Date of Approval: February 3, 2014

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 add a 2.7 mL cartridge presentation for use with the VETPEN automatic injection device.

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

2.7 mL cartridges and 10 mL multidose vials

I. Dispensing Status

Rx

J. Dosage Regimen

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.

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

Subcutaneous injection

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 add a 2.7 mL cartridge presentation for use with the VETPEN automatic injection device.

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. Dog

a. FIELD STUDY: EFFECTIVENESS AND SAFETY

(1) Study Title and Number:

Evaluation of the use of an insulin pen in diabetic dogs: a field clinical study. Study Number EX-5156-00

(2) Type of Study:

Field Effectiveness and Safety Study

(3) Study Dates:

March 2010 – May 2010

(4) Investigators and Locations:

Dr. Patrice Autret	La Chapelle Sur Erdre, France
Dr. Felix Pradies	St Aubin de Blaye, France
Dr. Laurent Faget	Cavignac, France
Dr. François Mens	Hagueneau, France
Dr. Philippe Dhalmann	Marseille, France
Dr. Fabrice Le Nepvou	Le Havre, France
Dr. Erol Cavdar	Hyeres, France
Dr. Marie-Christine Ritter	Geispolsheim, France
Dr. Laurent Dillie	Lille, France
Dr. Claude Muller-Fleurisson	Lomme, France
Dr. Pascal Etienne	Cadenet, France
Dr. Bruno Gauclere	Fonsegrives, France

(5) General Design:

This was a 21-day, open-label study to evaluate the usability of a refillable automatic injection device (VETPEN insulin pen). The first week was an adjustment period during which the owner learned to use the insulin pen.

(a) Purpose of Study:

The purpose of the study is to demonstrate that owners could use the insulin pen and that the use of the insulin pen is well accepted by the dogs and their owners and does not negatively impact the control of diabetes in the dogs.

(b) Description of Test Animals:

The study included 40 client owned diabetic dogs (11 intact males, 2 neutered males, 19 spayed females, and 8 intact females) representing various breeds and mixes, ranging in age from 5 to 15 years, and ranging in weight from 4.0 to 46.1 kg. Eligible dogs had uncomplicated and well-controlled diabetes mellitus and had been treated with VETSULIN for at least 4 months prior to enrollment.

(c) Drug Administration:

VETSULIN was administered subcutaneously using a VETPEN insulin pen loaded with a pre-filled 2.7 mL VETSULIN cartridge and 29 gauge/12 mm insulin pen needle. There are two insulin pen sizes. The small insulin pen provides doses of 0.5 IU to 8 IU in 0.5 IU increments per injection. The large insulin pen provides doses of 8 IU to 16 IU in 1 IU increments. The choice of insulin pen was dependent on the dose. The initial insulin dose was the dose at enrollment. The investigators could adjust the insulin dose as needed during the study.

(d) Variables Measured:

On Study Days 0 and 21, the investigator conducted a physical examination and interviewed the owner about the presence or absence of polyuria, polydipsia, polyphagia, and weight loss. Telephone interviews with the owners were conducted twice a week to monitor the use of the pen and the condition of the dog. On the final visit or during a withdrawal visit, a final interview was conducted to define the overall acceptance of the insulin pen based on a Yes/No response to the three final questions:

The owner answered the first two questions based on the assessment on the final study day:

Were you able to learn how to use the insulin pen?
Overall was the insulin pen well tolerated by your pet?

The investigator answered the third question based on the clinical assessment of the dog's diabetes during the final examination:

Was diabetes control negatively impacted by the use of the insulin pen?

(e) Criteria for Success/Failure:

Success was defined as a minimum of 70% positive responses for each of the three final questions (i.e. "Yes" for the first two questions and "No" for the third question).

(f) Statistical Methodology:

The percentage of positive responses was calculated for the three final questions.

(6) Results:

Of 40 dogs enrolled in the study, two dogs whose owners did not adjust to using the insulin pen during the adjustment period were excluded from the effectiveness analysis. Therefore, all 40 dogs enrolled in the study were included in the safety evaluation and 38 were included in the effectiveness evaluation. Thirty-four of the 38 dogs completed the Study Day 21 visit. Four dogs were withdrawn between Study Days 8 and 21 and were included in the analysis on the basis of owner responses and investigator evaluations when they were withdrawn. Thirty-seven of the 38 owners (97.4%) said they were able to learn how to use the insulin pen. Thirty-five of the 38 owners (92.1%) said the insulin pen was well tolerated by the dogs. For 34 of the 38 dogs (89.5%), the investigators said that the control of diabetes was not negatively affected by the use of the insulin pen.

(7) Adverse Reactions:

Loss of diabetic control was reported in 10 dogs, 3 of which were withdrawn from the study. In 4 dogs, the loss of control resolved after dose adjustment while still using the insulin pen. For the remaining 3 dogs, the loss of diabetic control was reported at the end of the study and outcome was not documented. Two dogs had injection site reactions: edema in one dog and two instances of crusting in another. Poor appetite and weight loss was reported in one dog.

(8) Conclusions:

VETSULIN administered by the VETPEN insulin pen loaded with a pre-filled 2.7 mL VETSULIN cartridge is a safe and effective injection system for the administration of VETSULIN to diabetic dogs.

2. Cat

a. FIELD STUDY: EFFECTIVENESS AND SAFETY

(1) Study Title and Number:

Evaluation of the use of an insulin pen in diabetic cats: a field clinical study. Study Number EX-5157-00

(2) Type of Study:

Field Effectiveness and Safety Study

(3) Study Dates:

March 2010 – April 2010

(4) Investigators and Locations:

Dr. Patrice Autret	La Chapelle Sur Erdre, France
Dr. Felix Pradies	St Aubin de Blaye, France
Dr. Laurent Faget	Cavignac, France
Dr. François Mens	Hagueneau, France
Dr. Philippe Dhalmann	Marseille, France
Dr. Erol Cavdar	Hyeres, France
Dr. Marie-Christine Ritter	Geispolsheim, France
Dr. Laurent Dillie	Lille, France
Dr. Claude Muller-Fleurisson	Lomme, France
Dr. Pascal Etienne	Cadene, France
Dr. Corinne Laruelle	Le Havre, France
Dr. Bruno Gauclere	Fonsegrives, France

(5) General Design:

This was a 21-day, open-label study to evaluate the usability of a refillable automatic injection device (VETPEN insulin pen). The first week was an adjustment period during which the owner learned to use the insulin pen.

(a) Purpose of Study:

The purpose of the study is to demonstrate that owners could use the insulin pen and that the use of the insulin pen is well accepted by the cats and their owners and does not negatively impact the control of diabetes in the cats.

(b) Description of Test Animals:

The study included 36 client owned diabetic cats (27 males and 9 females - all neutered) representing various breeds and mixes ranging in age from 5 to 21 years, and ranging in weight from 2.3 to 9.5 kg. Eligible cats had uncomplicated and well-controlled diabetes mellitus and had been treated with VETSULIN for at least 4 months prior to enrollment.

(c) Drug Administration:

VETSULIN was administered subcutaneously using a VETPEN insulin pen loaded with a pre-filled 2.7 mL VETSULIN cartridge and a 29 gauge/12 mm pen needle. There are two insulin pen sizes. The small insulin pen provides doses of 0.5 IU to 8 IU in 0.5 IU increments per injection. The large insulin pen provides

doses of 8 IU to 16 IU in 1 IU increments. The choice of insulin pen was dependent on the dose. The initial insulin dose was the dose at enrollment. Investigators could adjust as needed based on clinical signs and blood glucose levels, if measured.

(d) Variables Measured:

On Study Days 0 and 21, the investigator conducted a physical examination and interviewed the owner about the presence or absence of polyuria, polydipsia, polyphagia, and weight loss. Telephone interviews with the owners were conducted twice a week to monitor the use of the insulin pen and the condition of the cat. On the final visit or during a withdrawal visit, a final interview was conducted to define the overall acceptance of the insulin pen based on a Yes/No response to the three final questions:

The owner answered the first two questions based on the assessment on the final study day:

Were you able to learn how to use the insulin pen?
Overall was the insulin pen well tolerated by your pet?

The investigator answered the third question based on the clinical assessment of the cat's diabetes during the final examination

Was diabetes control negatively impacted by the use of the insulin pen?

(e) Criteria for Success/Failure:

Success was defined as a minimum of 70% positive responses for each of the three final questions (i.e. "Yes" for the first two questions and "No" for the third question).

(f) Statistical Methodology:

The percentage of positive responses was calculated for the three final questions.

(6) Results:

All 36 cats completed the Study Day 21 visit. Thirty-six owners (100%) said they were able to learn how to use the insulin pen. Thirty-four owners (94.4%) said the insulin pen was well tolerated by the cats. For thirty-five cats (97.2%), the investigators said that the control of diabetes was not negatively affected by the use of the insulin pen.

(7) Adverse Reactions:

Loss of diabetic control was reported in three cats, all of which resolved after dose adjustment while still using the insulin pen.

Hypoglycemia (glucose ≤ 50 mg/dL) was reported in one cat. The cat recovered with supportive care and dose adjustment.

(8) Conclusions:

VETSULIN administered by the VETPEN insulin pen loaded with a pre-filled 2.7 mL VETSULIN cartridge is a safe and effective injection system for the administration of VETSULIN to diabetic cats.

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 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 in a 2.7 mL cartridge for use with the VETPEN automatic injection device, 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 marketing exclusivity beginning on the date of approval. The three years of marketing exclusivity applies only to the 2.7 mL cartridge presentation for use with the VETPEN automatic injection device for which this supplement is approved.

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.