Date of Approval: March 24, 2008

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.

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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. 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. 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 ± SD (mg/dL)	Mean glucose nadir ± 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 (µmol/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) ± 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 ≤ 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
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Jennifer L. Hodge, DVM	Cary	North Carolina
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Kristi Lively, DVM	Center Farragut	Tennesee
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 ± SD (IU per injection)	1.4 ± 0.5	1.4 ± 0.6	2.2 ± 0.8	2.8 ± 1.1	3.3 ± 1.6	3.3 ± 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

1. Ettinger S.J. "Diseases of the endocrine pancreas." In *Textbook of Veterinary Internal Medicine: Disease of the Dog and Cat,* 2nd Edition, Philadelphia, PA WB Saunders;

2. Fleeman L.M. and Rand J.S. “Management of Canine Diabetes.” *Veterinary Clinics of North America: Small Animal Practice.* Philadelphia, PA WB Saunders; September 2001; 31(5); 862-863.

3. Nelson R.W. and Feldman E.C. “Diabetes Mellitus.” In *Canine and Feline Endocrinology and Reproduction*, 2nd Edition, Philadelphia, PA WB Saunders; 1996; 339-391.

4. Schaer M. “Disease of the Endocrine Pancreas (Islet Cells).” In Morgan, Rhea V. *Handbook of Small Animal Practice*, 3rd Edition, Philadelphia, PA WB Saunders; 1997; 463-467.

5. Greco D. All those Insulins! Proc 22nd ACVIM 2004; 540-541.

6. Rand J.S. “Current understanding feline diabetes: Part 1, Pathogenesis.” *Journal of Feline Medicine and Surgery* 1999; 1:143-153.

7. Rand J.S. and Martin G.J. “Management of Feline Diabetes Mellitus.” *Veterinary Clinics of North America: Small Animal Practice.* Philadelphia, PA WB Saunders; September 2001; 31(5); 881-913.

8. Ettinger S.J. “Diabetes Mellitus.” In *Textbook of Veterinary Internal Medicine: Disease of the Dog and Cat*, 5th Edition, Philadelphia, PA WB Saunders; 2000; 1438-1460.

9. Bertoy E.H., Nelson D.H., and Feldman E.C. “Effect of lente insulin for treatment of diabetes mellitus in 12 cats.” *JAVMA* 1995; 206(11):1729-1731.

10. Broussard J.D. and Peterson P.E. “Comparison of two ultralente insulin preparations with protamine zinc insulin in clinically normal cats.” *Am J Vet Res*. 1994; 55(1):127-131.

11. Nelson R.W., Feldman E.C., and DeVries S.E. “Use of ultralente insulin in cats with diabetes mellitus.” *JAVMA* 1992; 200(12):1828-1829.

12. Wallace M.S., Peterson M.E., and Nichols C.E. “Absorption kinetics of regular, isophane, and protamine zinc insulin in normal cats.” *Domestic Animal Endocrinology* 1990; 7(4):509-515.

13. Moise N.S. and Reimers T.J. “Insulin therapy in cats with diabetes mellitus.” *JAVMA* 1983; 182(2):158-164.

14. Monroe W.E. “Managing Feline Diabetes.” abstract of presentation at annual meeting of the AVMA 2000.

15. Goosens M.M.C., Nelson R.W., Feldman E.C., and Griffey S.M. “Response to Insulin treatment and survival in 104 cats with diabetes mellitus (1985-1995).” *J Vet Inter Med.* 1998; 12:1-6.

16. Martin G.J. and Rand J.S. “Pharmacokinetic and Pharmacodynamic Study of Caninsulin in Cats with Diabetes Mellitus.” Internal Study Report 2000.