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FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-236

VETSULIN

Porcine insulin zinc suspension
Injectable 40 IU/mL
Dogs and Cats

The effect of the supplement is to 1) change the starting dose in dogs and 2) add an indication for use in cats: For the reduction of hyperglycemia and hyperglycemia-associated clinical signs in cats with diabetes mellitus

Sponsored by:

Intervet Inc.

2008-141-236

FOIS

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I. GENERAL INFORMATION:

A. File Number: NADA 141-236

B. Sponsor: Intervet Inc.
P.O. Box 318
29160 Intervet Lane
Millsboro, DE 19966

Drug Labeler Code: 057926

C. Proprietary Name(s): VETSULIN

D. Established Name(s): Porcine insulin zinc suspension

E. Pharmacological Category: Hormone

F. Dosage Form(s): Injectable

G. Amount of Active Ingredient(s): 40 international units (IU) insulin/mL

H. How Supplied: 2.5 and 10 mL multidose vials

I. How Dispensed: Rx

J. Dosage(s): DOGS

The initial recommended VETSULIN dose is 0.5 IU insulin/kg body weight. Initially, this dose should be given once daily concurrently with, or right after a meal.

The veterinarian should re-evaluate the dog at appropriate intervals and adjust the dose based on clinical signs, urinalysis results, and glucose curve values until adequate glycemic control has been attained. In the US clinical study, glycemic control was considered adequate if an acceptable blood glucose curve was achieved (reduction in hyperglycemia and a nadir of 60 - 160 mg/dL), clinical signs of hyperglycemia (polyuria, polydipsia, and ketonuria) were improved, and hypoglycemia (blood glucose < 50 mg/dL) was

avoided. Twice daily therapy should be initiated if the duration of insulin action is determined to be inadequate. If twice daily treatment is initiated, the two doses should be 25% less than the once daily dose required to attain an acceptable nadir. For example, if a dog receiving 20 units of VETSULIN once daily has an acceptable nadir but inadequate duration of activity, the VETSULIN dose should be changed to 15 units twice daily.

Further adjustments in dosage may be necessary with changes in the dog's diet, body weight, or concomitant medication, or if the dog develops concurrent infection, inflammation, neoplasia, or an additional endocrine or other medical disorder.

CATS

The initial recommended dose in cats is 1 to 2 IU per injection. The injections should be given twice daily at approximately 12 hour intervals. For cats fed twice daily, the injections should be given concurrently with, or right after each meal. For cats fed *ad libitum*, no change in feeding schedule is needed. The veterinarian should re-evaluate the cat at appropriate intervals and adjust the dose based on clinical signs, urinalysis results, and glucose curve values until adequate glycemic control has been attained.

Further adjustments in dosage may be necessary with changes in the cat's diet, body weight, or concomitant medication, or if the cat develops concurrent infection, inflammation, neoplasia, or an additional endocrine or other medical disorder.

K. Route(s) of Administration:

VETSULIN should be administered subcutaneously using a U-40 insulin syringe and should be given 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.

- L. Species/Class(es):** Dogs and Cats
- M. Indication(s):** VETSULIN (porcine insulin zinc suspension) is indicated for the reduction of hyperglycemia and hyperglycemia-associated clinical signs in dogs and cats with diabetes mellitus.
- N. Effect(s) of Supplement:** This supplement provides for a new starting dose in dogs and for the use of VETSULIN in cats

II. EFFECTIVENESS:

A. Dosage Characterization:

Dog

In the original approval (Freedom of Information (FOI) Summary dated April 1, 2004) the starting VETSULIN dose was 1 IU/kg plus a weight dependent supplement. Based on a review of existing literature and a re-evaluation of the data from the US field study, the new starting dose is 0.5 IU/kg.

Several insulin therapy starting dose recommendations have been described in the literature.¹⁻⁵ It is preferable to begin therapy at a low dose because it is easier to adjust for hyperglycemia than to treat an acute hypoglycemic crisis. Ettinger recommends 0.5 to 1 IU/kg body weight as an initial dose of insulin in dogs administered in the morning followed by 10 to 25 percent of the patient's daily food intake.¹ Fleeman and Rand suggest an initial insulin dose of 0.5 IU/kg if the blood glucose value is 360 mg/dL or greater and an initial dose of 0.25 IU/kg in those dogs with blood glucose levels less than this.² Nelson and Feldman recommend a starting dosage of 0.5 IU/kg given as a single morning injection when intermediate-acting insulin is used as initial treatment of diabetic dogs.³ This dose can also be administered as a divided dose, approximately 12 hours apart to mimic physiologic insulin concentrations and provide greater availability.⁴ An even more conservative treatment regimen recommends a starting insulin dose of 0.4 to 0.7 IU/kg given once or twice daily; and for most dogs, if intermediate acting insulin is used twice daily, lowering the starting dosage to 0.4 to 0.5 IU/kg.⁵ Most authors agree that initial insulin therapy should be conservative and that incremental increases should be based on resolution of clinical signs and blood glucose monitoring.

In the US field study which provided substantial evidence of effectiveness supporting the original approval, the majority of VETSULIN doses administered were less than 1.0 IU/kg during the period effectiveness was evaluated. See Table 1 below.

Table 1: Doses of VETSULIN (IU/kg) by dose ranged administered during the US field study in dogs completing the study

Dose = d (IU/kg)	Number of Doses	Total Doses
$d \leq 0.5$	33	182
$0.5 < d < 1.0$	149	
$1.0 \leq d < 1.5$	59	71
$d > 1.5$	12	
Total doses	253	253

At a ratio of more than 2.5:1, the majority of VETSULIN doses administered were less than 1.0 IU/kg compared to doses of 1.0 IU/kg or more.

The starting dose of insulin varies 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. Although insulin treatment 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, review of the existing field study data and the literature cited support 0.5 IU/kg of VETSULIN as a safe and effective starting dose.

Cat

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. Initial insulin zinc suspension dose rates for cats of 1 to 2 IU per injection given every twelve hours are reported in the literature.^{8, 14}

Exogenous insulin is customarily classified as fast-, intermediate-, or long-acting. These characteristics are primarily dependent on the absorption rate from the injection site, which is generally varied by the addition of protamine (PZI and NPH insulin) or variation in crystal size (IZS and extended IZS insulin). VETSULIN (Insulin zinc suspension porcine) is classified as an intermediate-acting insulin. In cats, the peak activity following subcutaneous administration of VETSULIN occurs between 1.5 and 8 hours, and the duration of activity varies between 8 and 12 hours.¹⁶

B. Substantial Evidence:

Dog

CVM did not require effectiveness studies for this supplemental approval. The FOI Summary for the original approval of NADA 141-236 dated April 1, 2004, contains a summary of studies that demonstrate effectiveness of the drug for dogs.

Cat

(1) FIELD STUDY: EFFECTIVENESS AND SAFETY

- (a) Study Title and Number: Pilot efficacy and safety study of porcine insulin zinc suspension for reducing hyperglycemia and hyperglycemia-associated signs of diabetes mellitus in cats. Study Number 2017-001-00
- (b) Type of Study: Field Effectiveness and Safety Dose Confirmation Study
- (c) Study Dates: January 2002 - October 2002
- (d) Investigators and Locations:

Name	City	State
Elizabeth A. Dole, DVM	Syracuse	New York
Maire S. Mahanes, DVM	Charlottesville	Virginia
Keith P. Richter, DVM Jennifer Deberry, DVM	Rancho Santa Fe	California
Douglas R. Santen, DVM	Denver	Colorado
Nancy L. Suska, DVM	Alexandria	Virginia

(e) General Design

1. Purpose of Study: To confirm a starting dose of 1 to 2 IU VETSULIN per injection and evaluate the effectiveness and safety of VETSULIN to reduce hyperglycemia and hyperglycemia-associated signs in cats with diabetes mellitus over a 60 day treatment period.
2. Description of Test Animals: The study included 14 client owned diabetic cats (10 male and 4 female - all neutered) representing various breeds ranging in age from 5 to 14 years, and ranging in weight from 3.40 to 6.97 kg.
3. Control and Treatment Groups: 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 cats. All cats received treatment with VETSULIN. No control animals were used.

4. Inclusion Criteria: Cats were enrolled in the study based on a diagnosis of diabetes mellitus according to the following criteria: (1) Two fasting blood glucose concentration measurements > 250 mg/dL, (2) glycosuria, (3) and one or more of the following: polyuria, polydipsia, polyphagia, weight loss despite good appetite, or ketonuria (without signs of severe ketoacidosis).
5. Dose Form: 40 IU/mL porcine insulin zinc suspension (commercial formulation)
6. Drug Administration: Twice daily injection at approximately 12 hour intervals
 - i. Dosage amount, frequency, and duration: An initial dose of 1 to 2 IU per injection was administered. Clinical signs and blood glucose curve results were evaluated at Days 7, 14, 30, and 60 of treatment, and the dose was adjusted, if needed. Interim evaluations and dose adjustments were allowed at any time to attain or maintain acceptable diabetic control.
 - ii. Route of administration: subcutaneous injection
7. Variables Measured: At Days 0, 7, 14, 30 and 60, the investigator made an evaluation of diabetes control based on the presence or absence of clinical signs of diabetes mellitus (polydipsia, polyuria, polyphagia, abnormal activity, and weight loss on Day 0; polydipsia, polyuria, polyphagia, abnormal activity, and unacceptable weight trend on Days 7, 14, 30, and 60) in conjunction with 10 hour blood glucose curve results. Physical examinations and owner interviews occurred at each scheduled visit. Hematology, serum chemistry panels, and serum fructosamine were evaluated prior to treatment and at Days 30 and 60 of treatment.
8. Criteria for Success/Failure: The investigator recorded the assessment of diabetes control first as a continuous evaluation on a visual analogue scale (VAS) that ranged from 0-100 with a score of 0 indicating good control and a score of 100 indicating no control of diabetes mellitus, and secondly as a categorical evaluation of good, adequate, or poor diabetes control.

Reduction of hyperglycemia was evaluated by comparing blood glucose curve results obtained prior to insulin therapy (Day 0) to results from curves following therapy initiation (Days 7, 14, 30, and 60). Individual animal blood glucose means and study population blood glucose curve means and mean nadirs (lowest glucose measurement) were calculated and the results following treatment were compared to pre-treatment values to determine if a clinically significant reduction in blood glucose occurred.

Study population serum fructosamine means pre-treatment were compared to values at Days 30, and 60 to determine if a clinically significant reduction in fructosamine occurred.

9. Statistical Methodology: The measure of effectiveness was the change of the primary variables (VAS, blood glucose, blood glucose nadir, and fructosamine) during the study compared with Day 0. For animals that withdrew from the study prior to completion, missing data for the primary effectiveness variables were populated using a last observation carried forward (LOCF) method. The endpoints were analyzed as a repeated measures general linear mixed model using the MIXED procedure of SAS Version 9.1.3.

The two-sided 90% confidence intervals on the proportion of cats whose average blood glucose was below 300 mg/dL and whose blood glucose nadir was below 200 mg/dL were constructed based on the binary response of whether or not a cat's glucose was below the threshold and were analyzed as repeated measures generalized linear mixed models using the GLIMMIX procedure of SAS Version 9.1.3.

(f) Results: Mean VAS scores improved during the study period. VAS score mean, mean change, and range are summarized in Table 2.

Table 2: Mean VAS score, mean change and range of change

VAS (mm)	Day 0 (n=14)	Day 7 (n=14)	Day 14 (n=14)	Day 30 (n=13)	Day 60 (n=12)
Mean score ± SD*	95 ± 10	65 ± 28	43 ± 26	40 ± 32	20 ± 23
Mean change ± SD	-	30 ± 29	52 ± 26	55 ± 32	74 ± 25
Range of change	-	0 to 99	4 to 87	6 to 92	5 to 98

*SD = Standard Deviation

Categorical evaluation of diabetes control showed improvement from poor to adequate or good over the study period. All cats were evaluated as poor diabetic control at the start of the study. By Day 60, five cats were judged to have good diabetic control, 6 to have adequate control, and 1 to have poor control. Categorical evaluation results are summarized in Table 3.

Table 3: Categorical evaluations summary

Categorical Score	Day 0 (n=14)	Day 7 (n=14)	Day 14 (n=14)	Day 30 (n=13)	Day 60 (n=12)
Poor	14 (100%)	10 (72%)	6 (43%)	5 (38%)	1 (8%)
Adequate	0	3 (21%)	7 (50%)	4 (31%)	6 (50%)
Good	0	1 (7%)	1 (7%)	4 (31%)	5 (42%)

Study population glucose curve means and mean nadirs for Days 0, 7, 14, 30, and 60 were calculated to evaluate for reduction of hyperglycemia. The mean blood glucose concentration was progressively reduced from 354 ± 68 mg/dL pre-treatment (Day 0) to 162 ± 107 mg/dL at the end of the study (Day 60). The mean

blood glucose nadir was likewise reduced from 321 ± 77 mg/dL pre-treatment (Day 0) to 99 ± 84 mg/dL (Day 60). Blood glucose concentration mean and mean nadir results are summarized in Table 4.

Table 4: Mean blood glucose concentration and nadir comparison for 10-hour blood glucose curves

Day	Mean glucose \pm SD (mg/dL)	Mean glucose nadir \pm SD (mg/dL)
0	354 ± 68	321 ± 77
7	329 ± 94	253 ± 94
14	265 ± 107	181 ± 103
30	231 ± 119	171 ± 117
60	162 ± 107	99 ± 84

Mean fructosamine decreased at Days 30 and 60 compared to pre-treatment. As was observed with the VAS score, the serum fructosamine concentration varied between cats. The mean fructosamine concentrations and range for fructosamine at each time are summarized in Table 5.

Table 5: Serum fructosamine: mean and range

Serum Fructosamine (μ mol/L)			
	Pre-treatment (n=14)	Day 30 (n=13)	Day 60 (n=12)
Mean	660	546	462
SD	69	150	157
Range	569 to 787	301 to 848	229 to 707

All cats received insulin injections twice daily at approximately 12-hour intervals. Initial doses were 1 to 2 units per injection. The dose was adjusted to effect and was variable. The mean dose and dose range are summarized in Table 6.

Table 6: VETSULIN dose range for study cats

Dose	Day 7 (n=14)	Day 14 (n=14)	Day30 (n=13)	Day 60 (n=12)
Mean dose (IU per injection) \pm SD	1.7 ± 0.7	2.7 ± 0.9	3.2 ± 0.8	3.6 ± 1.8
Minimum dose (IU per injection)	1	1	2	1
Maximum dose (IU per injection)	3	4	5	7

- (g) Adverse Reactions: No injection site reactions were reported by cat owners or investigators. No clinical signs attributable to hypoglycemia were observed.

Hypoglycemia (defined as blood glucose \leq 50 mg/dL) without clinical signs occurred in six cats on eight occasions and were treated empirically with oral caloric supplements in four cases. Four cats reported to have normal activity at enrollment were reported to be lethargic or to have decreased activity at six times during the study treatment period. Lethargy and decreased activity did not appear to be associated with hypoglycemia. Blood glucose curve values were normal to elevated five of the six times lethargy or decreased activity were reported, and the investigators increased or did not change the insulin dose in all but one case. Lethargy resolved for two cats and improved for one cat by the end of the study. The fourth cat was euthanized shortly after the Day 14 evaluation at the owner's request. Chronic pancreatitis and glomerulonephropathy were diagnosed on necropsy.

One cat died shortly after the Day 30 evaluation. The owner did not notify the investigator and the cat was not available for necropsy.

Other abnormal signs reported during the treatment period not noted on the pretreatment history or physical examinations were: foul odor to stool, diarrhea; dull coat; rapid, shallow breathing; stiff gate in rear; gallop rhythm; pruritus and alopecia.

Hematology and serum chemistry results from blood samples collected pre-treatment were compared to those from samples obtained following treatment initiation (Days 30 and 60). Blood work results were available for 13 cats through Day 30 and 12 cats through Day 60. No consistent changes in hematology or serum chemistry values were noted.

- (h) Conclusions: Treatment with VETSULIN is safe and effective for the reduction of hyperglycemia and hyperglycemia-associated clinical signs in cats with diabetes mellitus. The most common clinical signs reported during treatment were lethargy and decreased activity.
- (i) Extended use: Cats enrolled in the study were allowed to continue treatment with VETSULIN after study completion. Of the 14 cats enrolled, 12 cats continued with extended use therapy. Investigators evaluated the cats approximately every 4 months. The mean post-study extended use was 116 weeks with a range of 22 to 242 weeks. Four cats left extended use therapy due to diabetic remission from 22 to 181 weeks after beginning extended use treatment. One cat was reported to have 3 instances of hypoglycemia (all related to accidental overdosing or concomitant condition), and 1 cat was reported to have 1 instance of hypoglycemia related to diabetic remission but still receiving insulin injections. No other adverse reactions were reported. Two cats died of unknown causes at 131 and 148 weeks after starting extended use treatment. One cat was euthanized for acute rear leg paralysis related to a suspected aortic thromboembolism, and one cat died after being hit by a car. One cat was changed to a different insulin because of VETSULIN supply issues. One cat was removed from extended use because the owner chose to discontinue treatment. Two cats remained on extended use therapy as of this reporting.

(2) FIELD STUDY: EFFECTIVENESS AND SAFETY

- (a) Study Title and Number: Pivotal efficacy and safety study of porcine insulin zinc suspension for reducing hyperglycemia and hyperglycemia-associated signs of diabetes mellitus in cats. Study Number 2017-003-00
- (b) Type of Study: Field Effectiveness and Safety Dose Confirmation Study
- (c) Study Dates: April 2005 - September 2006
- (d) Investigators and Locations:

Name	City	State
Katherine Beachy, DVM Elizabeth Eilers, DVM	Greensboro	North Carolina
Lynn Buzhardt, DVM Jason St. Romain, DVM	Zachary	Louisiana
Elizabeth A. Carroll, DVM	Durham	North Carolina
Terry Clekis, DVM	Bradenton	Florida
Jennifer DeBerry, DVM Keith Richter, DVM	San Diego	California
Elizabeth A. Dole, DVM	Syracuse	New York
Patrick S. Hackett, DVM Jennifer Bledsoe, DVM	Knoxville	Tennessee
Jennifer L. Hodge, DVM	Cary	North Carolina
Edward Jezbera, DVM	Riverside	California
Kristi Lively, DVM	Center Farragut	Tennessee
Maire S. Mahanes, DVM	Charlottesville	Virginia
Alyce M. Meyer, DVM	Albany	New York
Douglas R. Santen, DVM	Denver	Colorado
Roger Sifferman, DVM	Springfield	Missouri
Nancy L. Suska, DVM	Alexandria	Virginia

(e) General Design

1. Purpose of Study: To confirm the effectiveness and safety of VETSULIN to reduce hyperglycemia and hyperglycemia-associated signs in cats with diabetes mellitus over a 60 day treatment period and to provide additional evidence of effectiveness and safety over a 180 day treatment period.
2. Description of Test Animals: The study included 78 client owned diabetic cats (53 male and 25 female - all neutered) representing various breeds ranging in age from 3 to 17.5 years and ranging in weight from 1.9 to 10.8 kg. A total of 77 cats were included in the analysis of effectiveness.

3. Control and Treatment Groups: 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 cats. All cats received treatment with VETSULIN. No control animals were used.
4. Inclusion Criteria: Cats were enrolled in the study based on a diagnosis of diabetes mellitus according to the following criteria: (1) Two fasting blood glucose concentration measurements > 250 mg/dL, (2) glycosuria, (3) and one or more of the following: polyuria, polydipsia, polyphagia, weight loss despite good appetite, or ketonuria (without signs of severe ketoacidosis).
5. Dosage Form: 40 IU/mL porcine insulin zinc suspension (commercial formulation)
6. Drug Administration: Twice daily injection at approximately 12 hour intervals
 - i. Dosage amount, frequency, and duration: An initial dose of 1 to 2 IU per injection was administered. During the primary effectiveness portion of the study, clinical signs and blood glucose curve results were evaluated at Days 7, 14, 30, and 60 of treatment, and the dose was adjusted, if needed. Between Day 60 and 180, scheduled evaluations with optional blood glucoses were done at Days 90, 120, and 150 of treatment. At Day 180 (conclusion of the study) clinical signs and blood glucose curve results were evaluated, and the dose was adjusted, if needed. Interim evaluations and dose adjustments were allowed at any time to attain or maintain acceptable diabetic control.
 - ii. Route of administration: subcutaneous injection
7. Variables Measured: At Days 0, 7, 14, 30, 60, and 180 the investigator made an evaluation of diabetes control based on the presence or absence of clinical signs of diabetes mellitus (polydipsia, polyuria, polyphagia, abnormal activity, and weight loss on Day 0; polydipsia, polyuria, polyphagia, abnormal activity, and unacceptable weight trend on Days 7, 14, 30, 60, and 180) in conjunction with 10 hour blood glucose curve results. Physical examinations and owner interviews occurred at each scheduled visit. Hematology, serum chemistry panels, and serum fructosamine were evaluated prior to treatment and at Days 30, 60, and 180 of treatment.
8. Criteria for Success/Failure: A visual analogue scale (VAS), mean blood glucose, and mean blood glucose nadir were evaluated as primary variables for effectiveness evaluation. The investigator recorded the assessment of diabetes control as a continuous evaluation on a VAS that ranged from 0-100 with a score of 0 indicating good control and a score of 100 indicating no control of diabetes mellitus.

Reduction of hyperglycemia was evaluated by comparing blood glucose curve

results obtained prior to insulin therapy (Day 0) to results from curves following therapy initiation on Days 7, 14, 30, and 60 (primary effectiveness period). Data for the Day 180 evaluation was also analyzed. Individual animal blood glucose means and study population blood glucose curve means and mean nadirs were calculated and the results following treatment were compared to pre-treatment values to determine if a clinically significant reduction in blood glucose occurred. Study population serum fructosamine was measured as a secondary variable. Pre-treatment means were compared to values at Days 30, 60, and 180 to determine if a significant reduction in fructosamine occurred.

11. Statistical Methodology: The measure of effectiveness was the change of the primary variables (VAS, blood glucose and blood glucose nadir) during the study compared with Day 0. For animals that withdrew from the study prior to completion, missing data for the primary effectiveness variables were populated using a last observation carried forward (LOCF) method. The endpoints were analyzed as a repeated measures general linear mixed model using the MIXED procedure of SAS Version 9.1.3.

The two-sided 90% confidence intervals on the proportion of cats whose average blood glucose was below 300 mg/dL and whose blood glucose nadir was below 200 mg/dL were constructed based on the binary response of whether or not a cat's glucose was below the threshold and were analyzed as repeated measures generalized linear mixed models using the GLIMMIX procedure of SAS Version 9.1.3.

(f) Results:

Four cats (5%) went into diabetic remission during the study. One cat went into remission prior to Day 60 and three between Day 60 and Day 180 of the study. A significant reduction of visual analogue scale score was observed when comparing Day 0 to Days 7, 14, 30, 60, and 180. The visual analogue scale score improved by Day 60 as summarized in Table 7.

Table 7: Analysis of visual analog scale

Day	Estimates (mm)		Analysis	
	LS* Means	Change: Day 0 – Day	t-test	P-Value
0	93.8	--	--	--
7	72.9	21.0	7.60	<0.001
14	55.0	38.8	12.59	<0.001
30	42.8	51.0	14.82	<0.001
60	31.2	62.6	18.95	<0.001
180	25.0	68.9	21.57	<0.001

*LS = Least Square

Blood glucose curve mean and mean nadir values between Day 0 and Days 7, 14, 30, 60 and approximately 180, were compared and tested for significant difference. The number and percentage of cats with blood glucose <300 mg/dL and the number and percentage of cats with blood glucose nadir <200 mg/dL at each time point were analyzed.

The average blood glucose concentration on Days 7, 14, 30, 60 and 180 was reduced compared to Day 0 as summarized in Table 8.

Table 8: Analysis of mean blood glucose

Day	Estimates (mg/dL)		Analysis	
	LS Means	Change: Day 0 – Day	t-test	P-Value
0	394.1 (n=77)	--	--	--
7	359.2 (n=77)	34.9	3.18	0.002
14	302.4 (n=77)	91.7	5.99	<0.001
30	277.3 (n=76)	119.6	6.82	<0.001
60	210.8 (n=72)	177.5	10.14	<0.001
180	212.1 (n=65)	174.7	10.25	<0.001

The average blood glucose nadir on Days 7, 14, 30, 60 and 180 were reduced compared to Day 0 as summarized in Table 9.

Table 9: Analysis of mean blood glucose nadir

Day	Estimates (mg/L)		Analysis	
	LS Means	Change: Day 0 – Day	t-test	P-Value
0	343.3 (n=77)	--	--	--
7	293.2 (n=77)	50.0	4.11	<0.001
14	234.3 (n=77)	108.9	6.58	<0.001
30	200.7 (n=76)	142.6	7.96	<0.001
60	145.7 (n=76)	197.6	11.69	<0.001
180	155.9 (n=73)	187.4	11.84	<0.001

The number and percentage of cats with a mean blood glucose < 300 mg/dL on Days 7, 14, 30, 60, and 180 were increased compared to Day 0. These values and their 90% lower confidence bounds are summarized in Table 10.

Table 10: Proportion of animals whose average blood glucose < 300 mg/dL

Day	Proportion < 300 mg/dL	90% Confidence Interval Limits	
		Lower	Upper
0	4/77=5.2%	2.1%	11.5%
7	18/77=23.4%	15.6%	33.5%
14	36/77=46.8%	36.3%	58.2%
30	42/76=55.3%	44.9%	66.6%
60	57/76=75.0%	65.6%	83.7%
180	52/73=71.2%	62.2%	81.4%

The number and percentage of cats with a mean blood glucose nadir < 200 mg/dL on Days 7, 14, 30, 60, and 180 were increased compared to Day 0. These values and their 90% lower confidence bounds are summarized in Table 11.

Table 11: Proportion of animals whose blood glucose nadir < 200 mg/dL

Day	Proportion < 200 mg/dL	90% Confidence Interval Limits	
		Lower	Upper
0	0/77=0%	--	--
7	13/77=16.9%	9.2%	25.5%
14	27/77=35.1%	23.7%	47.1%
30	40/76=52.6%	40.8%	66.0%
60	55/76=72.4%	62.6%	83.4%
180	51/73=69.9%	60.8%	82.3%

The mean fructosamine concentration on Day 0 was significantly (P <0.0001) reduced on Days 30, 60, and 180 compared to Day 0 as summarized in Table 12.

Table 12: Analysis of fructosamine

Day	n	Mean	SD
0	77	607.3	102.7
30	75	487.8	133.3
60	75	453.7	145.1
180	72	454.8	145.9

Most cats were started on 1 to 2 IU twice daily at approximately 12 hour intervals. Two cats were started on once daily insulin and one cat was started at 3 IU twice

daily. The dose was adjusted to effect during the study. The mean dose and dose range are summarized in Table 13.

Table 13: Mean, minimum and maximum VETSULIN dose by Day

Dose	Initial dose (n=78)	Day 7 (n=78)	Day 14 (n=78)	Day 30 (n=76)	Day 60 (n=72)	Day 180 (n=66)
Mean dose \pm SD (IU per injection)	1.4 \pm 0.5	1.4 \pm 0.6	2.2 \pm 0.8	2.8 \pm 1.1	3.3 \pm 1.6	3.3 \pm 1.8
Minimum dose (IU per injection)	1	0.5	0.5	1	0	0
Maximum dose (IU per injection)	3	3	4	6	8	8

(g) Adverse Reactions: Hypoglycemia (defined as blood glucose <50 mg/dL) occurred in 61 cats at some time during the study. Fifteen instances of hypoglycemia with associated clinical signs were reported in 13 cats (16.7%, 13/78). Clinical signs of hypoglycemia were generally mild in nature, including lethargy, diarrhea, decreased appetite/anorexia, vomiting, and hypothermia. One cat had seizures following accidental overdosing by the owner and during the subsequent dose adjustment period. The cat responded to supportive therapy and had no further hypoglycemic episodes. In all cases, the clinical signs resolved following symptomatic treatment and/or dose adjustment.

Polyneuropathy was reported in 4 cats. Two cases occurred while the dose was still being adjusted. One of these cats had almost no signs of polyneuropathy by Day 180. Two injection site reactions were reported: one as a mildly thickened subcutaneous tissue reaction and the second as mild bruising. One cat died while on study and three cats were euthanized.

Other abnormal signs reported during the treatment period not noted on the pretreatment history or physical examinations are presented in Table 14.

Table 14: Abnormal clinical signs observed

Clinical Sign	Instances	# of cats
Vomiting	27	23
Lethargy	21	16
Diarrhea / abnormal stools	19	13
Anorexia/ Decreased Appetite	16	14
Dermatologic Condition	14	13
Respiratory	7	6
Urinary Tract Disorder	10	7
Dehydration	4	2
Weight Loss	2	2
Polydipsia	2	2
Polyuria	2	2
Behavioral	2	2
Renal Disease	1	1

Hematology and serum chemistry results from blood samples collected pre-treatment were compared to those from samples obtained following treatment initiation (Days 30, 60, and 180). Blood work results were available for 75 cats through Day 30, 71 cats through Day 60, and 65 cats through Day 180. No consistent changes were noted.

- (h) Conclusions: Treatment with VETSULIN is safe and effective for the reduction of hyperglycemia and hyperglycemia-associated clinical signs in cats with diabetes mellitus. The most common adverse reactions reported were hypoglycemia, vomiting, diarrhea, lethargy, and anorexia/decreased appetite.
- (i) Extended use: Cats enrolled in the study were allowed to continue treatment with VETSULIN after study completion. Of the 78 cats enrolled, 61 cats continued with extended use therapy. The mean post-study extended use was 45 weeks with a range of 1 to 83 weeks. Four cats left extended use therapy because they went into diabetic remission at 17 and 72 weeks after beginning extended use treatment. Thirteen cats were removed from extended use and euthanized after 3 to 70 weeks of extended use therapy, primarily because of deteriorating health and poor quality of life. One cat died of unknown causes after 20 weeks of extended use therapy.

Four cats were reported to have one episode of hypoglycemia, one cat was reported to have two instances of hypoglycemia, and one cat was reported to have 4 instances of hypoglycemia. The following clinical observations occurred infrequently during the extended use study and may be directly attributed to the drug or may be secondary to the diabetic state or other underlying conditions in the cats: seizure, lethargy, vomiting, diarrhea, constipation, increased liver enzymes with icterus, weight loss, dental disease, inappropriate elimination, pancreatitis, anorexia, decreased appetite, limping/abnormal gait, respiratory disease, dyspnea, pleural effusion, sneezing, cough, polydipsia, polyuria, cystitis, behavioral change,

conjunctivitis, otitis, and gingivitis.

III. TARGET ANIMAL SAFETY:

A. Dog

CVM did not require target animal safety information for this supplemental approval. The FOI Summary for the original approval of NADA 141-236 dated April 1, 2004, contains a summary of target animal safety for dogs.

B. Cat

Insulin is an endogenous hormone whose mechanisms of action and effect have been extensively studied. Insulin tolerance in the cat and the effects of hypoglycemia that result 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 feline and human diabetes.^{3, 6-16}

Porcine insulin zinc suspension safety in cats was confirmed by the US field studies. Hypoglycemia, lethargy, vomiting, and two injection site reactions were the primary reactions reported. Additional support for the safety of VETSULIN is provided by data from field studies conducted in Australia that included long term evaluation of cats (up to 52 weeks of treatment) and US field study post-study extended use (up to 258 weeks of treatment). Adverse reactions reported during extended use with VETSULIN include hypoglycemia, seizure, lethargy, vomiting/diarrhea, constipation, increased liver enzymes with icterus, weight loss, inappropriate elimination, pancreatitis, decreased appetite/anorexia, limping/abnormal gait, respiratory disease, dyspnea, pleural effusion, sneezing, cough, polyuria, polydipsia, cystitis, and behavioral change.

In years of clinical experience in the more than 20 countries where porcine insulin zinc suspension is currently registered for animal use, few problems have been reported with VETSULIN use in cats. During the 1998-2007 period, 47 cases of adverse events in 50 cats treated with porcine insulin zinc suspension were reported to Intervet International and Intervet Inc. Events included death, seizures, lack of effectiveness/dysregulation, hypoglycemia, allergic or skin reaction, lethargy, vomiting/diarrhea, injection pain, hyperthermia, nystagmus, polyuria, polydipsia, and abnormal behavior.

IV. HUMAN FOOD SAFETY:

This drug is intended for use in dogs and cats, which are non-food animals. Because this new animal drug is not intended for use in food producing animals, CVM did not require data pertaining to drug residues in food (i.e., human food safety) for approval of this NADA.

V. USER SAFETY:

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to VETSULIN: 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.

VI. 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 Part 514. The data demonstrate that VETSULIN, when used according to the label, is safe and effective for the reduction of hyperglycemia and hyperglycemia-associated clinical signs in dogs and cats with diabetes mellitus.

A. Marketing Status:

This product may be dispensed only by or on the lawful order of a licensed veterinarian (Rx marketing status). Adequate directions for lay use cannot be written 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.

B. Exclusivity:

Under section 512(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for THREE years of marketing exclusivity beginning on the date of the approval. The three years of marketing exclusivity applies only to the new species for which this supplement is approved.

C. Supplemental Applications:

This supplemental NADA required a reevaluation of the safety or effectiveness data in the original NADA (21 CFR §514.106(b)(2)).

D. Patent Information:

The sponsor did not submit any patent information with this application.

VII. ATTACHMENTS :

Facsimile labeling is attached as indicated below:

Package Insert
Owner Information sheet
Vial Label (2.5mL and 10 mL)
Box Label (2.5 mL and 10 mL)

VIII. LITERATURE CITED

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vetsulin[®]

(porcine insulin zinc suspension)

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NADA 141-236. Approved by FDA

CAUTION

Federal law restricts this drug to use by or on the order of a licensed veterinarian

DESCRIPTION

vetsulin[®] is a sterile aqueous zinc suspension of purified porcine insulin.

Each mL contains:	purified porcine insulin	40 IU	(30% amorphous and 70% crystalline)
	Zinc (as chloride)	0.08 mg	
	Sodium acetate trihydrate	1.36 mg	
	Sodium chloride	7.0 mg	
	Methylparaben (preservative)	1.0 mg	

pH is adjusted with hydrochloric acid and/or sodium hydroxide

INDICATION

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

DOSAGE AND ADMINISTRATION

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

FOR SUBCUTANEOUS INJECTION IN DOGS AND CATS ONLY

vetsulin[®] should be mixed by gentle rolling of the vial prior to withdrawing the dose from the vial. Using a U-40 insulin syringe, the injection should be administered subcutaneously, 2 to 5 cm (3/4 to 2 in) from the dorsal midline, varying from behind the scapulae to the mid-lumbar region and alternating sides.

Always provide the Owner Information Sheet with each prescription.

Dogs

The initial recommended vetsulin[®] dose is 0.5 IU insulin/kg body weight. Initially, this dose should be given once daily concurrently with, or right after a meal.

The veterinarian should re-evaluate the dog at appropriate intervals and adjust the dose based on clinical signs, urinalysis results, and glucose curve values until adequate glycemic control has been attained. In the US clinical study, glycemic control was considered adequate if an acceptable blood glucose curve was achieved (reduction in hyperglycemia and a nadir of 60 - 160 mg/dL), clinical signs of hyperglycemia (polyuria, polydipsia, and ketonuria) were improved, and hypoglycemia (blood glucose < 50 mg/dL) was avoided. Twice daily therapy should be initiated if the duration of insulin action is determined to be inadequate. If twice daily treatment is initiated, the two doses should be 25% less than the once daily dose required to attain an acceptable nadir. For example, if a dog receiving 20 units of vetsulin[®] once daily has an acceptable nadir but inadequate duration of activity, the vetsulin[®] dose should be changed to 15 units twice daily.

Further adjustments in dosage may be necessary with changes in the dog's diet, body weight, or concomitant medication, or if the dog develops concurrent infection, inflammation, neoplasia, or an additional endocrine or other medical disorder.

Cats

The initial recommended dose in cats is 1 to 2 IU per injection. The injections should be given twice daily at approximately 12 hour intervals. For cats fed twice daily, the injections should be given concurrently with, or right after each meal. For cats fed *ad libitum*, no change in feeding schedule is needed. The veterinarian should re-evaluate the cat at appropriate intervals and adjust the dose based on clinical signs, urinalysis results, and glucose curve values until adequate glycemic control has been attained.

Further adjustments in dosage may be necessary with changes in the cat's diet, body weight, or concomitant medication, or if the cat develops concurrent infection, inflammation, neoplasia, or an additional endocrine or other medical disorder.

CONTRAINDICATIONS

Dogs and cats known to have a systemic allergy to pork or pork products should not be treated with vetsulin[®]. vetsulin[®] is contraindicated during periods of hypoglycemia.

WARNINGS

User Safety: For use in animals only. Keep out of the reach of children. Avoid contact with eyes. In case of contact, immediately flush eyes with copious amounts of water for 15 minutes. Accidental injection may cause clinical hypoglycemia. In case of accidental injection, seek medical attention immediately. Exposure to product may induce a local or systemic allergic reaction in sensitized individuals.

Animal Safety: Owners should be advised to observe for signs of hypoglycemia (see Owner Information Sheet). Use of this product, even at established doses, has been associated with hypoglycemia. An animal with signs of hypoglycemia should be treated immediately. Glucose should be given orally or intravenously as dictated by clinical signs. Insulin should be temporarily withheld and, subsequently, the dosage should be adjusted, if indicated.

Any change in insulin should be made cautiously and only under a veterinarian's supervision. Changes in insulin strength, manufacturer, type, species (animal, human) or method of manufacture (rDNA versus animal-source insulin) may result in the need for a change in dosage.

Appropriate diagnostic tests should be performed to rule out endocrinopathies in pets that are difficult to regulate (e.g., hyperadrenocorticism in dogs and hyperthyroidism in cats).

PRECAUTIONS

Animals presenting with severe ketoacidosis, anorexia, lethargy, and/or vomiting should be stabilized with short-acting insulin and appropriate supportive therapy until their condition is stabilized. As with all insulin products, careful patient monitoring for hypoglycemia and hyperglycemia are essential to attain and maintain adequate glycemic control and prevent associated complications. Overdosage can result in profound hypoglycemia and death. Progestogens, certain endocrinopathies, and glucocorticoids can have an antagonistic effect on insulin activity. Intact hitches should be ovariectomized. Progestogen and glucocorticoid use should be avoided.

Drug Interactions:

In the US clinical effectiveness studies, dogs and cats received various medications while being treated with vetsulin[®], including antimicrobials, antivirals, antifungals, antihistamines, analgesics, anesthetics/tranquilizers, diuretics, bronchodilators, corticosteroids (cats), NSAIDs, thyroid hormone supplementation, hyperthyroid medication (methimazole), internal and external parasiticides, anti-emetics, dermatological topical treatments and oral supplements, ophthalmic preparations containing antimicrobials and antiinflammatories, and various vaccines. No medication interactions were reported. This drug was not studied in dogs receiving corticosteroids.

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

Use in puppies and kittens: The safety and effectiveness of vetsulin[®] in puppies and kittens has not been evaluated.

ADVERSE REACTIONS

Dogs

In the field effectiveness and safety study, 66 dogs were treated with vetsulin[®]. Sixty-two dogs were included in the assessment of safety. Hypoglycemia (defined as blood glucose < 50 mg/dL) with or without associated clinical signs occurred in 35.5% (22/62) of the dogs at various times during the study. Clinical signs of hypoglycemia were generally mild in nature (described as weakness, lethargy, stumbling, falling down, and/or depression). Disorientation and collapse were reported less frequently and occurred

in 16.1% (10/62) of the dogs. Two dogs had a seizure and one dog died during the seizure. Although never confirmed, the presumptive diagnosis was hypoglycemia-induced seizures. In the rest of the dogs, hypoglycemia resolved with appropriate therapy and adjustments in insulin dosage.

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

The following clinical observations occurred in the field study following treatment with vetsulin[®] and may be directly attributed to the drug or may be secondary to the diabetic state or other underlying conditions in the dogs: hematuria, vomiting, diarrhea, pancreatitis, non-specific hepatopathy/pancreatitis, development of cataracts, and urinary tract infections.

Cats

In a field effectiveness and safety study, safety data was reported for 78 cats receiving vetsulin[®].

Hypoglycemia (defined as blood glucose < 50 mg/dL) was reported in 61 cats (88 total incidences). Fifteen of the occurrences (involving 13 cats) were associated with clinical signs described as lethargy, diarrhea, decreased appetite/anorexia, vomiting, and hypothermia. One cat had seizures following accidental overdosing by the owner and again during the subsequent dose adjustment period. The cat responded to supportive therapy and had no further hypoglycemic episodes. In all cases of hypoglycemia, the clinical signs resolved following symptomatic treatment and/or dose adjustment.

Polyneuropathy was reported in 4 cats. Two injection site reactions were reported: one as a mildly thickened subcutaneous tissue reaction and the second as a mild bruising.

The following clinical observations occurred in the field study following treatment with vetsulin[®] and may be directly attributed to the drug or may be secondary to the diabetic state or other underlying conditions in the cats: vomiting, lethargy, diarrhea, decreased appetite/anorexia, pancreatitis, dermal events, respiratory disease, urinary tract disorder, renal disease, dehydration, weight loss, polydipsia, polyuria, behavioral change, and ocular discharge/conjunctivitis.

In a smaller field effectiveness and safety study, 14 cats were treated with vetsulin[®]. Hypoglycemia was reported in 6 cats (8 total occurrences). Lethargy not associated with hypoglycemia was reported in 4 cats (6 total occurrences). The following clinical observations occurred in the field study following treatment with vetsulin[®] and may be directly attributed to the drug or may be secondary to the diabetic state or other underlying conditions in the cats: foul odor to stool, diarrhea, dull coat, rapid, shallow breathing, stiff gate in rear, gallop rhythm, and pruritus with alopecia.

During the 1998-2007 period, the following adverse events in 50 cats treated with porcine insulin zinc suspension were reported to Intervet International and Intervet Inc: Death, seizures, lack of effectiveness/dysregulation, hypoglycemia, allergic or skin reaction, lethargy, vomiting/diarrhea, injection pain, hyperthermia, nystagmus, PU/PD, and abnormal behavior.

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

GENERAL PHARMACOLOGY

Porcine insulin is similar in amino acid structure to canine insulin. vetsulin[®] is classified as intermediate acting insulin. In dogs, vetsulin[®] has two peaks of activity following subcutaneous administration (the first at around 4 hours and the second at around 11 hours) (1). The duration of activity varies between 14 and 24 hours (1). In cats, the peak activity following subcutaneous administration of vetsulin[®] occurs between 1.5 and 8 hours (2), and the duration of activity varies between 8 and 12 hours (2). The peak(s), duration of activity and dose required to adequately control diabetic signs will vary between individuals.

EFFECTIVENESS

Dogs

A total of 66 client-owned dogs were enrolled in and 53 completed the effectiveness and safety field study. The dogs completing the study included 22 breeds of purebred and various mixed breed dogs ranging in age from 4 to 14 years, and ranging in weight from 4.2 to 51.3 kg. Of the dogs completing the study, 25 were spayed females and 28 were male (21 neutered and 7 intact).

Dogs were started on vetsulin[®] at a dose of 1 IU/kg plus a body weight-dependent dose supplement once daily. The initial treatment time to reach acceptable glycemic control (Dose determination period) ranged from 5 to 151 days. Dogs were evaluated for treatment effectiveness three times at 30-day intervals (Study Period). The blood glucose curve means and mean nadirs were compared pre- and post-treatment to assess effectiveness. The blood glucose curve mean was reduced from 370 mg/dL pre-treatment to 151 mg/dL, 185 mg/dL, and 184 mg/dL at the three treatment period evaluations. The blood glucose mean nadir was reduced from 315 mg/dL pre-treatment to 93 mg/dL, 120 mg/dL, and 119 mg/dL at the three treatment period evaluations. Sixty days after an adequate vetsulin[®] dose was initially established, 94%, 96% and 83% of study dogs experienced a reduction in polyuria, polydipsia, and ketonuria, respectively. Investigators reported adequate glycemic control an average of 81% of the time during the Study Period.

Cats

A total of 85 client-owned cats (53 males and 25 females—all neutered) of various breeds were enrolled in a 60 day field effectiveness and safety study with continued use up to Day 180. Seven cats were removed from the study prior to the Day 7 evaluation. The remaining cats ranged in age from 3 to 17.5 years and in weight from 1.9 to 10.8 kg. Seventy-two cats completed the study to Day 60 and 66 cats completed to Day 180. The cats were started on vetsulin[®] at an initial dose of 1 to 2 IU insulin twice daily. Scheduled evaluations occurred at Days 7, 14, 30, 60, and 180. Dose adjustments were allowed at and between the evaluations. Effectiveness was based on blood glucose curve mean, blood glucose nadir and improvement in clinical signs. Blood glucose curve means decreased from 394 mg/dL on Day 0 to 217 mg/dL on Day 60. The mean blood glucose nadir decreased from 343 mg/dL on Day 0 to 146 mg/dL on Day 60.

Fourteen client-owned cats (10 males and 4 females—all neutered) of various breeds were enrolled in a 60 day effectiveness and safety field study. The cats ranged in age from 5 to 14 years and in weight from 3.40 to 6.97 kg. Twelve cats completed the study. The cats were started on vetsulin[®] at an initial dose of 1 to 2 IU insulin twice daily. Scheduled evaluations occurred at Days 7, 14, 30, and 60. Dose adjustments were allowed at and between the evaluations. The blood glucose curve means decreased from 354 mg/dL on Day 0 to 162 mg/dL on Day 60. The mean blood glucose nadir decreased from 321 mg/dL on Day 0 to 99 mg/dL on Day 60.

HOW SUPPLIED

vetsulin[®] is supplied as a sterile injectable suspension in multidose vials containing either 2.5 mL or 10 mL of 40 IU/mL porcine insulin zinc suspension. Vials are supplied in cartons of one, 10 mL vial and cartons of ten, 2.5 mL vials.

STORAGE CONDITIONS

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

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

Distributed by: INTERVET INC.
Millsboro, DE 19966

Made in Germany

01/08

References

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

This summary contains important information about vetsulin®. You should read this information before you start giving your pet vetsulin® and review it each time your prescription is refilled. This sheet is provided only as a summary and does not take the place of instructions from your veterinarian. Talk to your veterinarian if you do not understand this information or if you want to know more about vetsulin®.

What is vetsulin®?

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

What is diabetes mellitus?

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

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

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

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

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

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

Who should not receive vetsulin®?

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

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

Talk to your veterinarian about:

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

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

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

Tell your veterinarian about:

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

How to give vetsulin® to your pet

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

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

Preparing the Dose:

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

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

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

Giving the injection:

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

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

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

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

Signs of hypoglycemia may occur suddenly and can include

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

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

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

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

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

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

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

Can vetsulin® be used with other medications?

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

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

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

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

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

How do I store vetsulin®?

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

What else should I know about vetsulin®?

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

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

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

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

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10 mL

See package insert for directions for use.

Indications: VETSULIN is indicated in the treatment of hypoglycemia and hypoadrenism in dogs and cats.

Contraindications: VETSULIN is contraindicated in dogs and cats with diabetes mellitus.

Warnings: VETSULIN should be used with caution in dogs and cats with hypoadrenism.

Adverse Reactions: VETSULIN may cause hypoglycemia, hypotension, and weight gain.

How Supplied: VETSULIN is supplied in a 10 mL vial.

Storage: VETSULIN should be stored at room temperature (20° to 25°C).

Caution: VETSULIN is a potent insulin and should be used with caution.

vetsulin[®]

(DEQIOE INSULIN ZINC SUSPENSION)

40 units per mL (U-40)

CAUTION: Federal Law restricts this drug to use by or on the order of a licensed veterinarian.

Manufactured by **INTERVET INC.**, Kenilworth, NJ 07033

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MADE IN CANADA

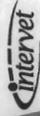
www.vetsulin.com

Approved by FDA

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1 of 1



vetsulin[®]

(porcine insulin zinc suspension)

CAUTION: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

10 x 2.5 mL



vetsulin[®]

(porcine insulin zinc suspension)

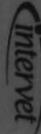


10 x 2.5 mL



vetsulin[®]

(porcine insulin zinc suspension)



10 x 2.5 mL



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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 (as chondrol) 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.

See package insert for directions for use.

Indication: VETSULIN[®] (porcine insulin zinc suspension) is indicated for the reduction of hyperglycemia and hyperglycemia associated clinical signs in dogs and cats with diabetes mellitus.

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Storage: 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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Made in Germany
www.vetsulin.com
NADA No. 141-236; Approved by FDA



Exp:

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vetsulin
(porcine insulin zinc suspension)
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Intervet
vetsulin
(porcine insulin zinc suspension)



Description: VETSULIN® is a sterile aqueous zinc suspension of purified porcine insulin.

See package insert for directions for use.

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

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

Intervet
vetsulin
(porcine insulin zinc suspension)

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Intervet
vetsulin
(porcine insulin zinc suspension)
10 mL

Intervet
vetsulin
(porcine insulin zinc suspension)

CAUTION: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

Each mL contains:
Purified Porcine Insulin (30% amorphous and 70% crystalline) 40 IU
Zinc (as chloride) 0.08 mg
Sodium acetate trihydrate 1.36 mg
Sodium chloride 7.0 mg
Methylparaben (preservative) 1.0 mg
pH is adjusted with hydrochloric acid and/or sodium hydroxide.



Lot/Exp:
Lacquer-free

