Date of Approval: April 1, 2004

FREEDOM OF INFORMATION SUMMARY

NADA 141-236

VETSULIN

Porcine insulin zinc suspension

VETSULIN (porcine insulin zinc suspension) is indicated for the reduction of hyperglycemia and hyperglycemia-associated clinical signs in dogs with diabetes mellitus.

Sponsored by:

Intervet, Inc.
P. O. Box 318
405 State St.
Millsboro, DE 19966

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1. GENERAL INFORMATION:

a.	File Number:	NADA 141-236
b.	Sponsor:	Intervet, Inc. P.O. Box 318 405 State St. Millsboro, DE 19966 Drug Labeler Code: 057926
c.	Established Name:	Porcine insulin zinc suspension
d.	Proprietary Name:	VETSULIN
e.	Dosage Form:	Injectable
f.	How Supplied:	2.5 and 10 mL multidose vials
g.	How Dispensed:	Rx
h.	Amount of Active Ingredient:	40 international units (IU) insulin/mL
i.	Route of Administration:	VETSULIN should be administered subcutaneously using a U-40 insulin syringe and should be given 2 to 5 cm from the dorsal midline, varying from behind the scapulae to the mid-lumbar region and alternating sides.
j.	Species/Class:	Canine

k. Recommended Dosage:
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 Table 1.

Table 1: Initial dose determination

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 field study, glycemic control was considered adequate if an acceptable blood glucose curve was achieved (reduction in hyperglycemia and a nadir of 60 to 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.

l. Pharmacological Category: Hormone

m. Indications: VETSULIN (porcine insulin zinc suspension) is indicated for the reduction of hyperglycemia and hyperglycemia-associated clinical signs in dogs with diabetes mellitus.

2. EFFECTIVENESS:

a. Dosage Characterization:

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.[1-8]

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.[8] 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.[1]

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 ten 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 $\pm$ 0.64 IU/kg).[9] One or two peaks in plasma insulin were noted following a single insulin injection, plasma insulin was elevated above baseline for 14 to 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 $\pm$ 0.5 IU/kg).[10] 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 5 to 13 mmol/L (90 to 234 mg/dL). Five of the eight dogs showed partial blood glucose control. These five dogs maintained glycemic control for 9 to 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 patients and for an individual patient 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 1 IU/kg plus a weight-dependent dose supplement as safe and effective.

b. Substantial Evidence:

EFFECTIVENESS AND SAFETY OF VETSULIN FOR REDUCING HYPERGLYCEMIA ASSOCIATED WITH DIABETES MELLITUS IN DOGS.

One multi-location field study was conducted between May 19, 1997, and May 9, 2001 to evaluate the effectiveness and safety of VETSULIN in the clinical

management of naturally occurring diabetes mellitus in dogs.

Study Director:
William E. Monroe, DVM, MS
Dept. of Small Animal Clinical Sciences
Virginia-Maryland Regional College of Veterinary Medicine
Blacksburg, VA

Cases were enrolled and managed by Investigators.

Investigators
William E. Monroe, DVM, MS, Blacksburg, VA
Edward A. Fallin, DVM, MS, Manakin-Sabot, VA
Mark R. Finkler, DVM, Roanoke, VA
John R. Hart, DVM, Rancho Santa Fe, CA
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Jennifer S. Shinn, DVM and Todd L. Towell, DVM, MS, Boulder, CO
Kimberly A. Williams, DVM, Annapolis, MD

Purpose: To assess the effectiveness and safety of VETSULIN for the reduction of hyperglycemia and hyperglycemia-associated clinical signs in dogs with diabetes mellitus.

General Design: The study objectives were achieved by comparing the relative effectiveness and safety of VETSULIN therapy to the pretreatment period. Dogs selected for inclusion in the study were those normally presented to the veterinary hospitals with diabetes mellitus. Only dogs with a definitive diagnosis of diabetes mellitus were enrolled in the study. A definitive diagnosis was established if the following criteria were met:

A blood glucose concentration >250 mg/dL AND one or more of the following:
- History of polyuria and polydipsia
- Weight loss despite good appetite
- Glucosuria
- Mild to moderate ketonuria
- A blood glucose concentration >250 mg/dL on another day.

Treatment was divided into two phases during the study, the Dose Determination Period and the Study Period. During the Dose Determination Period, the dog's daily VETSULIN dose was titrated by the investigator to achieve a blood glucose nadir of 60 to 160 mg/dL and attain adequate glycemic control. The investigator reevaluated dogs approximately every 4 to 7 days during the dose determination period. The VETSULIN dose was incrementally adjusted until an acceptable nadir was achieved. The Dose Determination Period continued until the

investigator was satisfied that adequate glycemic control had been attained. Adequate control was defined as a reduction in hyperglycemia with attainment of a suitable blood glucose curve and improvement of clinical signs relative to enrollment (Time 0).

At this point, the dog reached Study Time 1 and entered the Study Period phase of treatment. During the Study Period, glycemic control was re-evaluated at 30 ± 3 days (Study Time 2) and 60 ± 3 days (Study Time 3) after Time 1. The insulin dose was adjusted at these times, if needed, based on clinical signs reported by the owner, urine ketones measured at the recheck examination, and the Study Time glucose curve. Additional evaluations and dose changes were completed between study times if needed to maintain adequate glycemic control following the procedure described for the Dose Determination Period. The investigator initiated twice daily therapy during the Dose Determination or Study Periods if duration of insulin action was determined to be inadequate based on clinical signs and blood glucose curve/spot check results. If twice-daily treatment was initiated, VETSULIN injections were given approximately every 12 hours. The dose and diet were adjusted accordingly to achieve adequate control without hypoglycemia.

Animals: A total of 66 client-owned dogs were enrolled, and 53 completed the effectiveness and safety study. The patients completing the study included 22 breeds of purebred and various mixed breeds of 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).

Test Material: 2.5 mL and 10 mL multidose vials containing 40 IU of porcine insulin zinc suspension/mL.

Dosage: The initial VETSULIN dose was 1 IU/kg body weight plus a body weight-dependent dose supplement once daily as shown in Table 1. The dose was adjusted to achieve adequate glycemic control based on repeated blood glucose curve, urine ketone and clinical sign evaluations. Because a safe and effective insulin dose is highly variable among individual diabetics and for the same diabetic over time, the dose and frequency of administration was adjusted individually for each dog.

Route of Administration: Subcutaneous injection

Control: In accordance with 21 CFR 514.117(b)(4)(iv), the effects of VETSULIN were compared with experience historically derived from the predictable history of diabetes mellitus in dogs. The statistical analysis focused on the objective parameters evaluated at Study Times 1, 2, and 3 compared to the baseline values at Study Time 0 for each animal.

Study Duration: The Dose Determination Period needed to attain adequate

glycemic control ranged from 5 days to 151 days (mean: 42 days). This was followed by a 60 day Study Period.

Pertinent Variables Measured: Effectiveness was evaluated by comparing 12-hour blood glucose curve means and mean nadirs and the presence or absence of polyuria, polydipsia, and ketonuria pre-treatment (Time 0) and post-treatment (Times 1, 2, and 3). Investigator assessments of glycemic control during the Study Period were also compiled and evaluated. At each assessment, the investigator performed a physical examination, recorded body weight, and evaluated for injection site reactions. Any adverse events related to treatment that were reported by the owner were recorded. Pre- and post-treatment complete blood count and serum chemistry analyses were performed and evaluated for any significant changes.

Results: 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 2. Lower one-sided 95% confidence limits were calculated at each study time for each clinical response rate (95% confident that the general population response should be at least as good as the lower limit response of the study animals).

Table 2: Change in clinical signs of diabetes mellitus and lower 95% confidence limit on percentage improved.

Clinical Sign	Study Time	Result[a]			Proportion Improved	Percentage of dogs Improved (%)	Lower One - Sided 95% Confidence Limit[b] (%)
		Observation missing	Present	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% confidence limits.

Investigator assessments of adequate glycemic control are summarized in Table 3. In cases where control was judged inadequate, adequate control was generally attained with an adjustment of the VETSULIN dose or a change to twice daily administration.

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

Study Time	% Adequate (No./total)	% Inadequate (No./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 4.

Table 4: 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 5.

Table 5: 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.

Adverse Reactions: In the clinical effectiveness and safety study, 66 dogs were treated with VETSULIN. Sixty-two dogs were included in the assessment of safety. Hypoglycemia with or without associated clinical signs occurred in 35.5% (22/62) of the dogs at various times during the study. Clinical signs of hypoglycemia were generally mild in nature (described as weakness, lethargy, stumbling, falling down, and/or depression). Disorientation and collapse were reported less frequently and occurred in 16.1% (10/62) of the dogs. Two dogs had a seizure and one dog died during the seizure. Although never confirmed, the presumptive diagnosis was hypoglycemia-induced seizures. In the rest of the dogs, hypoglycemia resolved with appropriate therapy and adjustments in insulin

dosage.

Seven owners recorded the following observations about the injection site on the home monitoring forms: swollen, painful, sore, and a bleb under the skin.

The following clinical observations 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.

Extended Use: 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 animals approximately every 90 days.

The mean post-study survival time for extended use was 838 days (range of 41 to 1720 days). One owner reported three injection site reactions in one dog. The owner of this dog reported once that the injection site was painful and twice that there was a lump at the injection site. Seven dogs had one reported instance each that may have been related to hypoglycemia. Four dogs were reported as weak, one as lethargic, one as having decreased activity, and one as having had two seizures in a 4 month period. Following evaluation by the Investigator, the insulin dose was not changed for four dogs, was decreased for two dogs, and was increased for one dog. No other adverse reactions were reported. No findings that appeared to be related to treatment with VETSULIN were noted in dogs for which necropsy results were available.

3. TARGET ANIMAL SAFETY:

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.[1-10]

Porcine insulin zinc suspension safety in dogs was confirmed by the US field study. Dose-related hypoglycemia and occasional owner-observed injection site reactions were the primary events reported. Additional support for the safety of VETSULIN is provided by a study by Graham and Nash (unpublished) that included long term evaluation of dogs (up to 448 days of treatment) and US field study post-study extended use (41 to 1720 days of post-study treatment). No adverse events other than injection site reactions and hypoglycemia were

reported in any dog receiving long term therapy.

In years of clinical experience in the 20 countries where porcine insulin zinc suspension is currently registered for animal use, few problems have been reported with VETSULIN use in dogs. During the 1995-2001 period, the following adverse reactions in 19 dogs were reported to Intervet International. Six dogs were reported as destabilized and four as lack of expected effectiveness following a period of successful treatment. Two dogs developed edema of the head and neck that resolved when they were switched to another insulin product, and one dog developed a fibrous lump at the injection site. Two dogs dosed at typical porcine insulin zinc suspension doses developed hypoglycemia. One of those two dogs died. After an overdose of insulin, four dogs developed profound hypoglycemia which resulted in death in all four dogs.

4. HUMAN SAFETY:

This drug is intended for use in dogs, which are non-food animals. Because this new animal drug is not intended for use in food-producing animals, data on human safety pertaining to drug residues in food were not required for approval of this NADA.

Human Warnings are included on the product label as follows: "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".

5. AGENCY CONCLUSIONS:

The data submitted in support of this NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act and 21 CFR 514 of the implementing regulations. The data demonstrate that VETSULIN when used under the labeled conditions of use is safe and effective for the reduction of hyperglycemia and hyperglycemia-associated clinical signs in dogs with diabetes mellitus.

The drug is restricted to use by or on the order of a licensed veterinarian because professional expertise is judged to be critical in the diagnosis of diabetes mellitus, management of the condition and monitoring the possible adverse effects of the drug.

Under section 512 (c)(2)(F)(i) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for FIVE years of marketing exclusivity beginning on the date of approval because no active ingredient of the new animal drug has previously been approved.

6. ATTACHMENTS:

Facsimile Labeling is attached as indicated below:

a. Client Information sheet
b. Package Insert
c. Vial Label
d. Box Label

7. LITERATURE CITED

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