safety Data Sheet (SDS), contact Boehringer Ingelheim at 1-888-637-4251.

For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or online at http://www.fda.gov/reportanimalae.

Information for Cat Owners: Please refer to the Client Information Sheet for Cats for more information about PROZINC. PROZINC, like other insulin products, is not free from adverse reactions. Owners should be advised of the potential for adverse reactions and be informed of the associated clinical signs. Potential adverse reactions include: hypoglycemia, insulin antagonism/resistance, rapid insulin metabolism, insulin-induced hyperglycemia (Somogyi Effect), and local or systemic reactions. The most common adverse reaction observed is hypoglycemia. Signs may include: weakness, depression, behavioral changes, muscle twitching, and anxiety. In severe cases of hypoglycemia, seizures and coma can occur. Hypoglycemia can be fatal if an affected cat does not receive prompt treatment. Appropriate veterinary monitoring of blood glucose, adjustment of insulin dose and regimen as needed, and stabilization of diet and activity help minimize the risk of hypoglycemic episodes. The attending veterinarian should evaluate other adverse reactions on a case-by-case basis to determine if an adjustment in therapy is appropriate, or if alternative therapy should be considered.

Effectiveness: A total of 187 client-owned cats were enrolled in a 45-day field study, with 176 receiving PROZINC. One hundred and fifty-one cats were included in the effectiveness analysis. The patients included various purebred and mixed breed cats ranging in age from 3 to 19 years and in weight from 4.6 to 20.8 pounds. Of the cats included in the effectiveness analysis, 101 were castrated males, 49 were spayed females, and 1 was an intact female.

Cats were started on PROZINC at a dose of 0.1-0.3 IU/lb (0.2-0.7 IU/kg) twice daily. Cats were evaluated at 7, 14, 30, and 45 days after initiation of therapy and the dose was adjusted based on clinical signs and results of 9-hour blood glucose curves on Days 7, 14, and 30.

Effectiveness was based on successful control of diabetes which was defined as improvement in at least one blood glucose variable (glucose curve mean, nadir, or fructosamine) and at least one clinical sign (polyuria, polydipsia, or body weight). Based on this definition, 115 of 151 cases (76.2%) were considered successful. Blood glucose curve means decreased from 415.3 mg/dL on Day 0 to 203.2 mg/dL by Day 45 and the mean blood glucose nadir decreased from 407.9 mg/dL on Day 0 to 142.4 mg/dL on Day 45. Mean fructosamine values decreased from 505.9 µmol/L on Day 0 to 380.7 µmol/L on Day 45.

Cats that completed the effectiveness study were enrolled in an extended use field study. The mean fructosamine value was 342.0 µmol/L after a total of 181 days of PROZINC therapy.

How Supplied: PROZINC is supplied as a sterile injectable suspension in 10 mL and 20 mL multi-dose vials. Each mL of PROZINC contains 40 IU recombinant human insulin.

Storage Conditions: Store in an upright position under refrigeration at 36-46°F (2-8°C). Do not freeze. Protect from light. **Use the 10 mL vial within 60 days of first puncture. Use the 20 mL vial within 80 days of first puncture.**

Approved by FDA under NADA # 141-297

Marketed by:
Boehringer Ingelheim Animal Health USA Inc.
Duluth, GA 30096

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449986-01

Boehringer Ingelheim

Package Insert for Dogs

ProZinc®
(protamine zinc recombinant human insulin)

40 IU/mL

Caution: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

Description: PROZINC® is a sterile aqueous protamine zinc suspension of recombinant human insulin.

Each mL contains:

recombinant human insulin	40 International Units (IU)
protamine sulfate	0.466 mg
zinc oxide	0.088 mg
glycerin	16.00 mg
dibasic sodium phosphate, heptahydrate	3.78 mg
phenol (added as preservative)	2.50 mg
hydrochloric acid	1.63 mg
water for injection (maximum)	1005 mg

pH is adjusted with hydrochloric acid and/or sodium hydroxide.

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

Dosage and Administration: USE OF A SYRINGE OTHER THAN A U-40 SYRINGE WILL RESULT IN INCORRECT DOSING.

FOR SUBCUTANEOUS INJECTION ONLY.

DO NOT SHAKE OR AGITATE THE VIAL.

PROZINC should be mixed by gently rolling the vial prior to withdrawing each dose from the vial. Once mixed, PROZINC suspension has a white, cloudy appearance. Clumps or visible white particles can form in insulin suspensions: do not use the product if clumps or visible white particles persist after gently rolling the vial.

Using a U-40 insulin syringe, the injection should be administered subcutaneously on the back of the neck or on the side of the dog.

Always provide the Client Information Sheet with each prescription.

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 (see Clinical Pharmacology). 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.

Contraindications: PROZINC is contraindicated in dogs sensitive to protamine zinc recombinant human insulin or any other ingredients in PROZINC. PROZINC is contraindicated during episodes of hypoglycemia.

Warnings:
User Safety: For use in dogs and cats. 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 a local or systemic allergic reaction in sensitized individuals.

Animal Safety: Owners should be advised to observe for signs of hypoglycemia (see Client Information Sheet). Use of this product, even at established doses, has been associated with hypoglycemia. A dog with signs of hypoglycemia should be treated immediately. Glucose should be given orally or intravenously as dictated by clinical signs. Insulin should be temporarily withheld and, if indicated, the dosage adjusted.

Any change in insulin should be made cautiously and only under a veterinarian's supervision. Changes in insulin strength, manufacturer, type, species (human, animal) or method of manufacture (rDNA versus animal-source insulin) may result in the need for a change in dosage.

Appropriate diagnostic tests should be performed to rule out other endocrinopathies in diabetic dogs that are difficult to regulate.

Precautions: Dogs presenting with severe ketoacidosis, anorexia, lethargy, and/or vomiting should be stabilized with short-acting insulin and appropriate supportive therapy until their condition is stabilized. As with all insulin products, careful patient monitoring for hypoglycemia and hyperglycemia is essential to attain and maintain adequate glycemic control and to prevent associated complications. Overdose can result in profound hypoglycemia and death.

Glucocorticoids, progestogens, and certain endocrinopathies can have an antagonistic effect on insulin activity. Glucocorticoid and progestogen use should be avoided.

The safety and effectiveness of PROZINC in breeding, pregnant, and lactating dogs has not been evaluated.

The safety and effectiveness of PROZINC in puppies has not been evaluated.

Adverse Reactions: In a 182-day field study, 276 dogs received PROZINC. The most common adverse reactions were lethargy, anorexia, hypoglycemia, vomiting, seizures, shaking, diarrhea, and ataxia.

Table 1 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 1, 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 1. 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: The only change seen in complete blood count, serum chemistry, and urinalysis results was an elevation in mean cholesterol at Day 182 (432.6 mg/dL, normal range 131-345 mg/dL) compared to Day -1 (333.7 mg/dL).)

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 with some dogs experiencing more than one episode; 37 episodes were associated with clinical signs in 24 dogs, 40 episodes were without clinical signs in 27 dogs, and 3 were with unknown signs in 2 dogs. Clinical signs of hypoglycemia varied and included seizure, collapse, ataxia, staggering, trembling, twitching, shaking, disorientation, lethargy, weakness, and vocalization. Some dogs required hospitalization and intravenous dextrose while most recovered after receiving oral supplementation with a meal and/or oral glucose such as syrup. Two dogs were euthanized when the hypoglycemia did not resolve with supportive care. Hypoglycemia without clinical signs was defined as two consecutive blood glucose curve values < 60 mg/dL unaccompanied by clinical signs.

Diabetic ketoacidosis and pancreatitis: 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.

To report suspected adverse drug events, for technical assistance or to obtain a copy of the Safety Data Sheet (SDS), contact Boehringer Ingelheim at 1-888-637-4251.

For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or online at http://www.fda.gov/reportanimalae.

Clinical Pharmacology: PROZINC was administered subcutaneously to 10 healthy 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 at 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 (Table 2).

Table 2. 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

Information for Dog Owners: Please refer to the Client Information Sheet for Dogs for more information about PROZINC. PROZINC, like other insulin products, is not free from adverse reactions. Owners should be advised of the potential for adverse reactions and be informed of the associated clinical signs. Potential adverse reactions include hypoglycemia, insulin antagonism/resistance, rapid insulin metabolism, insulin-induced hyperglycemia (Somogyi Effect), and local or systemic reactions. The most common adverse reaction observed is hypoglycemia. Signs may include weakness, depression, behavioral changes, muscle twitching, and anxiety. In severe cases of hypoglycemia, seizures and coma can occur. Hypoglycemia can be fatal if an affected dog does not receive prompt treatment. Appropriate veterinary monitoring of blood glucose, adjustment of insulin dose and regimen as needed, and stabilization of diet and activity help minimize the risk of hypoglycemic episodes. The attending veterinarian should evaluate other adverse reactions on a case-by-case basis to determine if an adjustment in therapy is appropriate, or if alternative therapy should be considered.

Effectiveness: A total of 276 client-owned dogs were enrolled in an 84-day field study followed by a 98-day extended-use phase with 276 dogs receiving PROZINC. The dogs included various purebred and mixed breed dogs ranging in age from 2 to 16 years and in weight from 3.3 to 123 pounds. There were 128 neutered males, 8 intact males, 134 spayed females and 6 intact females. Two hundred twenty-four dogs (224) were included in the effectiveness analysis. Dogs were started on PROZINC at a dose of 0.2-0.5 IU/lb (0.5-1.0 IU/kg) once daily. Dogs were evaluated at 7, 14, 21, 28, 42, 63 and 84 days after initiation of therapy. The dose was adjusted based on clinical signs and results of 9-hour blood glucose curves on Days 7, 14, 21, 28, 42, 63 and 84.

Effectiveness was based on successful control of diabetes which was defined as improvement in at least one laboratory variable (blood glucose curve mean, blood glucose curve nadir, or fructosamine) and at least one clinical sign (polyuria, polydipsia, or weight loss). Based on this definition, 162 of 224 cases (72%) were considered successful.

How Supplied: PROZINC is supplied as a sterile injectable suspension in 10 mL and 20 mL multi-dose vials. Each mL of PROZINC contains 40 IU recombinant human insulin.

Storage Conditions: Store in an upright position under refrigeration at 36-46°F (2-8°C). Do not freeze. Protect from light. **Use the 10 mL vial within 60 days of first puncture. Use the 20 mL vial within 80 days of first puncture.**

Approved by FDA under NADA # 141-297

Marketed by:
Boehringer Ingelheim Animal Health USA Inc.
Duluth, GA 30096

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