

Date of Approval: May 15, 2018

**FREEDOM OF INFORMATION SUMMARY**  
**ORIGINAL NEW ANIMAL DRUG APPLICATION**

NADA 141-501

Semintra<sup>®</sup>

(telmisartan oral solution)

Oral Solution

Cats

For the control of systemic hypertension in cats

Sponsored by:

Boehringer Ingelheim Vetmedica Inc.

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**I. GENERAL INFORMATION**

**A. File Number**

NADA 141-501

**B. Sponsor**

Boehringer Ingelheim Vetmedica, Inc.,  
2621 North Belt Highway,  
St. Joseph, MO 64506-2002

Drug Labeler Code: 000010

**C. Proprietary Name**

Semintra®

**D. Product Established Name**

telmisartan oral solution

**E. Pharmacological Category**

Angiotensin II receptor blocker

**F. Dosage Form**

Oral solution

**G. Amount of Active Ingredient**

10 mg/mL

**H. How Supplied**

45 mL bottle with 35 mL volume

**I. Dispensing Status**

Rx

**J. Dosage Regimen**

The initial dose of Semintra® is 1.5 mg/kg (0.68 mg/lb) orally twice daily for 14 days, followed by 2 mg/kg (0.91 mg/lb) orally once daily. The dose may be reduced by 0.5 mg/kg (0.23 mg/lb) increments to a minimum of 0.5 mg/kg (0.23 mg/lb) orally once daily to manage Semintra®-induced hypotension. Semintra® can be administered directly into the mouth, or next to or on top of a small amount of food. Do not mix into food.

Semintra® should be administered using the dosing syringe provided in the package. The dosing syringe fits onto the bottle and has 0.1 mL incremental marks. The dose should be rounded to the nearest 0.1 mL. After administration

close the bottle tightly with the cap. Rinse the dosing syringe with water and let air dry.

If the cat vomits within 30 minutes of dosing, the cat may be re-dosed.

#### **K. Route of Administration**

Oral

#### **L. Species**

Cat

#### **M. Indication**

For the control of systemic hypertension in cats

### **II. EFFECTIVENESS**

The effectiveness of Semintra<sup>®</sup> (telmisartan oral solution) for the control of systemic hypertension in cats was demonstrated in two field effectiveness studies in client-owned cats (Study No. 2011028 and 2011029). Cats in the Semintra<sup>®</sup> group that completed Study 2011028 (28 days) were optionally enrolled in Study 2011029 (5 months) to evaluate the long-term safety and effectiveness of Semintra<sup>®</sup>. The most common adverse reactions reported in both studies were vomiting, diarrhea, lethargy, weight loss, decreased appetite, non-regenerative anemia and dehydration

The field effectiveness studies and the safety study were conducted with a 4 mg/mL telmisartan oral solution; the marketed formulation is a 10 mg/mL telmisartan oral solution. A pharmacokinetic study (Relative Bioavailability Study No. 2014367) demonstrated that the 4 mg/mL formulation used in the effectiveness and safety studies was bioequivalent to the 10 mg/mL final market formulation following a single oral dose of each solution.

A pharmacokinetic and pharmacodynamic study was conducted to determine if systemic exposure to the drug differed if the drug was administered in food. The study determined that systemic exposure is greater in fasted cats; however the field effectiveness studies support dosing with a small amount of food if necessary.

#### **A. Dosage Characterization**

An initial dose of 1.5 mg/kg twice daily for 14 days, followed by 2 mg/kg once daily, of orally administered telmisartan was selected for further evaluation for control of hypertension in cats based on the following study. A dose of 1 mg/kg once daily was selected for cats that develop clinical signs of hypotension at the 2 mg/kg once daily dose.

##### Laboratory Dose Selection Study

A pilot dose determination laboratory study was conducted to evaluate the effectiveness of multiple oral doses and dose strategies of telmisartan on the reduction of systolic blood pressure (SBP) in clinically normal, healthy laboratory cats within a 14-day time period. The secondary objective was to observe the effect of a 1 mg/kg once daily dose for maintaining the reduced SBP.

This study was a randomized, controlled, incomplete Latin square, crossover design. Twenty-eight normotensive, domestic shorthair cats weighing 5.4 - 17 pounds and one year of age and older were enrolled. There were three treatment periods and seven treatment groups (four cats per group): placebo, 1 mg/kg once a day, 1 mg/kg twice a day, 1.5 mg/kg once a day, 1.5 mg/kg twice a day, 2 mg/kg once a day, and 3 mg/kg once a day. The study also incorporated an acclimatization phase and a one-week washout between each treatment phase. In addition to the original design, a fourth treatment period was implemented following Period 3 without a washout to determine the effect of a reduction in dose to 1 mg/kg in all groups receiving telmisartan compared to placebo. The SBP was lower in the telmisartan groups compared to the placebo group at all time points. Based on results of Period 1, a dose of 1.5 mg/kg, administered twice a day, to reduce SBP in 14 days or less was chosen for further evaluation. The 2 mg/kg dose, administered once a day, was selected to maintain the reduced SBP after the initial 14 days.

## **B. Substantial Evidence**

### 1. Twenty-eight Day Field Effectiveness Study

**Title:** Evaluation of the safety and efficacy of orally administered telmisartan for hypertension in cats, Study No. 2011028.

**Study Dates:** *September 2012 to October 2015*

**Study Locations:** Thirty-one United States (US) and two Canadian veterinary clinics from the following locations participated in this study.

Campbell, California	Kansas City, Missouri
Lawndale, California	St. Louis, Missouri
Orange, California	Springfield, Missouri
Ventura, California	Randolph, New Jersey
Fort Collins, Colorado	Buffalo, New York
Hartford, Connecticut	Greensboro, North Carolina
Altamonte Springs, Florida	Morrisville, North Carolina
Largo, Florida	Columbus, Ohio
Woodstock, Georgia	Tulsa, Oklahoma
Chicago, Illinois	Beaverton, Oregon
Lawrence, Kansas	Philadelphia, Pennsylvania
Ann Arbor, Michigan	Alexandria, Virginia
Battle Creek, Michigan	Vancouver, Washington
Plymouth, Michigan	Milwaukee, Wisconsin
Stamford, Michigan	Ancaster, Ontario, Canada
Waterford, Michigan	Ottawa, Ontario, Canada
Plymouth, Minnesota	

**Study Design:** This was a multicenter, double-masked, randomized, placebo-controlled field study.

**Objective:** To evaluate the safety and effectiveness of telmisartan oral solution administered to cats for the control of hypertension associated with chronic kidney disease (CKD), hypertension associated with controlled

hyperthyroidism, or idiopathic hypertension over a 28-day treatment period. The study was conducted in accordance with Good Clinical Practice.

**Study Animals:** The study enrolled 288 client-owned cats with systemic hypertension (144 female, 144 male) of various breeds, 5 - 24 years old, and weighing 1.93 - 11.4 kg (4.2 - 25.1 lbs.). Cats included in the per protocol effectiveness evaluation had chronic renal disease (56.1%), idiopathic hypertension (29.9%), CKD and hyperthyroidism (11.3%), or hyperthyroidism (2.7%).

**Experimental Design:**

The cats were randomized to receive telmisartan or a vehicle control at a 2:1 ratio (192 cats in the telmisartan group and 96 cats in the control group).

**Treatment Groups:**

**Table II.1. Initial Dose from Day 0 to Day 14**

Group	Dosage	Number of Cats <sup>a</sup>
Telmisartan	1.5 mg/kg orally twice daily for 14 days, then 2 mg/kg orally once daily	192
Control	0.375 mL/kg orally twice daily for 14 days, then 0.25 mL/kg orally once daily	96

<sup>a</sup> Safety population = cats that received at least one dose of telmisartan or vehicle control

**Table II.2. Maintenance Dose After Day 14 Based on Systolic Blood Pressure**

SBP (mmHg)	Telmisartan Dosage	Control Dosage
> 180	Rescued from study	Rescued from study
120-180	2 mg/kg orally once daily	0.5 mL/kg orally once daily
< 120	1 mg/kg orally once daily <sup>a</sup>	0.25 mL/kg orally one daily <sup>a</sup>

<sup>a</sup> After a cat received 1 mg/kg telmisartan once daily or 0.25 mL/kg control once daily dosing for at least 14 days, additional dose reduction to 0.5 mg/kg once daily or 0.125 mL/kg once daily was allowed if SBP was <120 mmHg

**Inclusion Criteria:** Cats at least 1 year old, expected to live at least 6 months, voluntarily eating and drinking, on a stable diet for 14 days, with SBP between 160-200 mmHg; and hypertension associated with International Renal Interest Society (IRIS) CKD stage 1-3, hypertension associated with controlled hyperthyroidism, or idiopathic hypertension.

**Exclusion Criteria:** Pregnant, lactating, or intended for breeding; previously treated for hypertension within 7 days prior to the screening visit; severe hypertensive retinopathy including blindness, retinal detachment, hyphema or moderate to severe retinal bleeding; azotemia for a cause other than CKD; diagnosed or suspected acute renal failure; diagnosis or suspicion of active pyelonephritis; history of NSAID use within 14 days prior to screening; concurrent and uncontrolled hyperthyroidism, diabetes mellitus, liver disease,

congestive heart failure, or newly diagnosed or uncontrolled malignant neoplasia; or hematocrit <20%.

**Drug Administration:** The telmisartan group received telmisartan 4 mg/mL oral solution. The control group received the oral solution vehicle (no active ingredient). Cat owners administered the products directly into the cat's mouth with the dosing syringe, or by placing the dose near or on top of a small amount of food.

**Measurements and Observations:** Baseline physical examination, hematology, serum chemistry, urinalysis, indirect systolic blood pressure, and retinal photographs were obtained prior to the initial dose administration. Safety was monitored during the study by documentation of adverse events.

Physical examination parameters, SBP, and retinal photographs to assess hypertension-related target organ damage (TOD) were obtained on Days 0, 14, and 28; the Day 14 and Day 28 findings were compared to baseline. Blood and urine samples for hematology, serum chemistry, and urinalysis were collected on Days 0 and 28; the Day 28 findings were compared to Day 0 and evaluated for clinically significant changes. At Day 14 and at Unscheduled Visits, blood and urine samples were collected at the discretion of the Investigator. If an unscheduled visit was identified at the end of study visit, physical examination parameters, SBP, blood and urine, and retinal photographs were collected.

For the indirect SBP measurements, the same device model was used at all study sites. The SBP was obtained prior to other assessments and after the cat had acclimated to the examination room. Five readings were obtained using the forelimb, the lowest and highest readings were discarded, and the mean of the remaining three readings was recorded as the SBP measurement.

Retinal photographs were obtained after the SBP measurement and physical examination. The pupils were dilated prior to taking the retinal photographs. Retinal photographs were evaluated by a board certified veterinary ophthalmologist for diagnostic quality and for evaluation of hypertension-associated lesions.

**Statistical Methods:** Change in mean SBP from baseline to Day 14 for the treatment and control groups was evaluated using a mixed model with covariate. The model included the fixed effects of treatment group and covariates baseline mean SBP and treatment group by baseline mean SBP interaction; and the random effects of site and site by treatment group interaction. Treatment group least squares means of the Change in mean SBP from baseline to Day 14 and 95% confidence intervals were reported. Change from baseline to Day 28 summary for treatment and control groups included means and 95% confidence intervals.

**Results:**

**Effectiveness:** The change in group mean SBP from baseline (Day 0) to Day 14 was calculated. There was a statistically significant difference ( $p=0.0005$ ) between the group mean SBP of the telmisartan and control groups. The

telmisartan group had a mean decrease in SBP of 23.2 mmHg; and the control group had a mean decrease in SBP of 7.3 mmHg (see Table II.3).

**Table II.3. Primary Variable Group Mean SBP Assessment at Day 14**

Treatment Group	N	LSM SBP change from baseline to Day 14 (mmHg) <sup>a</sup>	Lower 95% CI (mmHg) <sup>b</sup>	Upper 95% CI (mmHg) <sup>b</sup>	p-value comparison to control
Telmisartan	141	-23.2	-28.1	-18.2	0.0005
Control	79	-7.3	-13.4	-1.2	n/a

<sup>a</sup> LSM: Least Squares Means

<sup>b</sup> CI = Confidence Interval

A clinically relevant reduction in group mean SBP was predefined to be  $\geq 20$  mmHg in the telmisartan group from baseline to Day 28. The mean of the treatment group at Day 28 minus the mean of the treatment group at baseline (Day 0) was calculated. The result was an arithmetic mean decrease of 23.9 mmHg in the telmisartan group (Table II.4).

**Table II.4. Clinical Relevance Assessment in the Telmisartan Group at Day 28 (SBP values in mmHg)**

Treatment Group	N <sup>a</sup>	Mean change	Lower 95% CL <sup>b</sup>	Upper 95% CL <sup>b</sup>	Median	Min.	Max.
Telmisartan	121	-23.9	-27.8	-20.0	-23.4	-74.0	34.7

<sup>a</sup> The number of cats available at Day 28 for comparison is less than at enrollment due to removal of cats for hypertension rescue or adverse reactions

<sup>b</sup> CL = Confidence Limit

The distribution of SBP change from baseline for the telmisartan and control groups at Visit 2 (Day 14) and Visit 3 (Day 28) are presented in Table II.5.

**Table II.5. Distribution of Change in SBP from Baseline for the Telmisartan and Control Groups at Visits 2 and 3**

Change in SBP from baseline	Telmisartan Day 14 (N=141)	Control Day 14 (N= 79)	Telmisartan Day 28 (N=121)	Control Day 28 (N= 50)
Increase	19 (13.5%)	28 (35.4%)	19 (15.7%)	12 (24.0%)
Decrease < 20 mmHg	44 (31.2%)	31 (39.2%)	35 (28.9%)	24 (48.0%)
Decrease $\geq 20$ mmHg	78 (55.3%)	20 (25.3%)	67 (55.4%)	14 (28.0%)

Dose Reduction to 1 mg/kg once daily: Cats that had SBP <120 mmHg were allowed a dose reduction to 1 mg/kg once daily. In the telmisartan group eleven cats had their dose reduced at Day 14 and eight cats had the dose reduced at Day 28. If a cat had hypotension at a dose of 1 mg/kg once daily, then the dose could be reduced again to 0.5 mg/kg once daily. In the



telmisartan group three cats had their dose reduced to 0.5 mg/kg once daily at Day 28 or at unscheduled visits.

Hypertension rescue: Cats were removed from the study if they had SBP >180 mmHg at Day 14. The percentage of cats that required hypertension rescue was lower in the telmisartan group compared to the control group (21.1% and 40.5%, respectively).

Physical Examination: No clinically relevant changes were observed in physical examination findings from baseline to Day 14 and Day 28, within treatment group and when the two treatment groups were compared.

Retinal Photographs: The retina was evaluated for hypertension-associated target organ damage (TOD). Retinal photographs were independently reviewed by a board certified veterinary ophthalmologist. The assessment for retinal TOD included comparison of retinal photographs taken at baseline to Day 14 and Day 28, and scoring as "better", "same", or "worse." Most cats in the telmisartan and control groups were the same at Day 14 (87% and 89.1%, respectively) and Day 28 (83.7% and 86.5%, respectively). A higher percentage of telmisartan cats scored "better" compared to control (11.5% and 8.1%, respectively) at Day 28. The telmisartan and control groups had similar incidences of "worse" scores (2.9% and 2.7%, respectively) at Day 28.

Clinical Pathology: There were no clinically relevant changes for clinical pathology variables during the study. Individual occurrences of clinically relevant anemia are summarized under Adverse Reactions.

IRIS Staging for CKD: The IRIS 2015 guidelines for staging CKD in cats based on serum creatinine were summarized at baseline and Day 28, and cats were scored as "better", "same", or "worse". The summaries include 109 cats that had CKD or CKD and hyperthyroidism as pre-existing conditions, and clinical pathology samples for both baseline and Day 28.

**Table II.6. IRIS Stage Assessment in the CKD Effectiveness Population at Day 28 Compared to Baseline**

<b>Treatment Group</b>	<b>Better</b>	<b>Same</b>	<b>Worse</b>	<b>Total</b>
Telmisartan	12 (14.8%)	64 (79.0%)	5 (6.2%)	81
Control	5 (17.9%)	21 (75.0%)	2 (7.1%)	28

Concomitant Treatments: The most common concomitant treatments used during the study included (in order of frequency): anesthesia/sedatives/analgesia, antibiotics, vaccines, thyroid treatment, prescription diets, joint supplements, nutritional supplements, antiemetics, antiparasitics, and fluid therapy.

**Adverse Reactions:**

Safety was evaluated in 288 cats (192 telmisartan, 96 control) that received at least one dose of study drug. Adverse reactions were defined as abnormal (unfavorable and unintended) clinical signs that occurred after treatment,

regardless of causality. A serious adverse reaction was defined as an event that required hospitalization or medical intervention.

Adverse reactions that occurred in at least 5% of either treatment group are presented in Table II.7 below. One hundred fourteen cats (59.4%) in the telmisartan group and 42 cats (43.8%) in the control group had at least one adverse reaction during the study.

**Table II.7. Adverse Reactions in the 28-Day Study (2011028)<sup>a</sup>**

<b>Clinical Sign</b>	<b>Telmisartan N=192</b>	<b>Control N=96</b>
Vomiting	46 (24.0%)	14 (14.6%)
Diarrhea	18 (9.4%)	4 (4.2%)
Lethargy	13 (6.8%)	3 (3.1%)
Weight loss	13 (6.8%)	5 (5.2%)
Decreased appetite/inappetence	13 (6.8%)	7 (7.3%)
Non-regenerative anemia	11 (5.7%)	2 (2.1%)
Dehydration	10 (5.2%)	4 (4.2%)
Retinal lesions (target organ damage)	4 (2.1%)	6 (6.3%)

<sup>a</sup> Includes serious and non-serious adverse reactions

Additional adverse reactions that occurred in <5% of cats in the telmisartan group included (in order of decreasing frequency), anorexia, gagging, arrhythmia, cough, heart murmur and regenerative anemia.

Additional adverse reactions that occurred in 2-5% of cats in the control group included azotemia, not drinking, and renal failure.

Seven cats (five telmisartan group and two control group) either died or were euthanized during the study. Three telmisartan group cats were euthanized for neoplasia that was diagnosed during or shortly after the study, one cat died from a traumatic injury, and one cat had acute onset paralysis. None of the telmisartan group cat deaths were considered related to treatment. Two control group cats were euthanized or died from decompensated pre-existing CKD.

**Conclusions:** Telmisartan was safe and effective in controlling hypertension in cats when administered at an initial dose of 1.5 mg/kg orally twice daily for 14 days, followed by 2 mg/kg orally once daily. Dose reductions to 1 mg/kg were effective in managing hypotension (<120 mmHg) that resulted from use of telmisartan while maintaining hypertension control. The most common adverse reactions were vomiting, diarrhea, lethargy, weight loss, decreased appetite, non-regenerative anemia and dehydration.

## 2. Five-Month Field Safety and Effectiveness Study

**Title:** Extended Use Field Safety: An evaluation of the oral administration of telmisartan for the control of hypertension in cats. Study No. 2011029

**Study Dates:** November 2012 to February 2016

**Study Locations:** Twenty-six US and two Canadian veterinary clinics from the following locations participated in this study.

Campbell, California	Kansas City, Missouri
Lawndale, California	St. Louis, Missouri
Ventura, California	Springfield, Missouri
Hartford, Connecticut	Randolph, New Jersey
Altamonte Springs, Florida	Greensboro, North Carolina
Largo, Florida	Columbus, Ohio
Chicago, Illinois	Tulsa, Oklahoma
Lawrence, Kansas	Beaverton, Oregon
Ann Arbor, Michigan	Philadelphia, Pennsylvania
Battle Creek, Michigan	Alexandria, Virginia
Plymouth, Michigan	Vancouver, Washington
Stamford, Michigan	Milwaukee, Wisconsin
Waterford, Michigan	Ancaster, Ontario, Canada
Plymouth, Minnesota	Ottawa, Ontario, Canada

**Study Design:** This was a multicenter, unmasked, single treatment group field study. The study was conducted in accordance with Good Clinical Practice.

**Objective:** The objective of this study was to evaluate safety of telmisartan oral solution for five-months when administered to client-owned cats for the control of hypertension associated with CKD, hypertension associated with controlled hyperthyroidism, or idiopathic hypertension.

**Study Animals:** The study enrolled 107 client-owned cats with systemic hypertension (51 female, 56 male) of various breeds, 7 - 20 years old, and weighing 1.93 - 11.4 kg (4.2 - 25.1 lbs.). Cats enrolled in the study had CKD (58.9%), idiopathic hypertension (29%), CKD and hyperthyroidism (9.3%), or hyperthyroidism (2.8%).

**Inclusion Criteria:** Cats at least 1 year old, voluntarily eating and drinking, that were in the telmisartan group and successfully completed the 28-day study (2011028), and were expected to survive the duration of the study.

**Exclusion Criteria:** Cats met the removal criteria during the 28-day study (2011028), had azotemia not secondary to CKD, anemia (hematocrit <20%) that required treatment or was rapidly progressive, or the investigator believed that study inclusion put the cat at undue risk.

**Drug Administration:** All cats received telmisartan 4 mg/mL oral solution. Cats started this study at the same dose they were on at the end of the 28-day study (2011028). Ninety-seven cats were enrolled on a dose of 2 mg/kg orally once daily (90.7%), eight cats a dose of 1 mg/kg orally once daily (7.5%), and two cats a dose of 0.5 mg/kg orally once daily (1.9%). Most cats were maintained at the 2 mg/kg once daily oral dose for the duration of the study. Dose reductions to 1 mg/kg or 0.5 mg/kg once daily could be used to manage hypotension (SBP <120 mmHg). Cat owners administered the products

directly into the cat's mouth with the dosing syringe, or by placing the dose near or on top of a small amount of food.

**Measurements and Observations:** Baseline physical examination, hematology, serum chemistry, urinalysis, indirect systolic blood pressure, and retinal photographs were obtained prior to the initial dose administration in the 28-day study (2011028). Physical examination and SBP measurements were conducted on Days 28, 56, 98, 140, and 182. Retinal photographs and clinical pathology samples were obtained on Days 28, 98, and 182. Retinal photographs were evaluated for evidence of target organ damage (TOD) secondary to hypertension. Safety was monitored during the study by documentation of adverse events.

Day 28 and Day 182 hematology, serum chemistry, and urinalysis results were compared to the baseline results (Day 0) from the 28-day study (2011028) to determine the clinical significance of changes in laboratory values. At Days 56 and 140, and at Unscheduled Visits, blood and urine samples were collected at the discretion of the Investigator. If an unscheduled visit was identified as the end of study visit, physical examination parameters, SBP, blood and urine, and retinal photographs were collected.

The same devices were used at all sites for measurement of indirect systolic blood pressure. The SBP was obtained prior to other assessments and after the cat had acclimated to the examination room. Five readings were obtained using the forelimb, the lowest and highest readings were discarded, and the mean of the remaining three readings was recorded as the SBP measurement.

Retinal photographs were obtained after the SBP measurement and physical examination. The pupils were dilated prior to taking the retinal photographs. Retinal photographs were evaluated by a board certified veterinary ophthalmologist for diagnostic quality and for evaluation of hypertension-associated lesions.

**Statistical Methods:** Group mean SBP at baseline and Days 28, 56, 98, 140 and 182, and change from baseline at each Day were summarized as number of observations, mean, median, standard deviation, minimum, and maximum. Retinal photographs that were of diagnostic quality were evaluated on the same days and distribution of changes from baseline were reported. IRIS staging frequency distributions of status changes from baseline for each study day were reported.

**Results:**

One hundred-seven cats enrolled in the study; all cats that received at least one dose were included in the safety evaluation. Seventy-three (68.2%) cats completed the study (Day 182), 10 cats were rescued (8 due to hypertension, 2 due to hypotension), 10 cats were removed by the owner or for owner non-compliance, 8 cats were removed for new or worsening TOD, and 6 cats were removed for adverse reactions unrelated to TOD.

**Systolic Blood Pressure (SBP):** The change in SBP from baseline (Day 0) to Days 28, 56, 98, 140, and 182 was calculated for each cat. The group mean

SBP remained at or below 150 mmHg for the duration of the study (Table II.8).

**Table II.8. Group Mean Systolic Blood Pressure by Visit**

Visit	N	Mean SBP (mmHg)	Median (mmHg)	Standard Error (mmHg)	Minimum mean SBP (mmHg)	Maximum mean SBP (mmHg)
Baseline	107	176	175	1.1	160	200
Day 28	107	148	149	1.8	95	179
Day 56	102	148	148	2.0	105	195
Day 98	92	142	144	2.1	77	207
Day 140	81	145	148	2.0	89	184
Day 182	73	150	147	2.2	104	207

The group mean SBP from Days 28 - 182 were maintained at or below 150 mmHg. The range of SBP as presented in the minimum and maximum columns demonstrates that there was variability in individual SBP. Some cats experienced hypotension secondary to telmisartan treatment and some cats experienced lack of adequate SBP control (protocol definition for hypertensive rescue was SBP >180 mmHg).

**Table II.9. Distribution of Cats by SBP Range and Study Day<sup>a</sup>**

SBP Range (mm Hg)	Baseline N=107 n (%)	Day 28 N=107 n (%)	Day 56 N=102 n (%)	Day 98 N=91 n (%)	Day 140 N=80 n (%)	Day 182 N=69 n (%)
≤ 150	0 (0.0%)	58 (54.2%)	55 (53.9%)	61 (67.0%)	44 (55.0%)	41 (59.4%)
>150-160	4 (3.7%)	19 (17.8%)	19 (18.6%)	17 (18.7%)	21 (26.3%)	16 (23.2%)
>160-170	38 (35.5%)	18 (16.8%)	14 (13.7%)	10 (11.0%)	12 (15.0%)	7 (10.1%)
>170-180	28 (26.2%)	12 (11.2%)	10 (9.8%)	2 (2.2%)	3 (3.8%)	4 (5.8%)
> 180	37 (34.6%)	0 (0.0%)	4 (3.9%)	1 (1.1%)	0 (0.0%)	1 (1.5%) <sup>b</sup>

<sup>a</sup> SBP obtained at unscheduled visits are not represented. Three cats that were removed for >3 missed doses prior to SBP measurement are not included in the table.

<sup>b</sup> This cat had hypertension on the last study visit and is therefore not counted in the cats that were removed for hypertension rescue.

Most cats enrolled in study 2011029 maintained SBP <150 mmHg during the study. There was some individual variability and fluctuation from visit to visit, and it is difficult to determine whether these fluctuations are the result of stress during the visit, natural physiologic variation, or variability attributable to the measurement method itself. Eight cats were removed for hypertension; three of these cats had not received consistent dosing prior to rescue. The

three cats that had hypertension secondary to inconsistent dosing are not included in Table II.9 above.

Dose Reductions to manage hypotension: Twenty-six cats had dose reductions to 1 mg/kg once daily to manage hypotension. Of these 26 cats, 10 had an additional dose reduction to 0.5 mg/kg once daily, and 2 cats were later rescued for continued hypotension.

**Table II.10. Telmisartan Dose by Visit**

Visit	N	2 mg/kg n (%)	1 mg/kg n (%)	0.5 mg/kg n (%)
Day 28	107	97 (90.7%)	8 (7.5%)	2 (1.9%)
Day 56	98	87 (88.8%)	9 (9.2%)	2 (2.0%)
Day 98	90	78 (86.7%)	9 (10.0%)	3 (3.3%)
Day 140	80	71 (88.8%)	4 (5.0%)	5 (6.3%)
Day 182	73	64 (87.7%)	5 (6.8%)	4 (5.5%)

**Physical Examination:** There were no clinically relevant changes for the group as a whole for physical examination findings from baseline (28-day study 2011028) to Days 28, 56, 98, 140, and 182. There was a 0.19 kg decrease in group mean body weight from baseline to Day 182. This change for the group was considered not clinically relevant given the concurrent chronic diseases within the study population. Weight loss adverse reactions are summarized under Adverse Reactions in Table II.12.

**Retinal Photographs:** The retina was evaluated for hypertension-associated TOD. Retinal photographs were independently reviewed by a board certified veterinary ophthalmologist. The assessment for retinal TOD included assessment of retinal photographs at Days 28, 98, and 182, and scored as "better", "same", or "worse," when compared to baseline (28-day study 2011028). Only cats with baseline retinal photographs of the same eye were included for comparison.

Over the course of the study 10 out of 107 total cats (9.3%) developed or had worsening of hypertension-related retinal TOD.

**Table II.11. Evaluation of Change in Retinal Lesions Compared to Baseline**

Visit	N	Better	Same	Worse
Day 28	87	6 (6.9%)	77 (88.5%)	4 (4.6%)
Day 98	68	5 (7.4%)	59 (86.8%)	4 (5.9%)
Day 182	54	4 (7.4%)	48 (88.9%)	2 (3.7%)

**Clinical Pathology:** There were no clinically relevant changes for clinical pathology variables during the study. There was a decrease in mean hematocrit of 3.8% from baseline to Day 182. Individual occurrences of clinically relevant anemia are summarized under Adverse Reactions in Table II.12.

IRIS Staging for CKD: The IRIS 2015 guidelines for staging CKD in cats based on serum creatinine were summarized by study visit, and cats were scored as "better", "same", or "worse". Seventy-three cats had CKD as a pre-existing condition. Overall, 21.9% (n=16) of cats were considered worse at any point in the study, compared to 17.8% (n=13) that were considered better. Of the 16 cats that scored worse, only three cats (4.1%) progressed to IRIS stage 4 during the study. At study enrollment, two of those cats were IRIS stage 3 and one was IRIS stage 2.

Concomitant Treatments: The most commonly used concomitant treatments during the study included (in order of frequency): antibiotics, anesthesia/sedatives/analgesia, nutritional supplements, vaccines, prescription diets, antiparasitics, thyroid treatment, antiemetics, and fluid therapy.

**Adverse Reactions:**

Safety was evaluated in 107 cats that received at least one dose of telmisartan. Adverse reactions were defined as abnormal (unfavorable and unintended) clinical signs that occurred after treatment, regardless of causality. A serious adverse reaction was defined as an event that required hospitalization or medical intervention.

Table II.12 below includes serious and non-serious adverse reactions. Ninety-four cats (87.9%) had at least one adverse reaction during the study.

**Table II.12. Adverse Reactions in the 5-Month Study (2011029)<sup>a</sup>**

<b>Clinical Sign</b>	<b>Telmisartan N=107</b>
Weight loss	37 (34.6%)
Vomiting	32 (29.9%)
Dehydration	18 (16.8%)
Non-regenerative anemia	17 (15.9%)
Anorexia	14 (13.1%)
Diarrhea	12 (11.2%)
Lethargy	12 (11.2%)
Decreased appetite/inappetence	11 (10.3%)
Heart murmur	10 (9.3%)
Death, Euthanasia, Found dead	9 (8.4%)
Cough	8 (7.5%)
Retinal lesions (target organ damage)	6 (5.6%)

<sup>a</sup> Includes serious and non-serious adverse reactions

Additional adverse reactions observed in <5.0% of cats in the study population included (in order of decreasing frequency): elevated liver enzymes, renal failure, tachycardia, arrhythmia, azotemia, depression, loose stool, constipation, gagging, hypotension, regenerative anemia, renal insufficiency, and vocalization.

Nine cats died or were euthanized during the study. Of these cats four had confirmed or suspected neoplasia and one had acute onset paralysis, which were not treatment related. Four cats had progressive renal disease: one developed diabetes with progressive renal disease, two had progressive renal disease, and one had progressive hepatic and renal disease. It could not be determined if the progressive renal disease was the natural course of the pre-existing disease or treatment related.

**Conclusions:** Telmisartan was safe and effective in controlling hypertension in cats when administered at a dose of 2 mg/kg orally once daily. Dose reductions were effective in managing hypotension in most cats. The most common adverse reactions were weight loss, vomiting, dehydration, non-regenerative anemia, anorexia, diarrhea, and lethargy. These are clinical signs that also commonly occur in cats with chronic kidney disease (CKD), which comprised 68.2% of the study population. Cats should be monitored for these adverse reactions during treatment with telmisartan.

### 3. Pharmacokinetic Study (Relative Bioavailability)

**Title:** Plasma concentrations and pharmacokinetic parameters of telmisartan after single oral administration of 2 mg/kg telmisartan to healthy male and female cats as telmisartan 10 mg/mL oral solution for cats and telmisartan 4 mg/mL oral solution for cats. Study No. 2014367.

**Study Dates:** August 2016 to September 2016

**Study Location:** Fontenilles, France

**Study Design:**

The safety and effectiveness of the 10 mg/mL oral solution was supported by comparing the relative bioavailability of the 10 mg/mL (test) and 4 mg/mL (reference) solutions in a pharmacokinetic study.

**Objective:** The aim of this study was to compare the pharmacokinetic (PK) parameters of telmisartan after a single oral administration of 2 mg/kg of telmisartan 10 mg/mL oral solution versus telmisartan 4 mg/mL oral solution. This study was conducted in accordance with Good Laboratory Practice (GLP) regulations.

**Study Animals:** Twenty-four healthy cats (12 males and 12 females) were assigned to one of two treatment groups with six males and six females in each group. Cats were approximately 3 - 11 years of age, and weighing 2.5 - 5 kg (5.5 - 11 lbs.) at the start of the study.

**Experimental Design:** The study was a 2-sequence, 2-period, cross-over study. The Reference formulation was telmisartan 4 mg/mL oral solution and the Test formulation was telmisartan 10 mg/mL oral solution. It was conducted in two treatment periods (14 days apart) in 2 groups of 12 cats. Cats were randomly allocated according to Table II.13.



**Table II.13. Treatment Groups**

<b>Group</b>	<b>No. and Sex of Animals</b>	<b>Period 1</b>	<b>Period 2</b>
1	6 males + 6 females	Test	Reference
2	6 males + 6 females	Reference	Test

Drug Administration: Cats were fasted overnight by removing any remaining refused feed at least 12 hours prior to each treatment. Feed was then distributed 4 hours after dosing (after the corresponding blood sampling, when the cat was returned to its pen). The fasted state was selected to minimize any food effect on the pharmacokinetics.

The Test and Reference formulations were administered by the oral route directly into the mouth of each cat via syringe on Day 0 and Day 14 according to the experimental design. Both formulations were administered at the target dose of 2 mg telmisartan per kg of body weight corresponding to 0.2 mL Test formulation per kg body weight, and 0.5 mL Reference formulation per kg body weight. The total volume of the Test or Reference formulation to be administered was calculated for each cat based on the body weight recorded within 24 hours before each dosing. The volumes were rounded to the nearest 0.1 mL in order to reach individual doses of 2 mg/kg of telmisartan.

The mean  $\pm$  SD telmisartan dose administered was  $1.97 \pm 0.12$  mg/kg and  $2.00 \pm 0.06$  mg/kg for the Test formulation 10 mg/mL oral solution and the Reference formulation 4 mg/mL oral solution, respectively in Period 1. The mean  $\pm$  SD telmisartan dose administered was  $1.98 \pm 0.08$  g/kg and  $2.00 \pm 0.03$  mg/kg for the Test formulation 10 mg/mL and the Reference formulation 4 mg/mL, respectively in Period 2.

Measurements and Observations: All treated cats were observed prior to drug administration and around each post-administration blood sampling. Clinical observations were conducted for abnormal findings regarding behavior-posture-movements, respiratory signs, hypersalivation, ocular signs, skin-hair, and other abnormalities. The pen was checked for presence of abnormal feces (loose, watery, with blood) or abnormal urine, and for presence of vomit. The food remaining was also recorded, if any, from the sampling time of 4 hours to 24 hours for each day of dosing. Three cats vomited within the first two hours of dose administration (see Adverse Reactions).

Blood samples were taken from all treated cats at the following intervals after treatment: 15 minutes, 30 minutes, and 1, 2, 4, 6, 8, 12, 24, 30, 36, and 48 hours. Telmisartan concentrations in plasma were measured using a validated LC-MS/MS analytical method.

Statistical Methods: The analysis of variance for  $AUC_{0-t}$  and  $C_{max}$  as primary parameters was performed after natural logarithmic transformation.  $AUC_{0-t}$  and  $C_{max}$  were compared using a mixed effects model analysis with  $\alpha = 0.05$ . Fixed effects were treatment, sequence, period, gender, and the interactions between gender and treatment and gender and sequence. The random effect was animal nested in the gender sequence interaction.

Prior to the conduct of the study, the acceptance criteria for the Test/Reference (T/R) ratios and the 90% confidence intervals (CI) were adjusted based on safety and effectiveness data of the Reference formulation. The 90% CI criteria range was determined using the Relative Bioavailability Approach (RBA), and the justification and calculation of the limits used to establish RBA were established prior to initiating the study. The two formulations were considered to be pharmaceutical alternatives if the lower and upper confidence limits were totally included within the predetermined RBA interval ranging from 80% - 239% for  $C_{max}$  and 80% - 184% for  $AUC_{0-t}$ .

**Results:** Pharmacokinetic parameters were calculated using noncompartmental methods. There were significant ( $p < 0.05$ ) gender differences in the PK of telmisartan for both the formulations, but these differences were similar across both the formulations. Therefore, the observed differences did not affect the main study objectives as each subject served as its own control in this cross over study. The median time to maximum plasma concentration ( $T_{max}$ ) was lower for the Reference formulation 4 mg/mL (0.27 hour, range 0.25 - 1.03 hour) compared to the Test formulation 10 mg/mL (0.38 hour, range 0.25 - 1.00 hour). The mean terminal elimination half-life was similar between the genders ( $\sim 8$  hours). The mean maximum concentration ( $C_{max}$ ) and area under the plasma concentration versus time curve to the last quantifiable time point ( $AUC_{0-t}$ ) were significantly lower (53 - 57% and 57 - 59%, respectively) for female cats compared to male cats.

**Table II.14. Arithmetic Mean (CV%) Noncompartmental Parameters**

Formulation	Gender	$T_{max}^{\#}$ (hr)	$C_{max}$ (ng/mL)	$AUC_{0-t}$ (ng*hr/mL)	$AUC_{0-\infty}$ (ng*hr/mL)	$T_{1/2}$ (hr)
4 mg/mL (Reference)	Female (n=12)	0.25 (0.25-1.02)	206 (40.3)	216 (30.7)	217 (30.6)	8.47 (27.3)
4 mg/mL (Reference)	Male (n=12)	0.5 (0.25-1.03)	360 (33.5)	376 (25.3)	385 <sup>a</sup> (24.4)	8.20 <sup>a</sup> (16.9)
4 mg/mL (Reference)	Combined (n=24)	0.27 (0.25-1.03)	283 (45.3)	296 (38.7)	297 <sup>b</sup> (39.3)	8.34 <sup>b</sup> (22.6)
10 mg/mL (Test)	Female (n=12)	0.38 (0.25-0.55)	194 (39.1)	231 (37.6)	232 (37.5)	8.11 (30.6)
10 mg/mL (Test)	Male (n=12)	0.38 (0.25-1.00)	369 (36.0)	390 (31.0)	391 (30.8)	8.13 (41.3)
10 mg/mL (Test)	Combined (n=24)	0.38 (0.25-1.00)	282 (49.1)	310 (42.3)	311 (42.0)	8.12 (35.0)

CV% = percent relative standard deviation

# Median (minimum - maximum)

<sup>a</sup>n=11

<sup>b</sup>n=23

$C_{max}$  = maximum observed plasma concentration

$T_{max}$  = time to maximum concentration

$AUC_{0-t}$  = Area Under the Curve to the last quantifiable time point  $AUC_{0-\infty}$  = Area Under the Curve extrapolated to infinity

$T_{1/2}$  lambda = terminal elimination half-life

The upper and lower limits of the calculated confidence intervals are presented in the table below:

The 4 mg/mL and the 10 mg/mL formulations are considered bioequivalent even after excluding the three cats which vomited after drug administration (see Tables II.15 and II.16 below).

**Table II.15. Bioequivalence Assessment, All Cats Included (N=24/group)**

Pharmacokinetic parameters	Lower 90% confidence interval	Upper 90% confidence interval	Test to Reference Ratio	Intra-subject CV%
C <sub>max</sub> (ng/mL)	83.65	114.85	0.98	32.7
AUC <sub>0-t</sub> (ng*h/mL)	91.00	114.55	1.02	23.5

C<sub>max</sub> = maximum observed plasma concentration

AUC<sub>0-t</sub> = Area Under the Curve to the last quantifiable time point

CV% = percent relative standard deviation

**Table II.16. Bioequivalence Assessment, Excluding Cats That Vomited Within 2 Hours after Dosing (N=21\* for Test, N=24 for Reference)**

Pharmacokinetic parameters	Lower 90% confidence interval	Upper 90% confidence interval	Test to Reference Ratio	Intra-subject CV%
C <sub>max</sub> (ng/mL)	95.20	122.25	1.07	23.9
AUC <sub>0-t</sub> (ng*h/mL)	99.90	119.44	1.09	17.1

\* 3 cats were excluded due to vomiting within the 2 first hours after drug administration.

C<sub>max</sub> = maximum observed plasma concentration

AUC<sub>0-t</sub> = Area Under the Curve to the last quantifiable time point

CV% = percent relative standard deviation

**Adverse Reactions:** During the administration phase, vomiting was observed during the first two hours after administration for one cat in Period 1 and two cats in Period 2. Vomiting is a known adverse reaction after administration of the telmisartan 4 mg/mL oral solution. The other adverse reaction observed just after treatment was hypersalivation. These adverse reactions were classified as mild.

**Conclusions:** Although the a priori acceptance criteria for equivalence had been adjusted using the Relative Bioavailability Approach (RBA), the 90% confidence intervals met the traditional bioequivalence criteria of 80 - 125% for both C<sub>max</sub> and AUC<sub>0-t</sub>. Therefore, the 4 mg/mL and the 10 mg/mL formulations are considered bioequivalent.

### III. TARGET ANIMAL SAFETY

The safety of Semintra® (telmisartan oral solution) for the control of systemic hypertension in cats was demonstrated in a laboratory study (Study No. 6150-0337-06F-154) described below. During the 6 month study in healthy cats, there were no test article-related effects seen during cageside observations, physical examinations, veterinary examinations, and ophthalmology examinations. There were some renal

and red blood cell effects seen in clinical pathology and pathology parameters that are consistent with the known pharmacologic effects of administration of angiotensin receptor blockers in animals with normal blood pressures. There was greater systemic exposure of telmisartan in the female cats compared to the male cats. The difference in exposure did not present as a clinically detectable difference in effect in the safety study or in the field study.

The fed/fasted pharmacokinetic study (Study No. 6150-0337-07F-131) demonstrated that the systemic exposure to telmisartan was greater for fasted cats compared to fed cats. The laboratory safety study was conducted in fasted cats.

#### **A. Laboratory Margin of Safety Study**

**Title:** Six-Month Oral Target Animal Safety Study of Telmisartan in Cats. Study Number 6150-0337-06F-154.

**Study Dates:** May 2008 through November 2008

**Study Location:** Ashland, OH

##### **Study Design:**

**Objective:** The study objective was to evaluate the safety of telmisartan oral solution (4 mg/mL) when administered once daily to adult cats at 0, 1, 3, and 5 mg/kg body weight for 6 months. This study included an evaluation of plasma test article concentration. This laboratory safety study was conducted in accordance GLP regulations.

**Study Animals:** Thirty-two healthy cats (16 males, 16 females) were assigned to one of four treatment groups, with four males and four females in each group. Cats were approximately 9 - 13 months old, and weighed 4.1 - 5.6 kg for males and 2.3 - 3.8 kg for females at the start of the study.

**Experimental Design:** This was a masked, randomized, placebo controlled laboratory study. Thirty-two cats were randomly assigned to the treatment groups within weight block after stratification by sex (sex ratio of 1:1). Masking was maintained by separation of function. Persons performing masked observations or duties did not perform unmasked duties (dose administration). Masked observations and procedures included all clinical observations, ophthalmology examinations, collection and interpretation of clinical pathology samples, necropsy, and final pathology evaluation of dose related microscopic findings.

**Drug Administration:** Cats were dosed with saline or telmisartan by oral syringe after an overnight fast. Food was offered at least four hours after dosing. Individual doses were based on the most recent body weight.

**Table III.1: Treatment Group, Dosage, and Number of Animals**

<b>Group</b>	<b>Test or Control Article</b>	<b>Dosage (mg/kg)</b>	<b>Volume (mL)</b>	<b>Number and Gender of Animals</b>
1	Saline (control)	0	1.25	4 males, 4 females
2	Telmisartan	1	0.25	4 males, 4 females
3	Telmisartan	3	0.75	4 males, 4 females
4	Telmisartan	5	1.25	4 males, 4 females

Measurements and Observations: Evaluations included twice-daily cageside observations, physical examinations, veterinary examinations, ophthalmic examinations, indirect systolic blood pressure measurement, hematology, serum chemistry, urinalysis, coagulation, food consumption, body weight, telmisartan plasma concentration, necropsy, and histopathology. Masked personnel that did not have knowledge of treatment group assignment performed all observations, examinations, and collection of variables. See Table III.2 for the study schedule.

**Table III.2: Study Schedule**

<b>Observation or Measurement</b>	<b>Day or Week of Study</b>
Cageside Observation	Twice daily
Physical examination	Daily
Food consumption	Daily
Body weight	Weekly
Veterinary examination	Acclimation, weeks 0, 4, 8, 12, 16, 20, and 24
Ophthalmic examination	Acclimation, week 25
Blood pressure (indirect, systolic)	Acclimation, week 0, then every 2 weeks through week 24; Measured 4 - 8 hours post-dose
Telmisartan plasma concentration	Days 21 and 161 (weeks 2 and 23)
Clinical pathology: hematology, serum chemistry, urinalysis, coagulation	Acclimation, days 1, 8, 15, 28, and weeks 7, 12, 16, 20, and 25
Gross necropsy and histopathology	Days 182 and 183 (week 25)

**Statistical Methods:** Table III.3 lists the analysis endpoints for the study and their respective methods of analyses.

**Table III.3: Study Endpoints and Analysis**

<b>Analysis Endpoint</b>	<b>Statistical Analysis</b>
Bone Marrow Organ weights Absolute Relative to body wt. Relative to brain wt.	Analysis of Variance
Clinical pathology Serum chemistry Hematology Coagulation Urinalysis Body weight Food consumption Blood pressure	Repeated Measures of Analysis of Covariance  Profile plots

**Results:**

**Clinical Observations and Examinations:** All cats survived the study. There were no test article-related findings during cageside observations, physical examinations, veterinary examinations, and ophthalmology examinations.

Blood pressure was lower in the treated groups compared to the control group, starting at week 4 for Group 2, at week 2 for Group 3, and at week 0 (day 2) for Group 4. Mean blood pressure was statistically significantly lower than the control group in Group 2 at weeks 4, 12, 16, 20, 22, and 24 ( $0.0011 \leq p \leq 0.0849$ ); in Group 3 from weeks 4 through 24 ( $0.0001 < p \leq 0.0035$ ); and in Group 4 from weeks 4 through 24 ( $0.0001 < p \leq 0.0030$ ). The lower blood pressures in the treated groups persisted through study end. Decreased blood pressure is an expected pharmacologic effect of telmisartan, and was not associated with clinical abnormalities in this study.

**Food Consumption and Body Weight:** Compared to the control group, mean food consumption was significantly decreased in Group 3 at weeks 5, 8, 10, 16, 22, and 23 ( $0.013 \leq p \leq 0.0703$ ); and in Group 4 at weeks 5-7, 10, 14, 17, 19, 21, 23, and 25 ( $0.0144 \leq p \leq 0.0785$ ). However, there was no difference between the control and treated groups for body weight.

**Clinical Pathology:**

**Hematology**

Compared to the control group, the treated groups had lower red cell counts, lower hematocrit, lower hemoglobin, and lower absolute and percent reticulocytes. There were statistically significantly lower mean RBC counts for Group 2 compared to the control group at weeks 2, 12, 16, and 20 ( $0.0064 \leq p \leq 0.0369$ ); for Group 3 compared to the control group at weeks 2-25 ( $0.0001 < p \leq 0.0115$ ); and for Group 4 compared to the control group at weeks 2, 12, 16, 20, and 25 ( $0.0001 < p \leq 0.0241$ ). There were no clinical signs associated with the decreases in red cell count, hematocrit, and hemoglobin.

There was no clinically relevant difference between the control and treated groups for mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), white blood cells, or platelets.

#### Serum Chemistry

Blood Urea Nitrogen (BUN): When BUN data were grouped by sex, mean BUN was higher in the Group 3 and Group 4 females and Group 4 males compared to the control group during weeks 2-25. For the pooled male and female data, BUN was statistically significantly higher for Group 3 means at weeks 0, 12, and 16 ( $0.0753 \leq p \leq 0.0902$ ), and for Group 4 means at weeks 2, 4, 7, 12, 16, 20, and 25 ( $0.003 \leq p \leq 0.0701$ ), when compared to the control group. The elevated BUN was not associated with clinical signs.

There were no clinically relevant changes for albumin, alkaline phosphatase (ALP), amylase, bicarbonate, calcium, cholesterol, creatinine, total bilirubin, direct bilirubin, creatinine kinase, globulin, glucose, gamma glutamyl transferase (GGT), lactate dehydrogenase (LDH), LDH isoenzymes, phosphorous, potassium, sodium, total protein, and triglycerides in the treated groups when compared to the control group.

There were no clinically relevant effects on urinalysis and prothrombin time (PT) and activated partial thromboplastin time (APTT).

Although the statistical model did not include a test for a sex effect, the trend of female cats having test-article related effects more frequently than male cats may be associated with the difference in drug exposure between females and males. However, no adverse clinical signs were observed for either sex.

#### Pathology:

There was minimal gastric ulceration on necropsy of one Group 4 male cat. There were no other clinically relevant findings on gross necropsy in the control and treated groups.

Mean heart to brain weight ratio was statistically significantly decreased in Group 3 ( $p=0.0301$ ) and Group 4 ( $p=0.0057$ ) compared to the control group. There was no histologic evidence of myocyte damage.

The mean absolute kidney weight was statistically significantly decreased in Group 4 ( $p=0.0211$ ) compared to the control group. There was a treatment effect on kidney histopathology. Minimal to mild juxtaglomerular apparatus hypertrophy was present in two of four Group 2 males, one of four Group 3 males, all Group 4 males, and all Group 2, 3, and 4 females.

One Group 4 female cat had a mild generalized depletion of the hematopoietic cells in the bone marrow. In the Group 4 female cats, changes on bone marrow cytology considered possibly test-article related included reduced total erythroid percent (2/4), lower relative polyrubricyte count (3/4), lower basophilic rubricyte percent (1/4), lower erythroid maturation index (1/4), higher myeloid/erythroid ratio precursors (1/4), and minimal decreases in late erythroid precursors (2/4). The bone marrow histopathology and cytology findings are consistent with the decrease in the erythroid mass seen on clinical pathology. There were no clinical signs associated with this finding.

**Conclusions:** Telmisartan had an acceptable margin of safety when administered at 1, 3, or 5 mg/kg once daily in normal, normotensive cats for 6 months. The effects of telmisartan on hematology variables, BUN, blood pressure, heart weight, and the juxtaglomerular apparatus are consistent with the known pharmacologic effects of administration of angiotensin receptor blockers in normotensive animals. Elevation in BUN secondary to lower glomerular filtration rates is also a known effect of administration of an angiotensin receptor blockers to normotensive animals. The lower heart weight is thought to occur from decreased peripheral resistance that occurs secondary to vasodilation and decrease in blood pressure.

## **B. Pharmacokinetic Study**

**Title:** Effect of Prandial State on Pharmacokinetics of Telmisartan Solution in Cats Following Repeated Oral Administration, Study No. 6150-0337-07F-131.

**Study Dates:** October 2007 through December 2007

**Study Director and Location:** Las Cruces, NM

### **Study Design:**

**Objective:** To investigate the comparative pharmacokinetics of telmisartan oral solution, following repeated oral dosing, when administered once daily for five consecutive days to fed or fasted cats.

**Study Animals:** Twelve healthy cats (6 males and 6 females), approximately 7 months to 8 years of age, and weighed 3.8 - 5.5 kg.

**Experimental Design:** See Table II.17 below. The cats were randomly assigned to group A or B, and each group consisted of three males and three females. Cats were fed once daily at 24-hour intervals, and had access to fresh water. "Fed" cats were administered telmisartan approximately 45 minutes after food was offered (food was removed after 30 minutes, followed by dosing 15 minutes later). "Fasted" cats were fed approximately 4 hours after dosing, with the food removed approximately 0.5 hour later. The fasted interval prior to dosing for the latter group was thus approximately 19.5 hours. This study was conducted in accordance with GLP regulations.

**Drug Administration:** Telmisartan solution was dosed orally at 1 mg/kg once daily, and was administered on days 0-5 (Period 1) and days 44-49 (Period 2). Cats in Group A were fasted for Period 1 and fed for Period 2. Cats in Group B were fed for Period 1 and fasted for Period 2. Both groups had a 14-day washout interval between the dosing periods.

**Pharmacokinetic Assessments:** Blood samples were collected prior to dosing and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 4, 8, and 12 hours after dosing on Study Days 0, 5, 44, and 49. Blood samples were also collected prior to dosing and at 0.75 and 12 hours after dosing on Study Days 1 - 4 and 45 - 48.



**Table III.4: Study Design and Prandial State**

<b>Group</b>	<b>Period 1 Days 0 - 5</b>	<b>Period 2 Days 44 - 49</b>
A	fasted	fed
B	fed	fasted

**Results and Conclusions:** The study showed that mean peak drug concentrations after dosing occurred at 21 minutes for fasted cats and at 32 minutes for fed cats. The maximum plasma concentration ( $C_{max}$ ) and area under the time vs plasma concentration curve (AUC) were approximately 225% and 18% respectively, greater for fasted cats. While this study determined that systemic exposure is greater in fasted cats, the field studies support dosing with a small amount of food if necessary.

#### **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 Semintra® (telmisartan oral solution):

Not for human use. Keep out of reach of children.

Semintra® is an angiotensin II antagonist/angiotensin receptor blocker (ARB). Pregnant women should avoid contact with Semintra® because substances that act on the renin-angiotensin-aldosterone system (RAAS) such as angiotensin receptor blockers (ARBs) can cause fetal and neonatal morbidity and death during pregnancy in humans.

#### **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 Semintra®, when used according to the label, is safe and effective for control of systemic hypertension in cats.

##### **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 and monitor hypertension. Furthermore, professional expertise is required to monitor for and respond to adverse reactions.

##### **B. Exclusivity**

Semintra®, 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.