

Vetsulin[®] and 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. Vetsulin has two peaks of insulin activity. The amorphous fraction provides quick activity, which peaks at approximately 4 hours following subcutaneous administration. The crystalline fraction is more slowly absorbed, providing a later peak of activity 11 hours post-injection. The impact of Vetsulin on blood glucose peaks at 4–8 hours post-injection and lasts for 14–24 hours. Consequently, some dogs (approximately one third) can be maintained on once-daily injections of Vetsulin.

Vetsulin should not be used in dogs 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 associated complications. Overdosage can result in profound hypoglycemia and death. See package insert for full information regarding contraindications, warnings, and precautions.

CONVERTING TO VETSULIN

Caution should be exercised when changing from one insulin product to another. Due to the nature of the disease, it is difficult to set general guidelines; however, some recommendations can be made. Vetsulin therapy is ideally prescribed for newly diagnosed diabetics or in cases where a change in insulin is indicated.

Starting regulation of the non-complicated diabetic dog:

Two types of patients can be categorized as non-complicated:

1. Pets presented to the veterinarian after the owner has noted the appearance of clinical signs without general deterioration—that is, no ketoacidosis (DKA). These cases are not emergencies, although dogs without cataracts should be treated diligently to try to avoid this complication.
2. Pets that, after initial presentation with DKA and its successful treatment, are generally stable and without ketonuria.

During consultation:

- Perform a thorough physical examination and weigh the patient.
- Conduct laboratory testing including complete blood count, urinalysis (including sediment examination), and serum biochemistry profile.
- Rule out hyper/hypothyroidism, renal failure, inflammatory bowel disease, pancreatitis, exocrine pancreatic insufficiency, hyperadrenocorticism, growth hormone excess or acromegaly, neoplasia, and hepatic disease.
- Photograph the pet (entire body): optional, but often the only way to diagnose subsequent acromegaly.

When health status is known and diabetes mellitus confirmed:

- Explain thoroughly what diabetes mellitus is, that achieving regulation may take time (up to 1–2 months), and what the implications are for the family. Make sure the owner understands the treatment involved, and that the dog should be able to live a happy, healthy life with consistent treatment. This is crucial, as complete cooperation of the owner is essential to the success of the treatment.
- Treat existing infections or other medical conditions. Any disease will affect insulin metabolism.
- Introduce an appropriate diet.
- Begin treatment with Vetsulin® (porcine insulin zinc suspension).

STARTING VETSULIN

In-clinic:

- Weigh the pet. In the event of a fraction of a kilogram, round the body weight down rather than up. For example, a 12.9-kg dog should be dosed as a 12-kg patient. If the dog is grossly overweight, utilize the optimal body weight for calculating the starting dosage of Vetsulin.
- Establish a starting dosage based on the labeled dosage of one IU/kg plus the weight-based supplemental dose.
- Decide whether to begin with once- or twice-daily injections.
 - Some pet owners may do best by easing into the routine of diabetes management with once-daily injections. This is preferable to having an overwhelmed client who sees euthanasia as the only viable option. After acclimating to the once-daily injections, the client is more likely to willingly accept twice-daily injections, if needed.
 - Remember that hyperglycemia does not kill dogs; hypoglycemia does.
 - The majority of dogs (two thirds) will require twice-daily Vetsulin injections.
- Keep the pet 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 and frequency of meals
 - Exercise recommendations
- Discharge pet to owner's care for one week. This allows the patient and owner to get used to injections. Alternatively, some practitioners may prefer to complete the initial regulation in-clinic.

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 the entire week.

MONITORING AND ADJUSTING DOSE

The pet should be returned for evaluation 6–7 days after starting Vetsulin.

- Obtain owner's overall impression of the pet's progress.
- Reweigh the pet. Overall dosage of Vetsulin should be modified for significant weight gains or losses.
- Blood glucose sampling should be evaluated to determine if regulation is achieved.
- Adjustments in dose based on the glucose curve evaluation should be in increments of 10 percent. For example, if a dog is currently receiving 12 IU twice daily and has a blood glucose curve that indicates inadequate regulation, the dose should be increased 10 percent or one IU.
- Additional adjustments in dose should be made no more frequently than every 5–7 days.
- Once regulated on Vetsulin, the pet should be rechecked every 2–4 months.

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 this causes frothing, which can denature the insulin and 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. The silicon coating inside the syringe can 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 VS 100 IU

Vetsulin, from Intervet Inc., is the first registered veterinary insulin for the treatment of diabetes mellitus in dogs. Vetsulin is presented in a glass vial at a concentration of 40 IU per mL of solution. To avoid dosing errors when administering Vetsulin to pets it is important to use a U-40 syringe. **USE OF A SYRINGE OTHER THAN A U-40 SYRINGE WILL RESULT IN INCORRECT DOSING.**

Some pet owners may attempt to replenish their syringe inventories and/or insulin supply from their local human pharmacies. Pharmacies carry 100 IU/mL 1 mL and 50 IU/mL 0.5 mL syringes only. **They do not stock 40 IU/mL 1 mL syringes, nor do they stock Vetsulin.**

Using a 100 IU syringe with Intervet's Vetsulin would result in an animal receiving 2.5 times less insulin than required. Human insulins are formulated at a concentration of 100 IU/mL. If a client uses a 40 IU syringe with a 100 IU insulin preparation, they would be injecting 2.5 times the amount of insulin necessary, which could result in fatal hypoglycemia.

Most pharmacists are not aware of Vetsulin nor the 40 IU syringes recommended for use with this product. As noted above, substituting a 100 IU/mL 1 mL insulin product and/or a 100 IU/mL 1 mL syringe without proper dosage conversion could result in unsuccessful regulation, hypoglycemia, or even death.

As this potential situation can be fatal, it is strongly advised to educate clients to purchase both Vetsulin and the 40 IU syringes from your veterinary clinic.

PRODUCT INFORMATION

NADA NO. 141-236, Approved by FDA
Vetsulin® (PORCINE INSULIN ZINC SUSPENSION)

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 (30% amorphous and 70% crystalline)	40 IU
Zinc 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 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 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.

The initial recommended Vetsulin® dose is 1 IU insulin/kg body weight plus a body weight-dependent dose supplement as shown in the table below.

Body Weight	Dose +	Dose Supplement	Initial Dose
<10 kg (<22 lb)	(Weight in kg) x 1 IU/kg	1 IU	1 IU/kg + 1 IU
10 - 11 kg (22 - 24 lb)	(Weight in kg) x 1 IU/kg	2 IU	1 IU/kg + 2 IU
12 - 20 kg (25 - 44 lb)	(Weight in kg) x 1 IU/kg	3 IU	1 IU/kg + 3 IU
>20 kg (>44 lb)	(Weight in kg) x 1 IU/kg	4 IU	1 IU/kg + 4 IU

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/spot check 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.

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.

CONTRAINDICATIONS

Dogs 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: 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, especially hyperadrenocorticism in diabetic dogs that are difficult to regulate.

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 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 study, dogs received various medications while being treated with Vetsulin® including antimicrobials, NSAIDs, thyroid hormone supplementation, internal and external parasiticides, anti-emetics, dermatological topical treatments and oral supplements, and ophthalmic preparations containing antimicrobials and antiinflammatories. No medication interactions were reported. This drug was not studied in dogs receiving steroids.

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

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

ADVERSE REACTIONS

In the field effectiveness and safety study, 66 dogs were treated with Vetsulin®. Sixty-two dogs were included in the assessment of safety. Hypoglycemia 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.

During the 1995-2001 period, the following adverse reactions in 19 dogs treated with porcine insulin zinc suspension were reported to Intervet International: destabilization (defined as lack of adequate regulation), lack of expected efficacy, edema of the head and neck, development of a fibrous lump at the injection site, hypoglycemia and death following administration of typical doses (one death in two dogs) and overdosage (four deaths in four dogs).

To report adverse reactions, call 1-800-345-4735.

INFORMATION FOR DOG OWNERS

Please refer to the Client Information sheet for more information about Vetsulin®. Vetsulin®, like other drugs of this class, is not free from adverse reactions. Owners should be advised of the potential for adverse effects 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 primary adverse reaction observed is hypoglycemia. Signs may include weakness, depression, behavioral changes, muscle twitching, and anxiety. In cases of severe 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 Vetsulin® therapy is appropriate, or if alternative therapy should be considered.

GENERAL PHARMACOLOGY

Porcine insulin is similar in amino acid structure to canine insulin. Vetsulin® is classified as an intermediate acting insulin. 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). The peak(s), duration of activity and dose required to adequately control diabetic signs will vary between dogs.

EFFECTIVENESS

A total of 66 client-owned dogs were enrolled in and 53 completed the effectiveness and safety field study. The patients 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.

The injection frequency and effective dose range for dogs varied substantially:

Study Time	Dogs on SID therapy	Dogs on BID therapy	Range of SID doses (IU/kg)	Range of BID doses (IU/kg)	
				a.m. dose	p.m. dose
Time 0 (Initial dose)	51 (96%)	2 (4%)	0.94 - 1.28	1.06 - 1.07	1.06 - 1.07
Time 1	23 (43%)	30 (57%)	0.44 - 2.22	0.39 - 1.29	0.39 - 1.26
Time 2	23 (43%)	30 (57%)	0.33 - 2.19	0.40 - 1.25	0.39 - 1.22
Time 3	18 (34%)	35 (66%)	0.43 - 2.18	0.34 - 1.40	0.28 - 1.40

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.

References:

1. Graham P, Nash A, McKellar Q. "Pharmacokinetics of porcine insulin zinc suspension in diabetic dogs." *Journal of Small Animal Practice*. 1997. Vol 38, October: 434-438.

Distributed by:

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