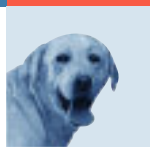
vetsulin™
(porcine insulin zinc suspension)



TREATMENT *for* DIABETES MELLITUS *in* DOGS

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TABLE *of* CONTENTS

INTRODUCTION

Diabetes mellitus is a common disorder in middle-aged and older dogs and is a complex disorder of carbohydrate, protein and lipid metabolism. It is a consequence of either an absolute or a relative deficiency of insulin, or peripheral cell insensitivity to insulin. Insulin is synthesized and released from beta cells in the pancreatic islets. Insulin assists with cellular uptake of glucose from the bloodstream, thus exerting a hypoglycemic effect. Within cells, insulin promotes anabolism (such as synthesis of glycogen, fatty acids and proteins) and counters catabolic events (reduces gluconeogenesis and inhibits fat and glycogen breakdown). Whereas insulin lowers blood glucose, there are opposing hormones (glucagon, cortisol, progesterone, adrenaline, thyroid hormone and growth hormone) that act to increase blood glucose. It is important to consider these counter-regulatory hormones, because changes in their blood concentrations will interfere with insulin actions. Changes in these hormones can occur in natural physiological conditions, in disease states, or as a consequence of drug administration.

In the absence of sufficient insulin, diabetic dogs will switch from glucose to fat metabolism for cellular energy. While this is initially beneficial, fat metabolism in unrecognized or untreated diabetics typically progresses to ketoacidosis and ultimately death.

Insulin treatment is the cornerstone of successful management, but dietary adjustments and a regular lifestyle are also important. In general, the prognosis is very good, provided that diagnosis is made at an early stage and treatment is administered properly. Open communication between client and veterinarian is also extremely important. Your encouragement of the client will largely influence the owner's motivation and compliance with treatment. Clients need to fully understand the disease to help achieve and maintain good diabetic stability and be highly motivated and committed to the management of their dog. The clinical staff has an important role in providing detailed client education, instruction and encouragement.

PREVALENCE

Estimates of the prevalence of diabetes mellitus in dogs ranges from 1:100 to 1:2000. The disease occurs mostly in adult and elderly dogs, but is also seen in young dogs of both sexes.

CLASSIFICATION

Several classification systems have been used to describe diabetes mellitus (DM). A human classification system recently revised in 1997 divides the disease into three types: Type 1 (previously insulin-dependent or juvenile-onset DM), Type 2 (previously non-insulin-dependent or adult-onset DM), and other specific types of diabetes mellitus (previously secondary or Type 3 DM). The most commonly recognized form in dogs is Type 1 (insulin-dependent DM). Dogs with the insulin-dependent form of the disease require daily insulin injections to control disease signs and delay the multisystemic disorders associated with the diabetic disease process. Untreated dogs commonly display severe weight loss, polydipsia and polyuria. They may experience dehydration and severe metabolic and electrolyte abnormalities if severe ketoacidosis develops. Untreated or improperly managed diabetic dogs suffer a decreased quality of life, and most die without appropriate therapy and monitoring.

ETIOLOGY OF DIFFERENT TYPES OF DIABETES MELLITUS

Primary Diabetes Mellitus

By the time diabetes mellitus is clinically recognized in dogs, they virtually all have Type 1 or insulin-dependent disease. This is characterized by beta cell destruction (often due to autoimmune destruction of the islets of Langerhans) and hypoinsulinemia. Insulin secretagogues, such as glucose or glucagon, fail to stimulate endogenous insulin production and there is an absolute requirement for exogenous insulin injections to control blood glucose levels.

Secondary Diabetes Mellitus

Diabetes mellitus can be secondary to severe inflammation or neoplasia of exocrine pancreatic tissue, which leads to loss of islet function. In these cases, diabetes is also complicated by exocrine pancreatic insufficiency. Diabetes mellitus can also occur when there is either overproduction of counteracting hormones or insulin resistance. Excessive growth hormone production can be seen in intact, cycling bitches. Progesterone produced during the luteal phase of the estrous cycle induces the production of growth hormone by the mammary gland, which counteracts the action of insulin.

Dogs with hyperadrenocorticism produce excessive amounts of glucocorticosteroids that stimulate gluconeogenesis and lead to an increase in the plasma glucose concentration. This stimulates insulin synthesis, which eventually results in exhaustion of the islets of Langerhans. Only about 10 percent of canine Cushing's syndrome cases are complicated by diabetes mellitus.

GLUCOSE TOXICITY

Glucose toxicity occurs when insulin secretion is reduced by prolonged hyperglycemia. Prolonged hyperglycemia can occur due to a number of causes. The prolonged and high-dose therapeutic use of glucocorticosteroids can induce diabetes mellitus.

The use of exogenous progestogens can lead to growth hormone excess. Progestogens also have an affinity for glucocorticosteroid receptors.

In obese dogs, tissue receptors have decreased insulin sensitivity. This leads to a greater demand for insulin, which can result in exhaustion of the islets of Langerhans.

POTENTIAL DIABETES MELLITUS

Potential diabetes mellitus, defined as impaired insulin synthesis and/or decreased sensitivity of tissue receptors to the effects of insulin, results in an increased blood glucose concentration that does not yet exceed the renal threshold.

Potential diabetes mellitus is seen in intact bitches during diestrus. At this stage, the problem may still be reversible by ovariohysterectomy, thus eliminating the progesterone source. Mild hyperglycemia may also be encountered in canine Cushing's syndrome. Here, too, reversal of the cortisol excess may prevent the development of diabetes mellitus.

PATHOGENESIS

Diabetes mellitus is a paradox: simultaneous extracellular hyperglycemia and intracellular glucose deficiency. The consequences of insulin deficiency or receptor insensitivity are reduced peripheral tissue utilization of glucose, amino acids and fatty acids. This results in the accumulation of glucose in the blood (hyperglycemia). Glucose is a small molecule and is freely filtered through the glomerulus in the kidney. In normal dogs, the renal tubules will reabsorb the filtered glucose. However, if the blood glucose rises above the renal threshold [approximately 180 mg/dl (10 mmol/L)], these tubular reabsorption mechanisms are overwhelmed and glucose appears in the urine. Glucose exerts an osmotic diuretic effect that leads to polyuria. To compensate, water consumption increases (polydipsia). Diabetic dogs tend to lose weight due to caloric loss with glucosuria and reduced peripheral tissue anabolism. Despite hyperglycemia, there is hypothalamic intracellular hypoglycemia that results in the stimulation of the hunger center and polyphagia. The consequences of this paradox are reflected in Figures 1 and 2.

FIGURE 1

INTRACELLULAR ENERGY SHORTAGE

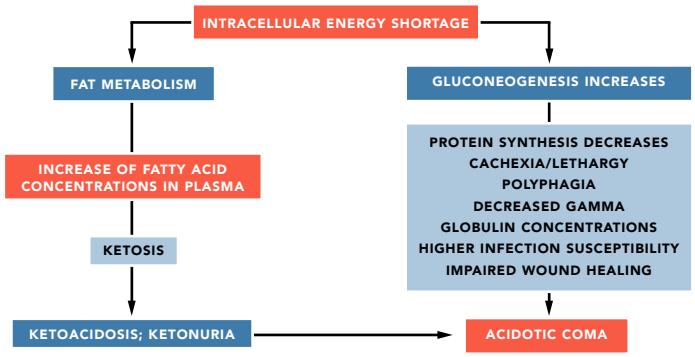
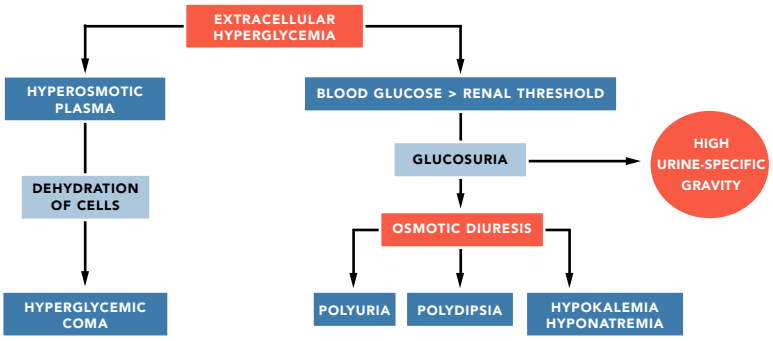


FIGURE 2

EXTRACELLULAR HYPERGLYCEMIA



Untreated or unrecognized diabetes mellitus may progress to diabetic ketoacidosis. In the absence of sufficient insulin, diabetic dogs will switch from glucose to fat metabolism for cellular energy. While fats are initially beneficial energy sources, lipid waste products (ketone bodies) accumulate in the blood and invoke severe and potentially life-threatening metabolic abnormalities. Diabetic ketoacidotic dogs can present with severe clinical signs (severe depression, anorexia, vomiting, dyspnea, collapse or coma). Owners may not have recognized or reported that the classic diabetic clinical signs were present. Without aggressive and determined management, ketoacidotic dogs may die.

CLINICAL SIGNS

There are three distinct clinical pictures in diabetes mellitus:

1. Uncomplicated
2. Complicated by ketoacidosis
3. Hyperosmolar syndrome

Signs of Uncomplicated Diabetes Mellitus:

The classical signs are:

- Polyuria/polydipsia
- Polyphagia
- Cachexia
- Increased susceptibility to infections (e.g. urinary tract infections)

Signs of Diabetes Mellitus Complicated by Ketoacidosis

In addition to the above signs, dogs with ketoacidosis may show:

- Severe depression
- Anorexia
- Vomiting
- Dyspnea
- Collapse or coma

Signs of Hyperosmolar Syndrome

- In dogs in which resistance of target tissues to insulin plays a role in the disease, insulin levels can be elevated.
- In these cases, ketosis is suppressed and plasma glucose concentrations can become very high.
- Dogs with hyperosmolar syndrome are usually comatose on presentation.

COMPLICATIONS OF DIABETES IN DOGS

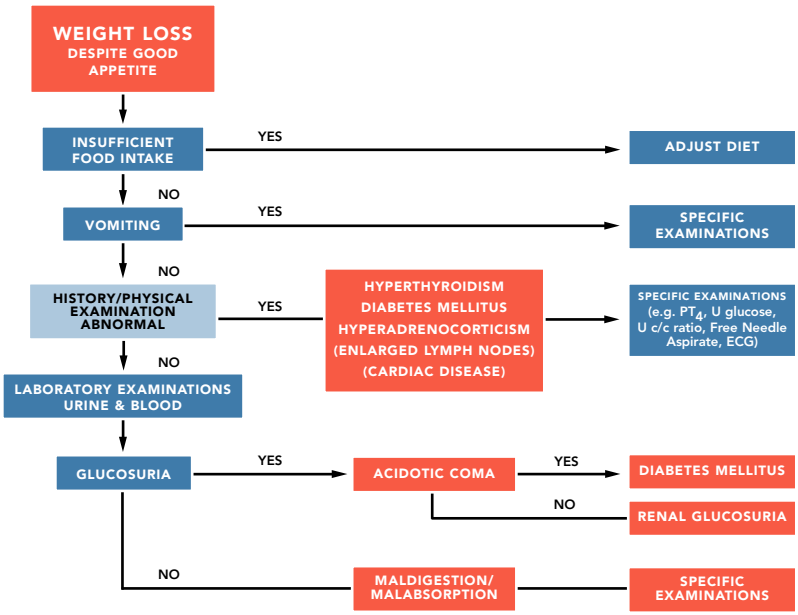
Chronic hyperglycemia can result in severe and debilitating illness. These include ketoacidosis (described above), recurrent infections (primarily urinary tract infections), cataract formation and (rarely) neuropathy. Cataract formation is the most common and irreversible complication of poor glycemic control in dogs. Cataract development can be alarmingly rapid with blindness occurring within a few weeks.

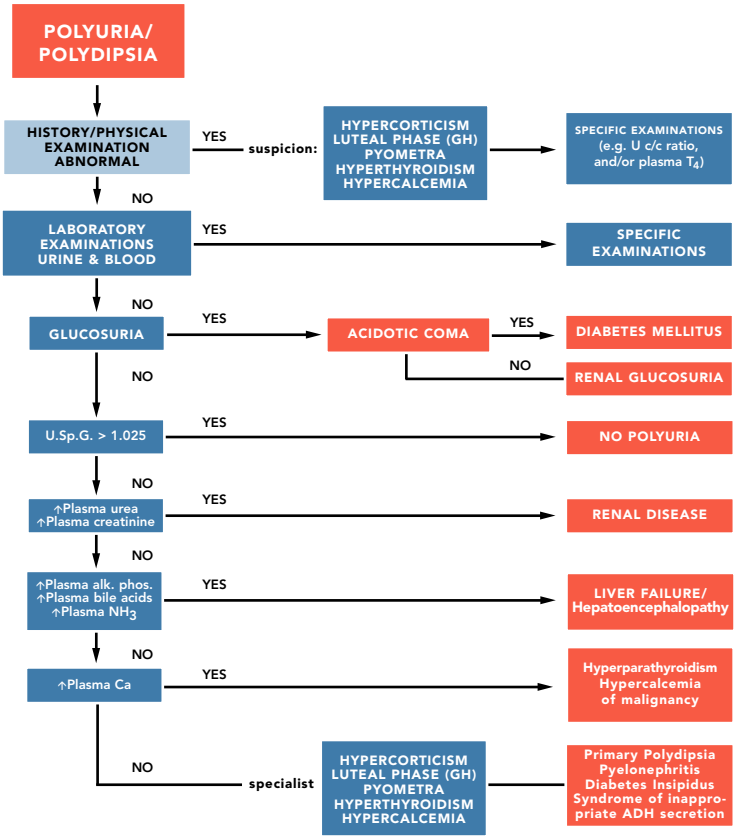
DIAGNOSIS

Diabetes mellitus is not the only cause of polyuria/polydipsia and weight loss. Each dog should be examined thoroughly to rule out any other causes before starting insulin treatment. A preliminary diagnosis of diabetes mellitus based on clinical signs must be confirmed by blood and urine tests. Reference values for blood glucose range from 80–120 mg/dl (4.4-6.7 mmol/l) in dogs. The renal threshold is around 180 mg/dl (10 mmol/l). If the blood-glucose concentration exceeds this threshold, glucose is excreted in the urine.

Differential Diagnosis: Weight Loss Despite a Good Appetite

Noticeable weight loss in a dog may cause concerned dog owners to visit their veterinarian. Although diabetes mellitus is a common diagnosis, other factors that can cause these clinical signs should be considered. The algorithm (right) can be used in determining an accurate diagnosis.





Differential Diagnosis: Polyuria/Polydipsia

Quite often, dog owners visit their veterinarian when their dog is urinating in the house and/or consuming large amounts of water. Although diabetes mellitus is a well-known cause of PU and PD, there are many other factors to consider. The algorithm (left) can be used in determining the cause of PU/PD.

MANAGEMENT OF DIABETES MELLITUS

General Considerations

Treatment of diabetes mellitus will only be successful if the dog owner understands all aspects of disease management, including dietary regulation and a regular exercise schedule. Investing time in a careful explanation of all aspects of diabetes management is strongly recommended.

The first aim of diabetic management is to eliminate the clinical signs without causing clinical hypoglycemia. Signs such as urinating indoors, repeatedly having to go outdoors to urinate, drinking from undesirable places (for example, the toilet bowl) or stealing food are often not well tolerated by owners. Resolution of the clinical signs improves the quality of life for both the dog and the owner. The next goal of therapy is to prevent diabetic complications such as hypoglycemia, blindness or peripheral neuropathies.

Ovariohysterectomy

If diabetes mellitus has been diagnosed in an intact bitch, immediate spaying is required to prevent further exposure to endogenous progesterone. If the dog is a good candidate for surgery, ovariohysterectomy should be carried out prior to insulin treatment, and intravenous fluid therapy should be administered.

If the bitch's condition is critical (dehydration, anorexia, uremia, severe hyperglycemia and glucosuria) and surgery is contraindicated, intravenous fluid therapy and insulin administration should be started to stabilize her condition.

Ovariohysterectomy should then be carried out as soon as the bitch's condition has improved sufficiently. On the day of surgery, pre-operative fasting will necessitate reducing the insulin dose to around 30 percent. Following surgery, regular monitoring of the blood glucose concentration is necessary until the bitch is in stable condition. The insulin response of target tissue cells will often improve following ovariohysterectomy and the insulin demand will decrease accordingly.

Diet

Volume and composition of meals should be identical from day to day. Commercial diets with a low soluble carbohydrate and a high fiber content provide a more gradual intestinal uptake of glucose. However, the low caloric density of such diets may be a problem in cachectic dogs that need to gain weight.

Types of Insulins

Insulin preparations can be divided into three categories:

Long-acting Insulins

Ultralente insulins
- 100 percent crystalline insulin

PZI insulins
- Contain protamine and zinc

Intermediate-acting Insulins

Lente insulins (e.g. Vetsulin™)
- Mixtures of 30 percent amorphous and 70 percent crystalline insulin in aqueous suspension

NPH insulins
- Contain protamine

Short-acting Insulins
- Soluble insulin and semilente insulin
- Intravenous administration possible

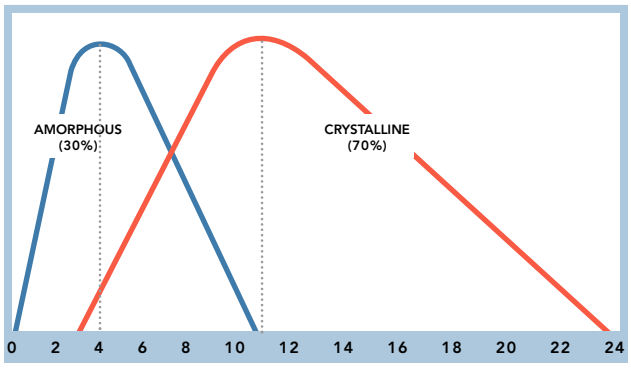
Due to differences in metabolism, the duration of activity of one type of insulin will vary from dog to dog. The source of the insulin can also differ. Vetsulin (porcine insulin zinc suspension), which contains porcine insulin, is similar to canine insulin. Recombinant human insulins are also available; however, human insulins differ from canine insulin by one amino acid.

USING VETSULIN™ (PORCINE INSULIN ZINC SUSPENSION) FOR TREATING DOGS WITH DIABETES

Pharmacokinetics of Vetsulin

Vetsulin is a sterile, aqueous suspension of purified porcine insulin. Vetsulin contains 40 IU per mL, consisting of 30 percent amorphous and 70 percent crystalline zinc insulin. Vetsulin is a lente, or intermediate-acting, insulin. In dogs, the amorphous fraction has peak activity approximately four hours after subcutaneous administration, and its effects last for about eight hours. Thereafter, the effect is maintained by the crystalline fraction, which has a slower onset of action and peak effects around 11 hours following injection. Afterward, the effect gradually declines to zero. Figure 3.

FIGURE 3



Schematic representation of Vetsulin concentration in dogs showing biphasic activity wherein amorphous activity peaks at 4 hours and crystalline activity peaks at 11 hours.

Vetsulin Dosing

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, two to five cm (three-fourths inch to two inches) from the dorsal midline, varying from behind the scapulae to the mid-lumbar region and alternating sides.

Initially, this dose should be given once daily concurrently with, or right after, a meal. The dog should be re-evaluated at appropriate intervals and the dose adjusted based on clinical signs, urinalysis results, and glucose curve values until adequate glycemic control has been attained. Glycemic control is considered adequate if an acceptable blood glucose curve was achieved (reduction in hyperglycemia and a nadir of 90–125 mg/dl), clinical signs of hyperglycemia (polyuria, polydipsia, and ketonuria) were improved, and hypoglycemia (blood glucose < 80 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 percent less than the once-daily dose required to attain an acceptable nadir. Further adjustments in dose 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.

Once the maintenance dose has been established and the dog is stable, a long-term management program must be implemented. The aim is to minimize variations in insulin requirement. This includes monitoring to detect underdosage or overdosage of insulin, and adjustment of dose, if required. Careful monitoring during maintenance will help limit the chronic problems associated with diabetes, including cataracts, etc.

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

INITIAL RECOMMENDED VETSULIN DOSE IS 1 IU INSULIN/KG BODY WEIGHT, PLUS A BODY-WEIGHT-DEPENDENT DOSE SUPPLEMENT, AS SHOWN.

Various approaches to maintenance have been described. The most clinically accepted approach is to have the owner monitor and record the dog's general health (including well-being, thirst and appetite) and check urine glucose daily. Dogs should be checked every two to four months (more often if there are problems) for general health, urine glucose and blood glucose level.

Adjustments to the insulin dose must be based on full analysis of clinical data and the blood glucose measurement.

The use of progestogens in dogs suffering from diabetes mellitus should be avoided. Ovariohysterectomy should be considered for intact bitches. Stress and irregular exercise must be avoided. Care must be taken with the use of corticosteroids. It is important to establish a strict feeding schedule in consultation with the owner that will include a minimum of fluctuations and changes.

It is extremely important that owners are able to recognize the signs of hypo- or hyperglycemia and respond appropriately. Polyuria, polydipsia and polyphagia in combination with weight loss, general bad condition, loss of hair or abnormal furry coat and lethargy are the most common clinical signs of hyperglycemia, and require administration of insulin to restore blood glucose levels to an acceptable range.

Vetsulin™ (porcine insulin zinc suspension): 40 IU v 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 dogs, 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 dog owners may attempt to replenish their syringe inventories and/or insulin supply from their local human pharmacies. Pharmacies carry U-100 (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 U-100 syringe with Intervet's Vetsulin would result in a dog receiving two and a half times less insulin than required. Human insulins are formulated at a concentration of 100 IU/mL. If a client uses a U-40 syringe with a 100 IU insulin preparation, they would be injecting two times the amount of insulin necessary, which could result in fatal hypoglycemia.

Most pharmacists are not aware of Vetsulin nor the U-40 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 and even death.

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

Starting Regulation With Vetsulin™ (porcine insulin zinc suspension)

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 have 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 dogs can be categorized as non-complicated:

1. Dogs 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. Dogs 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 dog.
- 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, hepatic disease.
- Photograph the dog (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 one to two 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 appropriate diet.
- Begin treatment with Vetsulin.

Starting Vetsulin™ (porcine insulin zinc suspension)

In-clinic:

- Weigh the dog. 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 dog. If the dog is grossly overweight, utilize the optimal body weight for calculating the starting dosage of Vetsulin.
- Establish a starting dose based on the labeled dosage of one IU/kg plus the weight-based supplemental dose.
- Begin with once-daily injections, then evaluate.
    - Some dog 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 ease of giving injections, the client is more likely to willingly accept twice-daily injections, if needed.
    - Remember that hyperglycemia does not kill dogs acutely; hypoglycemia does.
    - The majority of dogs (two-thirds) will require twice-daily Vetsulin injections.
- Keep the dog hospitalized for the day to verify that the starting dose does not cause hypoglycemia.
- Instruct owner:
    - The majority of dogs (two-thirds) will require twice-daily Vetsulin injections.
    - Injection technique
    - How to identify and treat hypoglycemia
    - Parameters to monitor at home
    - Preferred diet and frequency of meals
    - Exercise recommendations
- Discharge dog to owner's care for one week. This allows the dog and owner to acclimate to the injections. Alternatively, some practitioners may prefer to complete the initial regulation in the 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

Six to seven days after starting Vetsulin, the dog should be returned for evaluation.

- Obtain owner's overall impression of the dog's progress.
- Re-weigh the dog. 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 1 IU.
- Additional adjustments in dose should be made no more frequently than every five to seven days.
- Once regulated on Vetsulin, the dog should be rechecked every two to four months.

Feeding Schedule

Good glycemic control is dependent upon a controlled and consistent dietary intake. It is important to achieve and then maintain a normal body weight, because this is a strong indicator of good diabetic control. The dietary requirements of a diabetic dog are highly variable—diet must be individually tailored for each dog.

Body weight is a major factor in diet selections. Obese dogs require reduced caloric intake, either through feeding a calorie-restricted diet or by feeding a reduced quantity of the normal diet. Increasing physical activity will also be beneficial in obese dogs. On the contrary, underweight dogs may require calorie-rich diets such as pediatric or convalescent diets.

Another important consideration is the presence of concurrent disease, for example, renal failure or pancreatitis. It may be that the dietary management for these associated problems is more critical than a specific "diabetic" diet.

Dogs tend to gobble their food. Traditionally, the dog's daily food intake should be divided into two meals. The first meal is given around the time of the morning insulin injection, and the second meal is given approximately 7.5 hours (six to ten hours) later, at the time of peak insulin activity. Fiber-rich diets have been shown to slow the postprandial glucose surge in dogs, which consequently improves glycemic control.

Dose Adjustment

In dogs, dose adjustment should be managed in steps of 10 percent. Following adjustment, evaluation should not take place before the new dose has been given for a period of at least five to seven days. Although maintaining a normal blood glucose concentration throughout the entire day is not possible, the aim is to maintain blood glucose concentrations below the renal threshold for a substantial part of the day. This will result in the disappearance of most of the dog's clinical signs, which is the main goal of therapy.

MONITORING DIABETIC CONTROL

Clinical Signs

If the blood glucose concentration can be kept below the renal threshold, glucosuria will be prevented and there will be no polyuria or polydipsia. Water consumption less than 60 mL/kg/day usually indicates good diabetic control. Altered appetite and failure to maintain a normal body weight may suggest poor diabetic control.

How To Evaluate Treatment

Importance of clinical signs

The objective for the treatment of diabetes mellitus is to eliminate clinical signs of diabetes in the dog. Many tools, such as the glucose curve, are available to evaluate the success of insulin therapy. However, the temperament of the dog can make these procedures non-reliable (stress-induced hyperglycemia) or even impossible to perform. In these cases, the owner's evaluation of clinical signs will help the monitoring process.

Evaluation of insulin therapy

Clinical signs seen in diabetes mellitus are good indicators of glycemia. Hence, a dog with polyuria, polydipsia and weight loss will not have a normal blood glucose curve. This will not only be the case when the diagnosis is made, but can also be observed at home during regulation. Demonstration of these clinical signs indicates poor regulation or a concurrent disease (e.g., hyperadrenocorticism, infection, etc.).

When administering insulin, clinical signs will decrease as the optimal dose is approached. When glycemia is close to the renal threshold for glucose excretion, osmotic diuresis will stop or decrease significantly. To evaluate polyuria and polydipsia, the veterinarian can ask the owner to measure the water consumption in the morning and at night to determine if any differences occur during the day.

Weight of the dog must be evaluated on a regular basis. The goal is to have consistent weight. However, if the dog is receiving a weight-reducing diet, it can be difficult to distinguish whether the weight loss is due to the diet or to poor regulation. Presence of other clinical signs will give a good indication. If weight loss is seen despite an excellent appetite, this is an indication of poor regulation and the dog should be re-evaluated in the clinic.

The presence of any infections (cystitis, dental abscess, dermatitis, etc.) can affect treatment and must be reported by the owner. Cataracts should also be reported, as they will develop in the presence of hyperglycemia. In these cases, re-evaluation in the clinic is advisable.

Important:
Ideal regulation occurs when the owner is satisfied with the resolution of the dog's polyuria and polydipsia and the blood glucose curve remains below the renal threshold for the majority of the 24-hour day. Difficulties in obtaining ideal regulation can be associated with a variety of factors that should be identified and resolved.

SUMMARY OF CLINICAL SIGNS POSSIBLY ENCOUNTERED DURING REGULATION OF DIABETIC DOGS WITH VETSULIN

HYPOGLYCEMIA or blood glucose level too low	EUGLYCEMIA or normal blood glucose level	HYPERGLYCEMIA or blood glucose level too high
Restlessness, trembling or shivering, unusual movement or behavior, muscle twitching, unconsciousness (coma).	Normal behavior, normal water and food consumption.	Polyuria, polydipsia, polyphagia, weight loss, cataracts, rear limb weakness, lethargy, weakness.
Possible cause: insulin overdose, excessive exercise, insufficient food.	Good balance of insulin, food, exercise. Good health status.	Possible cause: insufficient insulin administration, concurrent disease, insulin resistance, glucose toxicity, infection.

Urine Monitoring

Urine testing can be helpful to detect diabetic instability. For example, prolonged or persistent ketonuria may warn of impending clinical ketoacidosis. Alternatively, increasing levels of urine protein, increasing urine pH, and/or the presence of blood or leukocytes may indicate a urinary tract infection.

Assessing glycemic control from urine glucose tests is much more difficult. Glucosuria is only seen when the renal threshold is exceeded. A positive urine glucose tells us that the blood exceeded 180 mg/dl at some point since the urinary bladder was last emptied. A negative urine glucose informs us that the blood glucose was maintained at less than 180 mg/dl since the bladder was last emptied. A negative or positive urine glucose correlates very poorly with blood glucose and does not determine the degree of hypoglycemia or hyperglycemia.

Changing trends in urine glucose levels are, therefore, probably more helpful. Persistently negative urine glucose may signal for a reduction in insulin dose if there are clinical signs of hypoglycemia supported by blood glucose tests. On the contrary, increasing urine glucose levels may lead to concerns that there are administration problems or the development of resistance to exogenous insulin.

Urine testing can provide useful information and may suggest the need for further clinical investigation. Due to the marked limitations of urine glucose testing, however, the dose of insulin should not be altered based on this information alone.

Glycosylated Blood Proteins

Glycosylated blood proteins are formed by the non-enzymatic, irreversible binding of glucose to blood proteins. Glycosylation of serum proteins, particularly albumin, produces fructosamine.

The amount of fructosamine produced is directly proportional to the blood glucose concentration: the higher the average daily blood glucose concentrations, the more fructosamine is made. Albumin is degraded after 14–21 days; therefore, the amount of fructosamine on any given day reflects the average blood glucose concentration over the previous two to three weeks.

Measuring fructosamine is a simple and inexpensive test. It requires one mL of serum or plasma, which can be collected at any time; the dog does not need to fast. Fructosamine is useful both for the diagnosis of diabetes mellitus and as a tool for monitoring control. If a baseline fructosamine level is obtained at the time of diagnosis, follow-up serial measurements can be taken as management progresses. If good glycemic control is achieved, there should be a reduction in fructosamine levels.

As with any test, fructosamine testing has limitations. Hypoproteinemia may lower fructosamine levels. Dogs in which diabetes is detected early may have a normal serum fructosamine because they have not been hyperglycemic long enough to increase fructosamine levels.

Glycosylated hemoglobin is formed when glucose binds to hemoglobin in the red blood cells. Glycosylated hemoglobin has a longer half-life than albumin, so it is not quite as useful as fructosamine for short- to medium-term diabetic monitoring.

Monitoring a Diabetic Dog with Fructosamine and Glycosylated Hemoglobin

Generally, monitoring blood glucose is a good way to evaluate regulation of the diabetic dog. It is inexpensive, accurate, rapid and requires only a drop of blood. However, in certain conditions it is not reliable, because blood glucose concentration is influenced by many factors. Consequently, blood glucose curves may not reflect the actual effect of the insulin treatment. Food intake, exercise, dog cooperation, use of a drug (e.g., xylazine, demetomidine, prednisolone, progestagens, megestrol acetate), and other conditions (e.g., hyperadrenocorticism, acromegaly) or stress can affect blood glucose concentrations. In these cases, therefore, blood glucose measurement will not be helpful and other methods of evaluation should be used. Observation of clinical signs and monitoring of glucosuria can be done on a regular basis, or veterinarians can rely on evaluation of fructosamine and glycosylated hemoglobin (GHb) in laboratory testing.

Fructosamine and GHb are two glycated proteins commonly used for monitoring diabetic human patients. These two proteins are markers of mean glucose concentration, and their concentration is proportional to the blood glucose concentration. The concentration of these proteins is not affected by stress; therefore, they are ideal for monitoring stressed, diabetic dogs. However, although fructosamine and GHb are good tools for determining regulation, they will not identify an underlying problem, nor will they replace glucose curves needed for adjustments of therapy. Rather, they give an idea of the control of the glycemia for a long period: fructosamine reflects the glycemic control for the previous two to four weeks, and GHb for the prior two to four months.

Fructosamine is preferred when rapid changes of dosage are needed. It is more commonly evaluated, because more analytical assays are available that are less time consuming and complicated. Interestingly, successful monitoring and regulation can be achieved with weekly (or monthly) measurements of serum fructosamine.

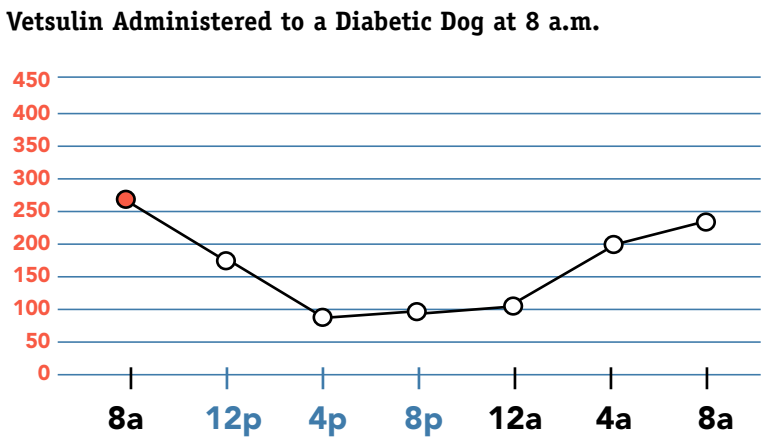
Test results and interpretation vary greatly depending on the literature consulted and the laboratory where the test is performed. Therefore, it is recommended to ask each laboratory for its guidelines for the purposes of interpretation.

To submit blood samples to the lab, tubes for serum (red-top tubes) must be used for fructosamine; and tubes for whole blood (EDTA tubes, lavender-top tubes) for GHb.

Blood Glucose Curves

The most accurate way to assess response to treatment is by generating a blood glucose curve. Ideally, the first sample should be taken just prior to insulin administration. Alternatively, after the dog has been given its first meal followed by the Vetsulin™ (porcine insulin zinc suspension) injection in the morning, the first blood sample should be taken as soon as possible. Thereafter, blood samples should be taken approximately every two hours throughout the day (12–24 hours). Prior to the insulin injection, the blood glucose is usually elevated. Following injection and absorption of Vetsulin, the blood glucose is expected to fall; at some point the glucose should plateau at its lowest blood concentration (the glucose nadir) after which it climbs again to approximately pre-injection levels. Blood glucose curves at the clinic only approximate how the diabetic dog responds to insulin at home. Feeding and exercise patterns are different and stress can markedly alter the glycemic response. Some clinicians teach their clients to perform blood glucose curves at home using blood from the pinna and portable glucometers.

Figure 4.
Example of 24-hour glucose curve



Interpreting the Glucose Curve

In conjunction with the presence or absence of clinical signs (+/- serum fructosamine levels) the glucose curve provides the information to determine whether the correct dose of Vetsulin has been selected for the individual dog. From the curve we can establish:

- Whether or not Vetsulin is effective in lowering the blood glucose level
- The rate of onset of Vetsulin activity
- The time to peak action of Vetsulin
- The glucose nadir
- The duration of Vetsulin activity

Ideally, Vetsulin should reduce the blood glucose, have a relatively rapid onset of action of two to four hours post-injection, and produce a blood glucose nadir around 90–125 mg/dl. The duration of the effect will determine if Vetsulin is administered once or twice daily.

How To Evaluate Treatment Using a Glucose Curve

Many tools are available to evaluate treatment, including:

1. Glucose curve
2. Punctual blood samples
3. Glucosuria monitoring
4. Clinical signs
5. Fructosamine and glycosylated hemoglobin

How to Complete a Glucose Curve

Feed and then inject the dog with Vetsulin™ (porcine insulin zinc suspension) as it is done at home (this may be done by the owner and then verified by the veterinarian). If the dog exercises at home during the day, the same exercise routine should be adhered to while in the clinic.

Blood Sampling:	• Just prior to insulin administration. • Then, in at least 60- to 120-minute intervals. • Over a period of 12 hours, ideally for 24 hours. • **Caution:** Be careful with small dogs to avoid anemia.

How to Interpret a Glucose Curve

Remember that:	• Stress can affect reliability of results. • This is only one tool among many others.
It helps to determine:	• Insulin effectiveness. Maximum and minimum glycemia, which should ideally be between 100 and 300 mg/dl (5.6–10 mmol/L).
Glucose nadir goal:	• 90–125 mg/dl (5.0–6.9 mmol/L)
Duration of insulin action:	• From the injection to a glycemia of 250 mg/dl (13.9 mmol/L). • **Goals:** SID 20 hours; BID 10–12 hours.

OWNER PARTICIPATION

Owners should be advised that stabilizing their dog might take as long as several months. During therapy, encourage pet owners to actively participate in monitoring their dog's progress. Initially, monitoring should be carried out on a daily basis; but once the dog is stable, this frequency can be decreased.

Many owners can be successfully instructed to take capillary blood samples, and to use a handheld glucometer. If this is not possible, the owner can be instructed to test the urine for the presence of glucose. Before dose rate changes are made, however, blood glucose concentrations should be confirmed.

Most owners quickly learn to give daily insulin injections. Remind owners that it is important to monitor their dog's food intake before giving the insulin injection. Dogs that are off their feed should have their insulin reduced by at least half. Significant dose adjustments may be required in dogs with gastroenteritis or a reduced appetite.

TREATMENT COMPLICATIONS

Hypoglycemia

If the insulin dose is too high, clinical signs of hypoglycemia may be observed. This serious and potentially fatal condition (which can also be triggered by events such as loss of appetite, vomiting or excessive exercise) may occur at any stage, even after stabilization has been achieved. The clinical signs include hunger, restlessness, shivering, ataxia, disorientation, convulsions and coma. However, some dogs just become very quiet and inappetent.

Hypoglycemic seizures observed by the owner should be treated immediately at the home rather than delaying treatment for the dog to be taken to a veterinary clinic. The owner should be instructed to pour a small amount of a sugar solution (e.g. Karo syrup) onto his or her finger and then to rub the solution onto the dog's gums. Absorption of the sugar occurs quickly and the dog usually responds in one to two minutes. The sugar solution should never be poured directly into the mouth because of the risk of aspiration pneumonia. Once the dog has responded to the sugar administration and is sternal, it may be fed a small, high-protein meal. Once the dog has stabilized, it should be transported for veterinary evaluation.

Problems with Regulation

If the response to insulin therapy is poor, a blood glucose curve should be made along with every effort to rule out other concurrent or underlying disorders.

Problems with Administration

Vetsulin™ (porcine insulin zinc suspension) has been specially developed for use in dogs and has a concentration of 40 IU/mL, making dilution unnecessary. Dilution should be avoided since it will alter the pharmacokinetics of the insulin.

Antibodies

Antibodies may be directed either against the insulin or against other foreign proteins in the preparation. The presence of antibodies is common and does not frequently lead to poor regulation. Antibody production is less likely if homologous insulin (same structure) is given. The porcine insulin in Vetsulin has a similar structure as canine insulin.

Other Hormones
When treating a dog for diabetes mellitus, medication with progestogens should be discontinued immediately. Intact bitches should be spayed. If dogs are being treated with corticosteroids, alternative treatment should be sought. If this is not feasible, efforts should be made to minimize the corticosteroid dose.

Stress, Infections and Obesity
Stress or infections (particularly infections of the oral cavity) can lead to a decline in the sensitivity of target tissues to insulin. Obese dogs have reduced insulin sensitivity.

Inadequate Insulin Dose–Persistence of Clinical Signs
Insufficient insulin will not lower blood glucose to an appropriate nadir. If the blood glucose level does not drop below the renal threshold level for most of the day, clinical signs (polyuria, polydipsia) will persist.

Rapid Metabolism/Short Duration of Action of Insulin
The duration of effect of any insulin preparation is highly variable between individuals. Insulin dosages that are effective in one dog may not be effective in another. In dogs where Vetsulin™ (porcine insulin zinc suspension) is metabolized more rapidly, once-a-day therapy may not be sufficient to prevent the onset of clinical signs 12–14 hours later. These dogs may require twice-daily therapy.

Length of Action of Insulin
In treating a diabetic dog, one daily injection of insulin may be sufficient. Short-acting insulin generally has a duration of one to ten hours; intermediate-acting insulins such as Vetsulin, NPH and human lente have a duration of 6–24 hours, and ultralente has a duration of 8–28 hours. These figures, however, are only generalities. In many dogs treated with intermediate- and long-acting insulins, length of action will be less than 24 hours.

However, insulin type is not the only responsible factor for the length of action. Variations in metabolic rate require that some dogs receive two daily injections of insulin. The short duration (or rapid metabolism) phenomenon can be seen not only at the beginning of the treatment, but also after many weeks or months. When this problem occurs, the dog could have glucose in the morning urine and the owner could report the presence of polyuria, polydipsia and weight loss.

The glucose curve is an ideal tool for differentiating the problem of short duration and Somogyi effect. In fact, it is easy to misdiagnose if only a few blood samples are taken. The rapid glucose drop could be missed prior to the rise of blood glucose, caused by compensatory mechanisms to stop hypoglycemia.

A rapid metabolism or a short duration of action can be seen when there is hyperglycemia [i.e., glycemia of more than 200–250 mg/dl (11–14 mmol/L)] 18 hours or less after the injection of insulin. This phenomenon has been observed as early as six hours after the administration of insulin.

There are two alternatives when a short length of action is identified: 1. Changing to a longer-acting insulin, or 2. Injecting the dog twice a day. This second alternative is the better choice for the dog, provided it does not conflict with the owner's schedule.

Decreasing the dose by 25 percent and administering two equivalent doses of insulin at 12-hour intervals is recommended. This should decrease the risk of hypoglycemia when there is an overlap in insulin effect. Each dose of insulin should be administered around the time of feeding, with each meal meeting 50 percent of the daily caloric requirements.

Somogyi Effect

An insulin dose that is slightly too high may bring about the Somogyi effect, otherwise known as rebound hyperglycemia. This is a chain of reactions through which the body attempts to counteract the decline in the blood glucose concentration. If the blood glucose concentration falls to less than 65 mg/dl (3.6 mmol/L), or if the blood glucose decreases rapidly regardless of the glucose nadir following injection of insulin, the dog may become hungry and restless or lethargic. In response to a declining glucose level in the CNS, epinephrine, cortisol, glucagon and growth hormone are released.

These hormones bring about an increase in the blood glucose concentration through gluconeogenesis, release of glucose from hepatic glycogen and increased peripheral resistance to insulin. Polyuria and polydipsia are seen, and this can easily be misinterpreted.

If the morning polyuria is thought to be the result of an insufficient insulin dose and a higher dose is given, the problem will be aggravated. An even more pronounced Somogyi effect will follow and, sooner or later, this may result in severe hypoglycemia when the counter-regulatory mechanisms are exhausted. Hyperglycemia can sometimes persist for as long as three days after a single hypoglycemic episode. As a result, blood glucose concentrations do not always normalize within a few days after lowering the insulin dose.

If the Somogyi effect is suspected, an alternative approach involves decreasing the dose by 10–25 percent and closely observing the clinical picture. If signs of polyuria or polydipsia become worse following dose adjustment, it is unlikely that a Somogyi effect was the cause of the regulation problems.

Conversely, if the polyuria and polydipsia disappear within two to three days, it is probable that the Somogyi effect was the cause.

Somogyi Overswing

What is Somogyi Overswing?

Somogyi overswing is the normal physiological response to hypoglycemia caused by a high insulin dose. It is also called insulin-induced hyperglycemia or Somogyi effect.

Why does it occur?

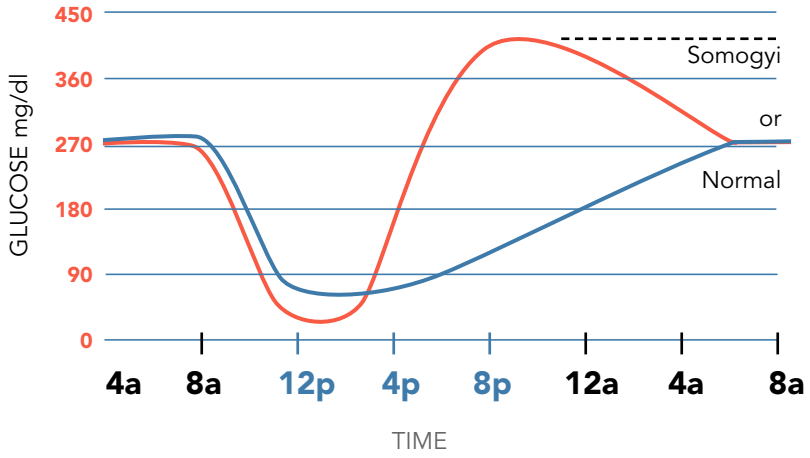
After the administration of a high dose of insulin, glycemia decreases rapidly [below 65 mg/dl (3.6 mmol/L)]. A chain of reactions which counteract hyperglycemia are initiated:

- Release of epinephrine, ACTH, glucagon and growth hormone
- Stimulation of lipolysis, gluconeogenesis and glucogenolysis

This results in rebound hyperglycemia (with or without ketosis) that cannot be controlled, as a diabetic dog does not secrete sufficient endogenous insulin. Glycemia can reach levels of 400 mg/dl (22 mmol/L) or greater.

Risk Factor

If insulin dose modifications are based on morning glucosuria, this will aggravate the problem and lead to severe hypoglycemia.



When to Suspect a Somogyi Overswing

- Minimal glycemia: < 65 mg/dl or 3.6 mmol/L
- Maximum glycemia: 400–800 mg/dl or 22–44 mmol/L
- Persistent morning glucosuria: > 1 percent or 1–2 g/dl (strips)
- Morning hyperglycemia: > 400–450 mg/dl or 22 mmol/L
- Clinical signs:
    1) Polyuria, polydipsia, weight loss
    2) Hypoglycemia (weakness, convulsions, ataxia, behavior changes)
- High insulin dose: close to 2.2 IU/kg and greater

Diagnosis

A 24-hour glucose curve showing hypoglycemia and consecutive hyperglycemia is the only diagnostic tool that can be used to detect a Somogyi Overswing.

Note: A Somogyi Overswing can sometimes persist for as long as three days after a hypoglycemic episode.

Eliminating the Problem

Decrease insulin dose by 10–25 percent, for up to three to five days. Glycemia and clinical signs should return to a more normal state. Note: A dog with a dose close to or exceeding 2.2 IU/kg (1 IU/lb) will need a greater reduction than a dog receiving a smaller dose.

Re-evaluate the dog seven to ten days later and adjust the dose, if necessary. (A glucose curve is strongly recommended.)

FAILURE TO RESPOND TO INSULIN OR "INSULIN RESISTANCE"

Some dogs appear to have no response to insulin; the blood glucose stays elevated for the duration of the glucose curve. Insulin resistance is diagnosed in dogs if the blood glucose does not fall after injecting more than 1.5 IU/kg, or more than 2.2 IU/kg is required to keep the blood glucose level below 300 mg/dl.

Prior to ruling in a diagnosis of insulin resistance, it is important to rule out administration problems:

- Is the insulin stored correctly?
- Is the insulin in date?
- Are the correct syringes being used to give the insulin?
- Who is giving the insulin?
- Where are the sites of insulin injection?
- What is the owner's technique for giving insulin?

The owner should be observed gently mixing Vetsulin™ (porcine insulin zinc suspension), drawing up the correct volume into the syringe, expelling the air and then successfully injecting the dog. The sites of injection should be examined for fibrosis, which could delay the absorption of the insulin.

Once it is determined that the owner's injection technique is correct, the veterinarian should administer the dog's next dose of Vetsulin from a new bottle. If there is still no response to Vetsulin, an intravenous trial with soluble insulin is required. If the blood glucose level falls following the intravenous administration of soluble insulin, then the dog is not insulin resistant; in this case an alternative site of injection, a different dose of insulin or another insulin preparation must be sought. If there is no response to intravenous soluble insulin, then investigation for the cause of the insulin resistance should be considered.

PROGNOSIS IN DIABETES MELLITUS

The prognosis for a diabetic dog depends, to a large extent, on the level of confidence, knowledge and dedication of its owner. These factors can be favorably influenced by good veterinary-client communication that provides encouragement to the owner. Most diabetic dogs can live relatively normal lives with periodic check-ups and testing. Well-regulated diabetic dogs can be expected to live normal lifespans in the absence of other concurrent diseases.

VETSULIN™ (PORCINE INSULIN ZINC SUSPENSION) EFFICACY DATA

The starting dose of insulin may vary significantly from the dose that achieves acceptable control of hyperglycemia and hyperglycemia-associated clinical signs. The goal at therapy initiation is to establish significant control of diabetic signs while avoiding hypoglycemia. Several insulin therapy starting dose recommendations have been described.

Few reports referring directly to the use of porcine insulin zinc suspension are available. Church compared the blood glucose response to neutral protamine Hagedorn insulin (NPH), protamine zinc insulin (PZI), and porcine insulin zinc suspension (IZS-P) in eight naturally occurring, previously untreated diabetic dogs. The author noted great variability in individual response to the different insulins, and in time, to peak activity between different dogs to different insulins, but noted no difference in overall response between dogs or insulins. Church concluded that IZS-P had a relatively predictable peak activity time compared to NPH and PZI, but that it was impossible to accurately predict an individual dog's response to a particular insulin formulation except in broad, generalized terms.

An initial porcine insulin zinc suspension dose of 1 IU/kg body weight plus a body weight-dependent dose supplement was described in small animal endocrinology notes provided to Dutch veterinary practitioners by Belshaw.

Two other published reports support the claim that the starting dose of 1 IU/kg plus a weight-dependent supplement proposed by Belshaw is safe and effective. In a study by Graham, Nash and McKellar, plasma insulin and glucose concentrations were measured in 10 stable, client-owned diabetic dogs of various breeds receiving once-daily porcine insulin zinc suspension injections ranging from 1.01 to 2.80 IU/kg (mean = 1.90 ± 0.64 IU/kg). One or two peaks in plasma insulin were noted following a single insulin injection; plasma insulin was elevated above baseline for 14–24 hours; and blood glucose levels were effectively and safely reduced. No adverse effects attributable to the insulin were reported. A study by Horn and Mitten evaluated eight clinically stable, client-owned diabetic dogs of various breeds receiving once-daily porcine insulin zinc suspension injections ranging from 0.7 to 2.3 IU/kg (mean 1.3 ± 0.5 IU/kg). Owner assessment of control of clinical signs of diabetes and 24-hour blood glucose curve results were obtained. Acceptable blood glucose maintenance was defined as a blood glucose between 90–234 mg/dL (5 to 13 mmol/L). Five of the eight dogs showed partial blood glucose control. These five dogs maintained glycemic control for 9–13 hours. Two dogs had blood glucose values in the acceptable range for 22 and 24 hours, respectively. One dog became distressed during hospitalization, and the blood glucose curve did not show an identifiable response to the insulin.

Although insulin dose varies between dogs—and for an individual dog over time due to differences in physiological state, concurrent disease conditions, endogenous insulin production, diet and/or exercise — the referenced studies support a starting Vetsulin dose of one IU/kg plus a weight-dependent dose supplement as safe and effective.

Field Trial Data

In the US field study, treatment with Vetsulin resulted in a reduction in blood glucose curve means and mean nadirs post-treatment relative to pre-treatment. The mean (± SD) blood glucose curve concentration was reduced from 370 ± 100 mg/dL at enrollment (Time 0) to 151 ± 75 mg/dL (Time 1), 185 ± 92 mg/dL (Time 2), and 184 ± 87 mg/dL (Time 3). The blood glucose mean nadir was reduced from 315 ± 93 mg/dL at enrollment (Time 0) to 93 ± 35 mg/dL (Time 1), 120 ± 62 mg/dL (Time 2) and 119 ± 60 mg/dL (Time 3).

Improvements in the incidence of polyuria, polydipsia and ketonuria after the initiation of Vetsulin treatment are summarized in Table 1. Lower one-sided 95 percent confidence limits were calculated at each study time for each clinical response rate (95 percent confident that the general population response should be at least as good as the lower limit response of the study dogs).

Table 1: Change in clinical signs of diabetes mellitus and lower than 95 percent confidence limit on percentage improved.

Clinical Sign	Study Time	RESULTS[a]			Proportion Improved	Percentage of Dogs Improved	Lower One-Sided 95% Confidence Limit[b]
		Observation Missing	Present[a]	Absent			
POLYURIA	0	1	49	3	NA	NA	NA
	1	0	2	51	47/49	96	88
	2	0	9	44	40/49	82	70
	3	0	3	50	46/49	94	85
POLYDIPSIA	0	0	50	3	NA	NA	NA
	1	0	2	51	48/50	96	88
	2	0	7	46	43/50	86	75
	3	0	2	51	48/50	96	88
KETONURIA	0	0	35	18	NA	NA	NA
	1	5	2	46	28/35	80	66
	2	3	2	48	30/35	86	72
	3	1	5	47	29/35	83	69

[a] For observation period 0, a missed observation of a clinical sign was considered to have been observed as absent. For treatment observation periods 1, 2 and 3, a missed observation of a clinical sign was considered to have been observed as present. This results in a conservative worst-case estimate of the proportion improved.
[b] The lower one-sided 95% confidence limits were obtained from StatXact 4 by using the lower limit from two-sided 90 percent confidence limits.

Investigator assessments of adequate glycemic control are summarized in Table 2. In cases where control was judged inadequate, adequate control was generally attained with an adjustment of the Vetsulin™ (porcine insulin zinc suspension) dose or a change to twice-daily administration.

Table 2: Investigator assessment of glycemic control: Study Times 1, 2 and 3.

Study Time	% Adequate (Number/total)	% Inadequate (Number/total)
Time 1	100 (53/53)	0 (0/53)
Time 2	66 (35/53)	34 (18/53)
Time 3	75 (40/53)	25 (13/53)

Titrating to an effective insulin dose and maintaining adequate glycemic control by dose adjustments was highly variable both between dogs and for any given dog over time. The frequency of administration and effective dose ranges for dogs completing the study are summarized in Table 3.

Table 3: Injection frequency and effective dose range for dogs completing the Vetsulin study (n=53).

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

The number of dose adjustments required to attain and maintain adequate glycemic control was also variable. Results are summarized in Table 4.

Table 4: Number of dose adjustments required to attain and maintain adequate glycemic control by weight class and study period (n = 53).

INTERVAL	RANGE IN NUMBER OF DOSE CHANGES BY WEIGHT CLASS			
	< 10 kg (n = 14)	10 – 11 kg (n = 5)	12 – 20 kg (n = 8)	> 20 kg (n = 26)
Dose determination period[a]	0 – 7	2 – 6	0 – 6	0 – 17
Between Time 1 and 2[b]	0 – 2	0 – 1	0	0 – 3
Between Time 2 and 3[c]	0 – 3	0 – 1	0 – 2	0 – 7

[a] 7 of 53 dogs required no dose adjustment. [b] 45 of 53 dogs required no dose adjustment.
[c] 27 of 53 dogs required no dose adjustment.

CONCLUSIONS: This study demonstrates that Vetsulin is safe and effective for reducing hyperglycemia and hyperglycemia-associated clinical signs in dogs with diabetes mellitus.

VETSULIN™ (PORCINE INSULIN ZINC SUSPENSION) SAFETY DATA

Insulin is an endogenous hormone whose mechanisms of action and effect have been studied for over 80 years. Insulin tolerance in the dog and the effects of hypoglycemia that results from overdosage have been well described. Regardless of insulin origin or formulation used, an increase in the dose above that which controls blood glucose concentrations will inevitably result in hypoglycemia. The safety of using various types of intermediate- and long-acting insulin to treat diabetes mellitus when dosed appropriately and accompanied by adequate monitoring of the disease process is supported by the extensive literature regarding canine and human diabetes.

Field Trial Data

In the US field 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 percent (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 percent (10/62) of the dogs.Two dogs each 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 also 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.

Dogs enrolled in this study were allowed to continue treatment with Vetsulin after study completion. Of the 66 dogs initially enrolled in the field study, 53 continued treatment into the extended use phase. Investigators evaluated the dogs every 90 days.

No findings that appeared to be related to treatment with Vetsulin were noted in dogs for which necropsy results were available.

vetsulin™
(porcine insulin zinc suspension)

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 ovariohysterectomized. 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 anti-inflammatories. 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 percent (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 percent (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 1IU/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 percent, 96 percent and 83 percent of study dogs experienced a reduction in polyuria, polydipsia, and ketonuria, respectively. Investigators reported adequate glycemic control an average of 81 percent 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.

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REFERENCE

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

REFERENCES

Church DB. (1981) The blood glucose response to three prolonged duration insulins in canine diabetes mellitus. *Journal of Small Animal Practice* Vol 22 pp 301-310.

Feldman EC & Nelson RW. (2004) *Diabetes Mellitus in Canine and Feline Endocrinology and Reproduction.* Eds. EC Feldman and RW Nelson. WB Saunders, Philadelphia.

Graham PA. (1996) Prognosis in diabetes mellitus. In: *Proceedings of Intervet International Symposium, New Aspects of Diabetes Mellitus*, European Society of Veterinary Internal Medicine, 6th Annual Congress 12 September 1996. pp 23-25.

Graham P, Nash A, McKellar Q. (1977) Pharmacokinetics of porcine insulin zinc suspension in diabetic dogs. *Journal of Small Animal Practice* Vol 38, pp 434-438.

Hess RS & Ward CR. (2000) Effect of insulin dosage on glycemic response in dogs with diabetes mellitus: 221 cases (1993-1998). *Journal of the American Veterinary Medical Association* Vol 216, pp 217-221.

Horn B & Mitten RW. (2000) Evaluation of insulin zinc suspension for control of naturally occurring diabetes mellitus in dogs. *Australian Veterinary Journal* Vol 78, pp 831-834.

Jensen AL. (1996) New developments in diagnosing and monitoring diabetes mellitus in dogs and cats with special emphasis on serum fructosamine. In: *Proceedings of Intervet International Symposium, New Aspects of Diabetes Mellitus*, European Society of Veterinary Internal Medicine, 6th Annual Congress 12 September 1996.

Mahaffey EA & Cornelius LM. (1982) Glycosylated Hemoglobin in Diabetic and Nondiabetic Dogs. *Journal of the American Veterinary Medical Association* Vol 180, pp 635-637.

Wess G & Reusch C. (2000) Capillary blood sampling from the ear of dogs and cats and use of portable meters to measure glucose concentration. *Journal of Small Animal Practice* Vol 41, pp 60-66.

For more information on treating dogs for diabetes mellitus, visit www.Vetsulin.com.

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