Now available in 10 mL and 20 mL bottles

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

The breakthrough you’ve been waiting for is here: now you can deliver glycemic control in most diabetic dogs WITH A SINGLE DAILY INJECTION.¹,²

GOOD NEWS:
• PROZINC® (protamine zinc recombinant human insulin) is now approved for cats and dogs*¹
• A study employing continuous glucose monitoring PROVES that once-daily dosing can be used to achieve diabetic control in dogs¹
• Diabetic control with PROZINC was attained at similar rates in both naïve and previously insulin-treated canine populations²

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.

* PROZINC is approved for twice-daily use in cats.²
1 Data on file at Boehringer Ingelheim.

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Extended duration of action

Biphasic daily glucose curve

Optimal blood glucose (BG) level may already be present right at the time of next insulin administration

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

1. Extended duration of action
2. Biphasic daily glucose curve
3. Optimal blood glucose (BG) level may already be present right at the time of next insulin administration

This is an example of the biphasic curve that is expected when dogs are well-controlled on PROZINC® (protamine zinc recombinant human insulin). The dark green line represents the mean of 28 days of BG curves, in the same dog, monitored with continuous glucose monitoring (CGM). The daily variation that may 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 was fed + PROZINC was administered.

IMPORTANT SAFETY INFORMATION: As with all insulin products, careful monitoring for hypoglycemia and hyperglycemia is essential to attain and maintain adequate glycemic control and to prevent associated complications. For more information, please see full prescribing information.

Check-Off (Qualify)
Identify if the customer is aware that PROZINC is now approved for dogs and offers proven once-daily dosing for most canine patients.

Doctor, are you familiar with PROZINC?
If YES, confirm and discuss the possibility of once-daily dosing for dogs
If NO, detail as the primary contact

Confidence
Clients with newly diagnosed diabetic dogs will be relieved to learn about once-daily dosing with PROZINC for dogs! A recent study that used continuous glucose monitoring PROVES that PROZINC delivers glycemic control for MOST canine patients with just a single injection each day.1

Invitation to neutral
Let's review the exciting new developments with PROZINC and once-daily dosing for dogs...

It's the customer's decision
...Now you have a single product that meets the needs of both diabetic cats and dogs that makes once-daily dosing a reality for most canine patients.
PROZINC is a sterile aqueous protamine zinc suspension of recombinant human insulin.

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

Dose and Administration: USE OF A SYRINGE OTHER THAN A U-40 SYRINGE WILL RESULT IN INCOMPLETE 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 may 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 sides of the thighs.

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 naive dogs is the lower end of the dose range. The 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 clinical 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 value and shape, nadir, and fructoseamine level) 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 >70 mg/dL, maximum blood glucose was <110 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 action, 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 concurrent 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 hyperglycemia.

Warnings: User Safety: For use in dogs and cats. Keep out of the reach of children. Avoid contact with eyes. In case of accidental contact, immediately flush eyes with running water for at least 15 minutes. If eye irritation develops, ocular 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 from diabetic dogs that are difficult to regulate.

Contraindications: Patients with hypoglycemia, anaphylaxis, larynx, 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. Glucocorticoids 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, shivering, 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, shakiness, disorientation, lethargy, weakness, and vocalization. In Table 1, the individual clinical signs that were observed during clinical signs of hypoglycemia are listed separately and a separate adverse reaction is provided for a single dog may have experienced more than one clinical sign of hypoglycemia.

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Number and Percentage</th>
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<tbody>
<tr>
<td>Anorexia</td>
<td>28 (10.1%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>21 (7.6%)</td>
</tr>
<tr>
<td>Seizures</td>
<td>16 (5.8%)</td>
</tr>
<tr>
<td>Shaking/trembling/twitching</td>
<td>13 (4.7%)</td>
</tr>
<tr>
<td>Diarrhea (includes bloody diarrhea)</td>
<td>9 (3.3%)</td>
</tr>
<tr>
<td>Disorientation/confusion</td>
<td>9 (3.3%)</td>
</tr>
<tr>
<td>Weakness</td>
<td>8 (2.9%)</td>
</tr>
<tr>
<td>Restlessness/anxiety/ agitation</td>
<td>6 (2.2%)</td>
</tr>
<tr>
<td>Cataract</td>
<td>6 (2.2%)</td>
</tr>
<tr>
<td>Hematuria</td>
<td>6 (2.5%)</td>
</tr>
</tbody>
</table>

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).

Table 1. Adverse reactions seen in the safety population (276 dogs)

Dose group | Onset of Action | Time to nadir | Duration of Action |
<table>
<thead>
<tr>
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<tr>
<td>0.5 IU/kg at a single site</td>
<td>1 to 14 hours</td>
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<tr>
<td>0.8 IU/kg at a single site</td>
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<td>1 to 10 hours</td>
<td>10 to 20 hours</td>
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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 and appropriate action. Potential adverse reactions include hypoglycemia, insulin antagonism/resistance, rapid insulin metabolism, insulin-induced hyperglycemia (Somogyi Effect), and local or systemic reactions. Potential adverse reactions include hypoglycemia, signs of hypoglycemia vary and include seizure, collapse, ataxia, staggering, trembling, twitching, shakiness, disorientation, lethargy, weakness, and vocalization. In severe cases of hypoglycemia, some dogs may exhibit 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 breeds and mixed breed dogs and ranged 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 randomized to receive PROZINC at 0.5 IU/kg (6 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 |
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Approved by FDA under NADA # 141-297

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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. The attending veterinarian should 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 regime 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 purebreds 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/kg (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 (blood glucose mean, nadir, or fructosamine) and at least one clinical sign (polysialosis, 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 of decreasing frequency: vomiting, hypoglycemia, anorexia/poor appetite, diarrhea, lethargy, cystitis/hematuria, upper respiratory infection, dry coat, hair loss, ocular discharge, abnormal vocalization, back 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 not similar to those reported in the first 45-day period 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.

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