Date of Approval: February 18, 2010

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-266

POSATEX Otic Suspension

Orbifloxacin, Mometasone Furoate Monohydrate and Posaconazole, Suspension
Dogs

For the treatment of otitis externa in dogs associated with susceptible strains of yeast (*Malassezia pachydermatis*) and bacteria (coagulase positive staphylococci, *Pseudomonas aeruginosa*, and *Enterococcus faecalis*).

Sponsored by:

Intervet, Inc.

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I. GENERAL INFORMATION:

A. File Number: NADA 141-266

B. Sponsor: Intervet, Inc.
56 Livingston Avenue
Roseland, NJ 07068

Drug Labeler Code: 000061

C. Proprietary Name(s):* POSATEX Otic Suspension

D. Established Name(s): Orbifloxacin, mometasone furoate monohydrate and posaconazole, suspension

E. Pharmacological Category: Antibacterial, anti-inflammatory, antifungal

F. Dosage Form(s): Topical suspension

G. Amount of Active Ingredient(s): Each gram of POSATEX Otic Suspension contains 10 mg orbifloxacin; mometasone furoate monohydrate equivalent to 1 mg mometasone furoate; and 1 mg posaconazole in a mineral oil based system containing a plasticized hydrocarbon gel.

H. How Supplied: 7.5 g, 15 g, 30 g in plastic bottles

I. How Dispensed: Rx

J. Dosage(s): Shake well before use. For dogs weighing less than 30 lbs. instill 4 drops of POSATEX Otic Suspension once daily into the ear canal. For dogs weighing 30 lbs. or more, instill 8 drops once daily into the ear canal. Therapy should continue for 7 consecutive days. Four drops of POSATEX Otic Suspension delivers approximately 1.0 mg of orbifloxacin, 0.1 mg of mometasone furoate monohydrate, and 0.1 mg of posaconazole.

K. Route(s) of Administration: Otic

L. Species/Class(es): Dogs

M. Indication(s): POSATEX Otic Suspension is indicated for the treatment of otitis externa in dogs associated

with susceptible strains of yeast (*Malassezia pachydermatis*) and bacteria (coagulase positive staphylococci, *Pseudomonas aeruginosa*, and *Enterococcus faecalis*).

* During the development of this product, the original proprietary name of ORBIMAX Otic was changed to POSATEX Otic Suspension. Wherever possible, the current proprietary name is used, but the reader should realize that ORBIMAX Otic refers to the same product as POSATEX Otic Suspension.

II. EFFECTIVENESS:

A. Dosage Characterization:

Orbifloxacin: The concentration of orbifloxacin in POSATEX Otic Suspension is 8.55 mg/mL. The MIC (minimum inhibitory concentration) $_{90}$ of orbifloxacin for field isolates of *Pseudomonas aeruginosa* and *Enterococcus faecalis* was ≥ 32 mcg/mL (the maximum MIC tested). MICs are used in conjunction with pharmacokinetics to predict the effectiveness of systemically administered antimicrobials. Topical administration of POSATEX Otic Suspension to an exudate and debris-free ear canal will result in local orbifloxacin concentrations that greatly exceed MICs evaluated for systemic administration. The concentration-dependent bactericidal action of fluoroquinolones supports once daily administration. Moreover, as orbifloxacin is incompletely and slowly absorbed from the external ear canal (Study Report 00209), and POSATEX Otic Suspension is reapplied daily, bacterial pathogens are exposed continually to high concentrations of orbifloxacin.

Posaconazole: The dose of 0.1% posaconazole is based on its relative *in vitro* potency to clotrimazole against canine isolates of *Malassezia pachydermatis*. *In vitro*, posaconazole has been shown to be at least ten times more potent than clotrimazole (Study Report 46431), which justifies a concentration of one tenth that used for clotrimazole in the approved veterinary otic products OTOMAX and MOMETAMAX (clotrimazole is formulated at a 1% concentration in these products).

Mometasone furoate monohydrate: The concentration, dose, and frequency of mometasone are derived from that already approved in another veterinary otic, MOMETAMAX. The effectiveness of mometasone in POSATEX Otic Suspension was demonstrated in the field study.

B. Substantial Evidence:

1. Component Anti-Inflammatory Effectiveness Study – Mouse Model

Component Anti-Inflammatory Efficacy of ORBIMAX (SCH 416547) in the Mouse Croton Oil Ear Assay – Study X00-244-01

Investigator: Karen E. Veley, B.S. Columbus, OH

Purpose:
To demonstrate component (mometasone) anti-inflammatory activity, and non-interference by the other active components orbifloxacin and posaconazole

GLP Compliance Statement: This nonclinical laboratory study was conducted in accordance with the U.S. Food and Drug Administration (FDA) Good Laboratory Practice (GLP) Regulations 21 CFR Part 58. The report accurately reflects the raw data obtained during the performance of the study.

General Design:
The study used a laboratory mouse model of irritant contact dermatitis. Mice were randomized to 8 treatment groups of 5 mice per group. The right ears of mice were treated with test articles and croton oil. Investigators were masked to test articles. The left ear of each mouse served as a control and was treated with the vehicle and croton oil. Ear swelling was measured and percent inhibition to swelling was calculated using the left ears as controls.

Test Animals:
40 male mice, 8 weeks old, 29.5 to 37.5 grams, Strain CRLCD1 (ICR)-BR

Treatment Groups (Test Articles applied to Right Ears):
1. Vehicle Control: the excipient base for POSATEX Otic Suspension (mineral oil based system containing a plasticized hydrocarbon gel) (this product was also used on left ears of all mice)
2. Orbifloxacin (10 mg/g) in vehicle
3. Mometasone (1 mg/g) in vehicle
4. Posaconazole (1 mg/g) in vehicle
5. Orbifloxacin (10 mg/g) and Mometasone (1 mg/g) in vehicle
6. Orbifloxacin (10 mg/g) and Posaconazole (1 mg/g) in vehicle
7. Mometasone (1 mg/g) and Posaconazole (1 mg/g) in vehicle
8. Orbifloxacin (10 mg/g), Mometasone (1 mg/g), and Posaconazole (1 mg/g) in vehicle [POSATEX Otic Suspension]

Procedure and Variables:
All products were applied to the anterior and posterior surfaces of mouse ears in volumes of 10 mcL per ear. Test article was applied to the right ear and vehicle was applied to the left ear 30 minutes before and again 15 minutes after 8% croton oil (in acetone) was applied. Mice were restrained with CO_2/O_2 anesthesia and ear thickness (swelling) was measured with digital calipers at 8 and 12 hours after application of croton oil. At 16 hours, mice were euthanized with CO_2 and ears were immediately measured again.

Percent inhibition to swelling was calculated for each mouse at 16 hours with the following formula: % inhibition = $(I_C-I_T)/ I_C$ *100%, where I_C and I_T are the ear

thickness (in mm) in the control (left) and treated (right) ear, respectively. Within each treatment group, individual percent inhibition results were averaged to calculate mean percent inhibition.

Statistical Analysis:
The mean percent inhibition was analyzed by a one-way ANOVA with the groups OMP (orbifloxacin, mometasone, and posaconazole), OP (orbifloxacin and posaconazole), and M (mometasone). Within this ANOVA, the contrasts OMP-M and OMP-OP were tested simultaneously using the Bonferroni correction at an α of 0.05.

Results:
The final (16 hour) sample time was used for comparisons between treatment groups, as the final sample was most relevant clinically. Mometasone provided maximum inhibition to swelling at 16 hours.

The mean percent inhibitions of OMP (12.576%) and M (9.717%) are not statistically significantly different. The mean percent inhibitions of OMP (12.576%) and OP (-8.244%) are statistically significantly different. All mice survived to the end of the study.

Conclusion:
This mouse model study demonstrated that by hour 16: 1) compared to the 3-way combination, the combination without mometasone provides significantly less anti-inflammatory activity; and 2) mometasone alone does not provide significantly more anti-inflammatory activity than the 3-way combination. Mometasone is essential to the anti-inflammatory effectiveness of POSATEX Otic Suspension.

2. Component Anti-Microbial Effectiveness Study – *In vitro*
Orbifloxacin-Posaconazole-Mometasone Drug Interaction Study - Report 46431

Investigator:
Steven D. Brown, Ph.D. and Maria Traczewski, M.T.
Wilsonville, OR

Purpose:
The purpose of the study was to document the *in vitro* activity of orbifloxacin and posaconazole against bacterial isolates and yeasts from the external ear or skin of dogs. Selected isolates were then used to assess whether there was any antagonistic or synergistic interaction between any two of the three components.

General Design and Samples Tested:
Minimum Inhibitory Concentrations (MICs) were determined for orbifloxacin, posaconazole, and mometasone (individually and combined). Microorganisms included 30 isolates of *Staphylococcus intermedius*, 50 isolates of *Pseudomonas*

aeruginosa, and 25 isolates of *Malassezia pachydermatis.* All isolates were collected from the ears and skin of dogs. For each isolate of bacteria or yeast, MICs for drug and drug combinations were compared for evidence of drug interaction.

Procedures:

Bacterial inocula were prepared following National Committee for Clinical Laboratory Standards (NCCLS) recommendations. American Type Culture Collection (ATCC) strains of *S. aureus* (29213), *P. aeruginosa* (27853), and *E. coli* (25922) were used as the control microorganisms and were included with each batch of testing. There are no NCCLS standards of susceptibility testing for yeast pathogens at the time of the study; however, the testing conditions were consistent and the *M. pachydermatis* (14522) quality control strain was used. Gentamicin and clotrimazole were included as controls and for comparisons. Cation adjusted Mueller-Hinton Broth (CAMHB) was used for bacterial testing. Both Sabouraud (SAB) Dextrose broth (pH 5) and the Emmons modification of Sabouraud Dextrose broth (pH 7) were used for testing *M. pachydermatis*. Initial screening tests were carried out with serial two-fold dilutions of the following agents:

Table 1: Combinations and Ranges of Active Agents Tested

Antimicrobial Agents and Mometasone	**Medium**	**Range of Concentration**
Orbifloxacin	CAMHB	16 to 0.016 mcg/mL
Gentamicin	CAMHB	16 to 0.016 mcg/mL
Orbifloxacin + Posaconazole (10:1 ratio)	CAMHB	16 to 0.016 + 1.6 to 0.0016 mcg/mL
Orbifloxacin + Mometasone (10:1 ratio)	CAMHB	16 to 0.016 + 1.6 to 0.0016 mcg/mL
Mometasone furoate	CAMHB	4.0, 2.0, 1.0 mcg/mL
Posaconazole	SAB	4.0 to 0.002 mcg/mL
Clotrimazole	SAB	32.0 to 0.008 mcg/mL
Posaconazole + Orbifloxacin (1:10 ratio)	SAB	1.0 to 0.001 + 10 to 0.01 mcg/mL
Posaconazole + Mometasone (1:1 ratio)	SAB	1.0 to 0.016 mcg/mL for each
Mometasone furoate	SAB	4.0, 2.0, 1.0 mcg/mL

Criteria for Comparison:

Synergism was defined as greater than or equal to a three-fold decrease in the MIC of either drug in combination as compared to the MIC of either drug alone. Antagonism was defined as greater than or equal to a three-fold increase in the MIC of either drug. Indifference was defined as an increase or decrease of less than or equal to two $\log_2$ dilutions of the combination as compared to either drug alone. MICs for posaconazole were compared to clotrimazole to justify the dose selection for posaconazole.

Results:
The combinations of orbifloxacin, posaconazole, and mometasone did not exhibit either synergism or antagonism against canine isolates of *Staphylococcus intermedius, Pseudomonas aeruginosa,* or *Malassezia pachydermatis.* Posaconazole was at least 60 times more potent against *Malassezia pachydermatis* than clotrimazole.

Conclusion:
Neither mometasone nor posaconazole added or detracted from the antibacterial effectiveness of orbifloxacin. Similarly, neither mometasone nor orbifloxacin added or detracted from the antimycotic effect of posaconazole. Study results support the use of posaconazole at one tenth the concentration of clotrimazole in OTOMAX and MOMETAMAX.

3. Field Study

A Negatively Controlled Study to Assess the Field Efficacy and Safety of ORBIMAX Otic Suspension (SCH 416547) administered once daily. Study C-00-055-00, Report 38341

Investigators and Locations:

Table 2: Field Study Investigators and Locations

Dr. Greg Tremoglie Glenmoore, PA	Dr. Dave Lukof Harleysville, PA
Dr. Karen Oberhansley Whitehouse Station, NJ	Dr. Ira Niedweske Iselin, NJ
Dr. Debbie Breitstein Englishtown, NJ	Dr. Charles Schwirck Somerville, NJ
Dr. Roger Sifferman Springfield, MO	Dr. Dean J. Rund Springfield, MO
Dr. Richard Benjamin Berkeley, CA	Dr. Robert Yelland San Leandro, CA

Purpose:
To assess the effectiveness and safety of POSATEX Otic Suspension in the treatment of canine otitis externa associated with bacteria and yeast.

General Design: Double-masked, randomized field study, using the POSATEX Otic Suspension excipient base as the control.

Test Animals and Treatment Groups: The test animals were client-owned dogs of multiple breeds, 4.8 months to 14.8 years of age, 5.3 lbs. to 167.6 lbs. body weight. Test dogs had the following histories of otitis externa: first occurrence (~ 40%), recurrent (46%), and chronic (~14%).

Table 3: Numbers of Dogs in Each Treatment Group

Treatment Group	**Number of Dogs Treated**	**Number of Dogs Evaluated for Effectiveness**
POSATEX Otic Suspension	143 dogs (67 females, 76 males)	122 dogs (56 females, 66 males)
Vehicle Control	48 dogs (24 females, 24 males)	38 dogs (18 females, 20 males)

Inclusion and Exclusion Criteria:

Dogs had to have otitis externa with concurrent bacterial and *Malassezia pachydermatis* infections in either one ear or both ears as determined by cytology. The otitis externa was of sufficient severity that the sum of the clinical scores (graded on a scale of 0-3) associated with discomfort, ear canal erythema, ear canal swelling and exudate quantity was greater than or equal to 5. If both ears qualified, only the right ear was evaluated. Dogs were excluded if they had otic foreign bodies, concurrent or recent medication that could confound study results (i.e. otic preparations; systemic corticosteroid, antibiotic, or antifungal therapy), occlusive masses, ruptured tympanic membranes, or if they were owned by staff or enrolled in other field studies.

Procedures:

A complete physical, hearing [clap] test, and otoscopic examination were performed. External ear canal cytology and culture samples were collected. Ears were cleaned with saline or water prior to the first treatment. Subsequent ear cleaning was not permitted. Affected ears were treated topically with POSATEX Otic Suspension or vehicle control once daily for 6 to 8 days. Dogs lighter than 30 lbs. were treated with 4 drops per affected ear. Dogs that weighed 30 lbs or more were treated with 8 drops per affected ear. Dogs were re-evaluated 2-7 days after completion of treatment.

Variables Evaluated:

Discomfort, ear canal erythema, and ear canal swelling were the primary variables. Primary variables were graded on a scale of 0 to 3, where 0 = none, 1 = mild, 2 = moderate, and 3 = marked. Secondary variables included odor (present or absent), pinna erythema (none, mild, moderate or marked), exudate quantity (none, trace, mild to moderate, or marked), and exudate type (serous, waxy, or purulent). Investigators and owners rated their overall evaluations as excellent (no obvious signs of discomfort – the dog has recovered and appears to be completely normal), good (occasional signs of discomfort – noticeably less discomfort, head shaking, and scratching than before treatment), fair (some reduction in signs of discomfort, but a definite indication of discomfort remains), or poor (no decrease in signs of discomfort). Hearing [clap test], ear canal cytology, and cultures were assessed pre and post-treatment.

Statistical Analysis:

For the primary clinical variables, POSATEX Otic Suspension was compared to the control using the Stratified Wilcoxon-Mann-Whitney Test with site as the strata. For the secondary clinical variables except Type of Exudate, the comparison was done using the Cochran-Mantel-Haenszel Test, again using site as strata. For Type of Exudate, homogeneity of the odds ratios and common odds ratio testing was performed.

Results:
Effectiveness was demonstrated by a highly statistically significant percent of dogs showing improvement in each of the primary variables.

Table 4: Percent of Dogs Showing Improvement in Primary Variables

Primary Variable	**POSATEX Otic Suspension Group**	**Control Group**	**p-values POSATEX Otic Suspension vs. Control**
Discomfort	88% (n=118)[a]	45% (n=38)	< 0.0001
Canal Erythema	81% (n=122)	39% (n=38)	< 0.0001
Canal Swelling	83% (n=107)	49% (n=35)	0.0001

[a] The number of animals in this group on which the percentage is based. The animals that were normal pre and post-treatment were excluded.

Effectiveness was supported by the results for investigator and owner overall evaluations and all of the secondary variables except Type of Exudate.

Table 5: Percent of Dogs Showing Improvement in Secondary Variables

Secondary Variable	**POSATEX Otic Suspension Group**	**Control Group**	**p-values POSATEX Otic Suspension vs. Control**
Pinna Erythema	83% (n=115)[a]	50% (n=36)	< 0.0001
Presence of Odor	66% (n=108)	21% (n=33)	< 0.0001
Quantity of Exudate	79% (n=121)	50% (n=38)	0.0007
Type of Exudate [b]	71% (n=17)	60% (n=5)	0.2381[c]
Investigator Evaluation [d]	75% (n=122)	21% (n=38)	< 0.0001
Owner Evaluation [d]	88% (n=122)	55% (n=38)	< 0.0001

[a] The number of dogs in this group on which the percentage is based. Dogs that were normal pre and post-treatment were excluded.
[b] Only cases with purulent exudate at either the pre and/or post treatment exam
[c] p-value for Type of Exudate applies to the test for common odds ratio being equal to 1.0.
[d] Percent of dogs rated "Excellent" or "Good"

Effectiveness was supported by the greater percent of POSATEX Otic Suspension group cases with no to mild signs in primary variables (discomfort, ear canal redness, and ear canal swelling) after treatment compared to the control group.

Table 6: Percent of Dogs with No to Mild Signs in Primary Variables[a]

Primary Variable	**Treatment Group**	**Pre-Treatment**	**Post-Treatment**
Discomfort	POSATEX Otic Suspension	22%	88%
	Control	26%	58%
Ear Canal Erythema	POSATEX Otic Suspension	16%	85%
	Control	21%	50%
Ear Canal Swelling	POSATEX Otic Suspension	52%	94%
	Control	42%	68%

[a] Based on 122 dogs in the POSATEX Otic Suspension group and 38 dogs in the control group

The otitis externa pathogens *Malassezia pachydermatis*, coagulase positive staphylococci, *Pseudomonas aeruginosa*, and *Enterococcus faecalis* were each isolated from at least ten dogs in the POSATEX Otic Suspension group that showed improvement in the primary variables and were rated as having a good or excellent overall response by investigators and owners.

In vitro susceptibility testing of orbifloxacin was performed by the broth microdilution method. The minimum inhibitory concentrations (MICs) of orbifloxacin against bacterial pathogens collected from the field study are summarized in the table below.

Table 7: Orbifloxacin MICs[a] (mcg/mL) for Field Study Pathogens

Genus	**# of isolates**	**MIC Range**	**MIC_{50}**	**MIC_{90}**
coagulase positive staphylococci	75	0.25 to 32	1	4
Pseudomonas aeruginosa	30	1.0 to 32	8	32
Enterococcus faecalis	24	4.0 to 32	8	32

[a] The maximum concentration of orbifloxacin tested was 32 mcg/mL.

The following MIC ranges and American Type Culture Collection (ATCC) Quality Control strains were used for susceptibility testing bacterial pathogens in the field study.

Table 8: Quality Control Ranges of MICs (mcg/mL) for Orbifloxacin

ATCC strain	**Range of MICs**
Staphylococcus aureus 29213	0.25-2
Enterococcus faecalis 29212	1-8
Escherichia coli 25922	0.015-0.12
Pseudomonas aeruginosa 27853	2-16

MIC_{50} and MIC_{90} are the minimum inhibitory concentrations for 50% and 90% of the isolates respectively. MICs are used in conjunction with pharmacokinetics to predict the *in vivo* effectiveness of systemically administered antimicrobials. Topical administration of POSATEX Otic Suspension, however, will result in local antimicrobial concentrations that greatly exceed serum and tissue levels resulting from systemic therapy. Therefore, susceptibility data may not predict the clinical response to POSATEX Otic Suspension. The assessment of success was based on clinical results, not microbiological results.

Adverse Reactions:

One dog with bilateral otitis externa developed hearing loss during treatment with POSATEX Otic Suspension. POSATEX Otic Suspension was discontinued and the condition resolved after one week.

Conclusion:
Compared to the placebo, a significant percent of dogs treated with POSATEX Otic Suspension showed improvement in discomfort, erythema, and swelling. POSATEX Otic Suspension improved clinical signs in dogs with otitis externa associated with one or more of the following organisms: *Malassezia pachydermatis*, coagulase positive staphylococci, *Pseudomonas aeruginosa*, and *Enterococcus faecalis*. Transient hearing loss developed in one dog during treatment with POSATEX Otic Suspension. Administration of POSATEX Otic Suspension should be discontinued immediately if hearing loss is detected.

III. TARGET ANIMAL SAFETY:

A. ORBIMAX Otic Suspension 21-Day Target Animal Safety Study in Dogs. Study Number 00036

Type of Study: 21-Day canine safety of POSATEX Otic Suspension at control, 1X, 3X, 5X dosage

Investigator: Patricia A. Turck. M.S.
Mattawan, MI

GLP Compliance Statement: This nonclinical laboratory study was conducted in accordance with the U. S. Food and Drug Administration (FDA) Good Laboratory Practice (GLP) Regulations 21 CFR Part 58. The report accurately reflects the raw data obtained during the performance of the study.

Purpose: The purpose of the study was to evaluate the safety of POSATEX Otic Suspension, when administered as an otic preparation to dogs at doses of 0 (vehicle control), 1X the clinical dose once per day, 3X (the clinical dose 3 times per day), and 5X (the clinical dose 5 times per day) for 21 consecutive days.

Test Animals: Forty-four (22 male, 22 female) Beagle dogs at least 8 months at study initiation were treated with the control or POSATEX Otic Suspension. Three dogs per sex in the 0X (control) and 1X group were designated for a recovery period.

Treatment Groups:

Table 9: Numbers of Dogs in Each Treatment Group

Treatment Group	Dose Level	Number and Gender of Animals
1	0	14 (7 male, 7 female)
2	1X	14 (7 male, 7 female)
3	3X	8 (4 male, 4 female)
4	5X	8 (4 male, 4 female)

Control: Vehicle [mineral oil and plasticized hydrocarbon gel (Plastibase 50W)]

Dosage Form: Otic Suspension. This formulation was final formulation.

Dosage Used: Clinical dose is 4 drops/ear for dogs weighing less than 30 lbs (13.6 kg) and 8 drops/ear for dogs weighing greater than or equal to 30 lbs ($\geq$ 13.6 kg). The clinical dose was administered once, three times, or five times per day to Groups 2, 3, and 4 respectively. The control article was administered at the same dose volume as the test article, and was administered five times per day in each ear. The dosing intervals were 2 hours ($\pm$0.5 hours) apart.

Route of Administration: The test and control articles were administered in each ear by otic dropper.

Study Duration: The test and control articles were administered for 21 consecutive days.

Pertinent Variables or Observations:

1. Cageside examination
2. Clinical observations
3. Physical examination
4. Ophthalmoscopic examination
5. Otoscopic examination
6. ACTH (adrenocorticotrophic hormone) stimulation test
7. Body weight
8. Food consumption
9. Hematology
10. Serum chemistry
11. Urinalysis
12. Fecal examination
13. Gross pathology
14. Organ weights
15. Histopathology

Results:
All animals survived to scheduled necropsy. Erythema of the ear pinnae was noted in the vehicle control and all treatment groups during the dosing period and was likely related to vehicle administration. The incidence in the 5X group was decreased compared to controls. Pain, swelling or heat, lasting between 1 and 3 days, were each noted in a different 5X dog early in the dosing period.

A slight, test article-related decrease in serum cortisol levels after ACTH stimulation testing on Day 21 was noted in the 5X group. Recovery period animals were euthanized without necropsy because the ACTH test results were normal in the 1X groups at the end of dosing.

No other test-article related changes were noted in any of the other variables or observations.

Conclusion:
POSATEX Otic Suspension was generally well-tolerated in the test animals. The decrease in serum cortisol concentration after adrenocorticotrophic hormone (ACTH) stimulation noted on Day 21 in the 5X treatment group is likely due to the POSATEX Otic Suspension administration. Although the erythema seen in all treatment groups is likely due to the vehicle, it should be considered a potential adverse reaction with POSATEX Otic Suspension administration. The local reaction of pain, swelling or heat in the 5X group was likely due to the POSATEX Otic Suspension administration.

B. SCH 416547 (ORBIMAX Otic): The Absorption and Excretion of SCH 416547 (^{3}H-Mometasone, ^{14}C-Posaconazole and ^{14}C-Orbifloxacin) following Administration of ORBIMAX Otic Ear Drops to Dogs. Study Number 00209

Type of Study: Pharmacokinetics/Metabolism

Investigator: Charles Heird, Ph.D.
Las Cruces, NM

Purpose: The purpose of this study was to determine the levels of total radioactive residues for each POSATEX Otic Suspension active ingredient in the urine, feces and plasma, following the administration of POSATEX Otic Suspension via ear drops to the external ear canal of Beagle dogs. Secondarily, the nature of the residues found in the urine and feces samples was investigated.

Test Animals: Six (3 male, 3 female) adult Beagle dogs

Treatment Groups:

Table 10: Treatment Groups and Dose Formulations

Gender	Radioactive Component	Non-Radiolabeled Components	Dose Formulation Number
1 male and 1 female	1.0% ^{14}C-SCH 51854 (orbifloxacin)	1.0% SCH 56592[a] & 0.1% SCH 32088	1
1 male and 1 female	1.0% ^{14}C-SCH 56592 (posaconazole)[a]	0.1% SCH 32088 & 1.0% SCH 51854	2
1 male and 1 female	0.1% ^{3}H-SCH 32088 (mometasone furoate)	1.0% SCH 56592[a] & 1.0% SCH 51854	3
[a] The ^{14}C-posaconazole and posaconazole concentration was at 10 times the intended formulation concentration due to low specific activity of the available ^{14}C-posaconazole and an anticipated very low absorption.			

Dosage Form: The study was conducted with a formulation identical to the final formulation with the exception of the inclusion of a 10X concentration of posaconazole.

Dosage Used: All animals were dosed with approximately 230-250 µL/ear with their appropriate dose formulation.

Route of Administration: Otic administration

Study Duration: 25 days

Pertinent Measurements/Observations:
1. Blood: At 4 and 8 hours, and 1, 2, 3, 7, 10, 14, 17, 21 and 24 days post-dosing
2. Urine and Feces: Once daily from Day 0 (pre-dosing day) to the end of study (24 days postdose)
3. Cage rinse with methanol

Recovery of radioactivity from the site of application was not determined.

Drug Analysis:
Total radiolabel in blood, urine, feces and metabolism cage was determined using liquid scintillation counting (LSC). Additionally, metabolic profiling of the filtered urine and extracts of fecal samples was conducted using HPLC/in-line radioactivity detection.

Results:
Based upon the amounts of radiolabeled compounds recovered from urine and feces, between 30 and 40% of the three drug components in the applied dose were systemically absorbed over a 24-day period. Of the three compounds, orbifloxacin was the least metabolized, with 87-89% of the total excreted ^{14}C label identified as parent drug, about 9-12% as polar metabolite(s), and 2-3% as non-polar metabolite(s). Mometasone and posaconazole showed an extensive metabolism, with between 80 and 90% of total label being excreted in urine and 70 to 99% in feces as polar metabolite(s), depending on drug component and sampling time. For mometasone, the parent drug and non-polar metabolite(s) were minimally excreted in feces. Cage wash residue was high and ranged from 7 to 36% of the dose, which was two to four times higher than the corresponding urine excretion amount.

Conclusion:
Substantial dermal absorption of posaconazole, mometasone and orbifloxacin occurs after aural administration of POSATEX Otic Suspension with posaconazole and mometasone being extensively metabolized but orbifloxacin only minimally so. The systemic risk due to the expected accumulation of the orbifloxacin and the major metabolites of the mometasone furoate and posaconazole following repeated dermal applications is reduced by the small aural dose amount and the restricted dose duration.

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. Federal law prohibits the extralabel use of this drug in food-producing animals.

V. USER SAFETY:

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to POSATEX Otic Suspension:

"**Keep out of the reach of children. Not for use in humans.** Individuals with a history of hypersensitivity to any of the components should avoid handling this product. In humans, there is a risk of user photosensitization within a few hours after excessive exposure to quinolones. If excessive accidental exposure occurs, avoid direct sunlight."

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 POSATEX Otic Suspension, when used according to the label, is safe and effective for the treatment of otitis externa in dogs associated with susceptible strains of yeast (*Malassezia pachydermatis*) and bacteria (coagulase positive staphylococci, *Pseudomanas aeruginosa*, and *Enterococcus faecalis*).

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 required to properly diagnose the disease and prescribe appropriate treatment.

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 approval. Exclusivity is based on new studies for substantial evidence of effectiveness and target animal safety.

C. Patent Information:

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