

HFA-305

199 1 2004

Date of Approval: \_\_\_\_\_

**FREEDOM OF INFORMATION SUMMARY**

**NADA 141-236**

**VETSULIN**

**Porcine insulin zinc suspension**

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

## Table of Contents

	<b>Page</b>
1. GENERAL INFORMATION:.....	3
2. EFFECTIVENESS:.....	4
a. Dosage Characterization: .....	4
b. Substantial Evidence: .....	5
3. TARGET ANIMAL SAFETY:.....	11
4. HUMAN SAFETY: .....	12
5. AGENCY CONCLUSIONS:.....	12
6. ATTACHMENTS: .....	13
7. LITERATURE CITED .....	13

Freedom of Information Summary  
NADA 141-236

**1. GENERAL INFORMATION:**

- a. File Number: NADA 141-236
- b. Sponsor: Intervet, Inc.  
P.O. Box 318  
405 State St.  
Millsboro, DE 19966
- Drug Labeler Code: 057926
- c. Established Name: Porcine insulin zinc suspension
- d. Proprietary Name: VETSULIN
- e. Dosage Form: Injectable
- f. How Supplied: 2.5 and 10 mL multidose vials
- g. How Dispensed: Rx
- h. Amount of Active Ingredient: 40 international units (IU) insulin/mL
- i. Route of Administration: VETSULIN should be administered subcutaneously using a U-40 insulin syringe and should be given 2 to 5 cm from the dorsal midline, varying from behind the scapulae to the mid-lumbar region and alternating sides.
- j. Species/Class: Canine
- k. Recommended Dosage: VETSULIN should be mixed by gentle rolling of the vial prior to withdrawing the dose from the vial. Using a U-40 insulin syringe, the injection should be administered subcutaneously, 2 to 5 cm (3/4 to 2 in) from the dorsal midline, varying from behind the scapulae to the mid-lumbar region and alternating sides. The initial recommended VETSULIN dose is 1 IU insulin/kg body weight plus a body weight-dependent dose supplement as shown in Table 1.

**Table 1: Initial dose determination**

<b>Body Weight</b>	<b>Dose</b>	<b>+ Dose Supplement</b>	<b>Initial Dose</b>
<10 kg (<22 lb)	(Weight in kg) x 1 IU/kg	1 IU	1 IU/kg + 1 IU
10 - 11 kg (22 - 24 lb)	(Weight in kg) x 1 IU/kg	2 IU	1 IU/kg + 2 IU
12 - 20 kg (25 - 44 lb)	(Weight in kg) x 1 IU/kg	3 IU	1 IU/kg + 3 IU
>20 kg (>44 lb)	(Weight in kg) x 1 IU/kg	4 IU	1 IU/kg + 4 IU

Initially, this dose should be given once daily concurrently with, or right after a meal. The veterinarian should re-evaluate the dog at appropriate intervals and adjust the dose based on clinical signs, urinalysis results, and glucose curve/spot check values until adequate glycemic control has been attained. In the US field study, glycemic control was considered adequate if an acceptable blood glucose curve was achieved (reduction in hyperglycemia and a nadir of 60 to 160 mg/dL), clinical signs of hyperglycemia (polyuria, polydipsia, and ketonuria) were improved, and hypoglycemia (blood glucose < 50 mg/dL) was avoided. Twice-daily therapy should be initiated if the duration of insulin action is determined to be inadequate. If twice-daily treatment is initiated, the two doses should be 25% less than the once daily dose required to attain an acceptable nadir.

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

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

**2. EFFECTIVENESS:**

**a. Dosage Characterization:**

The starting dose of insulin may vary significantly from the dose that achieves acceptable control of hyperglycemia and hyperglycemia-associated clinical signs. The goal at therapy initiation is to establish significant control of diabetic signs while avoiding hypoglycemia. Several insulin therapy starting dose recommendations have been described.<sup>1-8</sup>

Few reports referring directly to the use of porcine insulin zinc suspension are available. Church compared the blood glucose response to neutral protamine Hagedorn insulin (NPH), protamine zinc insulin (PZI), and porcine insulin zinc

Freedom of Information Summary  
NADA 141-236

suspension (IZS-P) in eight naturally occurring, previously untreated diabetic dogs.<sup>8</sup> The author noted great variability in individual response to the different insulins and in time to peak activity between different dogs to different insulins, but noted no difference in overall response between dogs or insulins. Church concluded that IZS-P had a relatively predictable peak activity time compared to NPH and PZI, but that it was impossible to accurately predict an individual dog's response to a particular insulin formulation except in broad, generalized terms.

An initial porcine insulin zinc suspension dose of 1 IU/kg body weight plus a body weight-dependent dose supplement was described in small animal endocrinology notes provided to Dutch veterinary practitioners by Belshaw.<sup>1</sup>

Two other published reports support the claim that the starting dose of 1 IU/kg plus a weight-dependent supplement proposed by Belshaw is safe and effective. In a study by Graham, Nash, and McKellar, plasma insulin and glucose concentrations were measured in ten stable, client-owned diabetic dogs of various breeds receiving once daily porcine insulin zinc suspension injections ranging from 1.01 to 2.80 IU/kg (mean =  $1.90 \pm 0.64$  IU/kg).<sup>9</sup> One or two peaks in plasma insulin were noted following a single insulin injection, plasma insulin was elevated above baseline for 14 to 24 hours, and blood glucose levels were effectively and safely reduced. No adverse effects attributable to the insulin were reported. A study by Horn and Mitten evaluated eight clinically stable, client-owned diabetic dogs of various breeds receiving once daily porcine insulin zinc suspension injections ranging from 0.7 to 2.3 IU/kg (mean  $1.3 \pm 0.5$  IU/kg).<sup>10</sup> Owner assessment of control of clinical signs of diabetes and 24 hour blood glucose curve results were obtained. Acceptable blood glucose maintenance was defined as a blood glucose between 5 to 13 mmol/L (90 to 234 mg/dL). Five of the eight dogs showed partial blood glucose control. These five dogs maintained glycemic control for 9 to 13 hours. Two dogs had blood glucose values in the acceptable range for 22 and 24 hours, respectively. One dog became distressed during hospitalization, and the blood glucose curve did not show an identifiable response to the insulin.

Although insulin dose varies between patients and for an individual patient over time due to differences in physiological state, concurrent disease conditions, endogenous insulin production, diet and/or exercise, the referenced studies support a starting VETSULIN dose of 1 IU/kg plus a weight-dependent dose supplement as safe and effective.

**b. Substantial Evidence:**

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

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

Freedom of Information Summary  
NADA 141-236

management of naturally occurring diabetes mellitus in dogs.

Study Director:

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

Cases were enrolled and managed by Investigators.

Investigators

William E. Monroe, DVM, MS, Blacksburg, VA  
Edward A. Fallin, DVM, MS, Manakin-Sabot, VA  
Mark R. Finkler, DVM, Roanoke, VA  
John R. Hart, DVM, Rancho Santa Fe, CA  
Steve Hill, DVM, MS, Rancho Santa Fe, CA  
David L. Panciera, DVM and Douglas R. Santen, DVM, Denver, CO  
Keith P. Richter, DVM, Rancho Santa Fe, CA  
Jennifer S. Shinn, DVM and Todd L. Towell, DVM, MS, Boulder, CO  
Kimberly A. Williams, DVM, Annapolis, MD

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

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

A blood glucose concentration >250 mg/dL AND one or more of the following:

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

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

Freedom of Information Summary  
NADA 141-236

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

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

Animals: A total of 66 client-owned dogs were enrolled, and 53 completed the effectiveness and safety study. The patients completing the study included 22 breeds of purebred and various mixed breeds of dogs ranging in age from 4.8 to 14 years, and ranging in weight from 4.2 to 51.3 kg. Of the dogs completing the study, 25 were spayed females and 28 were male (21 neutered and 7 intact).

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

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

Route of Administration: Subcutaneous injection

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

Study Duration: The Dose Determination Period needed to attain adequate

Freedom of Information Summary  
NADA 141-236

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

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

Results: Treatment with VETSULIN resulted in a reduction in blood glucose curve means and mean nadirs post-treatment relative to pre-treatment. The mean ( $\pm$  SD) blood glucose curve concentration was reduced from  $370 \pm 100$  mg/dL at enrollment (Time 0) to  $151 \pm 75$  mg/dL (Time 1),  $185 \pm 92$  mg/dL (Time 2), and  $184 \pm 87$  mg/dL (Time 3). The blood glucose mean nadir was reduced from  $315 \pm 93$  mg/dL at enrollment (Time 0) to  $93 \pm 35$  mg/dl (Time 1),  $120 \pm 62$  mg/dL (Time 2) and  $119 \pm 60$  mg/dL (Time 3).

Improvements in the incidence of polyuria, polydipsia, and ketonuria after the initiation of VETSULIN treatment are summarized in Table 2. Lower one-sided 95% confidence limits were calculated at each study time for each clinical response rate (95% confident that the general population response should be at least as good as the lower limit response of the study animals).

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

Clinical Sign	Study Time	Result <sup>a</sup>			Proportion Improved	Percentage of dogs Improved (%)	Lower One-Sided 95% Confidence Limit <sup>b</sup> (%)
		Observation missing	Present	Absent			
Polyuria	0	1	49	3	NA	NA	NA
	1	0	2	51	47/49	96	88
	2	0	9	44	40/49	82	70
	3	0	3	50	46/49	94	85
Polydipsia	0	0	50	3	NA	NA	NA
	1	0	2	51	48/50	96	88
	2	0	7	46	43/50	86	75
	3	0	2	51	48/50	96	88
Ketonuria	0	0	35	18	NA	NA	NA
	1	5	2	46	28/35	80	66
	2	3	2	48	30/35	86	72
	3	1	5	47	29/35	83	69

<sup>a</sup> For observation period 0, a missed observation of a clinical sign was considered to have been observed as absent. For treatment observation periods 1, 2, and 3, a missed observation of a clinical sign was considered to have been observed as present. This results in a conservative worst-case estimate of the proportion improved.

<sup>b</sup> The lower one-sided 95% confidence limits were obtained from StatXact 4 by using the lower limit from two sided 90% confidence limits.

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

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

Study Time	% Adequate (No./total)	% Inadequate (No./total)
Time 1	100 (53/53)	0 (0/53)
Time 2	66 (35/53)	34 (18/53)
Time 3	75 (40/53)	25 (13/53)

Titration to an effective insulin dose and maintaining adequate glycemic control by dose adjustments was highly variable both between dogs and for any given dog over time. The frequency of administration and effective dose ranges for dogs completing the study are summarized in Table 4.

**Table 4: Injection frequency and effective dose range for dogs completing the VETSULIN study (n=53).**

Study Time	Dogs on SID therapy	Dogs on BID therapy	Range of SID doses (IU/kg)	Range of BID doses (IU/kg)	
				a.m. dose	p.m. dose
Time 0 (Initial dose)	51 (96%)	2 (4%)	0.94 - 1.28	1.06 - 1.07	1.06 - 1.07
Time 1	23 (43%)	30 (57%)	0.44 - 2.22	0.39 - 1.29	0.39 - 1.26
Time 2	23 (43%)	30 (57%)	0.33 - 2.19	0.40 - 1.25	0.39 - 1.22
Time 3	18 (34%)	35 (66%)	0.43 - 2.18	0.34 - 1.40	0.28 - 1.40

The number of dose adjustments required to attain and maintain adequate glycemic control was also variable. Results are summarized in Table 5.

**Table 5: Number of dose adjustments required to attain and maintain adequate glycemic control by weight class and study period (n = 53).**

Interval	Range in number of dose changes by weight class			
	< 10 kg (n = 14)	10 - 11 kg (n = 5)	12 - 20 kg (n = 8)	> 20 kg (n = 26)
Dose determination period <sup>a</sup>	0 - 7	2 - 6	0 - 6	0 - 17
Between Time 1 and 2 <sup>b</sup>	0 - 2	0 - 1	0	0 - 3
Between Time 2 and 3 <sup>c</sup>	0 - 3	0 - 1	0 - 2	0 - 7

<sup>a</sup> 7 of 53 dogs required no dose adjustment. <sup>b</sup> 45 of 53 dogs required no dose adjustment. <sup>c</sup> 27 of 53 dogs required no dose adjustment.

**Conclusions:** This study demonstrates that VETSULIN is safe and effective for reducing hyperglycemia and hyperglycemia-associated clinical signs in dogs with diabetes mellitus.

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

dosage.

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

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

Extended Use: Dogs enrolled in this study were allowed to continue treatment with VETSULIN after study completion. Of the 66 dogs initially enrolled in the field study, 53 continued treatment into the extended use phase. Investigators evaluated the animals approximately every 90 days.

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

### **3. TARGET ANIMAL SAFETY:**

Insulin is an endogenous hormone whose mechanisms of action and effect have been studied for over 80 years. Insulin tolerance in the dog and the effects of hypoglycemia that results from overdosage have been well described. Regardless of insulin origin or formulation used, an increase in the dose above that which controls blood glucose concentrations will inevitably result in hypoglycemia. The safety of using various types of intermediate and long-acting insulin to treat diabetes mellitus when dosed appropriately and accompanied by adequate monitoring of the disease process is supported by the extensive literature regarding canine and human diabetes.<sup>1-10</sup>

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

Freedom of Information Summary  
NADA 141-236

reported in any dog receiving long term therapy.

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

**4. HUMAN SAFETY:**

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

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

**5. AGENCY CONCLUSIONS:**

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

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

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

Freedom of Information Summary  
NADA 141-236

**6. ATTACHMENTS:**

Facsimile Labeling is attached as indicated below:

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

**7. LITERATURE CITED**

- <sup>1</sup>Belshaw, BE. "Endocrinology Lecture Notes" Department of Clinical Sciences of Companion Animals, Utrecht University. 1985. 2-13.
- <sup>2</sup>Nelson RW. "Diabetes Mellitus." In *Saunders Manual of Small Animal Practice*. Eds. Stephen J. Birchard and Robert G. Sherding. W.B. Saunders Company, 1994. 249-256.
- <sup>3</sup>Nelson RW. "Diabetes Mellitus." In *Textbook of Veterinary Internal Medicine, Fifth Edition*. W.B. Saunders Company, 2000, vol. II. 1438-1460.
- <sup>4</sup>Nelson RW, and EC Feldman. "Diabetes Mellitus." In *Canine and Feline Endocrinology and Reproduction, Second Edition*. W.B. Saunders Company, 1996. 339-391.
- <sup>5</sup>Hoenig M. "Drugs Influencing Glucose Metabolism." In *Veterinary Pharmacology and Therapeutics, Seventh Edition*. Ed. H. Richard Adams. Iowa State University Press, 1995. 644-653.
- <sup>6</sup>Broussard JD, and MS Wallace. "Insulin Treatment of Diabetes Mellitus in the Dog and Cat." *Kirk's Current Veterinary Therapy XII Small Animal Practice*. Ed. Mark E. Peterson. W.B. Saunders Company, 1995. 393-398.
- <sup>7</sup>Schaer M. "Disease of the Endocrine Pancreas (Islet Cells)." In *Handbook of Small Animal Practice, Third Edition*. Ed. Rhea V. Morgan. W.B. Saunders Company, 1997. 463-467.
- <sup>8</sup>Church DB. "The blood glucose response to three prolonged duration insulins in canine diabetes mellitus." *J Small Anim Pract*, 1981. 22: 301-310
- <sup>9</sup>Graham PA, AS Nash, and QA McKellar. "Pharmacokinetics of porcine insulin zinc suspension in diabetic dogs." In *Journal of Small Animal Practice*, 1997. 38, October: 434-438.
- <sup>10</sup>Horn B, and RW Mitten. "Evaluation of insulin zinc suspension for control of naturally occurring diabetes mellitus in dogs." In *Australian Veterinary Journal*. 2000. 78, No. 12, December: 831-834.

**Dog Owner Information about  
vetsulin™ Injectable Insulin (porcine insulin zinc suspension)  
vetsulin™ for reduction of hyperglycemia and hyperglycemia-associated clinical signs in dogs 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 dog 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 any of 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 has inadequate levels of or an abnormal response to insulin. DM is common in middle age and older dogs. Daily insulin injections are usually necessary to treat DM. Vetsulin™ may help your dog effectively use food, aid in maintaining an acceptable blood sugar (glucose) level, and reduce or eliminate clinical signs commonly seen in dogs with DM. Diabetes mellitus may cause some or all of these signs or changes in your dog:

- 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)

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 dog 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 dog to dog but can be quite dramatic.
- In most dogs, improvement can be seen within a few days.
- 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™?**

- Dogs known to have a systemic allergy to pork or pork products.
- Dogs that have stopped eating or have greatly decreased appetite (anorexia), dogs that are vomiting, dogs that show signs of extreme drowsiness or fatigue (lethargy) and/or dogs showing 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 dog's condition.
- How often your dog may need to be examined by your veterinarian.
- The risks and benefits of using vetsulin™.

Tell your veterinarian if your dog 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)
- Cushing's Syndrome (Hyperadrenocorticism)
- Kidney disease

Tell your veterinarian about:

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

**How to give vetsulin™ to your dog**

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 dog, 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 dog, 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 dog 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, retaining the cap.
- Using a U-40 insulin syringe, pull the plunger back to draw air into the syringe to equal the vetsulin™ dose.
- Insert the syringe 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 (1-2 inches) from the midline of the back (middle of your dog'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 dog'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 and replace the cap on the needle 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 in my dog 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 dog shows signs of hypoglycemia?**

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

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 dog has a medical problem or side effect from vetsulin™ therapy. In particular, please contact your veterinarian if your dog shows any of the following:

- Excessive water consumption for more than 3 days
- Excess urination (including need to urinate at night for a dog 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 dog's blood sugar stable?**

- Your dog'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.

- "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 dog based on the response to vetsulin™.
- Your dog'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 dog'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 dog's response to insulin. Tell your veterinarian about all the medicines you have given your dog 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 dog's medications can be given together.

#### **What do I do in case my dog receives more than the prescribed amount of vetsulin™?**

If your dog 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 dog may need to be hospitalized for observation or treatment.

#### **What do I do if my dog 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 dog's next dose.
- If you cannot reach your veterinarian and your dog is eating and acting normal, give your dog 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 dog for which it was prescribed and for the condition for which it was prescribed.

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



Distributed by:  
INTERVET INC.  
Millsboro, DE 19966

Made in Holland

NADA NO. 141-236

## **vetsulin™ (PORCINE INSULIN ZINC SUSPENSION)**

### 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 (30% amorphous and 70% crystalline)	40 IU
Zinc 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 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 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.

The initial recommended vetsulin™ dose is 1 IU insulin/kg body weight plus a body weight-dependent dose supplement as shown in the table below.

<b>Body Weight</b>	<b>Dose</b>	<b>+ Dose Supplement</b>	<b>Initial Dose</b>
<10 kg (<22 lb)	(Weight in kg) x 1 IU/kg	1 IU	1 IU/kg + 1 IU
10 - 11 kg (22 - 24 lb)	(Weight in kg) x 1 IU/kg	2 IU	1 IU/kg + 2 IU
12 - 20 kg (25 - 44 lb)	(Weight in kg) x 1 IU/kg	3 IU	1 IU/kg + 3 IU
>20 kg (>44 lb)	(Weight in kg) x 1 IU/kg	4 IU	1 IU/kg + 4 IU

Initially, this dose should be given once daily concurrently with, or right after a meal. The veterinarian should re-evaluate the dog at appropriate intervals and adjust the dose based on clinical signs, urinalysis results, and glucose curve/spot check values until adequate glycemic control has been attained. In the US 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.

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.

## CONTRAINDICATIONS

Dogs 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: 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, especially hyperadrenocorticism in diabetic dogs that are difficult to regulate.

## 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 associated complications. Overdosage can result in profound hypoglycemia and death. Progestogens, certain endocrinopathies and glucocorticoids can have an antagonistic effect on insulin activity. Intact bitches should be ovariohysterectomized. Progestogen and glucocorticoid use should be avoided.

### Drug Interactions:

In the US clinical effectiveness study, dogs received various medications while being treated with vetsulin™ including antimicrobials, NSAIDs, thyroid hormone supplementation, internal and external parasiticides, anti-emetics, dermatological topical treatments and oral supplements, and ophthalmic preparations containing antimicrobials and antiinflammatories. No medication interactions were reported. This drug was not studied in dogs receiving steroids.

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

Use in puppies: The safety and effectiveness of vetsulin™ in puppies has not been evaluated.

## ADVERSE REACTIONS

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

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

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

The following clinical observations 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.

During the 1995-2001 period, the following adverse reactions in 19 dogs treated with porcine insulin zinc suspension were reported to Intervet International: destabilization (defined as lack of adequate regulation), lack of expected efficacy, edema of the head and neck, development of a fibrous lump at the injection site, hypoglycemia and death following administration of typical doses (one death in two dogs) and overdosage (four deaths in four dogs).

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

## INFORMATION FOR DOG OWNERS

Please refer to the Client Information sheet for more information about vetsulin™. Vetsulin™, like other drugs of this class, is not free from adverse reactions. Owners should be advised of the potential for adverse effects and be informed of the associated clinical signs. Potential adverse reactions include hypoglycemia, insulin antagonism/resistance, rapid insulin metabolism, insulin-induced hyperglycemia ("Somogyi Effect"), and local or systemic reactions. The primary adverse reaction observed is hypoglycemia. Signs may include weakness, depression, behavioral changes, muscle twitching, and anxiety. In cases of severe hypoglycemia seizures and coma can occur. Hypoglycemia can be fatal if an affected dog does not receive prompt treatment. Appropriate veterinary monitoring of blood glucose, adjustment of insulin dose and regimen as needed, and stabilization of diet and activity help minimize the risk of hypoglycemic episodes. The attending veterinarian should evaluate other adverse reactions on a case-by-case basis to determine if an adjustment in vetsulin™ therapy is appropriate, or if alternative therapy should be considered.

## GENERAL PHARMACOLOGY

Porcine insulin is similar in amino acid structure to canine insulin. Vetsulin™ is classified as an intermediate acting insulin. 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). The peak(s), duration of activity and dose required to adequately control diabetic signs will vary between dogs.

## EFFECTIVENESS

A total of 66 client-owned dogs were enrolled in and 53 completed the effectiveness and safety field study. The patients completing the study included 22 breeds of purebred and various mixed breed dogs ranging in age from 4.8 to 14 years, and ranging in weight from 4.2 to 51.3 kg. Of the dogs completing the study, 25 were spayed females and 28 were male (21 neutered and 7 intact).

Dogs were started on vetsulin™ at a dose of 1IU/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.

The injection frequency and effective dose range for dogs varied substantially:

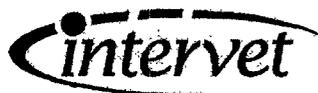
Study Time	Dogs on SID therapy	Dogs on BID therapy	Range of SID doses (IU/kg)	Range of BID doses (IU/kg)	
				a.m. dose	p.m. dose
Time 0 (Initial dose)	51 (96%)	2 (4%)	0.94 - 1.28	1.06 - 1.07	1.06 - 1.07
Time 1	23 (43%)	30 (57%)	0.44 - 2.22	0.39 - 1.29	0.39 - 1.26
Time 2	23 (43%)	30 (57%)	0.33 - 2.19	0.40 - 1.25	0.39 - 1.22
Time 3	18 (34%)	35 (66%)	0.43 - 2.18	0.34 - 1.40	0.28 - 1.40

#### 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.



Distributed by:  
INTERVET INC.  
Millsboro, DE 19966

Made in Holland

(date issued)

#### References

1. Graham P, Nash A, McKellar Q. "Pharmacokinetics of porcine insulin zinc suspension in diabetic dogs." *Journal of Small Animal Practice* Vol 38, October: 434-438.

2.5 mL

See package insert for directions for use.

Indication: VETSULIN<sup>®</sup> (pork insulin zinc suspension) is indicated for the reduction of hyperglycemia and hyperglycemia-associated clinical signs in dogs 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.

**vetsulin**  
(pork insulin zinc suspension)

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

Distributed by: INTERVET INC.  
Millsboro, DE 19966  
Made in Ireland  
www.vetsulin.com  
NADA No. 141-236, Approved by FDA



1000000

10 mL

See package insert for directions for use.  
Indications: VETSULIN™ (porcine insulin zinc suspension) is indicated for the reduction of hyperglycemia and hyperglycemia-associated clinical signs in dogs 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.

**vetsulin™**  
(porcine insulin zinc suspension)

CAUTION: Federal law restricts this drug to use by or on the order of a licensed veterinarian.  
Distributed by: INTERVET INC.  
Millsboro, DE 19966  
Made in Holland  
www.vetsulin.com



NADA No. 141-236, Approved by FDA

3

Lot/Exp:



004684-A

**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 chloride	0.08 mg
Sodium acetate trihydrate	1.38 mg
Sodium chloride	7.0 mg
Methyparaben (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 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.

**Distributed by:** INTERVET INC.  
Millsboro, DE 19966  
Made in Holland  
www.vetsulin.com

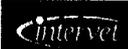
NADA No. 141-236, Approved by FDA



# vetsulin

(porcine insulin zinc suspension)

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



# vetsulin

(porcine insulin zinc suspension)

**Description:** VETSULIN<sup>VM</sup> is a sterile aqueous zinc suspension of purified porcine insulin. See package insert for directions for use.

**Indications:** VETSULIN<sup>VM</sup> (porcine insulin zinc suspension) is indicated for the reduction of hyperglycemia and hyperphosphatemia associated clinical signs in dogs 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.

**Distributed by:** INTERNET INC.  
Millsboro, DE  
19966  
Made in Holland  
www.vetsulin.com  
NADA No. 141-238. Approved by FDA



# vetsul<sup>in</sup>

(porcine insulin zinc suspension)

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

**Each mL contains:**  
Purified Porcine Insulin (30% amorphous and 70% crystalline) . . . 40 IU  
Zinc 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.

004685-A

100% POLYPROPYLENE  
**FPO**  
INTERNET INC.  
02170406855

Lot/Exp: