Date of Approval: November 23, 2009

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-298

SUROLAN

(miconazole nitrate, polymyxin B sulfate, prednisolone acetate)
Otic Suspension
Dogs

For the treatment of canine otitis externa associated with susceptible strains of yeast (*Malassezia pachydermatis*) and bacteria (*Staphylococcus pseudintermedius*)

Sponsored by:

Janssen Pharmaceutica NV

TABLE OF CONTENTS

I. GENERAL INFORMATION:

A. File Number: NADA 141-298

B. Sponsor:

Janssen Pharmaceutica NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

Drug Labeler Code: 012578

U.S. Agent: William Goodwine
Senior Director
Janssen Pharmaceutica Inc.
PMP Division
1125 Trenton-Harbourton Road
P.O. Box 200
Titusville, NJ 08560

C. Proprietary Name(s): SUROLAN otic suspension

D. Established Name(s): Miconazole nitrate, polymyxin B sulfate, prednisolone acetate

E. Pharmacological Category: Topical antifungal, antibacterial, and anti-inflammatory otic

F. Dosage Form(s): SUROLAN otic suspension is a white, opaque otic suspension

G. Amount of Active Ingredient(s): 23 mg/mL miconazole nitrate, 0.5293 mg/mL polymyxin B sulfate, 5 mg/mL prednisolone acetate

H. How Supplied: It is available in 15 mL and 30 mL plastic dispensing bottles with an applicator tip.

I. How Dispensed: Rx

J. Dosage(s): Shake well before use. The external ear should be thoroughly cleaned and dried before the initiation of treatment. Verify that the eardrum is intact. Instill 5 drops of SUROLAN in the ear canal twice daily and massage the ear. Therapy should continue for 7 consecutive days.

K. Route(s) of Administration: Otic

L. Species/Class(es): Dogs

M. Indication(s): SUROLAN is indicated for the treatment of canine otitis externa associated with susceptible strains of yeast (*Malassezia pachydermatis*) and bacteria (*Staphylococcus pseudintermedius*)

II. EFFECTIVENESS:

A. Dosage Characterization:

1. Study Title and Number: Uncontrolled clinical evaluation in Belgium and the Netherlands #V 2086

This field study was conducted in 1975 in Belgium and the Netherlands using 137 client-owned dogs. Clinical evaluation (discomfort, exudate, otoscopic appearance of the ear canal) determined the presence of otitis externa. All dogs received 3-5 drops of SUROLAN twice daily for a minimum of 7 days, and treatment was continued for up to 1 month or until a clinical cure was achieved. Of the 130 dogs that remained in the study, 56 were classified as subacute otitis externa and 74 as chronic. Otitis externa resolved in 85.7% of the dogs with subacute otitis externa and 55.4% of the dogs with chronic otitis externa. In a majority of the dogs, clinical resolution of otitis externa occurred either at day 7 or 14. The uncontrolled study demonstrated effectiveness of SUROLAN in dogs with otitis externa.

2. Study Title and Number*: In Vitro* Efficacy Study of the Antimicrobial Properties of SUROLAN Suspension, Study #IO ED-0200 and #IO ED-200A (amended)

This GLP study determined the susceptibility of representative bacterial and yeast pathogens associated with canine otitis externa to the active ingredients of SUROLAN. For each isolate, minimum inhibitory concentrations (MIC) of the antimicrobial constituents of SUROLAN, polymyxin B sulfate and miconazole nitrate, were determined individually as well as in a checkerboard series of combinations of the two drugs. Interference by the third active ingredient in SUROLAN, prednisolone acetate, was also evaluated.

Four test organisms representative of canine ear pathogens were used: the bacterial organisms *Escherichia coli*, *Staphylococcus pseudintermedius (previously S. intermedius)*, *Pseudomonas aeruginosa* and the fungal organism *Malassezia pachydermatis*. In Study #IO ED-0200, test organisms were clinical isolates collected from the Veterinary Teaching Hospital, Ontario Veterinary

Hospital, University of Guelph, Canada. For the amended study, additional *M. pachydermatis* isolates obtained from clinical cases enrolled in the SUROLAN International Field Trial (IO CC-0800) were used.

Statistical Methods: Outcomes, defined as the presence or absence of bacterial growth for each combination of drug concentrations, were dichotomized as 1 (slight or full growth) and 0 (no growth). To quantify and evaluate the significance of the effect of varying concentrations of miconazole and polymyxin in combination, logistic regression was performed.

The results showed a high susceptibility for all 4 test organisms to both polymyxin B sulfate and miconazole nitrate. SUROLAN vehicle and prednisolone acetate did not inhibit growth of any of the test or control organisms. All isolates remained susceptible to the drug constituents in the concentrations achieved by topical application of SUROLAN at the site of infection. The checkerboard titration results showed no negative inhibitory interactions between polymyxin B sulfate and miconazole nitrate to any of the organisms, or interference of prednisolone acetate. A synergistic interaction between the 2 drugs was demonstrated for *E. coli* and *P. aeruginosa*.

This study demonstrated the *in vitro* effectiveness and non-interference of the active constituents of SUROLAN (polymyxin B sulfate, miconazole nitrate, prednisolone acetate) against pathogenic bacteria and yeast commonly associated with canine otitis externa.

3. Study Title and Number: *In vivo* Efficacy Study of the Anti-inflammatory Properties of SUROLAN Suspension, Study #IO IR-0700.

This GLP study determined the anti-inflammatory effectiveness of SUROLAN using a laboratory animal ear skin inflammation model and determined whether the non-steroidal components of SUROLAN interfered with the anti-inflammatory effects of prednisolone acetate in the suspension. Eighty 9-week old female CD-1 domestic mice were used to test each active ingredient alone and in combination.

Twenty mcL of tetradecanoylphorbol acetate (TPA) was administered once to the lateral and medial pinnal surfaces of the right ear by means of an automatic microliter pipette. Ear inflammation was the main variable in the study illustrated by erythema and edema. The irritant TPA induced a clear and consistent ear inflammation with symptoms of skin redness and swelling. The mean erythema and edema scores for all treatments containing prednisolone were lower than those not containing prednisolone. Polymyxin B sulfate and miconazole nitrate did not interfere with the edema results among the groups containing steroids.

The study demonstrated that prednisolone is effective in reducing ear inflammation in mice and the other components within SUROLAN (polymyxin B sulfate and miconazole nitrate) do not interfere with prednisolone.

B. Substantial Evidence:

1. Study Title and Number: International field trial on the effectiveness of SUROLAN® Suspension compared to OTOMAX Ointment in the treatment of canine otitis externa #IO CC-0800

a. Type of Study: GCP Clinical field effectiveness study.

b. Study Dates: October 1, 2001 – November 25, 2002

c. Location(s) and Investigator(s): The study was conducted at 31 clinics in 4 geographical areas in the United States and Canada, which included Washington DC area, Seattle/Vancouver, Oakland, and Ontario.

Dr. Randell Benson Bethesda, MD	Dr. Peter Eeg Poolesville, MD	Dr. Peter Malnati White Plains, MD
Dr. Jim Reid Dr. Eric Chafetz Dr. Juli Westfall Vienna, VA	Dr. Steven Rogers Dr. David Jacobs Falls Church, VA	Dr. William Swartz Dr. Jennifer Schneider Herndon, VA
Dr. Fred Garrison Centerville, VA	Dr. Stephanie Lyons Washington, DC	
Dr. Hermann Bonasch San Lorenzo, CA	Dr. Rene Gandolfi Castro Valley, CA	Dr. Maurice Metcalfe Fremont, CA
Dr. Maureen Dorsey Dr. Cecilie Hart Oakland, CA	Dr. Deborah Rue Dr Carol Mertens Fremont, CA	Dr. Christine Stone-Payne Dr. Shian Lim Fremont, CA
Dr. Ted Rue Fremont, CA		
Dr. Melanie Caviness Dr. Margaret Hammon South Seattle, WA	Dr. Nick Nelson Dr. Kevin Stepaniuk Poulsbo, WA	Dr. Dave Luttinen Snohomish, WA
Dr. Lee Miles Seattle, WA	Dr. Brad Crauer Redmond, WA	

Dr. John Anderson Vancouver, BC Canada	Dr. Jack Brondwin Vancouver, BC Canada	Dr. Jessie Hare Delta, BC Canada

Location(s) and Investigator(s) cont'd

Dr. Robert Hopper Delta, BC Canada		
Dr. Richard Coultes Dr. Janice de St. Croix Dr. Michelle Holt Burlington, ON Canada	Dr. Isabel Hetram Dr. Vinny Hetram Dr. Daniel Yeulett South Caledonia, ON Canada	Dr. John McNally Dr. Chris Hamilton Dr. Heidi Hung Waterdown, ON Canada
Dr. Jane Burgess Dr. Kate Kuzminski Guelph, ON Canada	Dr. Joy Courey Dr. Sue Weninger Brampton, ON Canada	Dr. Nina Honda Dr. Ronald Fox Burlington, ON Canada
Dr. Barbara Drewry Guelph, ON Canada		

d. General Design

i. Purpose of Study: The objective of the study was to determine the effectiveness and safety of SUROLAN compared to OTOMAX when used under field conditions in North America and at proposed label directions in the treatment of bacterial and/or fungal canine otitis externa.

ii. Description of Test Animals: Three hundred and thirty-seven dogs (169 treated with SUROLAN and 168 treated with OTOMAX) were enrolled ranging in weight from 1.8 to 68.0 kg and age from less than 1 year to 20 years old. Of these, 176 (91 dogs treated with SUROLAN and 85 dogs treated with OTOMAX) were used to evaluate effectiveness and 322 dogs (161 treated with SUROLAN and 161 treated with OTOMAX) were used to evaluate safety. Some of the enrolled dogs completing the study were removed from the effectiveness or safety databases for protocol deviations.

iii. Control and Treatment Group(s): Dogs were randomly assigned either to the test article, SUROLAN, or to the active control, OTOMAX.

Table 1. Treatment groups

Treatment Group	Dose	Number and Sex of Animals
SUROLAN	5 drops BID	91 (45 F, 46 M)
OTOMAX	4 or 8 drops BID	85 (33 F, 52 M)

iv. Inclusion Criteria:

- Present with unilateral or bilateral clinical otitis externa.
- Have a minimum overall clinical score of 5, assessed from the 4 clinical examination variables.
- Have a confirmed bacterial and/or yeast infection from an ear swab as determined in a microbiological laboratory.

Only one ear of each dog was evaluated. An eligible dog with a bilateral ear condition had its right ear evaluated, assuming this ear scored a minimum of 5 in the clinical scoring. In case of the right ear not qualifying, the left ear was evaluated if the clinical score of that ear added up to 5.

v. Exclusion Criteria:

- Treated with local or systemic antimicrobial and/or anti-inflammatory therapy within the last 2 weeks (amended to 30 days).
- Treated with a depo form of corticosteroids within the last 4 months.
- Evidence of head tilt (inner/middle ear infection).
- Verified ruptured tympanic membrane.
- Concurrent infections of *Otodectes cynotis.*
- Poor general health or with high anesthetic risk.
- Pregnancy.

vi. Drug Administration:

Dosage amount, frequency, and duration: Treatments were administered into the ear canal twice a day for 7 consecutive days.

SUROLAN: 5 drops BID
OTOMAX: Dogs < 30lbs: 4 drops BID
Dogs ≥ 30 lbs 8 drops BID

vii. Variables Measured: Ear examination, tympanic membrane examination, hearing assessment, and ear swab sampling.

Ear Examination: Conducted prior to any swab collection or ear cleaning procedure. The chosen ear was examined at the initial visit and then 2-4 days after cessation of treatment. Four clinical signs of otitis externa were scored for severity as shown in the following table.

Table 2. Severity of clinical signs

Clinical Sign	Normal	Mild	Moderate	Marked
Pain/Discomfort	0	1	2	3
Swelling	0	1	2	3
Redness	0	1	2	3
Exudate	0	1	2	3

Tympanic membrane examination: The tympanic membrane was described as intact, ruptured, or not visible. A ruptured tympanic membrane disqualified the case from the study.

Ear swab sampling: One ear swab was collected for microbiology testing prior to any manipulation of the ear canal including cleaning. No further swabs were collected.

Samples were cultured to identify bacteria to the level of species and yeast to the level of genus.

Hearing assessment: The investigator assessed the gross hearing of the dog at the initial visit and then 2-4 days after cessation of treatment. A supplied high frequency audible dog whistle was used. Hearing was categorized as normal, reduced or absent.

viii. Criteria for Success/Failure:

The binary outcome: Improvement versus no improvement. "Improvement" was defined for each clinical parameter and the overall clinical parameter as a decrease of at least one level on the scale between the pre-treatment and post-treatment period, otherwise it was classified as "no improvement". Cases for which the difference between pre- and post-treatment was zero were excluded from any further analysis.

The continuous outcome: The degree of improvement or change in clinical score after treatment. If there was no improvement or if the score worsened, this was set to "0".

ix. Statistical Methods: For the binary outcome, a non-inferiority evaluation was used to compare SUROLAN with OTOMAX with respect to percent improvement for each clinical variable (pain/discomfort, swelling, redness, and exudate) and overall clinical variable (sum of the 4 clinical variables). The one-sided lower 95% confidence limit for the difference "SUROLAN – OTOMAX" was to be no less than -10% for treatment with SUROLAN to be considered non-inferior to treatment with OTOMAX.

e. Results

i. Binary Outcome: Improvement versus no-improvement. 96.7% of the cases treated with SUROLAN and 95.2% of the cases treated with OTOMAX had clinical improvement of the inflammatory symptoms. Among the total of 7 cases categorized as "no-improvement", 1 dog treated with SUROLAN experienced a worsening of the clinical signs while 2 dogs treated with SUROLAN and 4 dogs treated with OTOMAX had no change in clinical score

Table 3. Non-inferiority testing for each clinical examination variable and the overall clinical examination variable

Clinical Examination Variable	Group	Mean improve-ment[1] (%)	SUROLAN – OTOMAX (%)		
			95 % LL[2]	Difference	SE[3]
Pain/discomfort	SUROLAN	94.4	-4.0	2.7	3.9
	OTOMAX	91.7			
Swelling	SUROLAN	89.1	-10.0	-1.4	5.4
	OTOMAX	90.5			
Redness	SUROLAN	91.2	-4.0	5.1	5.3
	OTOMAX	86.1			
Exudate	SUROLAN	83.1	-9.0	1.0	6.1
	OTOMAX	82.1			
Overall	SUROLAN	96.7	-3.0	1.4	3.0
	OTOMAX	95.2			

[1] Mean improvement are back-calculated from the logit model [2] LL = Lower confidence limits (one-sided) [3] SE = Standard error

ii. Continuous Outcome: The degree of clinical improvement was demonstrated as a change in clinical score pre-treatment compared to post-treatment. On average the clinical ear score (pain/discomfort, redness, swelling and quantity of exudate) had improved by 5.6 points for SUROLAN and 5.5 points for OTOMAX. In more than 84% of

the dogs, the total clinical score decreased by 4 points or more. Two dogs treated with SUROLAN had no change in clinical score. Four dogs treated with OTOMAX had no change in clinical score.

Table 4. Mean and range of clinical score by treatment group.

Continuous Outcome	**SUROLAN N = 91**	**OTOMAX N = 85**
Pretreatment clinical score	7.5 (5 – 11)	7.3 (5 – 11)
Post treatment clinical score	2.0 (0 – 12)	1.8 (0 – 8)
Clinical Summary improvement	5.6 (0 – 10)	5.5 (0 – 10)

iii. Hearing: Three dogs (2 treated with SUROLAN and 1 treated with OTOMAX) had a hearing capacity change from normal to reduced between the initial examination and the final examination as assessed by the investigator. An additional dog treated with SUROLAN had normal hearing at the final examination as assessed by the investigator; however, on day 4 of treatment, the dog's owner noted that build-up of the medication in the ear decreased the dog's hearing. On follow-up on those dogs whose hearing was reduced at the final examination, 1 dog treated with SUROLAN and the 1 dog treated with OTOMAX had recovered and had normal hearing capacity. The other dog treated with SUROLAN was lost to follow-up.

iv. Microbiology: One hundred seventy-six dogs enrolled in the effectiveness database of the field study had positive ear swab culture results. Pre-treatment ear swab culture results often confirmed the presence of more than one potentially pathogenic organism. The most frequently cultured organisms were Gram-positive with 56% of dogs harboring staphylococcal isolates and 15% harboring streptococcal isolates. The second most common isolate was the yeasts at 52%. *Pseudomonas* spp. were present in 12.5% of enrolled dogs. Bacterial and yeast isolates identified pre-treatment are provided in Table 5.

Table 5. Frequency of isolation of potential otitis externa pathogens

Organism	Frequency of Pre-Tx Isolation [# of responsive cases]	
	SUROLAN (N=91)	**OTOMAX (N=85)**
Staph. pseudintermedius †	47 [45*]	46 [44]
Malassezia pachydermatis	40 [38*]	38 [36]
γ-non-hemolytic streptococci	14 [13]	5 [5]
Pseudomonas aeruginosa	9 [9]	10 [9]
Pseudomonas spp.	2 [2]	1 [1]
Yeast (unidentified)	6 [6]	7 [7]
Proteus mirabilis	6 [6]	5 [4]
β-hemolytic streptococci	6 [5]	0 [0]
α-hemolytic streptococci	4 [4]	1 [1]
Other staphylococci	1 [1]	5 [5]

† - formerly *Staph. intermedius*

* - denotes species for which there were a minimum of 10 evaluable, responsive cases with pre-treatment isolation of a pathogenic otitis externa species in this study

Staphylococcus pseudintermedius, Malassezia pachydermatis, and γ-non-hemolytic streptococci were identified pre-treatment in at least 10 cases that were clinically responsive to SUROLAN. The γ-non-hemolytic streptococci were not further identified down to the genus level and could therefore not be included in the indication. The required minimum of 10 evaluable, responsive cases was not reached for *Pseudomonas aeruginosa* and for all other organisms in this study. Therefore, the organisms included in the product indication are *Malassezia pachydermatis* and *Staphylococcus pseudintermedius*.

Susceptibility testing results of isolates in this study and of isolates in the *in vitro* study demonstrated a susceptibility of *Malassezia pachydermatis*, *Staphylococcus pseudintermedius,* and *Pseudomonas aeruginosa* to the active constituents of SUROLAN.

f. Adverse Reactions: There were 13 reported adverse reactions, 5 treated with SUROLAN and 8 treated with OTOMAX.

Table 6. Adverse reactions

Adverse Reaction	SUROLAN # of dogs	OTOMAX # of dogs
Reduced hearing	3*	1
Residue build-up	1	1
Pain upon drug application	1	0
Vomiting	0	4
Red Pustules on pinna	0	1
Head shaking	0	1
Total	5	8

* - One dog had normal hearing as assessed by the investigator during the final examination, however, the owner noted on day 4 of treatment that build-up of the medication in the ear decreased the dog's hearing.

g. Conclusion(s): SUROLAN is non-inferior to OTOMAX for the treatment of otitis externa in dogs.

III. TARGET ANIMAL SAFETY:

A. Study Title and Number: Laboratory Target Animal Safety (1X, 3X, 5X) Study in dogs for 42 consecutive days (6X treatment duration) #IO ED-0300

1. Name and Address of Study Director:

Dr. D. McKeown
Fergus, Ontario
Canada

2. General Design:

a. Animals: A total of 32 adult Beagle dogs were used in this study. Twenty-four dogs were treated with SUROLAN and 8 dogs were used as a control. Body weights ranged from 8.84 to 16.38 kg. Four males and four females were randomly assigned to four groups (4/sex/group).

b. Dosage Form: SUROLAN containing miconazole nitrate USP 23 mg/mL, polymyxin B sulfate USP 5500 IU/mL, prednisolone acetate USP 5 mg/mL (active ingredients).

Dosages: SUROLAN 10 drops daily (1X)
SUROLAN 30 drops daily (3X)
SUROLAN 50 drops daily (5X)
Placebo (saline) 50 drops daily

c. Route of Administration: All dogs underwent ear cleaning 3 days prior to the start of the study. SUROLAN or the saline placebo was administered externally into the ear using an Eppendorf® repeater pipette fitted with a broad rounded plastic tip. The tip was placed into the exterior portion of the ear and the product was administered. A new tip was used for each application.

d. Study Duration: Daily application(s) for 42 consecutive days (which is 6 X the recommended treatment duration). The study period included day -7 to day 56.

e. Pertinent Measurements/Observations: Veterinary clinical observations, general daily observations, temperature, feed consumption, behavior, ear assessments and hearing assessments, hematology, serum chemistry, urinalysis including urine sediment, fecal assessment, occult fecal blood, and body weight. Hearing was evaluated using a variable frequency dog whistle to test for responses to sound. A scale of 0 to 3 was used, with 0 being normal and 3 being severe deficit. Aural inflammation was evaluated using a scale of 0 to 3, with 0 being normal and 3 being severe inflammation. Behavior was evaluated using a scale of +1 to -2, with +1 being hyperactive, 0 being normal, and -2 being moribund.

f. Statistical Analysis: Continuous outcomes were analyzed by repeated measures analysis of variance. The fixed effects included in the model were sex, treatment group, day and their 2-way and 3-way interactions. Binary outcomes were analyzed by Chi-Square analysis and logistic regression.

3. Results:

a. Clinical Observations: There were no clinically significant treatment-related effects on body weight, feed consumption, behavior, or temperature.

b. Fecal Assessments: The majority of dogs in all treated groups and the control group had formed, moist and soft stools. One dog in the 3X group had loose, not well-formed stools on study day 28.

c. Occult Fecal Blood: One dog in the 3X group and one dog in the control group was positive for fecal occult blood on study day 28. All other dogs in all groups were negative for occult fecal blood.

d. Hearing Assessments: One dog in the control group was given a score of 2 (moderate deficit) on study day 14. This dog had normal hearing scores on all other study days. All other dogs in all groups were given normal hearing scores.

e. Ear Assessments:

Table 7. Ear assessments in the 1X, 3X and 5X treatment groups

Tx Group	Day 7	Day 14	Day 21	Day 35	Day 42
1X		Pale ears in 2 dogs	Pale ears in 2 dogs; 1 dog rubbed ears until tips bled	Mild inflammation in 2 dogs	
				Pink ears in 2 dogs	
3X	Pale inner ear in 1 dog	Pale ears in 4 dogs	Pale ears in 3 dogs	Mild inflammation in 1 dog	
			Painful ears in 2 dogs	Pink ears in 1 dog	Pink ears in 2 dogs
5X		Pale ears in 1 dog	Pale ears in 4 dogs	Mild inflammation in 6 dogs	Mild inflammation in 2 dogs
			Painful ears in 1 dog	Pink ears in 4 dogs	Pink ears in 2 dogs
				Painful ears in 1 dog	

Observations on study days 0, 28, and 56 in the 1X, 3X and 5X groups did not reveal any abnormalities. Waxy build-up and 2 instances of hyperemia occurred in the control group.

f. Veterinary Clinical Observations: One dog in the control group vomited on study day 28 and one dog in the 1X group vomited on study day 49. One dog in the 1X group had bleeding lacerations on the tips of both ears on study day 21 likely caused by the dog rubbing his ears due to the application of a topical otic product.

g. Hematology: The dose by day effect was statistically significant for leukocytes ($p < 0.10$) which was due to a severe adverse event resulting in leukocytosis in 1 dog in the 1X group, and unrelated to treatment with SUROLAN. Mild elevations in hemoglobin occurred in all groups, some of which may be the result of polydipsia and polyuria. See the urinalysis section.

h. Serum Chemistry: Beginning and beyond study day 14, 3 dogs in the 3X group had mild to moderate elevations in alkaline phosphatase (ALP). In the 5X group, only 1 dog had a mild increase in ALP on study day 42. In 1X, 3X and 5X groups, 5 dogs had mild increases in alanine transferase (ALT). Four dogs in the control group also had elevated ALT levels. The dose by day effect was statistically significant for gamma-glutamyl

transferase (GGT) ($p < 0.10$). The 1X, 3X, and 5X groups had significantly higher GGT means ($p < 0.10$) than the control group on study day 14. The 3X and 5X groups had significantly higher GGT means ($p < 0.10$) than the control group on study days 28 and 42. The 3X group had significantly higher GGT means than the control group on study day 56. One dog in the 3X group and one dog in the 5X group had large increases in GGT on study day 42. Otherwise, all elevations in GGT were mild in all groups beginning on study day 14 through study day 56. One dog each in the 1X, 3X and 5X groups and 1 dog in the control group had mild increases in blood urea nitrogen (BUN) during the study. Two dogs in the control group, 3 dogs in the 1X group, 3 dogs in the 3X group, and 2 dogs in the 5X group had mild elevations of chloride on study day 56. The above serum chemistry abnormalities were consistent with the absorption of a topical product containing a corticosteroid.

i. Urinalysis: In the 3X group, 2 dogs had a low urine specific gravity throughout the study, and in the 5X group, 1 dog had a low urine specific gravity during the study.

4. Conclusions**:**

Administration of SUROLAN at doses up to 5 times the recommended dose volume for 42 days in healthy Beagle dogs caused hypersensitivity reactions that included mild erythema and pale ears. In the 3X group, SUROLAN also caused painful and sensitive ear canals on examination in 2 dogs, and in the 5X group, SUROLAN caused hyperemia and sensitive ear canals on examination in 2 dogs. Changes in clinical pathology occurred in all SUROLAN treated groups consistent with the systemic absorption of topical corticosteroids. There were statistically significant elevations of GGT. There were also elevations in ALP, and chloride in the dogs treated with SUROLAN.

IV. HUMAN FOOD 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, 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 SUROLAN otic suspension:

Not for use in humans. Keep this and all drugs out of reach of children.

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 SUROLAN otic suspension, when used according to the label, is safe and effective for the treatment of canine otitis externa associated with susceptible strains yeast (*Malassezia pachydermatis*) and bacteria (*Staphylococcus pseudintermedius*).

A. Marketing Status:

This drug product is restricted to use by or on the order of a licensed veterinarian because professional expertise is required to determine the existence of, and microbiological components of, otitis externa. Additionally, veterinary expertise is needed to ensure that the tympanic membrane is intact prior to initial administration of the drug.

B. Exclusivity:

Under section 512(c)(2)(F)(ii) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for THREE years of marketing exclusivity beginning on the date of the approval.

C. Patent Information:

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

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

VII. ATTACHMENTS:

Facsimile Labeling:
Package Insert
Immediate container label 15 mL
Immediate container label 30 mL
Carton box 15 mL
Carton box 30 mL