

Vetsulin[®] and Feline Diabetes Mellitus

THE PRODUCT

Vetsulin[®] (porcine insulin zinc suspension) is an aqueous suspension containing 40 IU per mL of highly purified porcine insulin consisting of 30 percent amorphous and 70 percent crystalline zinc insulin. As a lente insulin, Vetsulin is classified as an intermediate-acting insulin. In cats, the peak activity following subcutaneous administration of Vetsulin occurs between 1.5 and 8 hours, and the duration of activity varies between 8 and 12 hours. The peak, duration of activity, and dose required to adequately control diabetic signs will vary between individuals. In general, cats require BID dosing of Vetsulin.

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 the reach of children. Animals presenting with severe ketoacidosis, anorexia, lethargy, and/or vomiting should be stabilized with short-acting insulin and appropriate supportive therapy until their condition is stabilized.

As with all insulin products, careful patient monitoring for hypoglycemia and hyperglycemia is essential to attain and maintain adequate glycemic control and prevent associated complications. Overdosage can result in profound hypoglycemia and death. See package insert for full information regarding contraindications, warnings, and precautions.

DIAGNOSING FELINE DIABETES MELLITUS

Diagnosing feline diabetes can be challenging. The diagnosis should be based on the presence of classic clinical signs that have been present for several weeks or months, such as polyuria (PU), polydipsia (PD), and weight loss despite a good appetite, coupled with corroborative laboratory tests showing hyperglycemia (>300 mg/dL) and glycosuria. A characteristic clinical sign of advanced feline diabetes is plantigrade stance.

In cats, stress can induce transient hyperglycemia that makes it harder to diagnose and manage diabetes. Because stress-induced hyperglycemia can result in blood glucose concentrations of 300 mg/dL to 400 mg/dL, it can confound the interpretation of blood glucose results. Persistent hyperglycemia and glycosuria should therefore be present to definitively establish the diagnosis of diabetes. It is also useful to measure serum fructosamine concentrations, since levels of fructosamine are normal in stress-induced hyperglycemia and elevated in sustained hyperglycemia.

Evaluating glucose accumulation in urine is a useful diagnostic tool in making a definitive diagnosis of diabetes in cats. Since it takes several hours of stress for detectable glucose to accumulate in the urine, glycosuria will not be present in cats with stress-induced hyperglycemia. In addition to the absence of glycosuria, none of the typical clinical signs of diabetes are present in cats with stress-induced hyperglycemia.

When a diagnosis of diabetes has been confirmed, begin treatment with Vetsulin® (porcine insulin zinc suspension).

STARTING VETSULIN

In-clinic:

- Weigh the cat to obtain a benchmark for future weight gain or loss.
- Start the cat on an injection of Vetsulin 1 to 2 IU BID, at approximately 12-hour intervals. The injection should be given concurrently with or right after meals for cats fed twice daily (no change in feeding schedule is required for cats fed *ad libitum*).
- Keep the cat hospitalized for the day to verify that the starting dosage does not cause hypoglycemia.
- Instruct owner:
 - Injection technique
 - How to identify and treat hypoglycemia
 - Parameters to monitor at home
 - Preferred diet
- Discharge cat to owner's care for 2–4 weeks. This allows the patient and owner to get used to injections.

At home, have the owner:

- Monitor and record water and food consumption.
- Monitor and record urine glucose and/or ketone bodies.
- Maintain starting dose and frequency of administration for 2–4 weeks (unless there's evidence of hypoglycemia).
- Return for evaluation 2–4 weeks after starting Vetsulin.

At the return visit:

- Reweigh cat.
- Obtain owner's overall impression of the cat's progress, especially with regard to PU and PD.
- Ideally, perform a serial blood glucose curve, with samples taken every 2 hours for the course of the day, to determine if regulation has been achieved, keeping in mind that cats often present with stress-induced hyperglycemia.
- Ideally, the blood glucose values will range between 120 and 350 mg/dL in a well-regulated diabetic cat. The dose will most likely need to be adjusted until adequate regulation is achieved.
- Adjust dose in increments of 1 IU per injection (BID), if necessary, based on the glucose curve evaluation.
- Allow at least 2–4 weeks between dose changes (unless there's evidence of hypoglycemia).
- Monitor fructosamine prior to and 2–3 weeks after dose changes in stressed cats.
- Once regulated on Vetsulin, cats should be rechecked every 2–4 months. It's important to keep in mind that cats, unlike dogs, can go into remission.

VETSULIN: HANDLE WITH CARE

Vetsulin, like many other insulin preparations, is a suspension. The active ingredients in Vetsulin are present in the precipitate and in the clear supernatant. Therefore, the vial must be gently agitated to ensure a homogeneous mixture for dosing accuracy. This may be done by slowly rotating and inverting the vial several times before withdrawal of each dose, or by rolling the vial between the palms of the hands. Vigorous shaking should be avoided because it can denature the insulin and cause frothing, which can interfere with accurate measurement of a dose.

Insulin preparations must look uniformly cloudy or milky before injection. Vetsulin vials should be stored upright in the refrigerator to avoid crystallization around the stopper.

In addition, clients should be advised not to reuse insulin syringes. One of the main concerns is the potential for staph infection, but the silicon coating inside the syringe may also contaminate the insulin vial with silicon. A white precipitate will form in the vial, which may interfere with the biological activity of the insulin.

VETSULIN: 40 IU/mL CONCENTRATION

Vetsulin is presented in a glass vial at a concentration of 40 IU per mL of solution, which facilitates more accurate dosing, especially of small pets like cats, and eliminates the need for diluting a higher-concentration human insulin. To avoid dosing errors when administering Vetsulin to cats, it is important to use a U-40 syringe.

USE OF A SYRINGE OTHER THAN A U-40 SYRINGE WILL RESULT IN INCORRECT DOSING.

Consequently, it is strongly advised that veterinarians educate clients on the need for and importance of using U-40 syringes with Vetsulin.

vetsulin®

(porcine insulin zinc suspension)

PRODUCT INFORMATION

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	(30% amorphous and 70% 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

vetsulin® should be mixed by gentle rolling of the vial prior to withdrawing the dose from the vial. 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.

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. In the US clinical study, 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. 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 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.

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 ovariectomized. 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 parasiticides, 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 gate 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 adverse reactions, call 1-800-345-4735.

GENERAL PHARMACOLOGY

Porcine insulin is similar in amino acid structure to canine insulin. vetsulin® is classified as intermediate acting insulin. In dogs, vetsulin® has two peaks of activity following subcutaneous administration (the first at around 4 hours and the second at around 11 hours) (1). The duration of activity varies between 14 and 24 hours (1). In 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), duration of activity and dose required to adequately control diabetic signs will vary between individuals.

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. 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 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 either 2.5 mL or 10 mL of 40 IU/mL porcine insulin zinc suspension. Vials are supplied in cartons of one, 10 mL vial and cartons of ten, 2.5 mL vials.

STORAGE CONDITIONS

Store in an upright position under refrigeration at 2° to 8° C (36° to 46° F). Do not freeze. Protect from light.

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

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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.

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