

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 a ntimicrobials, 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, lethargy, 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

Distributed by: INTERVET INC.
Millsboro, DE 19966

Made in Germany

01/08

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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Owner Information Sheet
vetsulin® Injectable Insulin (porcine insulin zinc suspension)
vetsulin® for reduction of hyperglycemia and hyperglycemia-associated clinical signs in dogs and cats with diabetes mellitus
Generic name: U-40 Purified Porcine Insulin Zinc Suspension

This summary contains important information about vetsulin®. You should read this information before you start giving your pet vetsulin® and review it each time your 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 this information or if you want to know more about vetsulin®.

What is vetsulin®?

vetsulin® is an aqueous suspension of porcine (pork) insulin. Insulin is a hormone produced by the pancreas (a large gland that lies near the stomach). This hormone is necessary for the body's correct use of food, especially sugar.

What is diabetes mellitus?

Diabetes mellitus (DM) occurs when a dog or a cat has inadequate levels of or an abnormal response to insulin. DM is common in middle age and older dogs and cats. Daily insulin injections are usually necessary to treat DM. vetsulin® may help your pet effectively use food, aid in maintaining an acceptable blood sugar (glucose) level, and reduce or eliminate clinical signs commonly seen with DM. Diabetes mellitus may cause some or all of these signs or changes:

- Excessive thirst (Polydipsia)
- Excessive urination (Polyuria)
- Excessive appetite (Polyphagia)
- Weight loss despite good appetite
- Glucose in the urine (Glycosuria)
- Ketones in the urine (Ketonuria)
- Cloudy eyes and vision loss (Diabetic cataracts: dogs)
- Weakness in back legs (Diabetic neuropathy: cats)

Untreated or improperly regulated diabetes may lead to changes in the acidity of the blood (diabetic ketoacidosis) with dehydration, vomiting, weakness, depression, coma, and death.

What kind of results can I expect when my pet is on vetsulin® for DM?

Although vetsulin® is not a cure for DM, it can help control or eliminate many of the complications associated with the disease (such as excessive thirst, urination, and weight loss) and prevent development of life threatening ketoacidosis.

- Response varies from animal to animal but can be quite dramatic.
- In most cases, improvement can be seen within a few days.
- In cats, treatment may lead to diabetes remission (insulin injections no longer required).
- If vetsulin® is discontinued or not given as directed, the signs of diabetes will likely return and life-threatening complications such as ketoacidosis may develop.

Who should not receive vetsulin®?

- Individuals known to have a systemic allergy to pork or pork products.
- Individuals that have stopped eating or have greatly decreased appetite (anorexia), are vomiting, show signs of extreme drowsiness or fatigue (lethargy) and/or show signs of severe ketoacidosis, should not receive vetsulin® until stabilized with appropriate supportive therapy.
- vetsulin® is for use in animals only. Keep out of reach of children. Seek medical attention immediately if accidental injection occurs.

What to tell/ask your veterinarian before using vetsulin®.

Talk to your veterinarian about:

- The signs of DM you have observed.
- What tests might be done before vetsulin® is prescribed.
- The importance of ovariohysterectomy (spaying), if your dog is an intact female.
- The importance of consistent daily injections, an appropriate and consistent diet, weight control, exercise, and home monitoring of your pet's condition.
- How often your pet may need to be examined by your veterinarian.
- The risks and benefits of using vetsulin®.

Tell your veterinarian if your pet has ever had the following medical problems

- Side effects when receiving other insulin products
- Digestive upset (vomiting and/or diarrhea)
- Liver disease
- Inflamed pancreas (Pancreatitis)
- Underactive thyroid (Hypothyroidism)
- Overactive thyroid (Hyperthyroidism)
- Cushing's Syndrome (Hyperadrenocorticism)
- Kidney disease

Tell your veterinarian about:

- Any medical problems or allergies that your pet has now or has had.
- All medicines that you are giving or plan to give your pet, including those you can get without a prescription.

How to give vetsulin® to your pet

Doses of insulin are measured in units. U-40 insulin contains 40 units/mL (1 mL = 1 cc). **Use vetsulin® with U-40 syringes only.** Use of a syringe other than a U-40 syringe will result in incorrect dosing. A licensed veterinarian must prescribe vetsulin® for your pet, and it should be administered according to your veterinarian's instructions.

Your veterinarian will determine the amount of insulin needed (based on the weight of your pet, clinical signs such as water consumption, and laboratory results), instruct you on proper storage and handling, show you how to draw the insulin from the bottle, and instruct you on how to administer the injection. Once you can do this correctly, your veterinarian will provide you with everything you need to care for your pet at home. vetsulin® should be administered with a U-40 insulin syringe according to the following instructions:

Preparing the Dose:

- Wash your hands
- Remove the vetsulin® bottle from the refrigerator and mix by gently rolling the bottle between your hands (do not shake).
- Carefully remove the cap from the needle.
- Using a U-40 insulin syringe, pull the plunger back to draw air into the syringe to equal the vetsulin® dose.
- Insert the syringe needle into the bottle and inject the air into the bottle.
- Turn the bottle and syringe upside down. Making sure the tip of the needle is in the vetsulin®, withdraw the correct dose into the syringe.
- Before removing the needle from the bottle, check the syringe for any air bubbles. If bubbles are present, hold the syringe straight up and tap its side until the bubbles float to the top.

Push them out with the plunger and withdraw the correct dose.

- Remove the needle from the bottle, being careful to not inject yourself.

Giving the injection:

- Injections should be given just under the skin (subcutaneously) 2-5cm (3/4-2 inches) from the midline of the back (middle of your pet's back running from tail to head), varying from just behind the shoulder blade to slightly in front of the hipbone.
- The injection site should be alternated between your pet's left and right side.
- Using your free hand, pinch up a fold of skin, insert the needle into the center of the fold as instructed by your veterinarian, and push the plunger in as far as it will go.
- Pull the needle out being careful to not inject yourself.
- Dispose of the syringe in an appropriate manner (sharps/biohazard disposal).

What are the possible side effects that may occur during vetsulin® therapy?

The most common side effect experienced with vetsulin® therapy is hypoglycemia (low blood sugar). Hypoglycemia can be caused by:

- Giving too much insulin
- Missing or delaying food
- Change in food, diet, or amount fed
- Change (increase) in exercise
- Infection or illness
- Change in the body's need for insulin
- Diseases of the adrenal, pituitary, or thyroid gland, or progression of liver or kidney disease
- Interaction with other drugs (such as progesterone or glucocorticoids)

Signs of hypoglycemia may occur suddenly and can include

- Weakness
- Depression
- Behavioral changes
- Muscle twitching
- Anxiety
- Seizures
- Coma
- Death

What do I do in case my pet shows signs of hypoglycemia?

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

Other side effects that can be seen include loss of effectiveness and local or systemic allergic reactions. It is important to contact your veterinarian immediately if you think your pet has a medical problem or side effect from vetsulin® therapy. In particular, please contact your veterinarian if your pet shows any of the following:

- Excessive water consumption for more than 3 days
- Excess urination (including need to urinate at night for a pet that usually sleeps through the night or inappropriate urination in the house)
- Reduced or loss of appetite
- Weakness, seizures, or severe mental depression
- Behavioral change, muscle twitching, or anxiety
- Constipation, vomiting, or diarrhea
- Signs of a bladder infection (small, frequent urinations, straining, blood in the urine)
- Swelling of the head or neck

What else can I do to keep my pet's blood sugar stable?

- Your pet's diet should be consistent and appropriate. A nutritionally complete, dry or canned pet food should be fed in consistent amounts at the same times each day or, at the discretion of your veterinarian, be available continuously.
- "Treats" and changes in diet should generally be avoided unless recommended by your veterinarian.
- Your veterinarian will advise you on how much and when to feed your pet based on the response to vetsulin®.
- Your pet's exercise should remain consistent. Consult with your veterinarian if you expect a major change in activity.
- Develop a schedule with your veterinarian for regular evaluations of your pet's diabetes.

Can vetsulin® be used with other medications?

Progesterone (such as megestrol) and glucocorticoids (such as cortisone, prednisone, dexamethasone, triamcinolone) should be avoided during vetsulin® therapy. Progesterone, glucocorticoids, and certain endocrine diseases may counter the effect of insulin. Other medications may also interfere with your pet's response to insulin. Tell your veterinarian about all the medicines you have given your pet in the past, and any medicines that you are planning to give with vetsulin®. This should include other medicines that you can get without a prescription. Your veterinarian may want to check that all of your pet's medications can be given together.

What do I do in case my pet receives more than the prescribed amount of vetsulin®?

If your pet is given too much vetsulin®, severe (life-threatening) hypoglycemia (low blood sugar) can result. Contact your veterinarian immediately. If your veterinarian is not available, seek other veterinary advice at once. Your pet may need to be hospitalized for observation or treatment.

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

- A missed or inadequate dose may cause temporary recurrence of signs (such as excess thirst and urination) but is not life threatening.
- Contact your veterinarian as soon as possible for advice on your pet's next dose.
- If you cannot reach your veterinarian and your pet is eating and acting normal, give your pet the usual dose at the next regularly scheduled injection time.

How do I store vetsulin®?

vetsulin® should be stored in an upright position under refrigeration (2-8 Degrees Celsius / 36-46 Degrees Fahrenheit). Do not freeze. Protect from light.

What else should I know about vetsulin®?

This sheet provides a summary of information about vetsulin®. If you have any questions or concerns about vetsulin® or DM, talk to your veterinarian.

As with all prescribed medicines, vetsulin® should only be given to the pet for which it was prescribed and for the condition for which it was prescribed.

It is important that your veterinarian periodically evaluate your pet's response to vetsulin® at regular checkups that include blood glucose monitoring. Your veterinarian will best determine if your pet is responding as expected.

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

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