



vetsulin[®]
(porcine insulin zinc suspension)



THE ONLY

veterinary insulin approved
FOR BOTH DOGS AND CATS.

For more than 20 years, veterinarians worldwide have relied on Vetsulin[®] for proven efficacy and unparalleled technical support.*





Vetsulin[®] (porcine insulin zinc suspension) is the ideal first choice for diabetic dogs.

AN IDENTICAL AMINO ACID MATCH TO CANINE INSULIN.

- ▶ Porcine insulin is preferred for dogs because it has the same amino acid sequence as canine insulin
 - Minimizes risk of anti-insulin antibodies in dogs
- ▶ Human insulin and canine insulin have a different amino acid sequence

WHY VETSULIN IS PREFERABLE TO HUMAN INSULIN FOR DOGS

	Vetsulin	NPH [†]
FDA approved for veterinary use	YES	NO
Matches canine insulin, minimizing risk of anti-insulin antibodies	YES	NO
More accurate dosing with 40 IU/mL	YES	NO
Dispensed by the veterinary clinic for quality control	YES	NO
Technical support from diabetes professionals	YES	NO
Client education tools	YES	NO



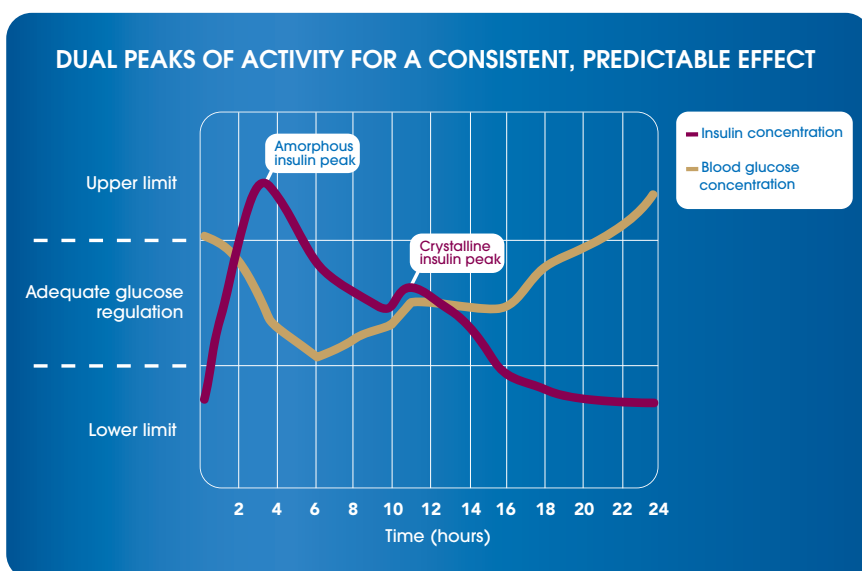
Vetsulin should not be used in dogs or cats known to have a systemic allergy to pork or pork products. Vetsulin is contraindicated during periods of hypoglycemia. Keep out of reach of children. As with all insulin products, careful patient monitoring for hypoglycemia and hyperglycemia is essential to attain and maintain adequate glycemic control and prevent associated complications. Overdosage can result in profound hypoglycemia and death. The safety and effectiveness of Vetsulin in puppies and kittens, breeding, pregnant, and lactating dogs and cats has not been evaluated. See package insert for full information regarding contraindications, warnings, and precautions.



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PROVEN EFFICACY IN DIABETIC DOGS.

- ▶ Quick onset of activity—Amorphous insulin fraction activity peaks at about 4 hours post-injection and lasts 8 hours¹
- ▶ Sustained effect—Crystalline insulin fraction is slowly absorbed, causing activity to peak at 11 hours post-injection¹
- ▶ Duration of activity—14 to 24 hours^{2,3}



About one-third of dogs may be adequately regulated with once-daily dosing.^{2,3}

EFFECTIVELY CONTROLS BLOOD GLUCOSE LEVELS AND REDUCES CLINICAL SIGNS OF DIABETES.¹

▶ **81%**
of diabetic dogs achieved adequate control of blood glucose levels during study period¹

▶ **96%**
reduction in polydipsia¹

▶ **94%**
reduction in polyuria¹

▶ **83%**
reduction in ketonuria¹



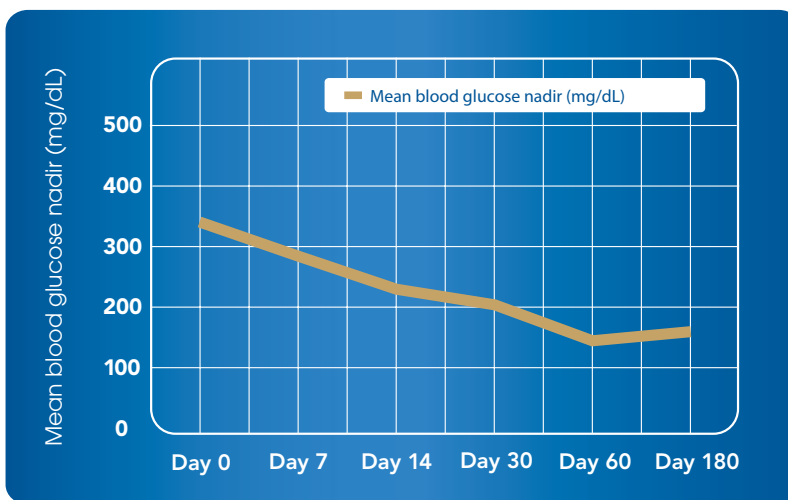
Vetsulin[®] (porcine insulin zinc suspension) fits the therapeutic needs of diabetic cats.

OFFERS A PREDICTABLE ONSET AND DURATION OF EFFECT IN CATS.⁴

- ▶ Intermediate-acting lente insulin
- ▶ Peak activity occurs between 1.5 and 8 hours post-injection⁴
- ▶ Duration of activity up to 12 hours⁴
- ▶ May help minimize the risk of hypoglycemia versus longer-acting insulin that is administered twice daily



REDUCED ALL MAJOR DIABETES INDICATORS TO WITHIN NORMAL RANGE.^{5,6}



The combination of 40 IU/mL concentration and a 0.5-mL syringe makes Vetsulin easier to accurately dose in cats.

BY DAY 60:

- ▶ 75% of cats had a mean blood glucose nadir <300 mg/dL⁵
- ▶ 72% of cats had a mean blood glucose nadir <200 mg/dL⁵
- ▶ The mean blood glucose nadir of all cats was 145.7 mg/dL⁵
- ▶ Mean fructosamine concentration was significantly reduced ($P < 0.001$)⁵

See back cover for full prescribing information.



EASY, ACCURATE DOSING.

- ▶ The 40 IU/mL concentration of Vetsulin allows more precise dose measurement for cats at low IU doses
 - A human study revealed that errors in dosing are common when doses of less than 2.0 U of U-100 insulin are dispensed⁷
 - Attempts to administer doses of 0.5 U or 1.0 U of U-100 insulin resulted in overdosage of 95% and 66%, respectively⁷
- ▶ A 0.5-mL U-40 syringe for cats also helps achieve more exact dosing

ECONOMICAL.

- ▶ At a starting dose of 1 to 2 IU per cat per injection, Vetsulin is very cost-effective
- ▶ The same inventory can be used for dogs or cats

REMISSION RATES IN CATS ARE SIMILAR FOR LENTE INSULIN (VETSULIN) AND INSULIN GLARGINE WHEN:⁸

Diet is controlled

Insulin management is started early in the course of the disease

Good glycemic control is achieved and maintained





Vetsulin[®] (porcine insulin zinc suspension) provides an effective option for both canine and feline patients.

CONVENIENT DOSING FOR DOGS AND CATS.

- ▶ Starting dose for dogs: 0.5 IU/kg once daily per label
- ▶ Starting dose for cats: 1–2 IU twice daily (not weight dependent)
 - Should not exceed 2 IU twice daily for the first 2–4 weeks
- ▶ U-40 syringes—available from Merck Animal Health—make it easier to dose accurately
 - 2 syringe sizes available—1 mL and 0.5 mL



ADMINISTRATION AND STORAGE.

- ▶ Prior to use, vials of Vetsulin should be shaken thoroughly until a homogeneous, uniformly milky suspension is obtained
- ▶ Vetsulin contents should be used within 42 days after the vial is first punctured
 - The in-use stability is confirmed when stored at 25°C (77°F)/60% relative humidity

Vetsulin is the only veterinary insulin with proven efficacy in helping manage diabetes in both dogs and cats.

Available in 10 mL bottle with 2 syringe sizes—1 mL and 0.5 mL





vetsulin[®]
(porcine insulin zinc suspension)

AN INSULIN THAT FITS THE NEEDS OF YOUR PRACTICE.

EXTENSIVE PROFESSIONAL SUPPORT AND RESOURCES.

- ▶ Access to Merck Animal Health diabetes professionals who can provide the answers you need
- ▶ Patient tracking tools make monitoring blood glucose levels easier
- ▶ Conversion tools to transition a patient from another insulin to Vetsulin

CLIENT TOOLS THAT HELP MAKE DIABETES MANAGEMENT EASIER.

- ▶ Pet owner educational brochures deliver crucial information on feline and canine diabetes and its management with Vetsulin in a friendly, easy-to-understand format
- ▶ An administration guide and monitoring sheet make it easier for clients to properly handle and administer Vetsulin and track vital information about their pet's progress

REVENUE FOR YOUR PRACTICE.

- ▶ Opportunity to strengthen client relationships
- ▶ Generate income from dispensing product and syringes in clinic
- ▶ Increases customer contact and enhances patient monitoring

For general information and pet diabetes tools,
please visit www.vetsulin.com.

Customer Service: 800-521-5767

Pet Diabetes Technical Services: 800-224-5318



NADA 141-236, Approved by FDA

CAUTION

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

DESCRIPTION

vetsulin® is a sterile aqueous zinc suspension of purified porcine insulin.

Each mL contains:

- purified porcine insulin 40 IU (35% amorphous and 65% crystalline)
- Zinc (as chloride) 0.08 mg
- Sodium acetate trihydrate 1.36 mg
- Sodium chloride 7.0 mg
- Methylparaben (preservative) 1.0 mg
- pH is adjusted with hydrochloric acid and/or sodium hydroxide.

INDICATION

vetsulin® (porcine insulin zinc suspension) is indicated for the reduction of hyperglycemia and hyperglycemia-associated clinical signs in dogs and 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 IN DOGS AND CATS ONLY

Shake the vial thoroughly until a homogeneous, uniformly milky suspension is obtained. Foam on the surface of the suspension formed during shaking should be allowed to disperse before the product is used and, if required, the product should be gently mixed to maintain a homogeneous, uniformly milky suspension before use. Clumps or white particles can form in insulin suspensions; do not use the product if visible clumps or white particles persist after shaking thoroughly. Using a U-40 insulin syringe, the injection should be administered subcutaneously, 2 to 5 cm (3/4 to 2 in) from the dorsal midline, varying from behind the scapulae to the mid-lumbar region and alternating sides. Always provide the Owner Information Sheet with each prescription.

Dogs

The initial recommended vetsulin® dose is 0.5 IU insulin/kg body weight. Initially, this dose should be given once daily concurrently with, or right after a meal.

Twice daily therapy should be initiated if the duration of insulin action is determined to be inadequate. If twice daily treatment is initiated, the two doses should each be 25% less than the once daily dose required to attain an acceptable nadir. For example, if a dog receiving 20 units of vetsulin® once daily has an acceptable nadir but inadequate duration of activity, the vetsulin® dose should be changed to 15 units twice daily.

The veterinarian should re-evaluate the dog at appropriate intervals and adjust the dose based on clinical signs, urinalysis results, and glucose curve values until adequate glycemic control has been attained. Further adjustments in 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.

Cats

The initial recommended dose in cats is 1 to 2 IU per injection. The injections should be given twice daily at approximately 12 hour intervals. For cats fed twice daily, the injections should be given concurrently with, or right after each meal. For cats fed *ad libitum*, no change in feeding schedule is needed. The veterinarian should re-evaluate the cat at appropriate intervals and adjust the dose based on clinical signs, urinalysis results, and glucose curve values until adequate glycemic control has been attained. Further adjustments in 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

Dogs and cats known to have a systemic allergy to pork or pork products should not be treated with vetsulin®. vetsulin® is contraindicated during periods of hypoglycemia.

WARNINGS

User Safety: For use in animals only. Keep out of the reach of children. Avoid contact with eyes. In case of contact, immediately flush eyes with copious amounts of water for 15 minutes. Accidental injection may cause clinical 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 Owner Information Sheet). Use of this product, even at established doses, has been associated with hypoglycemia. An animal 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, subsequently, the dosage should be adjusted, if indicated. Any change in insulin should be made cautiously and only under a veterinarian's supervision. Changes in insulin strength, manufacturer, type, species (animal, human) 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 endocrinopathies in pets that are difficult to regulate (e.g., hyperadrenocorticism in dogs and hyperthyroidism in cats).

PRECAUTIONS

Animals presenting with severe ketoacidosis, anorexia, lethargy, and/or vomiting should be stabilized with short-acting insulin and appropriate supportive therapy until their condition is stabilized. As with all insulin products, careful patient monitoring for hypoglycemia and hyperglycemia are essential to attain and maintain adequate glycemic control and prevent associated complications. Overdosage can result in profound hypoglycemia and death. Progestogens, certain endocrinopathies, and glucocorticoids can have an antagonistic effect on insulin activity. Intact bitches should be ovariosterectomized. Progestogen and glucocorticoid use should be avoided.

Drug Interactions:

In the US clinical effectiveness studies, dogs and cats received various medications while being treated with vetsulin® including antimicrobials, antivirals, antifungals, antihistamines, analgesics, anesthetics/tranquilizers, diuretics, bronchodilators, corticosteroids (cats), NSAIDs, thyroid hormone supplementation, hyperthyroid medication (methimazole), internal and external parasitides, anti-emetics, dermatological topical treatments and oral supplements, ophthalmic preparations containing antimicrobials and antiinflammatories, and various vaccines. No medication interactions were reported. This drug was not studied in dogs receiving corticosteroids.

Reproductive Safety: The safety and effectiveness of vetsulin® in breeding, pregnant, and lactating dogs and cats has not been evaluated.

Use in puppies and kittens: The safety and effectiveness of vetsulin® in puppies and kittens has not been evaluated.

ADVERSE REACTIONS**Dogs**

In the field effectiveness and safety study, 66 dogs were treated with vetsulin®. Sixty-two dogs were included in the assessment of safety. Hypoglycemia (defined as blood glucose < 50 mg/dL) with or without associated clinical signs occurred in 35.5% (22/62) of the dogs at various times during the study. Clinical signs of hypoglycemia were generally mild in nature (described as weakness,

lethargy, stumbling, falling down, and/or depression). Disorientation and collapse were reported less frequently and occurred in 16.1% (10/62) of the dogs. Two dogs had a seizure and one dog died during the seizure. Although never confirmed, the presumptive diagnosis was hypoglycemia-induced seizures. In the rest of the dogs, hypoglycemia resolved with appropriate therapy and adjustments in insulin dosage. Seven owners recorded the following observations about the injection site on the home monitoring forms: swollen, painful, sore, and a bleb under the skin.

The following clinical observations occurred in the field study following treatment with vetsulin® and may be directly attributed to the drug or may be secondary to the diabetic state or other underlying conditions in the dogs: hematuria, vomiting, diarrhea, pancreatitis, non-specific hepatopathy/pancreatitis, development of cataracts, and urinary tract infections.

Cats

In a field effectiveness and safety study, safety data was reported for 78 cats receiving vetsulin®. Hypoglycemia (defined as blood glucose < 50 mg/dL) was reported in 61 cats (88 total incidences). Fifteen of the occurrences (involving 13 cats) were associated with clinical signs described as lethargy, diarrhea, decreased appetite/anorexia, vomiting, and hypothermia. One cat had seizures following accidental overdosing by the owner and again during the subsequent dose adjustment period. The cat responded to supportive therapy and had no further hypoglycemic episodes. In all cases of hypoglycemia, the clinical signs resolved following symptomatic treatment and/or dose adjustment. Polyneuropathy was reported in 4 cats. Two injection site reactions were reported: one as a mildly thickened subcutaneous tissue reaction and the second as a mild bruising.

The following clinical observations occurred in the field study following treatment with vetsulin® and may be directly attributed to the drug or may be secondary to the diabetic state or other underlying conditions in the cats: vomiting, diarrhea, decreased appetite/anorexia, pancreatitis, dermal events, respiratory disease, urinary tract disorder, renal disease, dehydration, weight loss, polydipsia, polyuria, behavioral change, and ocular discharge/conjunctivitis. In a smaller field effectiveness and safety study, 14 cats were treated with vetsulin®. Hypoglycemia was reported in 6 cats (8 total occurrences). Lethargy not associated with hypoglycemia was reported in 4 cats (6 total occurrences). The following clinical observations occurred in the field study following treatment with vetsulin® and may be directly attributed to the drug or may be secondary to the diabetic state or other underlying conditions in the cats: foul odor to stool, diarrhea, dull coat, rapid, shallow breathing, stiff gait in rear, gallop rhythm, and pruritus with alopecia. During the 1998–2007 period, the following adverse events in 50 cats treated with porcine insulin zinc suspension were reported to Intervet International and Intervet Inc. Death, seizures, lack of effectiveness/dysregulation, hypoglycemia, allergic or skin reaction, lethargy, vomiting/diarrhea, injection pain, hyperthermia, nystagmus, PU/PD, and abnormal behavior. To report suspected adverse drug experiences, call Merck at 1-800-224-5318. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS, or <http://www.fda.gov/AnimalVeterinary>

GENERAL PHARMACOLOGY

vetsulin® is a mixture of amorphous and crystalline insulin resulting in immediate and prolonged insulin activity. In dogs, vetsulin® may show two peaks of activity. In a laboratory study, 12 healthy adult Beagles were administered vetsulin® at a dose of 0.5 IU/kg. The onset of activity varied from 0.5 to 2 hours; the time to peak activity varied from 1 to 10 hours; and the duration of activity varied from 10 to 24 hours. In diabetic dogs, vetsulin® has two peaks of activity following subcutaneous administration (the first occurs at 2 to 6 hours and the second at 8 to 14 hours) (1). The duration of activity varies between 14 and 24 hours (1).

In cats, vetsulin® has a single peak of activity. In a laboratory study, 12 healthy adult cats were administered vetsulin® at a dose of 0.5 IU/kg. The onset of activity varied from 0.5 to 2 hours; the time to peak activity varied from 2 to 6 hours; and the duration of activity varied from 8 to 24 hours. In diabetic cats, the peak activity following subcutaneous administration of vetsulin® occurs between 1.5 and 8 hours (2), and the duration of activity varies between 8 and 12 hours (2).

The peak(s) of activity, duration of activity, and dose required to adequately control diabetic signs vary between individuals and may vary in the same individual from day to day. The time ranges should only be considered as initial guidelines.

EFFECTIVENESS**Dogs**

A total of 66 client-owned dogs were enrolled in and 53 completed the effectiveness and safety field study. The dogs completing the study included 22 breeds of purebred and various mixed breed dogs ranging in age from 4.8 to 14 years, and ranging in weight from 4.2 to 51.3 kg. Of the dogs completing the study, 25 were spayed females and 28 were male (21 neutered and 7 intact). Dogs were started on vetsulin® at a dose of 1 IU/kg plus a body weight-dependent dose supplement once daily. The initial treatment time to reach acceptable glycemic control (Dose determination period) ranged from 5 to 151 days. Dogs were evaluated for treatment effectiveness three times at 30-day intervals (Study Period). The blood glucose curve means and mean nadirs were compared pre- and post-treatment to assess effectiveness. Glycemic control was considered adequate if an acceptable blood glucose curve was achieved (reduction in hyperglycemia and a nadir of 60–160 mg/dL), clinical signs of hyperglycemia (polyuria, polydipsia, and ketonuria) were improved, and hypoglycemia (blood glucose < 50 mg/dL) was avoided. The blood glucose curve mean was reduced from 370 mg/dL pre-treatment to 151 mg/dL, 185 mg/dL, and 184 mg/dL at the three treatment period evaluations. The blood glucose curve mean nadir was reduced from 315 mg/dL pre-treatment to 93 mg/dL, 120 mg/dL, and 119 mg/dL at the three treatment period evaluations. Sixty days after an adequate vetsulin® dose was initially established, 94%, 96% and 83% of study dogs experienced a reduction in polyuria, polydipsia, and ketonuria, respectively. Investigators reported adequate glycemic control an average of 81% of the time during the Study Period.

Cats

A total of 85 client-owned cats (53 males and 25 females—all neutered) of various breeds were enrolled in a 60 day field effectiveness and safety study with continued use up to Day 180. Seven cats were removed from the study prior to the Day 7 evaluation. The remaining cats ranged in age from 3 to 17.5 years and in weight from 1.9 to 10.8 kg. Seventy-two cats completed the study to Day 60 and 66 cats completed to Day 180. The cats were started on vetsulin® at an initial dose of 1 to 2 IU insulin twice daily. Scheduled evaluations occurred at Days 7, 14, 30, 60, and 180. Dose adjustments were allowed at and between the evaluations. Effectiveness was based on blood glucose curve mean, blood glucose nadir and improvement in clinical signs. Blood glucose curve means decreased from 394 mg/dL on Day 0 to 217 mg/dL on Day 60. The mean blood glucose nadir decreased from 343 mg/dL on Day 0 to 146 mg/dL on Day 60. Fourteen client-owned cats (10 males and 4 females—all neutered) of various breeds were enrolled in a 60 day effectiveness and safety field study. The cats ranged in age from 5 to 14 years and in weight from 3.40 to 6.97 kg. Twelve cats completed the study. The cats were started on vetsulin® at an initial dose of 1 to 2 IU insulin twice daily. Scheduled evaluations occurred at Days 7, 14, 30, and 60. Dose adjustments were allowed at and between the evaluations. The blood glucose curve means decreased from 354 mg/dL on Day 0 to 162 mg/dL on Day 60. The mean blood glucose nadir decreased from 321 mg/dL on Day 0 to 99 mg/dL on Day 60.

HOW SUPPLIED

vetsulin® is supplied as a sterile injectable suspension in multidose vials containing 10 mL of 40 IU/mL porcine insulin zinc suspension. Vials are supplied in cartons of one, 10 mL vial.

STORAGE CONDITIONS

Store in an upright position under refrigeration at 2° to 8° C (36° to 46° F). Do not freeze. Protect from light. Use contents within 42 days of first vial puncture.

Additional information about vetsulin® and diabetes mellitus can be found at www.vetsulin.com

Distributed by: Intervet Inc (d/b/a Merck Animal Health)
Summit, NJ 07901

Made in Germany

02/13

References

- Graham P, Nash A, and McKellar Q. "Pharmacokinetics of porcine insulin zinc suspension in diabetic dogs." *Journal of Small Animal Practice*. 1997. Vol 38, October: 434-438.
- Martin G.J. and Rand J.S. "Pharmacokinetic and Pharmacodynamic Study of Caninsulin in Cats with Diabetes Mellitus" (2000), Internal Study Report.

*Vetsulin is known as Caninsulin® outside of the US.

†NPH insulin, or neutral protamine Hagedorn, is marketed under several different trade names.

References: 1. Graham PA, Nash AS, McKellar QA. Pharmacokinetics of a porcine insulin zinc suspension in diabetic dogs. *J Small Anim Pract*. 1997;38(10):434-438. 2. Monroe WE, Laxton D, Fallin EA, et al. Efficacy and safety of a purified porcine insulin zinc suspension for managing diabetes mellitus in dogs. *J Vet Intern Med*. 2005;19:675-682. 3. Horn B, Mitten RW. Evaluation of an insulin zinc suspension for control of naturally occurring diabetes mellitus in dogs. *Aust Vet J*. 2000;78(12):831-834. 4. Martin GJ, Rand JS. Pharmacology of a 40 IU/ml porcine lente insulin preparation in diabetic cats: findings during the first week and after 5 or 9 weeks of therapy. *J Feline Med Surg*. 2001;3(1):23-30. 5. Vetsulin® (porcine insulin zinc suspension) [Freedom of Information Summary]. Millsboro, DE: Intervet Inc.; 2008. 6. Data on file, Merck Animal Health. 7. Casella SJ, Mongilio MK, Plotnick LP, Hesterberg MP, Long CA. Accuracy and precision of low-dose insulin administration. *Pediatrics*. 1993;91(6):1155-1157. 8. Feldman EC. Diabetes remission in cats: which insulin is best? *Compend Contin Educ Vet*. 2009;31(7 Suppl A).