CLICK ONE OF THE BELOW TO LEARN MORE ABOUT PROZINC®

- HOW TO ADMINSTER PROZINC®
- LEARN MORE ABOUT PROZINC[®] & HOW TO MANAGE DIABETES FOR DOGS
- LEARN MORE ABOUT PROZINC[®] & HOW TO MANAGE DIABETES FOR CATS



EASY DOES IT.

YOUR GUIDE TO PREPARING AND ADMINISTERING YOUR CAT'S OR DOG'S **PROZINC®** (protamine zinc recombinant human insulin) WITH EASE.



PREPARING THE INJECTION

You may think it would be difficult to give your cat or dog an insulin injection, but with care and practice you will find that it is not. Ask your veterinarian to show you the correct method.

FOLLOW THESE STEPS TO FILL THE SYRINGE

Make sure you use the correct syringe.

PROZINC® (protamine zinc recombinant human insulin) must be

injected with a U-40 syringe. Use of other syringe sizes (e.g., U-100) may result in dosing errors.

PROZINC injections will become easy

for you and your cat or dog with just a little practice and these tips. 2

U-40 syringes are marked with numbers

U-40 syringes are marked with numbers indicating units of PROZINC.

Be sure to draw up the number of units prescribed by your veterinarian. Do not try to adjust your cat or dog's dosage without your veterinarian's supervision.

3

Gently roll the PROZINC vial between

your hands. This step mixes the insulin and also warms it so the injection will be more comfortable for your cat or dog.

NOTE: It is important that you roll the vial and not shake it. Shaking the vial may reduce the effectiveness of the insulin.



4

Before inserting the needle into the vial,

remove the cap from the plunger and needle and pull back the plunger to the prescribed dose of PROZINC® (protamine zinc recombinant human insulin).



Insert the needle into the top of the PROZINC vial and push the plunger all the way in to inject air into the vial.

NOTE: Injecting air into the vial reduces pressure and eases removal of insulin from the vial.





Now turn the vial upside down with the needle still

inserted. Make sure the tip of the needle is submerged in the insulin. Pull the plunger back a few units past the prescribed dose.



Keep the needle inserted in the vial.

NOTE: Drawing up this extra insulin now will help reduce air bubbles and make it easier to give the right dose. See the next steps.

7

Look for large air bubbles in the syringe. If you see any, gently tap the side of the syringe with your finger

to release them.



8

Now gently push the plunger back in to the prescribed dose (the number of units prescribed by your veterinarian). Take your thumb off the plunger and withdraw the needle from the vial.



9

After removing the needle from the vial,

check the syringe to make sure you have the correct amount of insulin ready.

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 a local or systemic allergic reaction in sensitized individuals.

ProZinc[®] (protamine zinc recombinant human insulin)

ADMINISTERING THE INJECTION TO YOUR CAT

Place your cat on a stable surface. Make sure to choose a distraction-free place your cat is familiar with.

2

Gently pull up a fold of skin **1 inch from the middle of the neck/back**, close to the shoulder blades or hip bones. This will ensure several places to rotate when giving twice daily administrations.

3

Quickly insert the needle into the fold of skin close to the body. The insulin needle is very thin and sharp. It won't hurt your cat, especially if you insert it quickly.



4

Pull the plunger back slightly to ensure no blood enters the syringe. If you see any blood in the syringe, discard it and start over with a new syringe. Gently push the plunger all the way in, pull out the needle, and reward your cat with petting.

6

Dispose of the syringe and needle in a sharps container. (Ask your veterinarian if a PROZINC® (protamine zinc recombinant human insulin) pet owner kit with sharps container is available.)

NOTE: If you don't have a sharps container, ask your veterinarian for alternative options. It's important to observe local regulations governing disposal of used syringes and needles. Visit **SafeNeedleDisposal.org** for more information.

7

Store PROZINC in the refrigerator.

PROZINC should be stored at a temperature between $36^{\circ}F$ and $46^{\circ}F$ ($2^{\circ} - 8^{\circ}C$).

IMPORTANT SAFETY INFORMATION: PROZINC is for use in dogs and cats only. Keep out of the reach of children. Owners should be advised to observe for signs of hypoglycemia (low blood sugar). 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 animal does not receive prompt treatment. PROZINC should not be used during episodes of hypoglycemia (low blood sugar). 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. The safety and effectiveness of PROZINC in puppies, kittens, or breeding, pregnant, and lactating animals has not been evaluated.



ADMINISTERING THE INJECTION TO YOUR DOG

Place your dog on a stable surface. Make sure to choose a distraction-free place your dog is familiar with.

2

Gently pull up a fold of skin **1 inch from the middle of the neck/back**, close to the shoulder blades or hip bones. This will ensure several places to rotate when giving twice daily administrations.

3

Quickly insert the needle into the fold of skin close to the body. The insulin needle is very thin and sharp. It won't hurt your dog, especially if you insert it quickly.



4

Pull the plunger back slightly to ensure no blood enters the syringe. If you see any blood in the syringe, discard it and start over with a new syringe. Gently push the plunger all the way in, pull out the needle, and reward your dog with petting.

6

Dispose of the syringe and needle in a sharps container. (Ask your veterinarian if a PROZINC® (protamine zinc recombinant human insulin) pet owner kit with sharps container is available.)

NOTE: If you don't have a sharps container, ask your veterinarian for alternative options. It's important to observe local regulations governing disposal of used syringes and needles. Visit **SafeNeedleDisposal.org** for more information.

7

Store PROZINC in the refrigerator.

PROZINC should be stored at a temperature between 36°F and 46°F (2° - 8°C).

IMPORTANT SAFETY INFORMATION: PROZINC is for use in dogs and cats only. Keep out of the reach of children. Owners should be advised to observe for signs of hypoglycemia (low blood sugar). 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 animal does not receive prompt treatment. PROZINC should not be used during episodes of hypoglycemia (low blood sugar). 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. The safety and effectiveness of PROZINC in puppies, kittens, or breeding, pregnant, and lactating animals has not been evaluated.

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 hydroxi	de.

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 reevaluate 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 nadirs 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, insulininduced hyperglycemia (Somogyi Effect), and local or systemic reactions. The most common adverse reaction observed is hypoglycemia. Signs may include: weakness, depression, behavioral changes, muscle witching, 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 $342.0 \ \mu mol/L$ 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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Revised 08/2019

449986-01



Client Information Sheet for Cats

ProZinc[®] (protamine zinc recombinant human insulin)

40 IU/mL

This summary contains important information about PROZINC. You should read this information before you start giving your cat PROZINC and review it each time the prescription is refilled. This sheet is provided only as a summary and does not take the place of instructions from your veterinarian. Talk to your veterinarian if you do not understand any of this information or if you want to know more about PROZINC.

What is PROZINC?

PROZINC is an aqueous protamine zinc suspension of recombinant human insulin that is used to reduce high blood sugar (hyperglycemia) in cats with diabetes mellitus. A veterinarian must prescribe PROZINC for your cat. **PROZINC should be given to cats only.** Keep out of reach of children. Seek medical attention immediately if you accidentally inject yourself with PROZINC.

What is diabetes mellitus?

Diabetes mellitus occurs when a cat has insufficient levels of, or an abnormal response to, insulin. The low insulin levels may result in high blood sugar (hyperglycemia) that could produce the following changes in your cat:

- Increased thirst
 Increased appetite
- High levels of sugar (glucose) in the urine (glucosuria)
- · Weight loss

- Increased urination
 - · Weakness in the back legs

What kind of results can I expect when my cat is on PROZINC for diabetes mellitus?

Although PROZINC is not a cure for diabetes mellitus, it can help reduce the levels of sugar (glucose) in the blood, which can help alleviate the clinical signs.

What should I discuss with my veterinarian before giving PROZINC?

Talk to your veterinarian about:

- · The signs of diabetes mellitus you have observed in your cat (for example, increased thirst and urination).
- The importance of proper PROZINC storage, handling, and administration techniques (for example, how
 to gently roll the vial prior to each use, the proper appearance of product after gently rolling, how to fill the
 U-40 syringe with the proper amount of insulin, and where and how to inject the insulin).
- · The importance of maintaining your cat under the same conditions for diet, exercise, environment, etc.
- The importance of follow-up visits for testing to determine if dose adjustments of PROZINC are necessary.
 Tell your veterinarian about:
- · Any side effects your cat has had when receiving other insulin products.
- · Any medical problems or allergies that your cat has now or has had in the past.
- All medications that you are giving your cat or plan to give your cat, including those you can get without a prescription.
- · If your cat is pregnant, nursing, or if you plan to breed your cat.

What are the possible side effects that may occur in my cat during PROZINC therapy?

PROZINC, like other drugs, may cause side effects. Serious side effects can occur with or without warning. Please contact your veterinarian immediately if you think your cat has a medical problem or side effect from PROZINC therapy. The most common insulin-related side effect is low blood sugar (hypoglycemia). Signs of low blood sugar (hypoglycemia) can occur suddenly and may include:

- Weakness
 Staggering gait
 Muscle twitching
 Coma
- Depression, lethargy, sluggishness
 Behavioral changes
 Seizures, convulsions
 Death

What actions do I take if my cat shows signs of low blood sugar (hypoglycemia)?

- If your cat is unconscious or having a seizure, this is a medical emergency. Take your cat to the veterinarian immediately.
- If your cat is conscious, rub approximately 1 tablespoon of corn syrup or honey on your
 cat's gums. When it is able to swallow, give corn syrup or honey by mouth until your cat is
 alert enough to eat. Feed the usual meal and contact your veterinarian.

When should my cat not be given PROZINC?

Do not give your cat its prescribed dose of PROZINC if it:

- Is experiencing an episode of low blood sugar (hypoglycemia). Common causes for low blood sugar include excessive doses of insulin, failure to eat, strenuous exercise, changes in the body's need for insulin, diabetes-inducing disease or drug effects.
- · Is not eating or is vomiting.
- Is sensitive to protamine zinc recombinant human insulin or any other ingredients in PROZINC.
- Do not give your cat its prescribed dose of PROZINC if you see clumps or visible white
 particles in the vial after gently rolling.

How should I give PROZINC to my cat?

PROZINC should be given with or right after a meal.

Give PROZINC with U-40 syringes only. Use of a syringe other than a U-40 syringe will result in incorrect dosing. Gently roll the vial until the PROZINC has a uniformly cloudy, white appearance. If there are clumps or visible white particles in the vial after gently rolling, do not use the PROZINC and call your veterinarian. PROZINC should be given according to your veterinarian's instructions. Your veterinarian will tell you what amount of PROZINC is right for your cat and instruct you on techniques for administration.

Can PROZINC be given with other medications?

PROZINC can be given with other medications, but the dose may need to be adjusted due to the medication resulting in either increased or decreased insulin requirements. Tell your veterinarian about all medications you have given your cat in the past, and any medications that you are planning to give with PROZINC. This should include medications that you can get for your cat without a prescription. Your veterinarian may want to ensure that all of your cat's medications can be given together.

What should I do if I inject more than the prescribed amount of PROZINC?

Contact your veterinarian immediately and, if your veterinarian is not available, seek other veterinary advice at once.

What should I do if my cat receives less than the prescribed dose, or I miss an injection?

- · Contact your veterinarian as soon as possible for advice on your cat's next dose.
- If you cannot reach your veterinarian and your cat is eating and acting normally, give your cat the usual dose at the next regularly scheduled injection time.

How should I store PROZINC?

PROZINC should be stored 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.

What else should I know about PROZINC?

This sheet provides a summary of information about PROZINC. If you have any questions or concerns about the product or diabetes mellitus, talk to your veterinarian.

As with all prescribed medications, PROZINC should only be given to the cat for which it is prescribed and for the condition for which it was prescribed.

It is important to periodically discuss your cat's response to PROZINC at regular checkups that may include blood glucose monitoring. Your veterinarian will best determine if your cat is responding as expected and should continue receiving PROZINC.

Approved by FDA under NADA # 141-297

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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:

CITIL 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
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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 \leq 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/Ib (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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Revised 08/2019

449986-01

Client Information Sheet for Dogs

ProZinc[®] (protamine zinc recombinant human insulin)

40 IU/mL

This summary contains important information about PROZINC. You should read this information before you start giving your dog PROZINC and review it each time the prescription is refilled. This sheet is provided only as a summary and does not take the place of instructions from your veterinarian. Talk to your veterinarian if you do not understand any of this information or if you want to know more about PROZINC.

What is PROZINC?

PROZINC is an aqueous protamine zinc suspension of recombinant human insulin that is used to reduce high blood sugar (hyperglycemia) in dogs with diabetes mellitus. A veterinarian must prescribe PROZINC for your dog. PROZINC should be given only to the dog for which it is prescribed. Keep out of reach of children. Seek medical attention immediately if you accidentally inject yourself with PROZINC.

What is diabetes mellitus?

Diabetes mellitus occurs when a dog has insufficient levels of, or an abnormal response to, insulin. The low insulin levels may result in high blood sugar (hyperglycemia) that could produce the following changes in your dog:

- · Increased thirst · Increased urination
- · Increased appetite
 - Weight loss
- High levels of sugar (glucose) in the urine (glucosuria)

What kind of results can I expect when my dog is on PROZINC for diabetes mellitus?

Although PROZINC is not a cure for diabetes mellitus, it can help reduce the levels of sugar (glucose) in the blood, which can help alleviate the clinical signs.

What should I discuss with my veterinarian before giving PROZINC?

Talk to your veterinarian about:

- · The signs of diabetes mellitus you have observed in your dog (for example, increased thirst and urination).
- · The importance of proper PROZINC storage, handling, and administration techniques (for example, how to gently roll the vial prior to each use, the proper appearance of product after gently rolling, how to fill the U-40 syringe with the proper amount of insulin, and where and how to inject the insulin).
- · The importance of maintaining your dog under the same conditions for diet, exercise, environment, etc.
- · The importance of follow-up visits for testing to determine if dose adjustments of PROZINC are necessary. Tell your veterinarian about:
- · Any side effects your dog has had when receiving other insulin products.
- · Any medical problems or allergies that your dog has now or has had in the past.
- · All medications that you are giving your dog or plan to give your dog, including those you can get without a prescription.
- · If your dog is pregnant, nursing, or if you plan to breed your dog.

What are the possible side effects that may occur in my dog during PROZINC therapy?

PROZINC, like other drugs, may cause side effects. Serious side effects can occur with or without warning. Please contact your veterinarian immediately if you think your dog has a medical problem or side effect from PROZINC therapy. The most common insulin-related side effect is low blood sugar (hypoglycemia).

Signs of low blood sugar (hypoglycemia) can occur suddenly and may include:

- Weakness Staggering gait Muscle twitching Coma
- · Depression, lethargy, sluggishness · Behavioral changes Seizures convulsions
 · Death
- What actions do I take if my dog shows signs of low blood sugar (hypoglycemia)?
- · If your dog is unconscious or having a seizure, this is a medical emergency. Take your dog to the veterinarian immediately.
- · If your dog is conscious, rub approximately 1 tablespoon of corn syrup or honey on your dog's gums. When it can swallow, give corn syrup or honey by mouth until your dog is alert enough to eat. Feed the usual meal and contact your veterinarian.

When should my dog not be given PROZINC?

Do not give your dog its prescribed dose of PROZINC if it:

- · Is experiencing an episode of low blood sugar (hypoglycemia). Common causes for low blood sugar include excessive doses of insulin, failure to eat, strenuous exercise, changes in the body's need for insulin, diabetes-inducing disease or drug effects.
- · Is not eating or is vomiting.
- · Is sensitive to protamine zinc recombinant human insulin or any other ingredients in PROZINC.
- · Do not give your dog its prescribed dose of PROZINC if you see clumps or visible white particles in the vial after gently rolling.

How should I give PROZINC to my dog?

PROZINC should be given with or right after a meal.

Give PROZINC with U-40 syringes only. Use of a syringe other than a U-40 syringe will result in incorrect dosing. Gently roll the vial until the PROZINC has a uniformly cloudy, white appearance. If there are clumps or visible white particles in the vial after gently rolling, do not use the PROZINC and call your veterinarian. PROZINC should be given according to your veterinarian's instructions. Your veterinarian will tell you what amount of PROZINC is right for your dog and instruct you on techniques for administration

Can PROZINC be given with other medications?

PROZINC can be given with other medications, but the dose may need to be adjusted due to the medication resulting in either increased or decreased insulin requirements. Tell your veterinarian about all medications you have given your dog in the past, and any medications that you are planning to give with PROZINC. This should include medications that you can get for your dog without a prescription. Your veterinarian may want to ensure that all your dog's medications can be given together.

What should I do if I inject more than the prescribed amount of PROZINC?

Contact your veterinarian immediately and, if your veterinarian is not available, seek other veterinary advice at once

What should I do if my dog receives less than the prescribed dose, or I miss an injection?

- · Contact your veterinarian as soon as possible for advice on your dog's next dose.
- · If you cannot reach your veterinarian and your dog is eating and acting normally, give your dog the usual dose at the next regularly scheduled injection time.

How should I store PROZINC?

PROZINC should be stored 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.

What else should I know about PROZINC?

This sheet provides a summary of information about PROZINC. If you have any questions or concerns about the product or diabetes mellitus, talk to your veterinarian. As with all prescribed medications, PROZINC should only be given to the dog for which it is prescribed and for the condition for which it was prescribed.

It is important to periodically discuss your dog's response to PROZINC at regular checkups that may include blood glucose monitoring. Your veterinarian will best determine if your dog is responding as expected and should continue receiving PROZINC.

Approved by FDA under NADA # 141-297

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No other information replaces the advice of your veterinarian. Please don't ever hesitate to contact your veterinary professional with questions about your cat or dog's diabetes or administering a PROZINC injection.





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prozinc[®] (protamine zinc recombinant human insulin)

NO NEED TO STRESS

INFORMATION AND TIPS TO HELP YOU MANAGE YOUR DOG'S DIABETES.

Your Dog Has Been Diagnosed WITH DIABETES



WHAT IS DIABETES?

Canine diabetes mellitus occurs when a dog's body doesn't produce enough insulin (or, less commonly, does not respond to the insulin it produces). This is often due to damage to the cells in the pancreas, the organ that produces insulin.

The underlying cause for canine diabetes is unknown. Dogs with diseases such as obesity and pancreatitis, however, are at increased risk. Additionally, some breeds are at a higher risk for developing diabetes, even if they are otherwise healthy.¹²

WHY IS INSULIN IMPORTANT?

Insulin works as the "key" that lets your dog's cells utilize glucose for energy. When diabetes disrupts this normal process, it results in a shortage of glucose within the cells and an excess of glucose in the bloodstream. It is this imbalance of glucose that contributes to the signs we see in diabetic dogs.

SOME SIGNS OF CANINE DIABETES ARE



Increased Thirst – drinking more water than usual



Urinating more than usual

Increased Appetite – eating more food than usual



Weight Loss, even with increased food intake



Lethargy and weakness

YOU'RE NOT ALONE.

If your dog was just diagnosed with diabetes or if your dog's diabetes has been difficult to control, providing the right care may seem overwhelming or frustrating. If you feel this way, you are not alone. In fact, more than 165,000 dogs in the US are diagnosed with diabetes, and this can be a challenging time for many of their owners.^{3,4}

THE GOOD NEWS IS THAT DIABETES IS MANAGEABLE.

With the right care and treatment, your diabetic dog can get back on track! Read on to learn what you should do to help.

Managing Your Dog's **DIABETES**

ProZinc[®] (protamine zinc recombinant human insulin)

TRY TO KEEP A REGULAR SCHEDULE FOR YOUR DOG, ESPECIALLY WHEN IT COMES TO THESE ACTIVITIES:



What your dog eats is very important. Discuss your dog's diet with your veterinarian to determine what kind of food is best for your dog. When your dog eats is also important, so be sure to keep your dog's feedings as close to the same time each day as you can. Meal time(s) should coincide with administration of insulin to enhance the effects of the insulin and reduce the chances of glucose spikes in the blood (hyperglycemia).



EXERCISE AND PLAY

Exercise can make a difference in maintaining healthy blood glucose levels. Like feeding, exercise should happen **consistently**, every day. Check with your veterinarian for what kinds of activity may be appropriate for your dog.

ROUTINE TIP

Maintaining routines may require the cooperation of others in your household. Get them involved and share the responsibility of providing the care that your dog needs. For a dog with diabetes, keeping a consistent routine goes a long way in helping their body maintain steady glucose levels.

VETERINARY VISITS

Be sure to discuss your dog's diabetes during **regular** veterinary appointments, which may include blood glucose monitoring. This will help your veterinarian determine whether your dog is responding as expected or if an adjustment in the insulin regimen is needed



INSULIN THERAPY

Lifestyle changes such as an exercise plan, a special diet, and regular visits to the veterinarian can help. However, most dogs with diabetes will also need **insulin** injections.

While healthy dogs have appropriate insulin production and respond properly to that insulin, diabetic dogs usually need to have their insulin supplemented through insulin injections.

Proper care is critical to keeping your diabetic dog healthy.

Your Veterinarian Prescribed **PROZINC**[®]

ProZinc[®] (protamine zinc recombinant human insulin)

PROZINC[®] (protamine zinc recombinant human insulin) is approved by the FDA specifically for veterinary use and will help you care for your dog easily and effectively.

HOW DOES PROZINC WORK?

PROZINC is designed for dogs with diabetes just like yours. Following injection, PROZINC safely and effectively maintains your dog's blood glucose levels throughout the day.

As with all prescribed medications, PROZINC should be given to only the dog for whom it was prescribed and only at the recommended dosage and frequency. If you have any questions or concerns about the product or about diabetes mellitus, talk to your veterinarian.

GIVING YOUR DOG PROZINC.



Give injections of PROZINC just before your dog eats a meal or immediately following.



Give the injections at the same time every day to help your dog's blood glucose levels stay as stable as possible



Keep a consistent feeding schedule to make it easier to ensure injections happen at the right time

Be sure to give your dog the number of units prescribed by your veterinarian. Do not try to adjust your dog's dosage without your veterinarian's supervision.

PROZINC® is extensively studied.

PROZINC was proven safe and effective in the largest canine diabetes study to date, so you can feel confident giving PROZINC to your dog to help manage diabetes.³



WARNING – 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 a local or systemic allergic reaction in sensitized individuals.

What To Expect With **PROZINC**[®]

ProZinc[®] (protamine zinc recombinant human insulin)

With patience and diligent use, PROZINC[®] (protamine zinc recombinant human insulin) can help bring your dog's clinical signs of diabetes and high blood glucose levels under control so your dog can live a happy and virtually normal life.

REGULATING YOUR DOG'S BLOOD GLUCOSE

It may take a month or longer to regulate your dog's blood glucose. But once it is regulated, you will notice an improvement in the signs of diabetes (excessive thirst, urination, and increased appetite). When these signs decrease or disappear, you'll know your dog's blood glucose levels are stabilizing and your dog is likely to feel better.

Even if the signs of diabetes are gone, it is important to have routine checkups so your veterinarian can assess your dog's response to insulin therapy, as well as check your dog for other health issues.

IMPORTANT SAFETY INFORMATION: PROZINC is for use in dogs and cats only. Keep out of the reach of children. 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 located at the end of brochure.

AFTER STARTING TREATMENT WITH PROZINC[®] IN CLINICAL TRIALS⁵:

In a study, 276 diabetic dogs received PROZINC and were re-evaluated after 84 days to determine treatment success based on improvements in drinking, urination, body weight, and blood sugar parameters.



What Is **HYPOGLYCEMIA?**



Hypoglycemia (low blood glucose) is a dangerous and potentially life-threatening condition that can occur if your dog has had too much insulin, too little food, or much more exercise than usual.

WAYS TO HELP YOUR DOG AVOID HYPOGLYCEMIA.

First, make sure to give your dog the correct dose of PROZINC® on a consistent schedule. Your veterinarian will show you how to properly administer PROZINC to your dog.

- Maintain a regular feeding schedule
- Provide the exact amount of food recommended by your veterinarian
- Do not give your dog any prescription or over-the-counter medications without your veterinarian's supervision—this includes vitamins and supplements

Even after your dog's glucose levels are stabilized from using PROZINC,

REGULAR VISITS TO YOUR VETERINARIAN ARE IMPORTANT

to monitor disease progress and to make dosing adjustments as necessary.

Hypoglycemia requires your immediate attention and can be fatal for your dog without prompt treatment, so it's important to recognize the signs:

- Weakness
- DepressionStaggering or

walking strangely

- Unusual behavior
 Muscle twitching

 - Seizure
 - Coma

What to do in an emergency. IF YOU SUSPECT YOUR DOG HAS LOW BLOOD GLUCOSE, FOLLOW THESE STEPS:

- *If your dog isn't conscious*, rub a tablespoon of corn syrup or honey on your dog's gums, and contact your veterinarian immediately.
- 2 *If your dog remains unconscious or is having a seizure*, take your dog to the veterinarian immediately.
- **If your dog is conscious**, or when your dog regains consciousness and is able to swallow, hand-feed corn syrup or honey until your dog is alert enough to eat normal food.

As soon as your dog is alert enough to eat, feed the next scheduled meal instead of waiting for mealtime, and call your veterinarian for advice. Remember that hypoglycemia is a dangerous condition that can't wait. It is a medical emergency that requires you to take immediate action.

ALWAYS KEEP CORN SYRUP OR HONEY ON HAND.

If your dog experiences a hypoglycemic episode, there may not be time to go out and buy it.

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.

Fach mL contains:

Each me contains.	
recombinant human insulin 4	0 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
nH is adjusted with hydrochloric acid and/or sodiun	n 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 and 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: "wice 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 doeing is initiated the two doese should a cach be appreciated by 25% loss. 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 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 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	Time To	Duration Of
	Action	Nadir	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	5 to >24	16 to >24
	hours	hours	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 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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Revised 08/2019

449986-01



Client Information Sheet for Dogs ProZinc[®]

(protamine zinc recombinant human insulin)

40 IU/ml

This summary contains important information about PROZINC. You should read this information before you start giving your dog PROZINC and review it each time the prescription is refilled. This sheet is provided only as a summary and does not take the place of instructions from your veterinarian. Talk to your veterinarian if you do not understand any of this information or if you want to know more about PROZINC.

What is PROZINC?

PROZINC is an aqueous protamine zinc suspension of recombinant human insulin that is used to reduce high blood sugar (hyperglycemia) in dogs with diabetes mellitus. A veterinarian must prescribe PROZINC for your dog. **PROZINC should be given only to the dog for which it is** prescribed. Keep out of reach of children. Seek medical attention immediately if you accidentally inject yourself with PROZINC.

What is diabetes mellitus?

Increased urination

Diabetes mellitus occurs when a dog has insufficient levels of, or an abnormal response to, insulin. The low insulin levels may result in high blood sugar (hyperglycemia) that could produce the following changes in your dog:

- · Increased thirst · Increased appetite
 - · High levels of sugar (glucose) in the urine (glucosuria)

Weight loss What kind of results can I expect when my dog is on PROZINC for diabetes mellitus?

Although PROZINC is not a cure for diabetes mellitus, it can help reduce the levels of sugar (glucose) in the blood, which can help alleviate the clinical signs.

What should I discuss with my veterinarian before giving PROZINC?

Talk to your veterinarian about:

- · The signs of diabetes mellitus you have observed in your dog (for example, increased thirst and urination).
- · The importance of proper PROZINC storage, handling, and administration techniques (for example, how to gently roll the vial prior to each use, the proper appearance of product after gently rolling, how to fill the U-40 syringe with the proper amount of insulin, and where and how to inject the insulin).
- · The importance of maintaining your dog under the same conditions for diet, exercise, environment, etc.
- · The importance of follow-up visits for testing to determine if dose adjustments of PROZINC are necessary.

Tell your veterinarian about:

- · Any side effects your dog has had when receiving other insulin products.
- · Any medical problems or allergies that your dog has now or has had in the past.
- · All medications that you are giving your dog or plan to give your dog, including those you can get without a prescription.
- If your dog is pregnant, nursing, or if you plan to breed your dog.

What are the possible side effects that may occur in my dog during PROZINC therapy?

PROZINC, like other drugs, may cause side effects. Serious side effects can occur with or without warning. Please contact your veterinarian immediately if you think your dog has a medical problem or side effect from PROZINC therapy. The most common insulin-related side effect is low blood sugar (hypoglycemia).

Signs of low blood sugar (hypoglycemia) can occur suddenly and may include:

- Weakness
- · Behavioral changes Coma · Depression, lethargy, sluggishness Seizures, convulsions
 - Death · Muscle twitching
- Staggering gait

What actions do I take if my dog shows signs of low blood sugar (hypoglycemia)?

- · If your dog is unconscious or having a seizure, this is a medical emergency. Take your dog to the veterinarian immediately.
- · If your dog is conscious, rub approximately 1 tablespoon of corn syrup or honey on your dog's gums. When it can swallow, give corn syrup or honey by mouth until your dog is alert enough to eat. Feed the usual meal and contact your veterinarian.

When should my dog not be given PROZINC?

Do not give your dog its prescribed dose of PROZINC if it:

- · Is experiencing an episode of low blood sugar (hypoglycemia). Common causes for low blood sugar include excessive doses of insulin, failure to eat, strenuous exercise, changes in the body's need for insulin, diabetes-inducing disease or drug effects.
- · Is not eating or is vomiting.
- Is sensitive to protamine zinc recombinant human insulin or any other ingredients in PROZINC.
- · Do not give your dog its prescribed dose of PROZINC if you see clumps or visible white particles in the vial after gently rolling.

How should I give PROZINC to my dog?

PROZINC should be given with or right after a meal.

Give PROZINC with U-40 syringes only. Use of a syringe other than a U-40 syringe will result in incorrect dosing. Gently roll the vial until the PROZINC has a uniformly cloudy, white appearance. If there are clumps or visible white particles in the vial after gently rolling, do not use the PROZINC and call your veterinarian. PROZINC should be given according to your veterinarian's instructions. Your veterinarian will tell you what amount of PROZINC is right for your dog and instruct you on techniques for administration.

Can PROZINC be given with other medications?

PROZINC can be given with other medications, but the dose may need to be adjusted due to the medication resulting in either increased or decreased insulin requirements. Tell your veterinarian about all medications you have given your dog in the past, and any medications that you are planning to give with PROZINC. This should include medications that you can get for your dog without a prescription. Your veterinarian may want to ensure that all your dog's medications can be given together.

What should I do if I inject more than the prescribed amount of PROZINC?

Contact your veterinarian immediately and, if your veterinarian is not available, seek other veterinary advice at once.

What should I do if my dog receives less than the prescribed dose, or I miss an injection?

· Contact your veterinarian as soon as possible for advice on your dog's next dose.

· If you cannot reach your veterinarian and your dog is eating and acting normally, give your dog the usual dose at the next regularly scheduled injection time.

How should I store PROZINC?

PROZINC should be stored 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.

What else should I know about PROZINC?

This sheet provides a summary of information about PROZINC. If you have any questions or concerns about the product or diabetes mellitus, talk to your veterinarian. As with all prescribed medications, PROZINC should only be given to the dog for which it is prescribed and for the condition for which it was prescribed.

It is important to periodically discuss your dog's response to PROZINC at regular checkups that may include blood glucose monitoring. Your veterinarian will best determine if your dog is responding as expected and should continue receiving PROZINC.

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IF YOU HAVE QUESTIONS REGARDING PROZINC® PLEASE CALL BOEHRINGER INGELHEIM TECHNICAL SUPPORT AT **1-888-637-4251**

No other information replaces the advice of your veterinarian. Please don't ever hesitate to contact your veterinary professional with questions about your pet's diabetes or administering a PROZINC injection.



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YOU CAN DO THIS.

INFORMATION AND TIPS TO HELP YOU MANAGE YOUR CAT'S DIABETES.

Your Cat Has Been Diagnosed WITH DIABETES



WHAT IS DIABETES?

Feline diabetes mellitus occurs when a cat's body doesn't produce enough insulin or doesn't respond effectively to insulin.

WHY IS INSULIN IMPORTANT?

Insulin works as the "key" that lets your cat's cells utilize glucose for energy. When diabetes disrupts this normal process, it results in a shortage of glucose within the cells and an excess of glucose in the bloodstream. It is this imbalance of glucose that contributes to the signs we see in diabetic cats.

YOU'RE NOT ALONE.

If your cat was just diagnosed with diabetes or if your cat's diabetes has been difficult to control, providing the right care may seem overwhelming or frustrating. If you feel this way, you are not alone. As many as half a million cats in the US are diagnosed with diabetes, and this can be a challenging time for many of their owners.¹²

THE GOOD NEWS IS THAT DIABETES IS MANAGEABLE.

SOME SIGNS OF FELINE DIABETES ARE:



Increased Thirst – drinking more water than usual



Urinating More Than Usual

(if you use clumping litter, you may notice more clumps or larger clumps than you would normally see in the litter box)



Increased Appetite – eating more food than usual



Weight Loss, even with increased food intake

With the right care and treatment, your diabetic cat can get back on track! Read on to learn what you should do to help.

Managing Your Cat's **DIABETES**

ProZinc[®] (protamine zinc recombinant human insulin)

TRY TO KEEP A REGULAR SCHEDULE FOR YOUR CAT, ESPECIALLY WHEN IT COMES TO THESE ACTIVITIES:



What your cat eats is very important. Discuss your cat's diet with your veterinarian to determine what kind of food is best for your cat. When your cat eats is also important, so be sure to keep your cat's feedings as close to the same time each day as you can.



ACTIVITY AND PLAY

For a cat with diabetes, exercise can make a difference in maintaining a healthy blood glucose level. Like feeding, activity should happen **consistently**, every day.

ROUTINE TIP

Establishing and maintaining new routines may require the cooperation of others in your household. Get them involved and share the responsibility of providing the care that your cat needs. For a cat with diabetes, keeping a consistent routine goes a long way in helping your cat's body maintain steady glucose levels.

VETERINARY VISITS

Be sure to discuss your cat's diabetes during **regular** veterinary appointments, which may include blood glucose monitoring. This will help your veterinarian determine whether your cat is responding as expected or if an adjustment in the insulin regimen is needed.



INSULIN THERAPY

For cats with diabetes, lifestyle changes such as an activity plan, a special diet, and regular visits to the vet can help. However, most cats with diabetes will also need **insulin** injections.

While healthy cats have appropriate insulin production to meet their requirements, diabetic cats usually need to have their insulin supplemented through injections.

Proper care is critical to keeping your diabetic cat healthy.

Your Veterinarian Prescribed **PROZINC**[®]

ProZinc[®] (protamine zinc recombinant human insulin)

PROZINC® (protamine zinc recombinant human insulin) is approved by the FDA specifically for use in cats and will help you care for your cat easily and effectively.

HOW DOES PROZINC WORK?

PROZINC is designed just for diabetic cats like yours. Most cats have a fast metabolism, which means their bodies break down food and other substances very quickly. PROZINC is a twice-a-day insulin for cats, and releases insulin over a 12-hour period to help maintain your cat's blood glucose levels throughout the day.

As with all prescribed medications, PROZINC should only be given to the cat for whom it was prescribed and at the dosage and frequency for which it was prescribed. If you have any questions or concerns about the product or about diabetes mellitus, talk to your veterinarian.

GIVING YOUR CAT PROZINC.



Injections of PROZINC should be given before your cat eats a meal or just afterward.



Give the injections at the same time every day, approximately 12 hours apart, to help regulate your cat's blood glucose levels.



Keeping a consistent feeding schedule makes it easier to ensure injections happen at the right time.

Be sure to give your cat the number of units prescribed by your veterinarian. Do not try to adjust your cat's dosage without your veterinarian's supervision.

PROZINC® is extensively studied.

PROZINC was proven safe and effective in the largest feline diabetes clinical trial to date, so you can feel confident giving PROZINC to your cat to help manage diabetes.³



WARNING – 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 a local or systemic allergic reaction in sensitized individuals.

What To Expect With **PROZINC**[®]

(protamine zinc recombinant human insulin)

With patience and diligent care, PROZINC® (protamine zinc recombinant human insulin) can help bring your cat's clinical signs of diabetes and blood glucose under control so your cat can live a happy and virtually normal life.

REGULATING YOUR CAT'S BLOOD GLUCOSE

It may take a month or longer to regulate your cat's blood glucose. But once it is regulated, you will notice an improvement in the signs of diabetes (increased thirst, urination, and appetite). When these signs decrease or disappear, you'll know your cat's blood glucose is stabilizing and your cat is likely to feel better.

Even if the signs of diabetes are gone, it is important to have routine checkups so your veterinarian can assess your cat's response to insulin therapy.

IMPORTANT SAFETY INFORMATION: PROZINC is for use in dogs and cats only. Keep out of the reach of children. 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, diarrhea, and ataxia. Many of the adverse reactions, such as lethargy, seizures, and ataxia, are associated with hypoglycemia. Glucocorticoid and progestogen use should be avoided.

The safety and effectiveness of PROZINC in 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 located at the end of brochure.

IN A CLINICAL FIELD TRIAL, MOST CATS TREATED WITH PROZINC[®] SHOWED IMPROVEMENT WITHIN 45 DAYS³:





In fact, ABOUT HALF of the cats in the studies showed IMPROVEMENT IN JUST 7 DAYS^{3,4}

REMISSION

While there is no actual cure, it is possible for your cat's diabetes to go into remission. This happens when the concentration of glucose in your cat's blood stays at a normal level for at least 4 weeks without insulin treatment.⁵ It is important to remember that even if your cat's diabetes is in remission, and your cat has been taken off PROZINC, your cat is still considered "diabetic" and should continue to be monitored closely.

What Is **HYPOGLYCEMIA?**



Hypoglycemia (low blood glucose) is a dangerous and potentially life-threatening condition that can occur if your cat has too much insulin, too little food, or much more activity than usual.

WAYS TO HELP YOUR CAT AVOID HYPOGLYCEMIA.

First, make sure to give your cat the correct dose of PROZINC[®] (protamine zinc recombinant human insulin) on a consistent schedule.

- Maintain a regular feeding schedule
- Provide the exact amount of food recommended by your veterinarian
- Do not give your cat any prescription or over-the-counter medications without your veterinarian's supervision—this includes vitamins and supplements

Even after your cat's glucose levels are stabilized on PROZINC,

REGULAR VISITS TO YOUR VETERINARIAN ARE IMPORTANT

to monitor disease progress and to make dosing adjustments as necessary.

Hypoglycemia requires your immediate attention and can be fatal for your cat without prompt treatment, so it's important to recognize the signs:

- Extreme lethargy
- Unusual behavior

- Depression
- Lack of Coordination
- Loss of Consciousness
- Muscle twitching
- Seizure
- Coma

What to do in an emergency.

IF YOU SUSPECT YOUR CAT HAS LOW BLOOD GLUCOSE, FOLLOW THESE STEPS:

- *If your cat isn't conscious*, rub a tablespoon of corn syrup or honey on your cat's gums, and contact your veterinarian immediately.
- 2 *If your cat remains unconscious or is having a seizure*, take your cat to the veterinarian immediately.
- **3** *If your cat is conscious*, or when your cat regains consciousness and is able to swallow, hand-feed corn syrup or honey until your cat is alert enough to eat normal food.
- As soon as your cat is alert enough to eat, feed the next scheduled meal instead of waiting for mealtime, and call your veterinarian for advice. Remember that hypoglycemia is a dangerous condition that can't wait. It is a medical emergency that requires you to take action immediately.

ALWAYS KEEP CORN SYRUP OR HONEY ON HAND.

When you need it, there may not be time to go out and buy it.

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, hep	tahydrate 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 hydrochlori	c acid and/or sodium hydroxide.

Indication: PROZINC (protamine zinc recombinant human insulin) is indicated for the reduction of hyperglycemia and hyperglycemiaassociated 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/AnimalVeterinary/SafetyHealth.

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 μ mol/L on Day 0 to 380.7 μ mol/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 $\mu mol/L$ 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.

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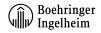
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Revised 02/2019

449986-00



Client Information Sheet for Cats

ProZinc[®] (protamine zinc recombinant human insulin)

40 IU/mL

This summary contains important information about PROZINC. You should read this information before you start giving your cat PROZINC and review it each time the prescription is refilled. This sheet is provided only as a summary and does not take the place of instructions from your veterinarian. Talk to your veterinarian if you do not understand any of this information or if you want to know more about PROZINC.

What is PROZINC?

PROZINC is an aqueous protamine zinc suspension of recombinant human insulin that is used to reduce high blood sugar (hyperglycemia) in cats with diabetes mellitus. A veterinarian must prescribe PROZINC for your cat. **PROZINC should be given to cats only.** Keep out of reach of children. Seek medical attention immediately if you accidentally inject yourself with PROZINC.

What is diabetes mellitus?

Diabetes mellitus occurs when a cat has insufficient levels of, or an abnormal response to, insulin. The low insulin levels may result in high blood sugar (hyperglycemia) that could produce the following changes in your cat:

- Increased thirst
- Increased appetite
- · High levels of sugar (glucose) in the urine (glucosuria)
- Increased urination
- Weight loss
- · Weakness in the back legs

What kind of results can I expect when my cat is on PROZINC for diabetes mellitus?

Although PROZINC is not a cure for diabetes mellitus, it can help reduce the levels of sugar (glucose) in the blood, which can help alleviate the clinical signs.

What should I discuss with my veterinarian before giving PROZINC?

Talk to your veterinarian about:

- The signs of diabetes mellitus you have observed in your cat (for example, increased thirst and urination).
- The importance of proper PROZINC storage, handling, and administration techniques (for example, how to gently roll the vial prior to each use, the proper appearance of product after gently rolling, how to fill the U-40 syringe with the proper amount of insulin, and where and how to inject the insulin).
- The importance of maintaining your cat under the same conditions for diet, exercise, environment, etc.
- The importance of follow-up visits for testing to determine if dose adjustments of PROZINC are necessary.

Tell your veterinarian about:

- Any side effects your cat has had when receiving other insulin products.
- Any medical problems or allergies that your cat has now or has had in the past.
- All medications that you are giving your cat or plan to give your cat, including those you can get without a prescription.
- If your cat is pregnant, nursing, or if you plan to breed your cat.

What are the possible side effects that may occur in my cat during PROZINC therapy?

PROZINC, like other drugs, may cause side effects. Serious side effects can occur with or without warning. Please contact your veterinarian immediately if you think your cat has a medical problem or side effect from PROZINC therapy. The most common insulin-related side effect is low blood sugar (hypoglycemia). Signs of low blood sugar (hypoglycemia) can occur suddenly and may include:

Weakness

Staggering gait

Muscle twitching

Seizures, convulsions

- Depression, lethargy, sluggishness
 Behavioral changes
 - Death

Coma

What actions do I take if my cat shows signs of low blood sugar (hypoglycemia)?

- If your cat is unconscious or having a seizure, this is a medical emergency. Take your cat to the veterinarian immediately.
- If your cat is conscious, rub approximately 1 tablespoon of corn syrup or honey on your cat's gums. When it is able to swallow, give corn syrup or honey by mouth until your cat is alert enough to eat. Feed the usual meal and contact your veterinarian.

When should my cat not be given PROZINC?

Do not give your cat its prescribed dose of PROZINC if it:

- Is experiencing an episode of low blood sugar (hypoglycemia).
 Common causes for low blood sugar include excessive doses of insulin, failure to eat, strenuous exercise, changes in the body's need for insulin, diabetes-inducing disease or drug effects.
- Is not eating or is vomiting.
- Is sensitive to protamine zinc recombinant human insulin or any other ingredients in PROZINC.
- Do not give your cat its prescribed dose of PROZINC if you see clumps or visible white particles in the vial after gently rolling.

How should I give PROZINC to my cat?

PROZINC should be given with or right after a meal.

Give PROZINC with U-40 syringes only. Use of a syringe other than a U-40 syringe will result in incorrect dosing. Gently roll the vial until the PROZINC has a uniformly cloudy, white appearance. If there are clumps or visible white particles in the vial after gently rolling, do not use the PROZINC and call your veterinarian. PROZINC should be given according to your veterinarian's instructions. Your veterinarian will tell you what amount of PROZINC is right for your cat and instruct you on techniques for administration.

Can PROZINC be given with other medications?

PROZINC can be given with other medications, but the dose may need to be adjusted due to the medication resulting in either increased or decreased insulin requirements. Tell your veterinarian about all medications you have given your cat in the past, and any medications that you are planning to give with PROZINC. This should include medications that you can get for your cat without a prescription. Your veterinarian may want to ensure that all of your cat's medications can be given together.

What should I do if I inject more than the prescribed amount of PROZINC?

Contact your veterinarian immediately and, if your veterinarian is not available, seek other veterinary advice at once.

What should I do if my cat receives less than the prescribed dose, or I miss an injection?

- Contact your veterinarian as soon as possible for advice on your cat's next dose.
- If you cannot reach your veterinarian and your cat is eating and acting normally, give your cat the usual dose at the next regularly scheduled injection time.

How should I store PROZINC?

PROZINC should be stored 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.

What else should I know about PROZINC?

This sheet provides a summary of information about PROZINC. If you have any questions or concerns about the product or diabetes mellitus, talk to your veterinarian.

As with all prescribed medications, PROZINC should only be given to the cat for which it is prescribed and for the condition for which it was prescribed.

It is important to periodically discuss your cat's response to PROZINC at regular checkups that may include blood glucose monitoring. Your veterinarian will best determine if your cat is responding as expected and should continue receiving PROZINC.

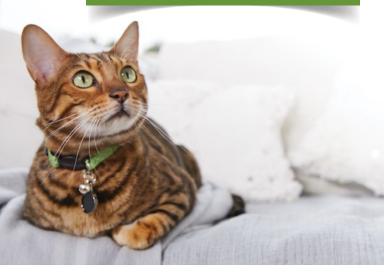
Approved by FDA under NADA # 141-297

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Revised 02/2019

IF YOU HAVE QUESTIONS REGARDING PROZINC® PLEASE CALL BOEHRINGER INGELHEIM TECHNICAL SUPPORT AT **1-888-637-4251**



No other information replaces the advice of your veterinarian. Please don't ever hesitate to contact your veterinary professional with questions about your cat's diabetes or administering a PROZINC injection.



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