Date of Approval: April 10, 2013

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-236

VETSULIN

Porcine insulin zinc suspension

Injectable Suspension

Dogs and Cats

The effect of the supplement is to change the specification for non-extractable (NE) insulin.

Sponsored by:

Intervet, Inc.

Table of Contents

I. General Information

A. File Number

NADA 141-236

B. Sponsor

Intervet, Inc.
556 Morris Ave.
Summit, NJ 07901

Drug Labeler Code: 000061

C. Proprietary Name

VETSULIN

D. Established Name

Porcine insulin zinc suspension

E. Pharmacological Category

Hormone

F. Dosage Form:

Injectable Suspension

G. Amount of Active Ingredient

40 international units (IU) insulin/mL

H. How Supplied

10 mL multidose vials

I. Dispensing Status

Rx

J. Dosage Regimen

1. 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.

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 each 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.

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. 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.

2. 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 of other medical disorder.

K. Route 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

Dogs and Cats

M. 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.

N. Effect of Supplement

The effect of the supplement is to change the specification for non-extractable (NE) insulin.

II. EFFECTIVENESS

A. Dosage Characterization

1. Dogs

   This supplemental approval does not change the previously approved dosage. The FOI Summary for the supplemental approval of NADA 141-236, dated March 24, 2008, contains dosage characterization information for dogs.

2. Cats

   This supplemental approval does not change the previously approved dosage. The FOI Summary for the supplemental approval of NADA 141-236, dated March 24, 2008, contains dosage characterization information for cats.

B. Substantial Evidence

1. Dogs

   a. Study Title and Number:

      Pharmacodynamic profile of a zinc insulin suspension (VETSULIN/CANINSULIN 40 IU porcine insulin/mL) in healthy Beagle dogs. Study code: S11376-00-CAN-OTH-CN

   b. Type of Study:

      Laboratory pharmacodynamic

   c. Investigator:

      G. Le Traon
      Angers, France

   d. General Design:

      (1) Purpose of Study:

         To evaluate the pharmacodynamic profile of VETSULIN (porcine insulin zinc suspension 40 IU/mL) with a non-extractable (NE) insulin content in the lower end (61%) of the proposed specification of 58%-72% when administered to healthy Beagles.

      (2) Drug Administration:

         Twelve fasted healthy adult Beagles received a single subcutaneous injection of VETSULIN at a dose of 0.5 IU/kg.

      (3) Variables Measured:

         (a) Plasma glucose concentration:

            Blood samples were collected within an hour before injection, immediately before injection, and 0.5, 1, 2, 4, 6, 8, 10, 12,

and 24 hours after injection. At each sampling time, a blood glucose concentration was measured immediately using a portable glucometer in order to identify hypoglycemia.

(b) Pharmacodynamic calculations:

The effect of insulin on plasma glucose concentrations was assessed individually for each dog using the following parameters:

(i) Glucose nadir (mg/dL):

Minimum plasma glucose concentration

(ii) Time to glucose nadir (hour)

(iii) Duration of action (hour):

Time for plasma glucose concentration to reach 80% of baseline concentration in 2 consecutive samples. The parameter was set at 24 hours if the plasma glucose concentration did not return to at least 80% of baseline value within 24 hours.

(iv) Onset of action (hour):

Time to reduction in plasma glucose concentration by at least 10% of baseline value

e. Results:

(1) Pharmacodynamic parameters

Table 1: Summary of pharmacodynamic parameters in healthy dogs (n=12)

Parameter	Value
Glucose nadir (mg/dL)	51 ± 9.4 [mean ± SD]
Glucose nadir as % baseline	49 ± 8.8 [mean ± SD]
Time to glucose nadir (hour)	8 (1-10) [median (range)]
Onset of action (hour)	1 (0.5-2) [median (range)]
Duration of action (hour)	12 (10-24) [median (range)]

(2) Safety:

Hypoglycemia was defined as blood glucose values below 40 mg/dL, using the portable glucometer. Hypoglycemia was recorded in three dogs, one of which had trembling as an associated clinical sign.

f. Conclusions:

The study using healthy adult Beagles describes the pharmacodynamics of VETSULIN with a NE content of 61%. Onset of action ranged from 0.5 to 2 hours (median 1 hour); time to glucose nadir ranged from 1 to 10 hours (median 8 hours); and duration of action ranged from 10 to 24 hours (median 12 hours). Three dogs experienced biochemical hypoglycemia and one dog had associated trembling.

2. Cats

a. Study Title and Number:

Pharmacodynamic profile of a zinc insulin suspension (VETSULIN/CANINSULIN 40 IU porcine insulin/mL) in healthy cats. Study code: S11375-00-CAN-OTH-FL

b. Type of Study:

Laboratory pharmacodynamic study

c. Investigator:

G. Le Traon
Angers, France

d. General Design:

(1) Purpose of Study:

To evaluate the pharmacodynamic profile of VETSULIN (porcine insulin zinc suspension 40 IU/mL) with a non-extractable (NE) insulin content in the lower end (61%) of the proposed specification of 58%-72% when administered to healthy adult cats.

(2) Drug Administration:

Twelve fasted healthy adult cats received a single subcutaneous injection of VETSULIN at a dose of 0.5 IU/kg.

(3) Variables Measured:

(a) Plasma glucose concentrations:

Blood samples were collected within an hour before injection, immediately before injection, and 0.5, 1, 2, 4, 6, 8, 10, 12, and 24 hours after injection. At each sampling time, a blood glucose concentration was measured immediately using a portable glucometer in order to identify hypoglycemia.

(b) Pharmacodynamic calculations:

The effect of insulin on plasma glucose concentrations was assessed individually for each dog using the following parameters:

(i) Glucose nadir (mg/dL):

Minimum plasma glucose concentration

(ii) Time to glucose nadir (hour)

(iii) Duration of action (hour):

Time for plasma glucose concentration to reach 80% of baseline concentration in 2 consecutive samples. The parameter was set at 24 hours if the plasma glucose concentration did not return to at least 80% of baseline value within 24 hours.

(iv) Onset of action (hour):

Time to reduction in plasma glucose concentration by at least 10% of baseline value

e. Results:

(1) Pharmacodynamic parameters

Table 2: Summary of pharmacodynamic parameters in healthy cats (n=9)*

Parameter	Value
Glucose nadir (mg/dL)	34 ± 7.1 [mean ± SD]
Glucose nadir as % baseline	36 ± 7.7 [mean ± SD]
Time to glucose nadir (hour)	2 (2-6) [median (range)]
Onset of action (hour)	1 (0.5-2) [median (range)]
Duration of action (hour)	12 (8-24) [median (range)]

*Onset of action calculations are based on 12 cats, whereas the calculations for the other parameters are based on nine cats. Three cats left the study because they needed oral glucose supplementation to treat clinical signs of hypoglycemia.

(2) Safety:

Hypoglycemia was defined as blood glucose values below 40 mg/dL using the portable glucometer. Hypoglycemia was recorded in all cats. Clinical signs of hypoglycemia included: weakness, trembling, loss of balance, hypothermia, blindness, disorientation, slight convulsions, loss of consciousness, vomiting, and uncontrolled defecation.

f. Conclusions:

The study using healthy adult cats describes the pharmacodynamics of VETSULIN with a NE content of 61%. Onset of action ranged from 0.5 to 2 hours (median 1 hour); time to glucose nadir ranged from 2 to 6 hours (median 2 hours); and duration of action ranged from 8 to 24 hours (median 12 hours). All cats experienced biochemical hypoglycemia defined as glucose readings < 40 mg/dL using the portable glucometer. Three cats were removed from the study after requiring oral glucose supplementation to alleviate clinical signs of hypoglycemia. Four cats showed signs but did not receive supplementation.

III. TARGET ANIMAL SAFETY

A. Dogs

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. Cats

CVM did not require target animal safety information for this supplemental approval. The FOI Summary for the supplemental approval of NADA 141-236, dated March 24, 2008, contains a summary of target animal safety for cats.

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 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

This approval does not qualify for marketing exclusivity under section 512(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act.

C. Supplemental Applications

This supplemental NADA did not require a reevaluation of the safety or effectiveness data in the original NADA (21 CFR 514.106(b)(2)).

D. Patent Information

For current information on patents, see the Animal Drugs @ FDA database or the Green Book on the FDA CVM internet website.