J Vet Intern Med 2011;25:440–445

Retrospective Comparison of the Efficacy of Fluconazole or Itraconazole for the Treatment of Systemic Blastomycosis in Dogs

A.S.W. Mazepa, L.A. Trepanier, and D.S. Foy

Background: Itraconazole is recommended for treatment of blastomycosis in dogs. Some evidence suggests that fluconazole might be less hepatotoxic than itraconazole.

Objectives: To compare (1) incidence of clinical remission and death; (2) treatment duration; (3) total drug cost; (4) incidence of relapse; and (5) incidence of increased ALT activities in dogs with blastomycosis treated with fluconazole or itraconazole.

Animals: One hundred and forty-four dogs with systemic blastomycosis treated with itraconazole or fluconazole from 1998 to 2008.

Methods: Retrospective case review. Information obtained included signalment, body weight, clinical signs, drug regimen, treatment duration, time to clinical remission, and laboratory results.

Results: Neither treatment efficacy between fluconazole (75% remission) and itraconazole (90% remission) nor relapse rate (18% for itraconazole, 22% for fluconazole) was significantly different ($P = .13, .75$, respectively). Treatment duration was significantly longer for fluconazole (median 183 days) than for itraconazole (138 days; $P = .001$). Costs for fluconazole (median \$1,223) were significantly less than for itraconazole (\$3,717; $P < .001$). Incidence of increased ALT activities was not significantly different between groups (17% [3/18] for fluconazole, 26% [6/23] for itraconazole; $P = .71$).

Conclusions: Fluconazole is associated with survival to clinical remission in 75% of dogs with blastomycosis. Although dogs receiving fluconazole were treated longer, drug costs were one-third those of itraconazole. Hepatotoxicosis, as estimated by increases in serum ALT activity, can be observed with similar incidence for both drugs.

Key words: Alanine aminotransferase; Blastomyces; Canine; Fungal disease.

Blastomycosis is a common, systemic fungal infection endemic throughout several regions of the United States, including the Ohio River Valley, Mid-Atlantic states, and regions of upstate New York. The causative agent is *Blastomyces dermatitidis*, a dimorphic fungus that exists in both an environmental mycelial and a mammalian host-associated yeast form.

Itraconazole, a synthetic triazole antifungal, is the treatment of choice for blastomycosis based on data in both humans and dogs.[1–3] Therapy with itraconazole is associated with remission rates of 68–75%; however, treatment can be for as long as 6 months in some cases.[1,4,5] The high cost of itraconazole and the extended treatment course necessary can sometimes lead to euthanasia, instead of treatment, because of financial constraints. Recently, fluconazole has become available in a generic form and can cost as little as one-tenth that of brand-name itraconazole. Generic itraconazole is also available, but absorption can be unpredictable, potentially leading to inconsistent blood concentrations and decreased efficacy.[6] In addition to lower cost, the use of fluconazole results in a lower incidence of hepatotoxicosis when compared with itraconazole in rodents.[7]

Abbreviations:

ALT	alanine aminotransferase
UW-VMTH	University of Wisconsin Veterinary Medical Teaching Hospital

We hypothesized that fluconazole would have comparable efficacy to itraconazole for induction of clinical remission in dogs with systemic blastomycosis, and would result in lower total drug cost. In addition, we hypothesized that fluconazole would have a lower incidence of hepatotoxicicosis than itraconazole. The primary aims of this retrospective study were, therefore, to compare the following outcomes in dogs with blastomycosis treated with either fluconazole or itraconazole at standard dosages: (1) incidence of clinical remission or death; (2) treatment duration to remission; (3) total drug cost; (4) incidence of relapse; and (5) incidence of increases in serum ALT activities.

Materials and Methods

The medical records of dogs with systemic blastomycosis that were presented to the University of Wisconsin Veterinary Medical Teaching Hospital (UW-VMTH) from January 1998 to December 2008, and that were treated with either fluconazole or itraconazole, were retrospectively reviewed. The criteria for inclusion in the study were (1) a cytologic or histopathologic diagnosis of blastomycosis, or consistent clinical signs combined with a positive urine Blastomyces antigen test and response to treatment with antifungal drugs[8]; and (2) adequate medical record information to determine drug dosing, duration and compliance of administration, evidence of drug toxicity, and documentation of clinical remission through

From the Department of Medical Sciences, School of Veterinary Medicine, University of Wisconsin—Madison, Madison, WI (Trepanier, Foy); and the Department of Clinical Sciences, College of Veterinary Medicine, North Carolina State University, Raleigh, NC (Mazepa). This work was performed at the School of Veterinary Medicine, University of Wisconsin—Madison, Madison, WI.

Corresponding author: Daniel S. Foy, Department of Medical Sciences, School of Veterinary Medicine, University of Wisconsin , 2015 Linden Drive, Madison, WI 53706; email: dfoy@svm.vetmed.wisc.edu.

Submitted July 27, 2010; Revised January 8, 2011; Accepted February 7, 2011.

10.1111/j.1939-1676.2011.0710.x

VMTH rechecks. Dogs were excluded from the study if they were treated with both itraconazole and fluconazole, or had received amphotericin B at any time. Dogs that had most or all follow-up care at another veterinary hospital were also excluded.

Signalment, history, clinical signs, and physical examination findings at the time of diagnosis were recorded for all dogs. Signs considered consistent with blastomycosis included cough, fever, skin lesions, lymphadenopathy, lameness with accompanying radiographs suggestive of osteomyelitis, or retinal lesions consistent with granulomas. All dogs were treated with either fluconazole or itraconazole, at approximately 5–10 mg/kg/d, for 1 month beyond clinical remission. Clinical remission was defined as resolution of all clinical signs, including absence of abnormalities on physical examination and ophthalmic examination (or remaining lesions considered inactive); chest or limb radiography (or interpreted as static over sequential radiographs taken 1 month apart); and imaging of any other affected sites. Results from CBCs, serum chemistry profiles, and imaging studies were recorded whenever performed. All dogs treated with itraconazole were treated with the brand-name formulation,[a] while all dogs treated with fluconazole were treated with the generic compound.[b] Total treatment costs to the clients were calculated for each dog, but were normalized to the cost of the drugs at a national pharmacy[c] as of November 2010, when the cost of brand name itraconazole was $17.07 for a 100 mg capsule, and the cost of generic fluconazole was $4.53 for a 200 mg tablet.

A semiquantitative disease-severity scoring system was developed to compare dogs treated with itraconazole versus dogs treated with fluconazole, in order to establish similarity between groups before treatment. Scoring parameters included fever, tachypnea, need for oxygen supplementation, pulmonary infiltrates or hilar lymphadenopathy on chest radiographs, ocular lesions, need for enucleation, peripheral lymphadenopathy, central nervous system signs, presence of skin lesions, prostatic involvement, and bone involvement. Dogs received a score of "1" if the clinical sign was present or if the body system was involved. A score of "0" was assigned if the clinical sign was not present or the body system was not involved. The highest possible score for an individual dog was "11."

Treatment efficacy was evaluated in several ways, including percentage of dogs that survived the first 2 weeks of treatment; percentage of dogs that reached clinical remission; percentage of dogs that died during treatment; duration of treatment to clinical remission; and representation to the VMTH with evidence of relapse of blastomycosis.

The incidence of increases in serum ALT activity above the reference range, occurring during azole antifungal therapy, which had no other reasonable alternative clinical explanation, was calculated. The magnitude of increase in serum ALT activity was also determined. If dogs were concurrently receiving other medications known to cause hepatotoxicity, such as phenobarbital, those dogs were censored from analysis of increases in ALT.

Wilcoxon's rank-sum testing was used to compare the fluconazole and itraconazole groups for baseline age, body weight, disease severity score at presentation, treatment duration to clinical remission, total drug cost, and increase in ALT activity. A 2-tailed Fisher's exact test was used to compare groups with regard to sex, survival at 2 weeks, representation for relapse, presence of individual factors comprising the disease severity score, and incidence of increases in ALT activities, with $P < .05$ considered statistically significant. A 90% confidence interval approach was used to test fluconazole therapy for noninferiority to itraconazole.

Results

Enrolled Patients

Medical records of 144 dogs with a diagnosis of blastomycosis were retrospectively reviewed. Dogs treated with itraconazole presented to the UW-VMTH from January 1998 through December 2005, and dogs treated with fluconazole presented from January 2003 through December 2008. Of 78 dogs treated with itraconazole, 31 dogs met inclusion criteria: 3 dogs died within 2 weeks of starting treatment, and 28 completed a full course of treatment. The other 47 dogs were excluded for incomplete medical records (n = 36), concurrent treatment with amphotericin B (n = 2), or initial treatment with itraconazole but switched to fluconazole (n = 9). Of 66 dogs treated with fluconazole, 36 dogs met the inclusion criteria; 9 dogs died within 2 weeks of starting treatment, and 27 completed a full course of treatment. The other 30 dogs were excluded for incomplete medical records (n = 26) or concurrent treatment with amphotericin B (n = 4).

Group Characteristics

Thirty-one dogs treated with itraconazole included 30 purebred dogs and 1 mixed breed dog. Major breeds represented included Labrador Retriever (8/28), Golden Retriever (4/28), Springer Spaniel (2/28), and German Shepherd (2/28). The median age at the time of diagnosis was 5.5 years (range, 1.2–12.3 years), with a median weight of 29.0 kg (6.4–52.0 kg). There were 17 male dogs (MI, 5/17; MC, 12/17) and 14 female dogs (FI, 4/14; FS, 10/14).

Thirty-six dogs treated with fluconazole included 31 purebred dogs and 5 mixed breed dogs. Major breeds represented included Labrador Retriever (12/36), Golden Retriever (4/36), and Newfoundland (2/36). The median age at the time of diagnosis was 5.0 years (0.8–11 years), with a median weight of 29.0 kg (6.2–49.0 kg). There were 22 male dogs (MI, 5/22; MC, 17/22) and 14 female dogs (FI, 1/14; FS, 13/14). No statistically significant differences were found in age ($P = .66$), weight ($P = .32$), or sex distribution ($P = .63$) between groups.

The median disease-severity score for dogs in both groups was 4, with a range of 2–8 for dogs treated with itraconazole and 1–7 for dogs treated with fluconazole (Table 1). No statistically significant difference was found in the overall disease-severity scores between groups ($P = .97$); however, dogs in the itraconazole treatment group were significantly more likely to have bone lesions ($P = .02$). All other assessed parameters were statistically similar between treatment groups.

Treatment Efficacy

Dogs treated with itraconazole received a median dose of 5.5 mg/kg/d, ranging from 4.6 to 10.8 mg/kg/d. The dogs treated with fluconazole received a median dose of 10.4 mg/kg/d, ranging from 2.9 to 19 mg/kg/d. Twenty-eight of 31 (90%) dogs treated with itraconazole and 27/36 (75%) dogs treated with fluconazole treatment survived beyond 2 weeks of therapy. The incidence of death in the first 2 weeks was 25 in the fluconazole group and 10% in the itraconazole group ($P = .13$). The efficacy data were also analyzed by noninferiority testing[9] to

Table 1. Clinical signs and disease severity scores (1–11) in 65 of 67 dogs with systemic blastomycosis treated with either itraconazole or fluconazole (5–10 mg/kg/d).

Clinical Finding	Itraconazole (n= 29)[a]	Fluconazole (n = 36)
Hilar lymphadenopathy or pulmonary infiltrates	27 (93%)	34 (94%)
Fever (>102.5°F)	22 (76%)	24 (67%)
Tachypnea (>50 breaths/min)	17 (59%)	13 (36%)
Ocular lesions	14 (48%)	13 (36%)
Skin lesions	11 (38%)	18 (50%)
Peripheral lymphadenopathy	9 (31%)	17 (47%)
Bone lesions	8 (28%)*	2 (6%)
Need for oxygen supplementation	5 (17%)	7 (19%)
Need for enucleation	4 (14%)	10 (28%)
Central nervous system signs	0 (0%)	3 (8%)
Prostatic involvement	0 (0%)	1 (3%)
Disease severity score (range)	4 (2–8)	4 (1–7)

Values for each clinical finding reported as the number of affected dogs and percent of each group, values for the overall disease severity score reported as median (range).

[a]Inadequate information to score disease in 2 of 31 dogs.

*Significantly higher than fluconazole group ($P = .02$).

determine whether fluconazole treatment could be considered equivalent to itraconazole for the treatment of blastomycosis in dogs. We determined the 95% confidence interval for the "true" difference between fluconazole and itraconazole efficacy, which was observed to be 15% less effective for fluconazole; the 95% confidence interval for this difference ranged from 33% less effective to 3% more effective for fluconazole. However, using a threshold for noninferiority such that fluconazole needs to be no more than 10% worse than itraconazole in efficacy, the 2 treatments were not proved to be equivalent when the full treatment period (including the first 2 weeks) was considered.

The median disease severity score for the subset of dogs treated with fluconazole and surviving to remission was 4 with a range of 1–7, while the subset of dogs treated with fluconazole that died had a median disease severity score of 5 with a range of 3–7. Disease severity scores for the survivors compared with nonsurvivors did not reach statistical significance ($P = .07$). When the components of the disease severity score were evaluated, dogs treated with fluconazole that died were significantly more likely to be tachypneic and require oxygen supplementation (both $P < .001$) than surviving dogs treated with fluconazole. All dogs surviving greater than 2 weeks beyond the initiation of therapy survived to clinical remission. Median duration of treatment (to 1 month beyond clinical remission) in the itraconazole group was 138 days (range, 54–237 days) and in the fluconazole group was 183 days (range, 73–296 days). Treatment duration was significantly longer, by about 45 days, in dogs treated with fluconazole than in dogs treated with itraconazole ($P = .001$). The rate of representation to the VMTH for relapse of blastomycosis was 5/28 (18%) for itraconazole and 6/27 (22%) for fluconazole, which was not significantly different between treatment groups ($P = .75$).

Evidence of Drug-Associated Increases in ALT Activities

Serum ALT activity was recorded before starting azole therapy, and at least once during the treatment period, in 41 of all 55 dogs that were followed to remission; 5 dogs in the itraconazole group and 9 dogs in the fluconazole group did not have ALT activity measured during the treatment period. Six of 23 dogs (26%) in the itraconazole group that were evaluated had ALT activities that increased out of the reference range after starting therapy, compared with 3/18 dogs (17%) receiving fluconazole; this difference was not significant ($P = .71$). The median magnitude of ALT elevation above the upper end of the reference range for itraconazole and fluconazole were 2.7 (range, 1.3– > 6.5) and 1.5 (range, 1.1–2.6), respectively, which was not significantly different ($P = .17$). For all 6 of the dogs in the itraconazole group with increases in ALT, itraconazole dosages were reduced and therapy was continued. Treatment with itraconazole was discontinued in only 1 dog because of progressively increasing ALT activity. Of the 3 dogs in the fluconazole group with increases in ALT, only 1 of the 3 dogs had its dosage reduced. All 3 dogs completed therapy without clinical signs of hepatotoxicosis.

Nine of the 144 dogs reviewed were censored from group analyses because of treatment with both itraconazole and fluconazole. In all 9 cases, therapy was initially started using itraconazole and was then subsequently switched to fluconazole. Three of the 9 (33%) cases were switched because of presumed itraconazole-induced hepatotoxicity, 3/9 (33%) cases were switched because of ophthalmic involvement and the potential for improved ocular penetration with fluconazole,[10,11] 2/9 (22%) cases were switched in order to reduce cost, and for 1 case the reason for switching could not be determined.

Total Drug Cost

The median monthly cost for itraconazole was $769.00, ranging from $256.35 to $2,050.80, and the median monthly cost for fluconazole was $203.85, ranging from $33.00 to $407.70. The median total cost of treatment in the itraconazole group was $3,717.00, ranging from $897.20 to $12,817.50, and the median total cost of treatment in the fluconazole group was $1,223.10, ranging from $220.80 to $3,057.75. Treatment with fluconazole was significantly less expensive than treatment with itraconazole, despite a longer treatment duration ($P < .001$).

Discussion

Blastomycosis is a serious, systemic fungal disease that commonly affects dogs and humans. Itraconazole is currently the recommended first-line treatment for both humans and dogs, but fluconazole has never been directly compared with itraconazole for the treatment of systemic blastomycosis.[1,4,12] No randomized, blinded studies comparing itraconazole and fluconazole therapy have been performed in people with blastomycosis. Therefore, treatment with itraconazole is based on small

open-label studies and anecdotal experience.[13,14] Two studies suggested that fluconazole was not as efficacious as itraconazole in the treatment of human blastomycosis,[15,16] therefore the use of fluconazole has remained limited in this disease. In 91 dogs treated with itraconazole at either 5 or 10 mg/kg/d, 75% responded to a 60-day itraconazole course while 25% died.[7] In a retrospective review, 21/31 dogs (68%) with blastomycosis responded initially to a 60 or 90-day course of itraconazole.[1] The response rates found in our study for itraconazole were apparently higher (90%); however, because the number of cases was low, this apparent difference is difficult to interpret, but could be because we treated for 1 month beyond clinical evidence of disease rather than for a fixed 60- or 90-day course.

When compared with itraconazole, we found a statistically similar overall remission rate for fluconazole (75%) as for itraconazole (90%) in our hospital, with no difference in efficacy (100%) beyond 2 weeks of treatment. It is possible that these remission rates would be statistically different with a larger sample size, and this difference, if real, might be clinically significant. The 95% confidence interval for difference in efficacy ranged from 33% less effective to 3% more effective for fluconazole. However, this testing utilized the remission rates of our study population, which feature an improved itraconazole remission rate than those reported previously, while the fluconazole remission rate was consistent with the rates previously reported for itraconazole remission.[1,4] The potential for fluconazole therapy to achieve remission rates up to 33% inferior to itraconazole therapy is concerning, and until prospective studies either disprove or verify this finding, the use of fluconazole in place of itraconazole must be weighed carefully. All dogs in both groups that survived the first 2 weeks went on to achieve clinical remission. The apparent difference between groups was in mortality at 2 weeks (10% for itraconazole and 25% for fluconazole). This may reflect a real difference in early efficacy between the 2 drugs, or may be because of other variability that could not be controlled for in this retrospective study design. Overall disease severity scores between the 2 treatment groups were similar, and no individual score was higher for the fluconazole dogs compared with the itraconazole dogs. However, when we separated the fluconazole group into dogs that died during the first 2 weeks of therapy (n = 9) and dogs that survived until clinical remission (n = 27), the difference in disease severity scores between the groups approached significance ($P = .07$). Of note, dogs treated with fluconazole and failing to survive were significantly more likely to experience tachypnea and require oxygen supplementation. This finding was not surprising, however, as dogs with severe lung involvement are more likely to fail therapy.[1] Similar analyses could not be performed for the 3 dogs in the itraconazole group that died, because of inadequate information for 2 of the dogs. Unfortunately, in order to determine whether a real 15% difference in 2-week survival is present between itraconazole and fluconazole treatments, a prospective study would need more than 300 dogs in each group to have 85% power to establish this as significant.

The incidence of representation for relapse of clinical signs was found to be relatively low and similar for both groups: 18% for itraconazole and 22% for fluconazole. This rate is similar to previous studies with relapse rates of 24 and 20%.[1,4] However, our relapse rate is based on representation to the VMTH for recurrent clinical signs, and represents a minimum incidence of relapse that may be an underestimation for both treatment groups.

Dogs administered fluconazole were treated for a significantly longer period of time (a median of 45 days longer) than dogs administered itraconazole. One likely explanation is that itraconazole might be more effective in clearing *Blastomyces* organisms in dogs; this is consistent with the finding that itraconazole has higher potency than fluconazole in vitro against human isolates of *B. dermatitidis*.[17,18] A 2nd contributing factor could be differences in monitoring between the 2 groups over time. The UW-VMTH switched from film radiography to digital radiography in April 2007; by that time, fluconazole had largely replaced itraconazole for the treatment of blastomycosis in dogs at the VMTH because of cost. Therefore, all dogs monitored with digital radiography, which is more sensitive for pulmonary lesions,[19] were in the fluconazole group. Because therapy was routinely continued until 1 month after the resolution of both clinical signs and radiographic evidence of active disease,[20] the use of sensitive digital radiography might have biased the fluconazole group to receive longer courses of therapy. Lastly, the lower cost of fluconazole, as compared with itraconazole, might have biased clinicians to prescribe a longer course of therapy, as additional months of treatment added little to the overall cost to the client.

A subset of dogs in the fluconazole group (n = 8) were also enrolled in a prospective study evaluating the diagnostic performance of the urinary *Blastomyces* antigen test, which dictated monthly evaluations and imaging throughout the course of treatment, as well as quarterly recheck exams for the 1st year after completing therapy. However, median treatment duration with fluconazole for these 8 dogs was 164 days (range, 73–230 days), which was not longer than the median treatment duration for the fluconazole group as a whole of 183 days.

The incidence of adverse effects in human patients treated with itraconazole was 39% in 1 prospective study, and included gastrointestinal upset, elevated liver enzymes, hypokalemia, and rash.[21] The overall incidence of itraconazole-associated hepatotoxicosis is approximately 1–5% in people.[22] In dogs with blastomycosis, 34% of dogs treated with of itraconazole (10 mg/kg/d) had increases in ALT activity, while the overall incidence of ALT increases was lower (12%) at the lower dosage of itraconazole (5 mg/kg/d).[7] Although the relative hepatotoxicosis of fluconazole versus itraconazole has not been characterized, fluconazole is less hepatotoxic than itraconazole in rats, both in vivo and in vitro.[7,23]

The incidence of drug-associated increases in ALT activity in our study was statistically similar between treatment groups (26% for itraconazole and 17% for fluconazole; $P = .71$). The magnitude of the elevation was also similar between groups, although the highest increase (> 6.5 times the upper end of the reference

range) was documented in the itraconazole group. This incidence for itraconazole is comparable to that previously reported in dogs with blastomycosis (12–34% depending on dosage)[7]; the incidence for fluconazole-associated hepatotoxicity in dogs has not been previously reported. It is important to note that 9 dogs were excluded from the study because of treatment with both itraconazole and fluconazole; 3 of these dogs changed therapy because of itraconazole-associated increases in ALT; no dogs had the reverse treatment change. Therefore, the rate of itraconazole-related hepatotoxicosis might be underestimated by this study. This study was underpowered to detect the observed 8% apparent difference in hepatotoxicity between itraconazole and fluconazole; more than 400 dogs in each group would have been necessary to show significance if this were a real difference. Of the 9 dogs excluded for combined fluconazole and itraconazole use, 5 dogs survived and 4 dogs had incomplete follow-up to determine the length of treatment necessary for disease remission. However, none of the dogs either died or were euthanized. The varied cases and presentation of the 5 dogs with adequate follow-up precluded further evaluation of a possible pilot study assessing the potential use of itraconazole followed by fluconazole.

The cost of therapy often dictates the treatment plan selected in veterinary medicine, and blastomycosis requires prolonged medical therapy. A treatment duration of 1 month past resolution of radiographic infiltrates, with a minimum of 90 days treatment, has been recommended for dogs with pulmonary blastomycosis.[20] In that study, the median time to resolution of radiographic signs was 185 days, which is comparable to treatment durations found in our study (138 days for itraconazole and 183 days for fluconazole). Even with a significantly longer duration of therapy, treatment with the generic formulation of fluconazole resulted in 3-fold lower costs to the client to achieve clinical remission. The markedly lower cost of fluconazole might allow some clients to pursue treatment that they might otherwise be unable to afford.

This retrospective study design had inherent limitations. It did not allow for dogs to have the same dosing and monitoring schedule. In addition, the switch to digital radiography could have resulted in more prolonged treatment for dogs treated with fluconazole later in the study period. With respect to hepatotoxicosis, other factors that may have resulted in increased ALT activity, such as concurrent illness or the use of other medications, might not have been documented in all cases, and conversely, ALT activities were not prospectively followed at each visit. Lastly, this was not a randomized study, therefore equality between the groups was more difficult to ensure. We attempted to address this limitation by using a disease severity index that compared the extent of disease and number of body systems involved between groups. Although there was no statistically significant difference in the disease severity index score between groups, there were more fluconazole dogs with CNS involvement, which has been associated with a worse prognosis.[1] Although no percentages reached significance, a higher percentage of dogs receiving itraconazole were reported tachypneic while a higher percentage of dogs receiving fluconazole required oxygen supplementation. Retrospectively, it was difficult to determine whether a clinician preference for itraconazole existed in tachypneic dogs and whether itraconazole was significantly beneficial for these dogs.

In conclusion, we have demonstrated that fluconazole is effective for the treatment of systemic blastomycosis in dogs, and was not significantly different in its effectiveness compared with itraconazole for long-term treatment in this population. However, equivalence between the 2 treatments could not be established in this sample size. Dogs treated with fluconazole required approximately 45 days longer of treatment to clinical remission, but there was a one-third lower total cost to client. Like itraconazole, fluconazole can cause apparent hepatotoxicity in some dogs, and serum ALT activities should be monitored for either drug regimen.

Footnotes

[a] Sporanox; Janssen-Ortho Inc, Raritan, NJ
[b] Fluconazole; IVAX Pharmaceuticals Inc, Miami, FL
[c] Walgreens Pharmacy; Deerfield, IL

Acknowledgments

The authors thank Nicholas Keuler, CALS Computer Lab, College of Agriculture and Life Sciences, for assistance with noninferiority analyses.

No outside funding was used to support this research.

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