Date of Approval: December 29, 2016

FREEDOM OF INFORMATION SUMMARY

APPLICATION FOR CONDITIONAL APPROVAL

Application Number 141-475

TANOVEA™-CA1

rabacfosadine for injection

Powder for Injection

Dogs

TANOVEA™-CA1 is indicated for the treatment of lymphoma in dogs.

Sponsored by:

VetDC, Inc.

Table of Contents

I. GENERAL INFORMATION

A. File Number

Application Number 141-475

B. Sponsor

VetDC, Inc.
320 E. Vine Dr., suite 218
Fort Collins, CO 80524

Drug Labeler Code: 086072

C. Proprietary Name

TANOVEA™-CA1

D. Product Established Name

Rabacfosadine for injection

E. Pharmacological Category

Anti-neoplastic

F. Dosage Form

Powder for injection

G. Amount of Active Ingredient

16.4 mg rabacfosadine per vial

H. How Supplied

TANOVEA™-CA1 is supplied in a 3 mL amber Type I glass vial with rubber stopper, aluminum over-seal, and plastic flip-off cap, packaged in a carton. Each vial contains 16.4 mg of rabacfosadine, as succinate salt.

I. Dispensing Status

Rx

J. Dosage Regimen

Administer TANOVEA™-CA1 at 1 mg/kg body weight as a 30-minute intravenous infusion, once every three weeks, for up to five doses. Stepwise dose reductions to 0.8 mg/kg and 0.66 mg/kg or dose delays may be used to manage adverse reactions.

TANOVEA™-CA1 is supplied as a sterile lyophilized powder for reconstitution before use. After reconstitution with 2 mL 0.9% Sodium Chloride Injection, USP, the reconstituted solution contains 8.2 mg/mL of rabacfosadine.

K. Route of Administration

Intravenous Injection

L. Species/Class

Dogs

M. Indication

TANOVEA™-CA1 is indicated for the treatment of lymphoma in dogs.

II. EFFECTIVENESS

Conditional Dose: The conditional dose for the indication "for the treatment of lymphoma in dogs" is 1 mg/kg, once every three weeks, for up to five doses. The safety data and the data to demonstrate reasonable expectation of effectiveness provide support for this conditional use.

A. Dosage Characterization

The dose of TANOVEA™-CA1 (rabacfosadine for injection) administered intravenously at 1 mg/kg once every three weeks for up to five doses, with dose reductions to 0.8 mg/kg and 0.66 mg/kg or dose delays to manage adverse reactions, is based on two pilot studies and three toxicity studies.

The two pilot studies (PC-193-2001[1] and PC-193-2017) used to support reasonable expectation of effectiveness provided effectiveness and field safety information supporting dosage characterization. Refer to the Reasonable Expectation of Effectiveness section for more information.

The three toxicity studies (TX-193-2009, TX-193-2010, and TX-193-2015) used to support target animal safety provided information supporting dosage characterization. The label dosage of rabacfosadine was based on determining the highest non-severely toxic dose (HNSTD) in dogs. Refer to the Target Animal Safety section for more information.

B. Reasonable Expectation of Effectiveness

Reasonable expectation of effectiveness for the treatment of lymphoma in dogs is based on the results of two field studies (PC-193-2001 and PC-193-2017). During development, rabacfosadine was also referred to as GS-9219.

1. Pilot Study

   Title: Efficacy Evaluation of GS-9219 in Naturally Occurring Non-Hodgkin's Lymphoma and Leukemia in Dogs. (PC-193-2001)

Study Design: The study evaluated several dosage regimens of rabacfosadine (not commercial formulation) in treatment-naïve dogs with T- or B-cell canine lymphoma and in dogs with relapsed or refractory, T- or B-cell canine lymphoma. Fifty dogs with lymphoma were enrolled and received one of four dosing regimens and were observed for dose-limiting adverse events. Rabacfosadine was administered using a 30-minute intravenous infusion in 5% Dextrose Solution for Injection, USP (2 mL/kg body weight).

Variables Measured: Response to treatment was evaluated using Response Evaluation Criteria in Solid Tumors (RECIST).[2] The following criteria were used to assess response outcomes for individual patients:

- Complete response (CR): complete disappearance of all measurable lymphoma.
- Partial response (PR): a > 30% decrease in the sums of the longest diameters of measurable affected nodes.
- Stable disease (SD): a 30% decrease to 20% increase in the sums of the longest diameters of measurable affected nodes.
- Progressive disease (PD): a > 20% increase in the sums of the longest diameters of measurable affected nodes or newly arising lesions.

Progression free survival (PFS) duration: the time from first dose to the first observation of disease progression or death due to any cause.

Result(s): Seventeen dogs received rabacfosadine at a dose between 0.66 and 1.2 mg/kg by intravenous infusion once every three weeks.

Three dogs received rabacfosadine at a dose of 1.2 mg/kg body weight by intravenous infusion, once every three weeks, for one to four doses. A summary of the results in these dogs is presented in Table 1 below.

Table 1. Effectiveness results for dogs receiving 1.2 mg/kg of rabacfosadine once every three weeks.

Dog	Naïve or Relapsed/Refractory*	Doses	Best Response	PFS (days)
GS-1001B	Naïve	4	CR	370
GS-1002B	Relapsed/Refractory	1	PR	8**
GS-1003B	Naïve	1	PR	8

* Relapsed vs. refractory disease not stated.
** The dog was withdrawn from the study by the owner while still in remission.

Five dogs received rabacfosadine at a dose of 1.0 mg/kg body weight by intravenous infusion, once every three weeks, for one to five doses. A summary of the results in these dogs is presented in Table 2 below.

Table 2. Effectiveness results for dogs receiving 1.0 mg/kg of rabacfosadine once every three weeks.

Dog	Naïve or Relapsed/Refractory*	Doses	Best Response	PFS (days)
GS-1004B	Relapsed/Refractory	2	PR	35
GS-1005B	Relapsed/Refractory	1	PR	22
GS-1006B	Naïve	5	CR	179
GS-1008B	Naïve	1	CR	23
GS-1011B	Relapsed/Refractory	5	CR	119

* Relapsed vs. refractory disease not stated.

Six dogs received rabacfosadine at a dose of 0.82 mg/kg body weight by intravenous infusion, once every three weeks, for one to five doses. A summary of the results in these dogs is presented in Table 3 below.

Table 3. Effectiveness results for dogs receiving 0.82 mg/kg of rabacfosadine once every three weeks.

Dog	Naïve or Relapsed/Refractory*	Doses	Best Response	PFS (days)
UW017**	Naïve	5	CR	751
UW018	Relapsed/Refractory	1	PD	9
UW019	Naïve	5	CR	280
UW020	Naïve	2	PR	30***
UW023	Relapsed/Refractory	3	PR	50
GS-1012B	Relapsed/Refractory	1	PD	8

* Relapsed vs. refractory disease not stated.
** The dog was administered 0.82 mg/kg for doses 1, 3, 4, and 5; and 1.0 mg/kg for dose 2.
*** The dog was withdrawn by the owner while still in remission.

Three dogs received rabacfosadine at a dose of 0.66 mg/kg body weight by intravenous infusion once every three weeks for two to five doses. A summary of the results in these dogs is presented in Table 4 below.

Table 4. Effectiveness results for dogs receiving 0.66 mg/kg of rabacfosadine once every three weeks.

Dog	Naïve or Relapsed/Refractory*	Doses	Best Response	PFS (days)
UW012	Relapsed/Refractory	5	CR	170
UW013	Naïve	5	CR	134
GS-1013	Relapsed/Refractory	2	PR	48

* Relapsed vs. refractory disease not stated.

Ten dogs administered rabacfosadine at various dosing regimens that achieved response (9 dogs with CR and 1 dog with PR), and then experienced recurrence of lymphoma, were subsequently retreated with rabacfosadine at a dose of 0.82 mg/kg once every 3 weeks for one to five doses. During the retreatment following recurrence of lymphoma, 5 of the dogs experienced a best response of CR, 1 dog experienced a best response of PR, 2 dogs

experienced a best response of SD, and 2 dogs had a best response of PD. PFS in the 6 dogs with CR or PR during retreatment ranged from 43 to 99 days.

Safety: Adverse events were reported using Veterinary Cooperative Oncology Group – common terminology criteria, VCOG-CTCAE v1.1.[3] Adverse reactions associated with rabacfosadine treatment when administered once every three weeks included lethargy, dehydration, fever, hyporexia/anorexia, weight loss, vomiting, diarrhea, tachypnea, dyspnea, pulmonary fibrosis, aspiration pneumonia, neurologic signs, otitis externa, alopecia, dermatopathy, proteinuria, increased creatinine, elevated liver enzymes, elevated bilirubin, neutropenia, thrombocytopenia, anemia, hypertriglyceridemia, hypoglobulinemia, hypoalbuminemia, increased creatine kinase, hypokalemia, and hypophosphatemia.

Most adverse reactions were Grade 1-2. Grade 3 reactions included hyporexia/anorexia, weight loss, vomiting, diarrhea, dehydration, otitis externa, aspiration pneumonia, neutropenia, thrombocytopenia, anemia, and bilirubinemia. Grade 4 reactions included tachypnea and neutropenia. Grade 5 reactions included dyspnea (secondary to pulmonary fibrosis) resulting in a life-threatening or fatal outcome. With the exception of pulmonary fibrosis, adverse reactions resolved either spontaneously, with supportive treatment, or by dose modification.

Additional adverse reactions seen at the other dosing regimens (i.e., more frequent dosing) included pruritic and erythemic lesions on the dorsum; exudation, crusting, erythema, and necrosis with epidermal sloughing on the ears, face, ventral neck and/or forelimbs; glucosuria; and type II pneumocyte hyperplasia.

Pharmacokinetics: Plasma concentrations of rabacfosadine and its active metabolites were measured in 8 dogs with lymphoma. Rabacfosadine was rapidly eliminated from plasma with a half-life of <0.5 hours. The primary metabolite, 9-(2-phosphonylmethoxyethyl)-N6-cyclopropyl-2,6-diaminopurine (cPrPMEDAP), had a plasma half-life of 6 hours. The cytotoxic metabolite 9-(2-phosphonylmethoxyethyl) guanine (PMEG) was not detected in plasma samples but was detected in high levels in peripheral blood mononuclear cells (PBMCs) within 24 hours of dosing and persisted with subsequent dosing in a similar manner in all dosage groups. The PBMC concentrations in the group treated with doses of 0.82 mg/kg rabacfosadine once every two weeks or once every three weeks were 131 and 1,420 nM for cPrPMEDAP and PMEG, respectively (median values from five dogs). Following the final dose on Day 5 in dogs administered 0.21 mg/kg rabacfosadine daily for five days, PBMC concentrations were comparable to those observed in dogs administered one dose of 0.82 mg/kg rabacfosadine despite approximately 4-fold lower plasma AUC0-t (median PBMC concentrations in 6 dogs of 120 and 2025 nM for cPrPMEDAP and PMEG, respectively).

2. Pilot Study

Title: Randomized Trial of 3 Dose Regimens of GS-9219 in Dogs with Relapsed B-cell Non-Hodgkin's Lymphoma. (PC-193-2017)

Study Design: The study evaluated several dosage regimens of rabacfosadine (not commercial formulation) in dogs with relapsed, B-cell canine lymphoma. Fifteen dogs with lymphoma were enrolled and received one of three dosing regimens. Dogs were between 5 to 10 years old and weighed 5.6 to 65 kg. Ten male castrated and five female spayed dogs were enrolled.

Variables Measured: Response to treatment was evaluated using RESIST criteria.

Result(s): Five dogs were administered rabacfosadine intravenously at a dose of 1.0 mg/kg in a volume of 2 mL/kg in 0.9% Sodium Chloride Injection, USP, over 30 minutes, once every three weeks, for one to six doses. A summary of the results in these dogs is presented in Table 5 below.

Table 5. Effectiveness results for dogs receiving 1.0 mg/kg of rabacfosadine once every three weeks.

Dog	Doses	Best Response	PFS (days)
001	6	CR	449
002	6	CR	365
007	1	PD	14
012*	5	SD	92**
017	2	SD	44

* The dog was administered 1.0 mg/kg for doses 1 and 5, 0.8 mg/kg for doses 2 and 3, and 0.92 mg/kg for dose 4.
** Censored

Safety: Adverse events were reported using Veterinary Cooperative Oncology Group – common terminology criteria, VCOG-CTCAE v1.1. Adverse reactions associated with rabacfosadine treatment when administered once every three weeks included hyporexia/anorexia, vomiting, diarrhea, pulmonary fibrosis, aspiration pneumonia, tachycardia, injected sclera, dermatopathy, neutropenia, anemia, increased blood urea nitrogen, elevated liver enzymes, hypertriglyceridemia, hypoglobulinemia, proteinuria, pyuria, and bacteruria.

Most adverse reactions were Grade 1-2. Grade 3 reactions included vomiting, aspiration pneumonia, and hypertriglyceridemia. Adverse reactions resolved either spontaneously, with supportive treatment or by dose modification.

Additional adverse reactions seen at the other dosing regimens (i.e., more frequent dosing) included dehydration; weight loss; lethargy; polyuria; hematuria; glucosuria; otitis externa; pruritic and erythemic lesions on the dorsum; exudation, crusting, erythema, and necrosis with epidermal sloughing on the ears, face, ventral neck and/or forelimbs; type II pneumocyte hyperplasia in the lungs; thrombocytopenia; increased bilirubin; increased

creatine kinase; increased creatinine; hypomagnesemia; hypoalbuminemia; and hypoproteinemia.

Conclusions: The two field studies support a reasonable expectation of effectiveness for the use of TANOVEA™-CA1 (rabacfosadine for injection) administered intravenously at 1.0 mg/kg, once every three weeks, for up to five doses for the treatment of lymphoma in dogs.

III. TARGET ANIMAL SAFETY

A. Toxicity Study

Title: An Acute Intravenous Infusion Toxicity Study of GS-9219 in the Beagle Dog. (Study No. TX-193-2009)

Study Dates: June 2006 to March 2007

Study Location: Senneville, Quebec, Canada

Study Design:

Objective: The objective of the GLP study was to investigate the potential acute toxicity of rabacfosadine (not commercial formulation) following a single 30-minute intravenous infusion in the dog.

Study Animals: There were 6 male and 6 female Beagle dogs per treatment group. Dogs were 7 to 8 months old and weighed 5.7 to 10.9 kg at the start of treatment. All dogs were healthy based on physical examination and clinical pathology (hematology and serum chemistry).

Experimental Design: Thirty male and 30 female dogs were randomly assigned to five treatment groups of 12 dogs each (6 males and 6 females). Males and females were randomized separately. Three dogs/sex/group were necropsied on Day 3 (main study) and 3 dogs/sex/group were necropsied on Day 21 (recovery group). The study was unmasked.

Table 6: Control and Treatment Groups

Treatment Group	Dose (mg/kg)	Number and Sex of Dogs
1	Vehicle (5% Dextrose for Injection, USP)	6 males 6 females
2	0.25	6 males 6 females
3	0.82	6 males 6 females
4	2.5	6 males 6 females
5	8.2	6 males 6 females

Drug Administration: The test and control articles were administered by a 30-minute intravenous infusion on Day 1, into the saphenous or cephalic vein. The test article was added to 5% Dextrose for Injection, USP for the infusion. The dose volume was 2 mL/kg bodyweight.

Measurements and Observations: Mortality and signs of ill health or reaction to treatment were evaluated twice daily. Physical examinations were performed daily. Food consumption was measured daily. Body weight was measured weekly and prior to necropsy. Hematology was evaluated three times pretreatment and on Days 1, 2, 3, 6, 9, 12, 15, 18, and 21. Serum chemistry was evaluated once pretreatment and on Days 1, 3 (main study animals only), weekly during the observation period, and on Day 21. Gross necropsy and histopathology were performed on Day 3 (main study) and Day 21 (recovery group). Toxicokinetics were evaluated on Day 1.

Statistical Method(s): For variables measured more than once throughout the study, a repeated measures analysis of covariance was used with treatment, sex, day, treatment by sex, treatment by day, sex by day and treatment by sex by day terms as fixed effects. Pretreatment values were used as a covariate and remained in the model regardless of statistical significance. All tests were conducted at alpha=0.10, except for the test for the three-way interaction, which was conducted at alpha=0.05. No additional analysis was performed if the three-way interaction was significant. Pairwise comparisons of each treatment group against control group (within sex, within day or overall) were evaluated at alpha=0.10 to follow up on significant effects involving treatment. No adjustments were made for multiple comparisons.

Results:

Mortality
All main study dogs survived to scheduled euthanasia on Day 3. All recovery dogs administered 8.2 mg/kg were either found dead or preterminally euthanized due to poor and deteriorating condition on Days 6 or 7. All remaining recovery dogs survived to scheduled euthanasia on Day 21.

Clinical Observations
Between Days 4-7, dogs in the recovery groups administered 8.2 mg/kg were observed to have decreased activity, weakness, dehydration, abnormal feces, vomiting, fur staining, salivation, thinness, prominent backbone, eyes partially closed, cold to touch, thin fur, head shaking, tremors, hunched posture, lying on side, decreased respiration, fever, tachycardia, and dermatologic changes (dry skin, red skin, scabs).

Starting on Day 4, there was an increased frequency of abnormal feces in dogs in the recovery group administered 2.5 mg/kg. This observation resolved by Day 10. Sporadic abnormal feces were reported in all treatment groups, including the control group.

During the recovery period, vomiting was reported in one dog administered 0.82 mg/kg and two dogs administered 2.5 mg/kg; suspected dehydration was reported in one dog administered 0.82 mg/kg and two dogs administered 2.5

mg/kg; and thinness or prominent backbone was reported in one dog administered 0.82 mg/kg and two dogs administered 2.5 mg/kg.

In all groups, including control, there were dermatologic changes (fur loss, thin fur, dry skin, red skin, skin lesions, scabs) with a higher incidence in the dogs administered 2.5 mg/kg.

Body Weight
There was no treatment-related effect on body weight noted in the main study dogs euthanized on Day 3.

Male dogs in the recovery group administered 8.2 mg/kg lost 15-19% of their weight by Day 6 compared to Day -1 (female weights were not provided).

Dose-dependent weight loss was observed in dogs in the recovery groups administered 0.82 and 2.5 mg/kg and there was a trend towards weight recovery in these groups.

Food Consumption
Treatment-related decreases in food consumption were noted in dogs administered 2.5 and 8.2 mg/kg, starting on Day 2 to 3. By Day 8 or 9, dogs administered 2.5 mg/kg began consuming food amounts similar to pre-study; however, they were offered supplemental food from Day 7 or 8 until the end of the study. One dog administered 0.82 mg/kg was offered supplemental food from Day 11 until the end of the study; the dog had lower food intake on Days 7 and 8.

Hematology
There was a dose-dependent decrease in white blood cell (WBC) parameters in dogs administered 0.82, 2.5, and 8.2 mg/kg. The nadir for the leukopenia and monocytopenia was at Day 6. The nadir for the neutropenia, eosinopenia, and basopenia was between Day 6 and 9. Recovery of the WBC parameters was generally seen by Day 12.

For neutropenia the VCOG grade was Grade 1 in dogs administered 0.82 mg/kg; Grade 1 to 3 in dogs administered 2.5 mg/kg; and Grade 1 on Days 1 and 2 and Grade 4 on Day 6 in dogs administered 8.2 mg/kg.

Serum Chemistry
There were no serum chemistry findings attributable to the test article.

One dog in the recovery group administered 8.2 mg/kg had several abnormalities likely due to severe dehydration and gastrointestinal loss including increased creatinine, blood urea nitrogen, and phosphorus and decreased sodium and chloride.

Pathology
Main Study Day 3: Dose-related macroscopic and microscopic changes were noted in the gastrointestinal tract (stomach, small intestines, and large intestines) in all treatment groups administered the test article. Changes included minimal to slight single cell necrosis in the epithelium of the stomach and minimal to slight crypt necrosis was noted in the duodenum, jejunum, ileum, cecum, and colon.

Lymphoid atrophy and necrosis was noted in the thymus, spleen, mesenteric lymph node, and gut associated lymphoid tissue (GALT) in dogs administered 2.5 and 8.2 mg/kg.

Minimal to moderate bone marrow hematopoietic hypocellularity was observed in all dogs administered 8.2 mg/kg.

Minimal single cell necrosis of the acinar epithelium of the prostate was observed in all males administered 8.2 mg/kg.

Minimal increased mitotic figures/single cell necrosis in the adrenal cortex was observed in one dog administered 2.5 mg/kg and in one dog administered 8.2 mg/kg.

Minimal renal tubular vacuolation was observed in one dog administered 8.2 mg/kg, minimal basophilia of the kidney was observed in one dog administered 8.2 mg/kg, and minimal basophilia and fibrosis of the kidney was observed in one dog administered 2.5 mg/kg.

Recovery Group Day 21: Dose-dependent single cell necrosis of the epithelium, mucosal atrophy, and mucosal inflammation was observed in the glandular mucosa of the stomach and dose-dependent duodenal crypt dilatation and inflammation was observed.

Slight lymphoid atrophy/necrosis was noted in the thymus of one dog administered 0.25 mg/kg and one dog administered 2.5 mg/kg.

Dose-dependent tubular degeneration/necrosis of the kidney was characterized by nuclear karyomegaly, cytoplasmic basophilia, and occasional single cell necrosis. Tubular degeneration/necrosis was noted in the preterminally euthanized animals administered 8.2 mg/kg.

Conclusion: The administration of a single 30-minute intravenous infusion of rabacfosadine in dogs was tolerated at dose levels of 0, 0.25, 0.82, and 2.5 mg/kg. A single dose of rabacfosadine administered at 8.2 mg/kg resulted in mortality due to gastrointestinal toxicity and severe neutropenia. Treatment-related vomiting, dehydration, thinness, body weight loss, and decreased food consumption were observed at ≥ 0.82 mg/kg; and abnormal feces were observed at ≥ 2.5 mg/kg. Hematological changes included dose-dependent reductions in white blood cells that reached a nadir on Days 6 and 9 and were reversible by Day 12 for doses ≤ 2.5 mg/kg. Dermatologic changes were reported in all groups, including the control group with a higher incidence in the dogs administered 2.5 mg/kg. Pathology changes included dose-dependent effects on the gastrointestinal tract, lymphoid tissue, bone marrow, prostate, adrenal cortex, and kidney. Following a 21-day recovery period, the majority of the changes in the intestines and lymphoid tissues reversed. Dose-dependent renal tubular degeneration/necrosis was still observed.

B. Toxicity Study

Title: A 5-Day Intravenous Infusion Toxicity Study of GS-9219 (with a 21-Day Recovery Period) in the Beagle Dog. (Study No. TX-193-2010)

Study Dates: July 2006 to March 2007

Study Locations: Senneville, Quebec, Canada

Study Design:

Objective: The objective of the GLP study was to investigate the potential toxicity of rabacfosadine (not commercial formulation) following daily 30-minute IV infusions in the dog for 5 days and to assess the reversibility, persistence, or delayed occurrence of effects, if any, after a 21-day recovery period.

Study Animals: There were 6 male and 6 female Beagle dogs per treatment group. Dogs were 7 months old and weighed 5.7 to 9.7 kg at the start of treatment. All dogs were healthy based on physical examination, hematology, and chemistry.

Experimental Design: Twenty four male and 24 female dogs were randomly assigned to four treatment groups of 12 dogs each (6 males and 6 females). Males and females were randomized separately. Three dogs/sex/group were necropsied on Day 6 (main study) and 3 dogs/sex/group were necropsied on Day 27 (recovery group). The study was unmasked.

Table 7: Control and Treatment Groups

Treatment Group	Dose (mg/kg)	Number and Sex of Dogs
1	Vehicle (5% Dextrose for Injection, USP)	6 males 6 females
2	0.082	6 males 6 females
3	0.25	6 males 6 females
4	0.82	6 males 6 females

Drug Administration: The test/control articles were administered once a day by a 30 minute intravenous infusion on Days 1 through 5, into the saphenous or cephalic veins. The test article was added to 5% Dextrose for Injection, USP for the infusion. The dose volume was 2 mL/kg bodyweight.

Measurements and Observations: Mortality and signs of ill health or reaction to treatment were evaluated twice daily. Physical examinations were performed daily. Food consumption was measured daily. Body weight was measured weekly and prior to necropsy. Hematology was evaluated three times pretreatment and on Days 1, 2, 3, 6, 9, 12, 15, 18, 21, 24, and 27. Serum chemistry was evaluated once pretreatment and on Days 1, 6, 14, 21 and 27. Gross necropsy and

histopathology were performed on Day 6 (main study) and Day 27 (recovery group). Toxicokinetics were evaluated on Day 1 and 5.

Statistical Method(s): For variables measured more than once throughout the study, a repeated measures analysis of covariance was used with treatment, sex, day, treatment by sex, treatment by day, sex by day and treatment by sex by day terms as fixed effects. Pretreatment values were used as a covariate and remained in the model regardless of statistical significance. All tests were conducted at alpha=0.10, except for the test for the three-way interaction, which was conducted at alpha=0.05. No additional analysis was performed if the three-way interaction was significant. Pairwise comparisons of each treatment group against control group (within sex, within day or overall) were evaluated at alpha=0.10 to follow up on significant effects involving treatment. No adjustments were made for multiple comparisons.

Results:

Mortality
All dogs survived to scheduled euthanasia.

Clinical Observations
In the main and recovery groups, dogs administered 0.82 mg/kg had vomiting, abnormal feces (soft, liquid, green, red), and were observed as thin. During the recovery period, dogs administered 0.82 mg/kg also had decreased appetite, decreased activity, suspected dehydration, and fever. The vomiting was mainly reported between Days 5 and 11. Five dogs reported with suspected dehydration were administered Lactated Ringers Solution by subcutaneous injection on several days between Days 7 and 21.

One dog administered 0.082 mg/kg vomited on Day 20.

During the recovery period, one dog administered 0.082 mg/kg and one dog administered 0.25 mg/kg were observed as thin.

In all groups, including control, there were dermatologic changes (fur loss, thin fur, dry skin, red skin, skin lesions, scabs) with a higher incidence in the groups administered drug.

Body Weight
There was a dose-dependent effect on body weight loss in dogs administered 0.25 and 0.82 mg/kg. The largest amount of weight loss occurred between Days -1 and 7, followed by between Days 7 and 14. Most dogs started regaining weight by the end of the study; however, 4 of 6 dogs administered 0.25 mg/kg and 6 of 6 dogs administered 0.82 mg/kg weighed less at Day 27 compared to their Day -1 values.

Food Consumption
There was a dose-dependent decrease in food consumption in dogs administered 0.25 and 0.82 mg/kg starting on Day 2 to 3 and persisting through the end of the study. All dogs in the recovery group administered 0.82 mg/kg received supplemental food from Days 7 to 9 until the end of the recovery period. One dog

administered 0.25 mg/kg received supplemental food from Day 15 until the end of the recovery period.

Hematology
There was a dose-dependent decrease of all WBC parameters in dogs administered 0.082, 0.25, and 0.82 mg/kg. The nadir for leukocytes was between Day 6 and 9. The nadir for lymphocytes and monocytes was at Day 6. The nadir for neutrophils, eosinophils, and basophils was at Day 9. Recovery of the WBC parameters was generally seen by Day 12.

Neutropenia was observed in dogs administered 0.25 and 0.82 mg/kg. In dogs administered 0.25 mg/kg, all neutropenia was VCOG Grade 1. In dogs administered 0.82 mg/kg, VCOG Grade 1 and 2 neutropenia was observed at Day 6 and VCOG Grade 4 neutropenia was observed at Day 6 and 9.

Serum Chemistry
Treatment-related changes in electrolytes (decreased sodium and chloride and increased phosphorus and potassium were noted in dogs administered 0.082, 0.25, and 0.82 mg/kg.

Incidences of Grade 1 hypoalbuminemia were observed in dogs administered 0.82 mg/kg during the study.

Pathology
Main Study Day 6: Decreased organ weight changes (absolute, percent body weight) were present in the spleen in dogs administered 0.25 and 0.82 mg/kg and in the thymus in dogs administered 0.82 mg/kg. A small thymus was observed in one dog administered 0.25 mg/kg and two dogs administered 0.82 mg/kg.

Dose-dependent macroscopic observations of dark foci of discoloration were noted in the small and large intestines in dogs administered 0.25 and 0.82 mg/kg.

Dose-dependent microscopic changes were noted in the gastrointestinal tract. In the stomach, minimal single cell necrosis was observed. In the small and large intestines, varying degrees and combinations of mucosal hemorrhage, dilatation of mucosal glands/crypts, necrosis of crypt epithelial cells, atrophy of the mucosa/villi, and edema and inflammation of the intestinal wall were present in dogs administered 0.25 and 0.82 mg/kg.

Dose-dependent lymphoid atrophy and necrosis was observed in the thymus and spleen in all dogs administered the test article. Dose-dependent lymphoid atrophy and necrosis was observed in the mesenteric lymph node, mandibular lymph node, and GALT in dogs administered 0.25 and 0.82 mg/kg.

Dose-dependent minimal to slight hematopoietic hypocellularity was observed in the bone marrow in all groups administered the test article.

Minimal to moderate degeneration/atrophy of the testicular seminiferous epithelium was present in male dogs from the groups administered 0.25 and 0.82 mg/kg.

Recovery Group Day 27: Decreased organ weights (absolute, percent body weight) were present in the thymus in dogs administered 0.25 and 0.82 mg/kg.

The histopathological changes in the recovery groups were only partially reversed in all treatment groups at all dose levels. Following the 21-day recovery period, treatment-related microscopic findings were present in the gastrointestinal tract, thymus, bone marrow, testis, pancreas, salivary gland, and kidney.

Dose-dependent minimal to slight mucosal hemorrhage and glandular or cryptal dilatation in the small and large intestines were observed in dogs administered 0.25 and 0.82 mg/kg. Dose-dependent single cell necrosis, mucosal atrophy, and inflammation in the stomach were noted in dogs from all groups administered the test article.

Dose-dependent lymphoid atrophy/necrosis in the thymus was observed in dogs from all groups administered the test article.

Slight hematopoietic hypocellularity was observed in the bone marrow in dogs administered 0.82 mg/kg.

Dose-dependent minimal to moderate degeneration/atrophy of the testicular seminiferous epithelium was present in males in all groups administered the test article.

Dose-dependent acinar cell necrosis in the pancreas was observed in dogs administered 0.25 and 0.82 mg/kg.

Dose-dependent glandular cell necrosis, atrophy, and/or inflammation were observed in the mandibular salivary gland in all groups administered the test article.

Dose-dependent minimal to slight tubular changes were observed in the kidneys characterized by varying combinations of dilatation, increased cellular basophilia, tubular cell degeneration and necrosis of individual tubular epithelial cells were present in all groups administered the test article.

Conclusion: The administration of rabacfosadine once daily for 5 days by a 30-minute intravenous infusion was tolerated at dose levels of 0.082, 0.25, and 0.82 mg/kg; however, at 0.82 mg/kg therapeutic intervention was necessary. Body weight loss and decreased food consumption were observed at ≥ 0.25 mg/kg; and vomiting, abnormal feces, decreased appetite, decreased activity, suspected dehydration, and fever were observed at 0.82 mg/kg. Hematological changes included dose dependent reductions in white blood cells that reached a nadir on Days 6 and 9 and were reversible by Day 12. Dermatologic changes were reported in all groups, including the control group with a higher incidence in the groups administered drug. Pathology changes included dose-dependent effects on the gastrointestinal tract, lymphoid tissue, bone marrow, male reproductive system, pancreas, salivary gland, and kidney. Following a 21-day recovery period, microscopic findings were present in the gastrointestinal tract, salivary gland, kidney and testes in all treated dogs, in the pancreas and thymus in dogs administered ≥ 0.25 mg/kg and in the bone marrow in dogs administered 0.82

mg/kg. The microscopic changes following the recovery period were minimal to slight in dogs administered 0.082 and 0.25 mg/kg, except for the changes in the testes.

C. Toxicity Study

Title: A 3-Cycle Once Weekly Intravenous Infusion Toxicity Study of GS-9219 (with a 21-Day Recovery Period) in the Beagle Dog. (Study No. TX-193-2015)

Study Dates: August 2007 to May 2008

Study Location: Senneville, Quebec, Canada

Study Design:

Objective: The objective of the GLP study was to investigate the potential toxicity of rabacfosadine (not commercial formulation) following daily 30-minute intravenous infusion once every 7 days in the dog for 3 doses and to assess the reversibility, persistence, or delayed occurrence of effects, if any, after a 21-day recovery period.

Study Animals: There were 6 male and 6 female Beagle dogs per treatment group. Dogs were 7 months old and weighed 4.9 to 8.9 kg at the start of treatment. All dogs were healthy based on physical examination, hematology, chemistry, and urinalysis.

Experimental Design: Twenty-four male and 24 female dogs were randomly assigned to four treatment groups of 12 dogs each (6 males and 6 females). Males and females were randomized separately. Three dogs/sex/group were necropsied on Day 16 (Main Study) and 3 dogs/sex/group were necropsied on Day 36 (Recovery Group). The study was unmasked.

Table 8: Control and Treatment Groups

Treatment Group	Dose (mg/kg)	Number and Sex of Dogs
1	Vehicle (5% Dextrose for Injection, USP)	6 males 6 females
2	0.25	6 males 6 females
3	0.50	6 males 6 females
4	1.0	6 males 6 females

Drug Administration: The test/control articles were administered by a 30 minute intravenous infusion once every 7 days for 3 administrations (Days 1, 8, and 15), into the cephalic vein. The test article was added to 5% Dextrose for Injection, USP for the infusion. The dose volume was 2 mL/kg bodyweight.

Measurements and Observations: Mortality and signs of ill health or reaction to treatment were evaluated twice daily. Physical examinations were performed

daily. Food consumption was measured daily. Body weight was measured twice weekly and prior to necropsy. Hematology and serum chemistry were evaluated once pretreatment and on Days 7, 10, 16, 22, 29, and 36. Urine was evaluated once pretreatment and on Days 16, 22, and 36. Electrocardiography was evaluated once pretreatment and on Days 1 and 15 at 1 to 2 hours after infusion initiation and at the end of the recovery period. Ophthalmic examination was performed once pretreatment, once during the week following the last dose, and once during the last week of the recovery phase. Gross necropsy and histopathology were performed on Day 16 (main study) and Day 36 (recovery group). Toxicokinetics were evaluated on Day 1 and 15.

Statistical Method(s): For variables measured more than once throughout the study, a repeated measures analysis of covariance was used with treatment, sex, day, treatment by sex, treatment by day, sex by day and treatment by sex by day terms as fixed effects. Pretreatment values were used as a covariate and remained in the model regardless of statistical significance. All tests were conducted at alpha=0.10, except for the test for the three-way interaction, which was conducted at alpha=0.05. No additional analysis was performed if the three-way interaction was significant. Pairwise comparisons of each treatment group against control group (within sex, within day or overall) were evaluated at alpha=0.10 to follow up on significant effects involving treatment. No adjustments were made for multiple comparisons.

Results:

Mortality
All dogs survived to scheduled euthanasia.

Clinical Observations
Mainly starting after the second dose, one dog in the control group, two dogs administered 0.50 mg/kg, and three dogs administered 1.0 mg/kg were observed as thin.

In all groups, including control, there were dermatologic changes (fur loss, thin fur, dry skin, red skin, skin lesions, scabs) with a higher incidence in the groups administered drug.

Body Weight
Dogs administered 1.0 mg/kg had decreased body weight.

Food Consumption
Dogs administered 1.0 mg/kg had decreased food consumption.

Hematology
Leukopenia was reported in one dog administered 1.0 mg/kg. VCOG Grade 1 neutropenia was observed in one dog administered 0.25 mg/kg and four dogs administered 1.0 mg/kg. Dose-dependent eosinopenia was seen in dogs administered the test article. Recovery of the WBC parameters was seen by Day 29.

Serum Chemistry
There were no serum chemistry findings attributable to the test article.

Urinalysis
There were no urinalysis findings attributable to the test article.

Electrocardiography
There were no electrocardiography findings attributable to the test article.

Ophthalmic Examination
There were no ophthalmic examination findings attributable to the test article.

Pathology
Main Study Day 16: Decreased organ weights (absolute, percent body weight) were present in the testes in male dogs in all groups administered the test article and in the thymus in dogs administered 0.50 and 1.0 mg/kg.

Dose-related minimal to moderate glandular necrosis with or without inflammation was observed in the stomach and minimal to moderate cryptal necrosis was observed in the cecum and colon in dogs from all groups administered the test article. Minimal cryptal necrosis of the ileum was noted in dogs administered 0.50 and 1.0 mg/kg.

Dose-related minimal to moderate lymphoid atrophy/necrosis was noted in the lymph nodes and GALT in in dogs from all groups administered the test article. Minimal to slight lymphoid atrophy was observed in the thymus in dogs administered 0.50 and 1.0 mg/kg. Minimal lymphoid atrophy/necrosis of the spleen was observed in dogs administered 1.0 mg/kg.

Non-dose dependent minimal to slight acute glandular necrosis was observed in the salivary gland in dogs from all groups administered the test article.

Macroscopically, small testes and epididymides were reported in 2 of 3 males administered 1.0 mg/kg. Non-dose dependent minimal to marked degeneration/atrophy of the seminiferous epithelium was observed in the testes in in male dogs from all groups administered the test article.

Non-dose dependent minimal tubular degeneration/necrosis with evidence of karyomegaly was observed in the kidneys in dogs from all groups administered the test article. Minimal to slight tubular vacuolation was observed in dogs administered 1.0 mg/kg.

Moderate pleural fibrosis was observed in one dog administered 0.25 mg/kg. Minimal splenic fibrosis was observed in one dog administered 0.25 mg/kg.

Recovery Group Day 36: Decreased organ weights (absolute, percent body weight) were present in the testes in male dogs in all groups administered the test article and in the thymus in dogs administered 0.50 and 1.0 mg/kg on Day 36.

Non-dose dependent minimal to slight glandular necrosis of the stomach was observed in dogs from all groups administered the test article.

Minimal necrosis/atrophy in the lymphoid tissues was observed in one dog administered 0.50 mg/kg and two dogs administered 1.0 mg/kg. Dose-dependent minimal lymphoid atrophy in the thymus was observed in dogs administered 0.50 and 1.0 mg/kg.

Dose-dependent minimal to moderate necrosis in the salivary glands was observed in dogs from all groups administered the test article.

Macroscopically, small testes and epididymides were reported in males in all groups administered the test article. Non-dose dependent degeneration/atrophy of the seminiferous epithelium in the testes was observed in dogs administered the test article with a slight increase in severity compared to the main study dogs.

Dose-dependent tubular regeneration was observed in the kidneys of dogs administered the test article, characterized by minimal to moderate tubular basophilia, dilatation, and thinning of the tubular epithelium. Karyomegaly and minimal tubular degeneration/necrosis was also observed.

Minimal adrenal fibrosis was observed in one dog administered 1.0 mg/kg.

Conclusion: The administration of a 30-minute intravenous infusion of rabacfosadine in dogs at dose levels of 0, 0.25, 0.50 and 1.0 mg/kg once every 7 days for 3 treatments was tolerated at all dose levels. Treatment-related findings included decreased body weight and food consumption at 1.0 mg/kg. Hematological changes included mild neutropenia predominantly at 1.0 mg/kg. Dermatologic changes were reported in all groups, including the control group with a higher incidence in the groups administered drug. Pathology changes included dose-dependent effects on the gastrointestinal tract and lymphoid tissue, and non-dose dependent effects on the salivary gland, male reproductive tract, and kidney. Following a 21-day recovery period, there was partial reversibility of the pathology changes.

D. Cardiovascular Study

Title: A Pharmacological Assessment of the Effect of GS-9219 on the Cardiovascular System of the Beagle Dog Using Telemetry (Study No. TX-193-2013)

Study Dates: July 2006 to March 2007

Study Location: Senneville, Quebec, Canada

Study Design:

Objective: The GLP study evaluated the pharmacological effects of rabacfosadine (not commercial formulation) on hemodynamic and electrocardiographic (ECG) parameters following a 30-minute IV infusion (dose volume of 2 mL/kg) in the Beagle dog via telemetry.

Study Animals: There were 4 male Beagle dogs implanted with telemetry devices. Dogs were 7 to 8 months old and weighed 11.5 to 12.4 kg at the start of treatment. All dogs were healthy based on physical examination, hematology, and chemistry.

Experimental Design: The 4 dogs received vehicle (dose 1), 0.3 (dose 2), and 3 mg/kg (dose 3) of rabacfosadine with a minimum washout period of 3 days and 7 days between dose 1 and 2, and dose 2 and 3, respectively.

Drug Administration: The test/control articles were administered by a 30-minute intravenous infusion. The dose volume was 2 mL/kg. Dextrose 5% for Injection, USP was used for the infusion.

Measurements and Observations: Mortality and signs of ill health or reaction to treatment was evaluated twice daily. Body weights were measured prior to randomization and on the day prior to dosing. Clinical observations were performed once pretreatment and following each dosing occasion. The following were evaluated: clinical signs, arterial blood pressures (mean arterial pressure, systolic blood pressure, diastolic blood pressure and pulse pressure), heart rate, quantitative ECG intervals, and a qualitative evaluation of the ECG waveforms were performed twice prior to each dose (at least 30 minutes apart) and at approximately 15, 30, 45 minutes and 1, 1.5, 2, 4, 6, 8, 10, 12, 24 hours post-dose for each dose level. On all dosing occasions the blood pressure and ECG waveforms were recorded continuously and all derived parameters logged as 5-minute means from approximately 2 hours prior to each dose to approximately 24 hours postdose.

Statistical Method(s): The results were presented using summary statistics (treatment mean and standard error of the mean (SEM)) for each variable. Either baseline-adjusted values or absolute values were computed for each time interval.

Results:

Mortality
All dogs survived to scheduled euthanasia.

Cardiovascular Parameters
There were no treatment-related effects on arterial blood pressure (mean, systolic, diastolic), heart rate, or ECG parameters.

Conclusion: At single intravenous doses of 0.25 and 2.5 mg/kg, rabacfosadine had no effect on the cardiovascular system.

E. Pilot Studies

Study Summary
In two multi-institutional field studies (PC-193-20011 and PC-193-2017) used to support reasonable expectation of effectiveness for the treatment of lymphoma (see **Reasonable Expectation of Effectiveness**), 22 dogs with untreated, relapsed, or refractory lymphoma received rabacfosadine (not commercial

formulation) as an intravenous infusion at doses of 0.66 to 1.2 mg/kg body weight administered once every three weeks for one to six doses.

Adverse Reactions
All dogs experienced at least one adverse reaction, however not all adverse reactions were seen in each dog. Adverse reactions associated with rabacfosadine when administered once every three weeks included:

General: lethargy, dehydration, fever

Gastrointestinal: hyporexia/anorexia, vomiting, diarrhea

Renal: increased creatinine, increased blood urea nitrogen, proteinuria, pyuria, bacteruria

Hepatic: elevated liver enzymes, elevated bilirubin

Cardiorespiratory: pulmonary fibrosis, aspiration pneumonia, tachypnea, dyspnea, tachycardia

Metabolic: weight loss

Hematologic: neutropenia, thrombocytopenia, anemia, hypertriglyceridemia, hypoproteinemia, hypoglobulinemia, hypoalbuminemia, increased creatine kinase, hypokalemia, hypophosphatemia

Ocular: injected sclera

Dermatologic: otitis externa, alopecia, dermatitis, pyoderma, ulcerations, excoriations

Most adverse reactions were VCOG Grade 1-2. Grade 3 reactions included hyporexia/anorexia, weight loss, vomiting, diarrhea, otitis externa, dehydration, aspiration pneumonia, neutropenia, thrombocytopenia, anemia, bilirubinemia, and hypertriglyceridemia. Grade 4 reactions included tachypnea, and neutropenia. Grade 5 reactions included dyspnea (secondary to pulmonary fibrosis).

Additional adverse reactions seen in dogs administered rabacfosadine at more frequent dosing schedules include:

- Dermatopathy including pruritic and erythemic lesions on the dorsum and exudation, crusting, erythema, and necrosis with epidermal sloughing on the ears, face, ventral neck and/or forelimbs.
- Glucosuria
- Type II pneumocyte hyperplasia

Conclusion
Rabacfosadine had a narrow margin of safety in the pilot effectiveness studies. Adverse reactions were common but manageable by monitoring patients regularly. With the exception of pulmonary fibrosis, adverse reactions resolved either spontaneously, or with supportive treatment, dose modification, or dose delay.

Overall Conclusion on Safety:

Rabacfosadine has a narrow margin of safety. The above studies support the safe use of rabacfosadine administered at a dose of 1.0 mg/kg as a 30-minute intravenous infusion, once every three weeks, for up to five doses for the treatment of lymphoma in dogs. Stepwise dose reductions to 0.8 mg/kg and 0.66 mg/kg or dose delays may be used to manage adverse reactions.

IV. HUMAN FOOD SAFETY

This drug is intended for use in dogs. 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

Based on excretion data and an extrapolation of the data for exposure, a 5-day human user safety precautionary period is recommended following treatment with TANOVEA™-CA1. The excretion data from study AD-193-2001 entitled "Distribution and Excretion of [^{14}C]-GS-9219 Following Intravenous Administration to Dogs" demonstrated that the majority of the radioactivity following a radiolabeled dose (76.5%) of [^{14}C]-GS-9219 was excreted in feces (41.4%), urine (31.5%), and cage rinse (3.83%) within first 48 hours post-administration. An additional 3.2% radioactivity was excreted by 120 hours post-administration. The radioactivity recovery was not complete. The collected urine and feces samples contained little parent drug and no active metabolite.

Assuming the excretion of the remaining radioactive dose is approximately 2% during each 24 hour period post 48 hours dose-administration, the extrapolated 90% recovery time for the full dose administered would be approximately 10 days. TANOVEA™-CA1 is not orally bioavailable. The accidental exposure to the full amount excreted over a 24-hour period would be a worst-case scenario. Exposure to the full 2% would require that the exposed person would come into contact with all excretions for a full 24-hour period and that these excretions would be introduced systemically. Therefore, the potential risk for human drug exposure with the 2% excretion per 24-hour period is minimal and a 5-day precautionary period is recommended.

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to TANOVEA™-CA1:

NOT FOR USE IN HUMANS. KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

Wear chemotherapy resistant gloves to prevent contact with feces, urine, vomit and saliva of treated dogs for 5 days following treatment. Place all waste materials in a plastic bag and seal before general disposal. Rabacfosadine is cytotoxic and can cause birth defects and affect female and male fertility. Pregnant and breast feeding women should not prepare or administer the product.

Special instructions for preparing and administering the product:

TANOVEA™-CA1 should be administered under the supervision of a veterinarian experienced in the use of cancer chemotherapeutic agents.

Use standard measures for the safe handling of cytotoxic drugs
- Wear chemotherapy resistant gloves, goggles and protective clothing
- Do not eat, drink or smoke while handling the product
- Do not store food in or near the preparation area

Accidental skin contact

- In case of accidental contact with the skin, wash the affected area immediately and thoroughly with soap and water

Accidental eye exposure

- Remove contact lenses
- Rinse the eyes with large amounts of tap water (use eyewash station if present) for at least 10 minutes while holding back the eyelid
- Seek medical advice immediately and show the package insert or label to the physician

Accidental self-injection

- Remove glove
- Let the wound bleed a few drops of blood
- Rinse the wound thoroughly with plenty of tap water
- Seek medical advice immediately and show the package insert or label to the physician

On the Client Information Sheet:

The following handling procedures will help minimize exposure to the active ingredient in TANOVEA™-CA1 for you and other members of your household:

- Cleaning up after your pet:
  - Avoid direct contact with urine, stool, vomit, and saliva for **5 days** after your dog is treated with TANOVEA™-CA1.
  - When cleaning up urine, stool, vomit, or saliva you should wear disposable chemotherapy resistant gloves and collect the contaminated material with disposable absorptive material (such as paper towels) and place them into a plastic bag. Carefully remove the gloves and place them in the bag and tie or fasten it securely for general household disposal. Wash your hands thoroughly afterwards. Check with your veterinarian to ensure you have the appropriate gloves.
  - You should not wash any items soiled with urine, stool, vomit, or saliva from your dog with other laundry.
  - Do not let your dog urinate or defecate in areas where people may come in direct contact with the urine or stool.

- Because TANOVEA™-CA1 may be present in the dog's saliva for **5 days** after treatment, take precautions in handling the dog's toys, food bowl, and water bowl. Wash food and water bowls separately from other items.

VI. AGENCY CONCLUSIONS

The data submitted in support of this application satisfy the requirements of section 571(b) of the Federal Food, Drug, and Cosmetic Act (FD&C Act). The data demonstrate that TANOVEA™-CA1, when used according to the label, is safe and has a reasonable expectation of effectiveness for the treatment of lymphoma in dogs.

A. Marketing Status

TANOVEA™-CA1 is conditionally approved for one year from the date of approval and is annually renewable for up to four additional one-year terms.

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 lymphoma, and to monitor safe use of the product, including treatment of any adverse reactions.

B. Exclusivity

TANOVEA™-CA1, as conditionally approved in our conditional approval letter, qualifies for SEVEN years exclusive marketing rights beginning as of the date of our approval letter. This drug qualifies for exclusive marketing rights under section 573(c) of the FD&C Act because it is a designated new animal drug under section 573(a) of the act. Except as provided in section 573(c)(2) of the act, we may not approve or conditionally approve another application submitted for such new animal drug with the same intended use as TANOVEA™-CA1. Exclusive marketing rights begin as of the date of our conditional approval letter.

C. Patent Information:

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

REFERENCES:

1. Vail DM, Thamm DH, Reiser H, Ray AS, Wolfgang GHI, Watkins WJ, Babusis D, Henne IN, Hawkins MJ, Kurzman ID, Jeraj R, Vanderhoek M, Plaza S. Assessment of GS-9219 in a pet dog model of non-Hodgkin's lymphoma. *Clin Cancer Res.* 2009 May 15;15(10):3503-10.
2. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, Van Oosterom AT, Christian MC, Gwyther SG. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst.* 2000; 92:205-16.

3. Veterinary Cooperative Oncology Group – common terminology criteria for adverse events (VCOG-CTCAE) following chemotherapy or biologic antineoplastic therapy in dogs and cats v1.0. *Vet Comp Oncol.* 2004; 2(4):194–213.