Date of Approval: November 10, 2016

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-474

Itrafungol™

itraconazole oral solution

Cats

For the treatment of dermatophytosis caused by *Microsporum canis* in cats.

Sponsored by:

Elanco US, Inc.

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I. GENERAL INFORMATION

A. File Number

NADA 141-474

B. Sponsor

Elanco US, Inc.
2500 Innovation Way
Greenfield, IN 46140

Drug Labeler Code: 058198

C. Proprietary Name

Itrafungol™

D. Product Established Name

Itraconazole oral solution

E. Pharmacological Category

Antifungal

F. Dosage Form

Oral solution

G. Amount of Active Ingredient

10 mg/ml

H. How Supplied

Itrafungol™ is available in a 52 mL bottle of oral solution, packed in a cardboard box with a graduated reusable dosing syringe.

I. Dispensing Status

Rx

J. Dosage Regimen

The daily dosage is 5 mg/kg (0.5 mL/kg) body weight administered once daily on alternating weeks for 3 treatment cycles. Cats are treated during weeks 1, 3, and 5, and left untreated during weeks 2 and 4.

K. Route of Administration

Oral

L. Species/Class

Cats

M. Indication

ITRAFUNGOL oral solution is indicated for the treatment of dermatophytosis caused by *Microsporum canis* in cats.

II. EFFECTIVENESS

A. Dosage Characterization

A dose of 5 mg itraconazole/kg body weight administered orally, once daily for 7 days on alternate weeks for a total of 21 dosing days, was chosen based on multiple studies conducted in cats either experimentally infected or naturally infected with *Microsporum canis.*

In a dose titration study, 27 European short hair domestic cats were infected with *Microsporum canis* (a strain isolated from dermatophytosis in naturally-infected cats) and administered itraconazole oral solution once daily for 14 consecutive days, starting three days after infection, at doses of 0, 1.25, 2.5, 5, and 10 mg/kg body weight. Clinical evaluation, microscopic examination, and cultures were performed at regular intervals before, during, and after treatment. Administration of itraconazole oral solution at 2.5 mg/kg for two weeks reduced the infection, but was insufficient for rapid clinical cure. Administration of itraconazole oral solution was effective when administered at 5 or 10 mg/kg body weight. Based upon study results, 5 mg/kg dose was selected for further evaluation.

The effectiveness of four different oral itraconazole treatment schedules was evaluated in a European field study using 77 cats naturally infected with *Microsporum canis*. The effectiveness of the four treatment schedules (5 mg/kg/day for 3 or 4 weeks, 5 mg/kg/day for 3 alternate treatment weeks, and 5 mg/kg/day every other day for 6 weeks) was evaluated based on clinical observations, Wood's lamp examination, and mycological examinations. A "good" to "excellent" clinical response was obtained in all 4 treatment groups at the end of the treatment schedule. However, the alternate week treatment schedule provided the best results at the end of a 4 week follow-up period. The highest percentage of mycologically negative animals was seen with the alternate day treatment schedule, followed by the alternate week schedule. Based on the overall clinical observations, Wood's lamp, and mycological results, the alternate week treatment schedule was selected.

The selected treatment schedule was further evaluated in a placebo controlled, blinded, randomized pilot laboratory effectiveness study using cats experimentally infected with *M. canis* by a previously described experimental infection model.[1] Forty-four cats (24 males and 20 females) were selected to enter the treatment period of the study. Cats were randomized into one of two treatment groups consisting of 22 cats each, and were administered either itraconazole oral solution at a dosage of 5 mg/kg/day (0.5 mL/kg), or control article (tap water) at a dosage

[1] Moriello KA, DeBoer DJ.1994. Development of an experimental model of *Microsporum canis* infection in cats. Vet Microbiol.42(4):289-95.

of 0.5 mL/kg. Treatment began on Day 0 and cats were dosed once daily for 7 days on alternate weeks for a total of 21 dosing days. A four week follow-up period occurred immediately after the treatment period, with study conclusion on Day 63. During the treatment and follow-up periods, collection of samples for mycological culture was performed weekly. Mycological cure was defined as two consecutive negative cultures by the end of the follow-up period (Day 63). In addition, clinical lesion scoring was performed once weekly during the treatment and follow-up periods. Mycological cure rates were higher in cats treated with itraconazole oral solution (68.2%) than cats administered the control article (4.5%) at Day 63. In addition, cats treated with itraconazole oral solution showed an improvement in total clinical lesion scores, which incorporated lesion area, erythema, induration, scaling/crusting, and satellite lesions. Based on these results, a dose of 5 mg/kg/day itraconazole oral solution, administered once daily for 7 days on alternate weeks for a total of 21 dosing days, was selected for use in cats naturally infected with *M. canis.*

B. Substantial Evidence

Laboratory Effectiveness Study

Title: Efficacy and Safety of Itraconazole 10 mg/mL Oral Solution for the Treatment of *Microsporum canis* Infection in Cats; KFI-013-EF-2514

Study Dates: March 2, 2015, through December 18, 2015

Study Location: Stouffville, ON, Canada

Study Design: Laboratory Effectiveness Study run according to Good Clinical Practices (GCP)

Objective: The objective of this laboratory study was to determine the efficacy and safety of itraconazole 10 mg/mL oral solution for the treatment of *M. canis* infection in cats using an alternating weekly protocol for a total of 21 days of treatment.

Study Animals: This study utilized purpose-bred domestic male and female short-haired cats that were 54 to 63 days of age at the time of experimental infection with *M. canis* on Day -28. Prior to Itrafungol™ treatment, 13 cats were found to shed coccidia oocysts and were treated with sulfadimethoxine, and seven of these same cats received a second course of sulfadimethoxine treatment, after which the coccidiosis outbreak was considered resolved.

Experimental Design: Eighty cats were randomly selected for the study based upon inclusion criteria. Cats were sorted by ascending study animal ID number and randomly assigned to cages 1 to 80, within 2 rooms. Each room contained eight banks of individual cages that housed five cats per bank. Within each room, banks of cages were randomly assigned to treatment groups. Within room-by-treatment group combinations, banks of animals were randomly assigned to 2 cohorts with dosing staggered by 1 day.

Inoculation with *Microsporum canis*: A highly fluorescent, field isolated strain of *M. canis* that produced large numbers of macroconidia was used to produce the

inoculum for the challenge infection. After replicate testing this isolate was found to have a mean itraconazole MIC of 0.021 µg/mL. Inoculum solution was prepared at an approximate concentration of $5x10^5$ spores/mL. Cats were inoculated on day -28 following sedation and clipping of the inoculation site (right lateral flank). Following inoculation, an occlusive bandage was applied to the inoculation site for at least 72 hours, followed by a light stockinette covering until day 0. Infection was confirmed by the presence of spores on microscopic examination of hair, positive Wood's lamp score, and a visible or palpable clinical lesion.

Drug Administration: Cats were dosed orally with either Itrafungol™ (itraconazole oral solution) or a control product (sterile water) once daily for seven days on alternate weeks for a total of 21 days of treatment, over a 5 week period as outlined below:

Table 1: Treatment Groups

Treatment Group	Number and Gender of Animals	Dose mg/kg
T0 Control Product (Sterile Water)	40 (20 male, 20 female)	0 mg/kg
T1 Itrafungol™ (itraconazole oral solution)	40 (19 male, 21 female)	5 mg/kg

Cats were treated once daily on the following days:
Cohort 1: Days 0 to 6, 14 to 20, and 28 to 34;
Cohort 2: Days 1 to 7, 15 to 21, and 29 to 35.

No topical therapy was used during the course of the study. A four week follow-up period followed the end of the treatment period.

Measurements and Observations: Mycological culture, primary lesion scores, Wood's lamp evaluation.

Mycological Culture: One fungal culture was obtained from the region of the inoculation site of each cat during acclimation (day -35), during the challenge period (days -14 and -2), and once weekly until the end of the study on day 63. The site was brushed at least 20 times using a clean, individually packaged toothbrush. Each sample was cultured for three weeks. Semi-quantitative results were recorded each week by counting the number of dermatophyte colonies per plate[2]. Each cat was then assigned a P score as follows:

- P0 (no colonies);
- P1 (1 to 5 colonies);

[2] DeBoer DJ, Moriello KA. 1995. Inability of two topical treatments to influence the course of experimentally induced dermatophytosis in cats. J Am Vet Med Assoc. 1:52-57.

- P2 (6 to 10 colonies);
- P3 (> 10 colonies).

The primary effectiveness variable was mycological cure by the end of the follow up period (Day 63). Mycological cure was defined as follows:

> Cured: Cats that showed two consecutive mycological culture P scores of P0 at any time during the treatment or follow up period with all subsequent P scores not exceeding P1.
> Not cured: Cats that did not show two consecutive mycological culture P scores of P0.

Secondary Variables: Primary lesion and Wood's lamp scores
The inoculation site of each cat was evaluated twice during the challenge period (days -14 and -2), and once weekly until the end of the study on day 63. The following parameters were subjectively evaluated and given a numerical score: degree of induration (thickening of dermis), erythema and scaling/crusting of the primary lesion (inoculation) site, and number of fluorescing hairs during Wood's lamp examination. Fluorescence of hair(s) was individually scored at three locations on the hair shaft including the base, mid-shaft, and tip. Wood's lamp cure was defined as no fluorescence at the base and mid-shaft of the hair.

Statistical Methods: Differences in mycological cures between the two treatment groups were evaluated using a generalized linear mixed model, assuming a binomial distribution and using a logit link. The model included treatment group as a fixed effect and room and cohort as random effects. Primary lesion scores and Wood's lamp scores were evaluated using a generalized linear mixed model assuming a multinomial distribution. The model included treatment group and baseline scores as fixed effects and room and cohort as random effects. Differences in Wood's lamp cure between treatment groups were evaluated using a generalized linear mixed model, assuming a binomial distribution and using a logit link. The model included treatment group as a fixed effect and room and cohort as random effects.

Results: Dermatophytosis lesions were successfully induced (all P3 scores) in all 85 cats at the end of the challenge period. Eighty (80) cats were included in the dosing period of the study. Dosing was well tolerated by all cats throughout the dosing period. There were no recorded dosing failures (spitting out or vomiting of Itrafungol™ or control product) during dose administration. One cat in the Itrafungol™-treated group vomited once within two hours of dose administration.

Primary Effectiveness Variable: Mycological cure rates at the end of the follow-up period were significantly different (P = 0.0003) in the Itrafungol™-treated group (24/40 or 60%) as compared to the control group (1/40 or 2.5%). Ten (10) of the 16 cats in the Itrafungol™-treated group that did not reach mycological cure had negative fungal cultures on Day 63. A total of six cats in the Itrafungol™-treated group had P scores of P1 or P2 at the end of the study, and two of these six cats had cultured negative at least once prior to Day 63. A total of 36/40 Itrafungol™-treated cats (90%) achieved at least one negative culture by the end of the study.

After replicate testing of *M. canis* isolates obtained from two cats that failed Itrafungol™ treatment, the mean itraconazole MICs were unchanged (0.026 and

0.035 µg/mL) when compared to the challenge strain (mean MIC of 0.021 µg/mL). Therefore, itraconazole MICs were indicative of susceptibility and below the value predictive of clinical effectiveness (1 µg/ml).[3]

Secondary Variables:

Primary Lesion Scores:

- Erythema scores were lower in the Itrafungol™-treated group as compared to the control group by Day 7. Between Days 7 and 14, erythema scores in the treated group notably declined with >85% of cats showing complete resolution from Day 14 onward. Erythema resolved in 100% of the treated cats on Day 49 and continued until the end of the study. Erythema in the control group fluctuated throughout the study. By Day 63, erythema remained in 30% of control cats.

- Induration (dermis thickening) scores were lower in the Itrafungol™-treated group as compared to the control group by Day 7. From Day 35 onward, the majority of cats (≥85%) in the treated group showed no signs of induration. By Day 63, 98% of treated cats showed clinical resolution of induration compared to 25% of control cats.

- Crust/scale scores were lower in the Itrafungol™-treated group as compared to the control group by Day 14. The majority of cats in the treated group (>90%) reached clinical resolution by Day 21. For the control group, areas of crust/scale were reported for the length of the study. By Day 63, 100% of cats in the treated group showed clinical resolution of crust/scale as compared to 53% in the control group.

Wood's Lamp Cure:

- From Days 7 through 28, prevalence of Wood's lamp cure (defined as no fluorescence at the base and mid-shaft of the hair) in the Itrafungol™-treated group steadily increased and remained high for the duration of the study. In contrast, the first Wood's lamp cure in the control group was not observed until Day 49. By Day 63, Wood's lamp cure in the treated group (39/40 or 97.5%) was numerically higher as compared to the control group (6/40 or 15%).

Adverse Reactions: Transient hypersalivation was observed in two cats in the Itrafungol™-treated group. One Itrafungol™-treated cat experienced vomiting within 2 hours of dosing (one episode on Day 1). Vomiting outside of the 2 hour post-dosing period was observed in 5 Itrafungol™-treated cats during the dosing period as compared to 4 cats in the control group. Episodes of diarrhea were observed in 9 cats (22.5%) in the Itrafungol™-treated group during the dosing period as compared to 7 cats (17.5%) in the control group. One Itrafungol™-treated cat showed mild increases in ALT and AST at the end of the dosing period. No related clinical signs were observed in this cat, and these values returned to

[3] Mancianti F, Zullino C, Papini R. Itraconazole susceptibility of feline isolates of *Microsporum canis*. Mycoses. 1997; 40:313-5.

normal by the end of the follow-up period. One cat in the Itrafungol™-treated group was noted to have lip erythema and lip induration once during the study.

Conclusions: Itrafungol™ (itraconazole oral solution) was effective for the treatment of *M. canis* infection in cats as determined by mycological cure. Itrafungol™ was well tolerated at the therapeutic dose of 5 mg/kg/day in cats treated once daily for seven days on alternate weeks for a total of 21 dosing days.

C. Supportive Effectiveness Data: European Field Effectiveness Study

Title: "Multicenter, double blind, field trial to compare the efficacy and safety of itraconazole with griseofulvin in the treatment of dermatophytosis in naturally infected cats." Study number: ITR-93CA-01

Study Dates: June 1994-April 1997

Study Locations: This study involved 53 investigators in 5 countries (Belgium, the Netherlands, France, Spain, and the United Kingdom). For statistical analysis, investigators were pooled into 18 "mega" centers.

Study Design:

Objective: The objective of the study was to compare the effectiveness and safety of itraconazole oral solution against an active control as systemic antimycotic treatment for cats naturally infected with *Microsporum canis.*

Study Animals: This study involved 514 client-owned cats; 266 received at least one dose of itraconazole oral solution and 248 cats received an active control. The cats were diagnosed with *M. canis* infection based upon clinical signs, positive Wood's Lamp examination, and mycological culture. All cats remained in their natural home environment throughout the study, and were separated from other cats not included in the study, wherever possible. The animals ranged in age from 6 weeks to 15 years, and the body weight ranged from 0.24 kg to 8.0 kg.

Drug Administration: Itraconazole 10 mg/ml oral solution was administered at 0.5 ml/kg once daily during the 1st, 3rd, and 5th weeks (no treatment during the 2nd and 4th weeks); this is equivalent to 5 mg/kg administered daily on alternating weeks for 3 treatment cycles. Cats were not treated with topical therapy and environmental decontamination was not employed.

Results: The primary effectiveness outcome measure was the rate of cured animals at the end of follow-up based on the clinical observation scores. "Cured" animals had to have a complete resolution of clinical lesions. Of the 207 cats that completed the treatment and follow-up, 175 (85%) treated with itraconazole oral solution were clinically cured. Of the 207 cats that completed the treatment and follow-up, 194 (94%) of the cats treated with itraconazole demonstrated either complete disappearance of fluorescence under UV lighting (i.e. Wood's Lamp negative) or fluorescence present only on the tips of the hairs at the end of follow-up.

Adverse reactions: Adverse reactions seen in the 266 cats that received at least one dose of itraconazole oral solution included 35 cases (13%) of one or more

elevated hepatic enzymes and 8 cases (3%) of gastrointestinal upset, including decreased appetite, vomiting, and/or diarrhea. Other infrequent adverse reactions included less than 3 cases each of somnolence, depression, and increased salivation.

Conclusions: This study supports the safety and effectiveness of itraconazole oral solution at the proposed dose and duration by demonstrating that itraconazole oral solution was effective in various home environments with different owners, and in a variety of cats of different breeds and ages.

III. TARGET ANIMAL SAFETY

A. Laboratory Margin of Safety Study

Title: Target Animal Safety study V14125-GLP

Study Dates: September 12, 2006, through February 7, 2007

Study Location: Ballina, Co. Mayo, Ireland

Study Design: Safety Study conducted in accordance with Good Laboratory Practices (GLP)

Objective: The purpose of this study was to determine the safety of ITRAFUNGOL™ (itraconazole oral solution) as a treatment for dermatophytosis in cats.

Study Animals: A total of 32 adult cats (9-22 months old) were used in this study. Twenty-four cats were administered Itrafungol™ and eight cats were administered a negative control (saline). Body weights ranged from 2.9 to 5.6 kg (on Day -1).

Experimental Design: Cats were blocked by sex, ranked within blocks by body weight, and then randomized to four treatment groups (four cats/sex/group). The study was blinded. The study director, veterinary histopathologist, and the persons that were involved in measurements and assessments of body weight, PEs, and clinical observations were all masked to treatment group.

Drug Administration: Cats were dosed via a dosing syringe orally once daily for seven days, on alternate weeks for 17 weeks (three times the recommended treatment duration), as outlined below:

Table 2: Treatment Groups

Treatment Group	Number and Gender of Cats	Dose mg/kg (mL/kg)
1 (0X/Negative Control)	4 male, 4 female	0 mg/kg (0.5 mL/kg)
2 (1X)	4 male, 4 female	5 mg/kg (0.5 mL/kg)
3 (3X)	4 male, 4 female	15 mg/kg (1.5 mL/kg)
4 (5X)	4 male, 4 female	25 mg/kg (2.5 mL/kg)

Measurements and Observations: Clinical observations, physical examinations, body weight, feed consumption, hematology, serum chemistry, urinalysis, and

complete gross and histopathology examinations. Blood samples for bioanalysis of itraconazole plasma levels were also taken.

Statistical Methods: For the continuous variables measured at more than one time point, such as hematology, serum biochemistry, quantitative urine parameters, body weight, feed consumption, and continuous physical examinations, a repeated measures analysis of covariance model was performed to test the effects of dose group, day, sex, dose group by day, dose group by sex, day by sex, and dose group by day by sex. Baseline measurements were included in the model as covariates. For continuous variables measured once, such as organ weights, an analysis of variance model was performed to test the effects of dose group, sex, and dose group by sex. Follow-up pairwise mean comparisons between the placebo group and the treated groups were performed, as necessary, using linear contrasts with significance level 0.10. For discrete variables, a Mantel Haenszel test controlling for sex between the placebo group and each of the treated groups combined and separately was applied. For all analyses, the individual cat was treated as the experimental unit.

Results:

Clinical Observations: The most common abnormal clinical observation related to treatment with Itrafungol™ was abnormal salivation. Abnormal salivation was noted in groups 1(0X), 3(3X), and 4(5X), and the incidence increased as the dose increased. A total of 13 cats experienced abnormal salivation (one from group 1, four from group 3, and all eight cats from group 4) for a total of 56 episodes of abnormal salivation.

One cat in group 4 (5X; Cat #26302) lost 22% of its body weight and had a number of episodes of vomiting, salivation, and anorexia during the treatment period. This cat also had renal lesions found on histopathology, as described below.

Clinical Pathology: Increasing trends were noted in alanine aminotransferase (ALT), aspartate aminotransferase (AST), and creatinine values in some cats treated with Itrafungol™ as compared to baseline values. Individual values rarely increased above the normal reference range and were not associated with adverse clinical signs.

Pharmacokinetics: Pharmacokinetic results showed that both maximum concentration (C_{max}) and area under the curve for 24 hours ($AUC_{0\text{-}24\ h}$) were higher on Day 112 compared to Day 0 for each group. In addition, as the dose level of itraconazole increased, both C_{max} and $AUC_{0\text{-}24\ h}$ increased on Day 0 and Day 112; however, increases in C_{max} and $AUC_{0\text{-}24\ h}$ values were less than proportional to dose level. The time at maximum concentration (T_{max}) was two hours for all individuals on Day 0 and Day 112 with the exception of one animal in the 3X group on Day 0; the T_{max} value for this animal was four hours.

Gross Pathology and Organ Weights: Adrenal glands were heavier for cats in group 4 (5X) compared to cats in group 1 (control) ($P = 0.0192$). There were no abnormal clinical signs of disease associated with these differences.

Histopathology: Histopathological examination of lung tissue samples revealed intra-alveolar foamy macrophages and intra-alveolar syncytial cells. Intra-alveolar foamy macrophages were found in a total of six animals, one cat from group 3 (3X) and five from group four (5X). Intra-alveolar syncytial cells were found in five animals from group 4 (5X). Abnormal renal findings included proximal convoluted tubule acute degeneration, which was found in three animals from group 2 (1X) and three animals from group 4 (5X). In addition, Cat #26302 in group 4 (5X) had proximal convoluted tubule acute degeneration, proximal convoluted tubule marked pallor, and focal mononuclear cell infiltration in the kidneys. No other significant histopathological findings were noted.

Conclusions:
Administration of Itrafungol™ (itraconazole oral solution) at 1X, 3X, and 5X the therapeutic dose for three times the recommended treatment duration in cats resulted in the presence of intra-alveolar foamy macrophages and renal proximal convoluted tubule degeneration. These adverse findings are likely related to exposure to Itrafungol™, specifically the vehicle component hydroxypropyl-β-cyclodextrin (HPβCD). There were no corresponding adverse clinical effects noted on observation or on clinical pathology analysis. In addition, similar changes have been described in literature in other species exposed to HPβCD and have been reported to be reversible. However, this study was not definitive regarding the pathologic nature of the findings; and, therefore, this study alone did not support the safe use of Itrafungol™ (itraconazole oral solution) in cats.

B. Laboratory Margin of Safety Study with Recovery

Title: "Non-Clinical Laboratory Study (GLP): Target Animal Safety Study of Itraconazole 10 mg/mL Oral Solution in Cats", Study Number KFI-013-SF-2113

Study Dates: July 21, 2014 – August 28, 2015

Study Location: Stouffville, Ontario, Canada

Study Design: Safety Study conducted in accordance with GLP

Objective: This study was designed to assess the safety of itraconazole oral solution (10 mg/mL) when administered to cats once daily at 5, 15, and 25 mg/kg for seven days on alternate weeks for 17 weeks, followed by an eight week recovery period. The study was further intended to assess if any of the histopathologic lesions seen in the earlier safety studies were noted after the eight week recovery period.

Study Animals: Purpose-bred domestic short-haired cats that were between 63 and 70 days of age, and 0.7 kg to 1.1 kg, at study initiation. Twenty-four cats were administered Itrafungol™ and eight cats were administered a negative control product.

Experimental Design: Thirty-two cats (16 M, 16 F) were stratified by gender and randomly assigned to one of four dose groups and into individual housing units. Within gender/dose group, cats were assigned to one of two cohorts (equal allocation of gender and dose group).

Drug Administration: Four dose groups were included in this study. Cats received either Itrafungol™ at 1X, 3X, or 5X the therapeutic dose or a negative control (saline). Cats were dosed orally once daily for seven days on alternate weeks for 17 weeks, which represents three times the recommended treatment duration. Following the 17 weeks of dosing, the cats were allowed to recover for 8 weeks prior to necropsy, during which they received no treatment.

Table 3: Treatment Groups

Treatment Group	Number and Gender of Cats	Dose mg/kg (mL/kg)
1 (0X/Negative Control)	4 male, 4 female	0 mg/kg (0.5 mL/kg)
2 (1X)	4 male, 4 female	5 mg/kg (0.5 mL/kg)
3 (3X)	4 male, 4 female	15 mg/kg (1.5 mL/kg)
4 (5X)	4 male, 4 female	25 mg/kg (2.5 mL/kg)

Measurements and Observations: Body weight, food consumption, clinical observations, physical examinations, hematology, clinical chemistry parameters, coagulation parameters, urinalyses, fecal analysis, organ weights, and post-mortem (gross and histopathologic) examination.

Statistical Methods: Analysis of variance was used to evaluate all continuous variables. Models included treatment, sex and the treatment-by-sex interaction as fixed effects; cohort was included in the model as a random effect. For variables measured more than once throughout the study, the following fixed effects were also included: time and the interactions treatment-by-time, sex-by-time and treatment-by-sex-by-time. If pre-treatment differences existed, the value closest to the first treatment administration was included as a covariate. Except for the three way interaction that was tested at alpha = 0.05, all tests were performed at alpha = 0.10. To follow up on significant effects involving treatment, mean comparisons between the zero dose group and each non-zero dose group were performed (within sex, within time or overall, as appropriate) using linear contrasts. No adjustments were made for multiple comparisons.

Results: All cats survived to the termination of the study.

Clinical observations: Hypersalivation during or immediately following dosing, vomiting, and loose stool were the most frequent abnormal clinical observations related to treatment with Itrafungol™. Hypersalivation was limited to the 3X and 5X groups and was observed in every dosing cycle. Vomiting was noted at similar levels in the control, 1X, and 3X groups; however, it occurred approximately twice as often in the 5X group. Mild gingival bleeding and perioral irritation (patchy alopecia and erythema) was noted in cats in the 3X and 5X groups.
Food consumption was consistently higher throughout the study in the control group than the groups administered Itrafungol™, and the control group gained more weight during the study than the groups administered Itrafungol™.
One cat in the 5X group exhibited inappetence progressing to anorexia, dehydration, and vomiting during the first dosing cycle. This cat had repeated episodes of inappetence during the second and third dosing cycles. This cat also

had markedly elevated ALT and AST values on Day 36 (693 U/L and 283 U/L, respectively), was treated with minimal supportive care, and recovered to complete the study. The elevated liver values improved by day 78 and returned to normal by day 120. Histopathological evaluation of the liver at the end of the study was unremarkable.

Clinical Pathology: Mild elevations in ALT values were sporadically noted in all groups; however, the number of affected cats increased as the dose increased (two cats in the control group, two cats in the 1X group, three cats in the 3X group, and four cats in the 5X group). In most cats, ALT values peaked just above the upper limit of the reference range and were continuing to trend upward or were elevated yet stable at the end of the study. The highest values noted for both AST and ALT occurred in the 3X and 5X treatment groups.
One cat in the 3X group demonstrated a continued upward trend in ALT and AST values from Day 35 until the end of the study (day 176). Markedly elevated ALT and AST values were evident in this cat during the acclimation period on Day -12, but had returned to normal values by Day -2. No correlating abnormalities were identified on gross or histopathologic examination.

Histopathology: One cat in the 1X treatment group had minimal, multifocal mononuclear cell infiltrate in the liver. This cat also had mildly elevated liver enzymes at the conclusion of the study.

Conclusions:
Clinical signs related to treatment with Itrafungol™ (itraconazole oral solution) for 17 alternating weeks were hypersalivation, vomiting, and loose stools that were mild to moderate and self-resolving. Treatment related elevations in ALT and AST were noted in cats in all treatment groups, but more frequently in the higher dose groups. Cats in the itraconazole treated groups ate less food and gained less weight than cats in the control group. The previous histopathologic findings seen in study V14125, specifically treatment related proximal convoluted tubule acute degeneration and intra-alveolar foamy macrophages, were not noted in this study after an 8 week recovery period. These results demonstrate that Itrafungol™ is safe for use at the intended dose of 5 mg/kg once daily for three alternating periods of seven consecutive days, each period separated by 7 days without treatment.

C. Reproductive Safety

In a repeated dose study conducted in 1993, 16 pregnant queens were administered itraconazole oral solution at 5 mg/kg bodyweight for a total of 21 days (7 days on alternate weeks) during gestation or lactation. The study revealed a high frequency of fetal resorption, abnormal fetuses, and abnormal maternal behaviors. Confounding factors, such as stress of the cats and infectious disease (*Chlamydia psittaci*) made it difficult to establish a definitive relationship between administration of itraconazole during pregnancy and the high incidence of fetal resorption (partial and total), abnormal fetuses, and inappropriate maternal behavior. However, the results of this study reveal potential reproductive safety risks and do not support the safe of use itraconazole oral solution in pregnant queens.

IV. HUMAN FOOD SAFETY

This drug is intended for use in cats. 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 Itrafungol™:

Not for use in humans. Keep this and all medications out of reach of children. Wash hands and exposed skin after use. In case of accidental contact with eyes, rinse thoroughly with water. In case of pain or irritation, seek medical advice. In case of accidental ingestion, rinse mouth with water and seek medical advice.

Special precautions for person administering the veterinary product to the animal: *Microsporum canis* dermatophytosis is a zoonotic disease (a disease that can be transmitted from animals to humans); therefore consult a physician if a suspected lesion occurs on a human. Wear protective gloves when handling the animal during treatment or when cleaning the syringe. Wash hands and exposed skin after handing the animal.

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 (FD&C Act) and 21 CFR part 514. The data demonstrate that Itrafungol™, when used according to the label, is safe and effective for the treatment of dermatophytosis caused by *Microsporum canis* in cats.

A. Marketing Status

The drug is restricted to use by, or on the order of, a licensed veterinarian because professional expertise is needed to diagnose and provide guidance in the treatment of dermatophytosis, and to monitor for and respond to adverse reactions.

B. Exclusivity

Itrafungol™, as approved in our approval letter, qualifies for FIVE years of marketing exclusivity beginning as of the date of our approval letter. This drug qualifies for exclusivity under section 512(c)(2)(F)(i) of the FD&C Act because this is the first time we are approving this active ingredient in a new animal drug application submitted under section 512(b)(1) of the FD&C Act.

C. Patent Information:

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