Date of Approval: December 21, 2021

FREEDOM OF INFORMATION SUMMARY

APPLICATION FOR CONDITIONAL APPROVAL

Application Number 141-552

CANALEVIA™-CA1

crofelemer delayed-release tablets

Dogs

CANALEVIA™-CA1 is indicated for the treatment of chemotherapy-induced diarrhea in dogs.

Sponsored by:

Jaguar Animal Health

Executive Summary

CANALEVIA™-CA1 (crofelemer delayed-release tablets) is conditionally approved for the treatment of chemotherapy-induced diarrhea in dogs. The mechanism of action of crofelemer in dogs is not fully characterized. However, the drug is approved for use in people to treat non-infectious diarrhea in adults with HIV/AIDS who take anti-retroviral therapy. In people, two types of chloride channels regulate the secretion of chloride ions and water by intestinal epithelial cells: (1) cyclic adenosine monophosphate-stimulated cystic fibrosis transmembrane conductance regulator chloride channels; and (2) calcium-activated chloride channels. Crofelemer acts by inhibiting both types of channels at the luminal membrane of intestinal epithelial cells, thereby blocking the secretion of chloride ions and the accompanying high volume water loss seen in diarrhea. The result is that the flow of chloride ions and water into the gastrointestinal (GI) tract is normalized.

CANALEVIA™-CA1 is labeled for a total daily dose of 250 mg for dogs weighing up to 140 pounds (up to 63.6 kg) and 500 mg for dogs weighing more than 140 pounds (more than 63.6 kg).

Based on a minor use assessment, FDA estimated the rate of occurrence of chemotherapy-induced diarrhea in dogs in the United States (U.S.) to be below the published "small number" of 70,000 dogs (New Animal Drugs for Minor Use and Minor Species, 21 CFR § 516.3, 2009) on an annual basis. Therefore, the use of CANALEVIA™-CA1 for the treatment of chemotherapy-induced diarrhea in dogs in the U.S. constitutes a minor use in a major species. Drugs intended for minor uses are eligible for conditional approval.

A conditionally approved animal drug has been shown to be safe and has a reasonable expectation of effectiveness. During the conditional approval period, the sponsor can legally market the drug for the labeled use while making active progress toward demonstration of substantial evidence of effectiveness. The conditional approval is valid for one year. The sponsor can ask FDA to renew the conditional approval annually for up to four more years, for a total of five years of conditional approval. To receive a renewal from FDA, the sponsor must show active progress toward proving substantial evidence of effectiveness for full approval.

Proprietary Name	Established Name	Application Type and Number	Sponsor
CANALEVIA™-CA1	crofelemer delayed-release tablets	Conditional Approval Application Application Number 141-552	Jaguar Animal Health

Safety and Reasonable Expectation of Effectiveness

The sponsor conducted a pilot clinical field effectiveness study in shelter-housed and client-owned dogs with general acute diarrhea. Enrolled dogs were between 2 months and 12 years of age with fecal scores of 4 (watery, liquid stool with little particulate matter visible) or 5 (severe watery stool with no particulate matter visible). Dogs in the treated group received packets of enteric-coated beads containing crofelemer (not the commercial formulation of CANALEVIA™-CA1), and

dogs in the control group received packets containing enteric-coated beads without crofelemer.

The effectiveness analysis included 24 dogs (12 treated and 12 control). A dog was considered a treatment success if its diarrhea resolved and didn't recur during the 3-day study. Resolution of diarrhea was defined as a fecal score of 1 (well-formed stool) or 2 (soft or very soft, moist stool that doesn't have a clear shape). On Day 3, 9 out of 12 dogs (75%) in the treated group were treatment successes compared to 3 out of 12 dogs (25%) in the control group. Additionally, diarrhea had resolved by 48 hours in 4 of the 12 dogs (33%) in the treated group compared to none of the dogs in the control group. Dogs in both groups had similar adverse reactions, such as decreased appetite, depressed attitude, and decreased activity level, which are also commonly seen in dogs with general acute diarrhea. The frequency of observed adverse reactions was similar between treated and control groups.

The pilot study enrolled dogs with general acute diarrhea, not chemotherapy-induced diarrhea. However, both types include secretory diarrhea, and therefore, the pathophysiology is sufficiently similar that the results of the pilot study can be extrapolated to support a reasonable expectation of effectiveness of crofelemer to treat chemotherapy-induced diarrhea in dogs.

The sponsor conducted four laboratory safety studies in healthy Beagle puppies and dogs: (1) a 9-day target animal safety study, (2) a 9-month target animal safety study, (3) a 30-day target animal safety study, and (4) a cardiovascular study. The 9-day study used the commercial formulation of CANALEVIA™-CA1 and was the pivotal target animal safety study used to support the drug's safety in dogs. The 9-month, 30-day, and cardiovascular studies did not use the commercial formulation of CANALEVIA™-CA1. These three studies provided relevant information about the safety of crofelemer in dogs and were also used to support the drug's approval for use in people.

The total daily dose of crofelemer used in the four laboratory safety studies ranged from 0 mg/kg to 600 mg/kg. In all four studies, crofelemer caused GI side effects, including abnormal feces, vomiting, decreased food consumption, and decreased weight gain. At the end of the three target animal safety studies, the dogs were necropsied and had irritation, discoloration, and congestion of their GI tract. In general, the GI effects were dose-dependent, with a higher incidence seen at higher doses. Clinical pathology findings included decreases in serum albumin, total protein, cholesterol, calcium, and sodium and an increase in potassium in dogs that received 600 mg/kg/day of crofelemer. Similar clinical pathology changes were seen in dogs that received 175 mg/kg/day of crofelemer but to a lesser extent. Dogs that received 600 mg/kg/day of crofelemer had a microcytic, hypochromic anemia with mild (inadequate) regeneration and thrombocytosis. The cardiovascular study showed no crofelemer-related effects on cardiovascular parameters.

The sponsor conducted three pilot clinical studies in shelter-housed and client-owned dogs which provided relevant field safety information to support the safety of crofelemer in dogs. Dogs were between 2 months and almost 16 years of age and had either general acute diarrhea or chemotherapy-induced diarrhea. Dogs that had chemotherapy-induced diarrhea were older (age range was 7 to 12 years). Two of the pilot studies used the commercial formulation of CANALEVIA™-CA1; the other one did

not. The adverse reactions seen in dogs in the pilot studies were similar to those reported in the laboratory safety studies.

The safety studies described above (three laboratory target animal safety studies, one laboratory cardiovascular study, and three pilot field studies) support the safe use of CANALEVIA™-CA1 in dogs.

Conclusions
Based on the data submitted by the sponsor for the approval of CANALEVIA™-CA1, FDA determined that the drug is safe and has a reasonable expectation of effectiveness when used according to the label.

Table of Contents

I. GENERAL INFORMATION

A. File Number

Application Number 141-552

B. Sponsor

Jaguar Animal Health
200 Pine St.
suite 600
San Francisco, CA 94104

Drug Labeler Code: 086149

C. Proprietary Name

CANALEVIA™-CA1

D. Drug Product Established Name

Crofelemer delayed-release tablets

E. Pharmacological Category

Antidiarrheal

F. Dosage Form

Delayed-release tablet

G. Amount of Active Ingredient

125 mg of crofelemer per tablet

H. How Supplied

White, unscored enteric-coated tablets containing 125 mg of crofelemer packaged in bottles containing 60 tablets.

I. Dispensing Status

Prescription (Rx)

J. Dosage Regimen

Administer 1 tablet orally twice daily for 3 days for dogs weighing ≤ 140 pounds. Administer 2 tablets orally twice daily for 3 days for dogs weighing > 140 pounds. Tablets should not be broken, crushed, or chewed. If the tablet is chewed, one additional dose may be administered. Give with or without food.

K. Route of Administration

Oral

L. Species/Class

Dogs

M. Indication

CANALEVIA™-CA1 is indicated for the treatment of chemotherapy-induced diarrhea in dogs.

II. EFFECTIVENESS

The conditional dose and reasonable expectation of effectiveness for CANALEVIA™-CA1 for the treatment of chemotherapy-induced diarrhea in dogs is supported by clinical effectiveness data obtained from a pilot study in dogs with diarrhea that were administered crofelemer (not commercial formulation) orally twice a day for 3 days. Although the pilot study enrolled dogs with general acute diarrhea, based upon the current understanding of the pathophysiology of chemotherapy-induced diarrhea, the results can reasonably be extrapolated to support a reasonable expectation of effectiveness for crofelemer for the treatment of chemotherapy-induced diarrhea in dogs. In addition, crofelemer is approved for use in humans for symptomatic relief of non-infectious diarrhea in adult patients with HIV/AIDS on antiretroviral therapy.

A. Dosage Characterization

The dose of CANALEVIA™-CA1 (crofelemer delayed-release tablets) administered orally every 12 hours for six doses is based on a pilot study (CANA-001a, see Reasonable Expectation of Effectiveness). The formulation used in the study was not the commercial formulation. The dose range of 1.9 to 12.9 mg/kg administered during the pilot study correlates to the dose of one 125 mg tablet for dogs weighing less than 140 pounds.

B. Reasonable Expectation of Effectiveness

1. Pilot Study

Title: A Randomized, Blinded, Controlled Study to Assess the Clinical Efficacy of SP-303 (crofelemer) in Alleviating Clinical Signs Associated with Secretory Diarrhea in Dogs. (Study No. CANA-001a)

Study Dates: November 2014 to June 2017

Study Locations:

Albuquerque, NM	Las Cruces, NM
Austin, TX	Media, PA
Belgrade, MT	Middletown, CT
Boulder, CO	Norristown, PA
Burlingame, CA	North Haven, CT
Greenwich, RI	Reno, NV
Jacksonville, FL	Washington, NY
Largo, FL	Woolwich Township, NJ

Study Design:

Objective: To assess the clinical effectiveness of crofelemer administered orally in alleviating clinical signs of diarrhea in dogs and to identify the optimum endpoint to define effectiveness in future proposed clinical field studies.

Study Animals: The study was conducted in shelter-housed (n = 53) and client-owned (n = 8) dogs with diarrhea. Dogs between the age of two months and 12 years with a fecal score of 4 or 5 (see fecal score below) were included. Dogs were allowed to be fed prescription diets and receive concomitant medications such as non-steroidal anti-inflammatory drugs, antibiotics, and antiemetics.

Experimental Design: A randomized, masked, vehicle controlled, multicenter pilot clinical field study conducted in dogs with diarrhea.

Drug Administration: Crofelemer was administered to 29 dogs at a dose range of 1.9 to 12.9 mg/kg orally every 12 hours for three days. Crofelemer was administered as packets containing enteric-coated beads containing 40 mg of the active ingredient. The vehicle control was administered to 32 dogs as packets containing enteric-coated beads without the active ingredient.

Inclusion Criteria:
- Fecal score of 4 or 5 (watery or liquid stools with little or no particulate matter; see fecal score below)
- Male or female; intact or sterilized
- Between 2 months of age and 12 years of age
- Weight between 2 and 40 kg
- Any breed or mix

Exclusion Criteria:
- Dogs with other medical conditions which in the opinion of the investigator would preclude them from being enrolled into the study
- Dogs with a fecal test result positive for helminths, coccidia, or giardia
- Fecal score of 3 or below (milder diarrhea; see fecal score below)
- Dogs with bloody diarrhea and/or a suspicion of parvovirus
- Dogs who have been treated with any prohibited medications within seven days of enrollment (metronidazole, albendazole, probiotics, aminopentamide, and sulfadimethoxine)

Measurements and Observations: Baseline physical examination, hematology, chemistry, fecal examination, and fecal score were obtained. Fecal scores were obtained every four hours during the three-day treatment period. Fecal scores were based on a modified version of the Purina Fecal Scoring System[1].

Fecal Score:
1. Well-formed stools with slightly moist surface which leaves marks when picked up
2. Soft or very soft, moist, amorphous
3. Viscous liquid with some particulate matter
4. Watery, liquid stools with little particulate matter visible

5. Severe watery diarrhea, no particulate matter visible
6. Hemorrhagic diarrhea

Daily assessments included body temperature; fecal scores; and a scored assessment of general attitude, hydration status, appetite, and reaction to abdominal palpation. The scores were:

Attitude:
0. Normal
1. Slightly depressed
2. Moderately depressed
3. Severely depressed, not responsive to stimuli

Hydration:
0. Normal
1. Mild dehydration
2. Moderate dehydration; requires subcutaneous fluids
3. Severe dehydration; requires intravenous fluids

Appetite:
0. Ate all
1. Ate most
2. Ate little
3. Did not eat

Abdominal Palpation:
0. Normal/benign
1. Slight pain (acts uncomfortable)
2. Moderate pain (vocalizes or resists palpation)
3. Severe pain (does not tolerate palpation)

Statistical Method: The resolution of diarrhea was considered treatment success and was defined as a fecal score of 1 or 2. After a dog achieved resolution of diarrhea during the three-day study, subsequent fecal scores had to be maintained as a 1 or 2 in order to be considered a treatment success. The proportion of resolution of diarrhea and the corresponding 95% confidence interval (Clopper-Pearson) was calculated. Fisher's exact test was conducted to compare whether the proportion between the crofelemer group and vehicle control group were equal.

Results: Thirty-seven dogs were excluded from the effectiveness analysis because they had a medical condition precluding enrollment; a fecal test result positive for helminths, coccidia, or giardia; a fecal score of 3 or below; bloody diarrhea or parvovirus; or treatment with albendazole, fenbendazole, metronidazole, probiotics, aminopentamide, pyrantel, ponazuril, or sulfadimethoxine in the 7 days prior to screening or during the study. The remaining 24 dogs consisted of 12 dogs who received crofelemer and 12 dogs who received vehicle control.

The overall proportion of cases achieving resolution (success) are 75% and 25% for the crofelemer group and the vehicle control group, respectively.

There is a potential difference between treatments (P = 0.04). The results and the corresponding 95% confidence interval (Clopper-Pearson) are shown as follows in Table II.1.

Table II.1. Overall Proportion of Dogs Achieving Resolution of Diarrhea per Treatment Group and Corresponding Confidence Interval

Group	Crofelemer	Vehicle Control
Success Rate	9/12 (75%)	3/12 (25%)
95% Confidence Interval	42.8, 94.5	5.5, 57.2

Resolution of diarrhea was evaluated for each dog per 24 hour treatment block where hour 0 was defined as the time of the first dose administration. See Table II.2 below for results of resolution per 24 hour treatment block.

Table II.2. Number of Dogs Achieving Resolution of Diarrhea per 24 Hour Treatment Block

Treatment block	Crofelemer N = 12	Vehicle Control N = 12
≤ 24 hours	2 (17%)	0 (0%)
> 24 hours and ≤ 48 hours	2 (17%)	0 (0%)
> 48 hours and ≤ 72 hours	5 (42%)	3 (25%)

Adverse Reactions: All dogs were included in the safety evaluation for the study. Dogs who had vomiting or had abnormal scores for general attitude, activity, hydration status, appetite, or reaction to abdominal palpation are summarized in Table II.3.

Table II.3. Adverse Reactions in Study CANA-001a

Adverse Reactions[1]	Crofelemer N = 29	Vehicle Control N = 32
Appetite decreased	7 (24%)	9 (28%)
Attitude depressed	5 (17%)	5 (16%)
Activity decreased	4 (14%)	4 (13%)
Dehydration[2]	4 (14%)	5 (16%)
Abdominal palpation indicated pain[3]	3 (10%)	5 (16%)
Vomiting	1 (3%)	2 (6%)

[1]Dogs may have experienced more than one occurrence and more than one type of abnormal assessment during the study
[2]Two crofelemer treated dogs and one vehicle control dog were administered fluid therapy
[3]One of these vehicle control dogs was reported to not allow abdominal palpation at one timepoint on Day 2

Conclusion: The study results support a reasonable expectation of effectiveness for the use of CANALEVIA™-CA1 (crofelemer delayed-release tablets) administered orally twice a day for three days, for the treatment of chemotherapy-induced diarrhea in dogs.

III. TARGET ANIMAL SAFETY

The following studies support the safe use of crofelemer administered twice daily for three days for the treatment of chemotherapy-induced diarrhea in dogs. In the following studies, crofelemer is also referred to as SP-303 and CANALEVIA™-CA1. Four laboratory safety studies were performed in healthy Beagle puppies and dogs. Three pilot clinical field studies, performed in dogs with either acute diarrhea or chemotherapy-induced diarrhea, were used to assess field safety. Two multi-dose safety studies (Study WIL-288022 and Study WIL-288006), the cardiovascular safety study (Study MPI 1310-012), and the pilot study CANA-001b did not use the commercial formulation. The impact on the evaluation of safety due to formulation differences has not been evaluated.

A. A 9-Day Target Animal Safety Study

Title: Target Animal Margin of Safety Study to Evaluate CANALEVIA™ Tablets in Puppies. (Study No. 2530-001)

Study Dates: December 2016 to April 2017

Study Location: Mattawan, MI

Study Design:

Objective: To evaluate the safety of the test article, CANALEVIA™-CA1 tablets, in Beagle dogs after twice daily oral tablet administration for nine days.

Study Animals: Thirty-two healthy Beagle dogs (16 males, 16 females), aged approximately four months old on Study Day 0, weighing 4 to 6.8 kg, determined as healthy based on physical examination and clinical pathology.

Experimental Design: The study was a randomized, masked laboratory study conducted in accordance with the Good Laboratory Practice (GLP) regulations.

Drug Administration: Dogs in the CANALEVIA™-CA1 treatment groups were administered the commercial formulation of CANALEVIA™-CA1 tablets, containing 125 mg of crofelemer per tablet, twice daily for 9 days. Dogs were fasted 6 hours prior to each dose administration and 4 hours after dosing. The control group was sham dosed by simulating the dosing procedure in the same manner as the CANALEVIA™-CA1 treatment groups and received nothing by mouth. If a dog vomited within 2 hours of dose administration and 1 or more tablets were visible, then the animal was re-dosed with the same number of tablets visible in the vomitus.

Table III.1 Treatment Groups and Doses

Treatment Group	Treatment	Dose Level (mg/kg BID[1])	Total Daily Dose Range (mg/kg)	Number of Dogs
1	Sham Dose	0	0	4 male 4 female
2	CANALEVIA™-CA1	27.2	50-98	4 male 4 female
3	CANALEVIA™-CA1	54.3	99-147.1	4 male 4 female
4	CANALEVIA™-CA1	162.9	294.1-343.1	4 male 4 female

[1]BID - Twice daily dosing

Measurements and Observations:

- Stool samples were evaluated on Study Days -11, -1, and Study Day 9. Fecal analysis performed was by direct smear and float.
- Body weights were measured on Study Day -1, Study Day 2, and Study Day 5; these weights were used for dose calculation.
- Food consumption was measured twice daily, morning and evening during Study Days -26 to Study Day 9.
- Observations for mortality, morbidity, and availability of food and water were conducted twice daily.
- Cageside clinical examinations were conducted twice daily from Study Day -14 to Study Day -1.
- Cageside clinical examinations were conducted on dose administration days at hours 1, 2, 6, 8, and 10 after the first (AM) daily dose and 1, 2, 6, and 10 hours after the second (PM) daily dose. Dogs were monitored post-dosing for

any choking, drooling, gagging, or vomiting associated with the swallowing of whole tablets.

- Detailed clinical observations were conducted once daily on dose administration study days at 2 hours post-dosing.
- Physical examinations were conducted on Study Day -1 and prior to necropsy.
- Ophthalmoscopic exams were conducted pre-study and prior to necropsy by a veterinary ophthalmologist using tropicamide solution 1% for mydriasis.
- Electrocardiographic examinations were performed pre-study on Study Day -1 and prior to the final dose.
- Blood and urine samples for clinical pathology evaluations were collected from all animals twice pre-study on Study Day -11 and Study Day -1 and prior to necropsy. The analysis performed included complete blood count, clinical chemistry, coagulation (prothrombin time, activated partial thromboplastin time, and fibrinogen), and urinalysis.
- Crofelemer assay blood samples were collected on Study Day 0 (prior to the morning dose and at approximately 1, 2, 6, and 10 hours after the morning dose) and Study Day 9 (prior to the final dose and at approximately 1, 2, 6, 10, 18, and 24 hours after the last dose). Plasma samples were analyzed for Epigallocatechin.
- Necropsy examinations were performed on Study Day 10, organ weights were recorded, and selected tissues were examined microscopically.

Statistical Methods: The experimental unit was the individual animal. For continuous variables measured only once during the study, analysis of variance with treatment, sex, and treatment-by-sex interaction as the fixed effect was used to test for difference among treatment groups. If treatment-by-sex interaction was significant, pairwise comparisons of each treatment group versus control using linear contrasts were performed within sex. If treatment-by-sex interaction was not significant and treatment main effect was significant, pairwise comparison of each treatment group versus control for pooled sexes were performed. Analysis of covariance was used to analyze continuous variables that were measured once post-treatment and at least once pre-treatment. Treatment, sex, treatment-by-sex interaction were included in the models as fixed effects. Pre-treatment measure was included in the models as a covariate regardless of its statistical significance. Baseline values were defined as the values prior to and nearest to the first dosing. For continuous variables measured more than once post-treatment, repeated measures analysis of covariance was used to test for difference among treatment groups. The model includes treatment, time, sex, and all interactions as fixed effects. Time was modeled as a repeated factor, with animal as the subject of repeated measurements. The covariance structure was chosen from autoregressive (1) [AR(1)], heterogeneous AR(1) [ARH(1)], compound symmetry (CS), heterogeneous CS (CSH), and spatial covariance structure [SP(POW)], based on the minimum Akaike information criterion (AIC). In addition, baseline values were included as a covariate regardless of its significance. All above fixed effects were tested at $\alpha = 0.1$ except the treatment-by-sex-by-time interaction, which was tested at $\alpha = 0.05$.

Results: Mortality and Morbidity: There were no deaths or clinically significant illness during the study.

Clinical Observations: Findings included mucoid, soft, watery, or red discolored feces; vomiting; and lacrimation. The findings of red discolored feces, watery feces, mucoid feces, and vomiting were dose dependent and were increased in Group 4 (162.9 mg/kg dose). Five dogs in Group 4 had vomiting with tablets present in the vomitus.

Table III.2 Clinical Observations During the Study by Dose Group (Number of Observations)

Observation[1]	**0 mg/kg BID[2]**	**27.2 mg/kg BID**	**54.3 mg/kg BID**	**162.9 mg/kg BID**
Feces soft	216	248	124	224
Feces watery	76	83	63	147
Feces discolored red	4	19	50	125
Vomiting	5	11	2	23
Feces mucoid	1	2	2	6
Lacrimation	2	1	8	6

[1]Observations that occurred more than once per individual were counted.
[2]BID - Twice daily dosing

Clinical Pathology and fecal analysis: There were dogs in all groups positive for coccidia on fecal analysis.

Three dogs had a decreased hematocrit (reference range 37.2-52%) at study end compared to pre-study: one Group 2 (27.2 mg/kg) male with hematocrit of 39.6% prior to dosing and 35.8% on Study Day 9, one Group 4 (162.9 mg/kg) female with hematocrit of 40.7% prior to dosing and 36.4% on Study Day 9, and one Group 4 female with hematocrit of 36.4% prior to dosing and 36.1% on Study Day 9.

There were no clinically significant effects on body weight, physical examination findings, food consumption, ophthalmoscopic examination findings, electrocardiogram (ECG), or necropsy findings for any of the groups during the study.

Toxicokinetics: Toxicokinetic data was not evaluated due to insufficient bioanalytical method validation data.

Conclusions: The study demonstrated that CANALEVIA™-CA1 has an adequate margin of safety for the treatment of chemotherapy-induced diarrhea in dogs when administered orally according to the dosing instructions in the labeling. CANALEVIA™-CA1 administered orally twice a day for nine days at doses of 0, 27.2, 54.3, and 162.9 mg/kg did not produce systemic toxicity. The administration of CANALEVIA™-CA1 resulted in dose-dependent increases in red discolored feces, and at 162.9 mg/kg, an increased incidence of vomiting, watery feces, and mucoid feces. Clinical observations in all groups included mucoid, soft, or watery feces and observations of vomiting and lacrimation.

B. A 9-Month Target Animal Safety Study

Title: A 9-Month Oral Toxicity Study of Enteric Coated SP-303 in Dogs. (Study No. WIL-288022)

Study Dates: March 1998 to December 1998

Study Location: Ashland, OH

Study Design:

Objective: To evaluate the toxicity potential of enteric coated SP-303 (crofelemer) tablets when administered orally to dogs for 9 months.

Study Animals: Thirty-two healthy Beagle dogs (16 males and 16 females), aged approximately six months at first dose administration, weighing 9.3 kg to 10.4 kg for the males and 7.8 kg to 9.9 kg for the females at first dose administration.

Experimental Design: The study was a randomized laboratory study conducted in accordance with GLP regulations. The study was not masked.

Drug Administration: The dogs were dosed by oral administration once a day for 273 or 274 days. The study utilized SP-303 tablets containing 250 mg and 500 mg of crofelemer. Dogs in Group 1 received placebo tablets at a number equivalent to that used for test article administration in Group 4 rounded down to the nearest whole 500 mg tablet. Doses of SP-303 tablets were rounded up to the next whole 250 mg tablet. Individual doses were prepared by counting out the number of tablets required and placing them into gelatin capsules.

Table III.3. Treatment Groups

Treatment Group	Treatment	Dosage Level (mg/kg) Once a Day	Number and Sex of Animals
1	Placebo	0	4M, 4F
2	SP-303	50	4M, 4F
3	SP-303	175	4M, 4F
4	SP-303	600	4M, 4F

Measurements and Observations: Clinical observations were performed during drug administration and approximately two to three hours following treatment throughout the study. Detailed physical examinations were performed on all animals weekly, beginning one week prior to treatment and lasting until study termination. Individual body weights were recorded pre-study, Study Day 0, and weekly until study termination. Individual food consumption was recorded daily pre-study and until study termination. Ophthalmological examinations were performed pre-treatment and during the last week of the study (Week 38). ECGs were performed pre-treatment and during study Weeks 19 and 38. Blood and urine were collected for clinical pathology (hematology, clinical chemistry, coagulation parameters, and urinalysis) pre-study, on Study Day 136 (Week 19), and prior to necropsy (Week 38). At the end of the study, dogs were euthanized

and select organ weights were recorded and tissues were collected for gross pathology and histopathology.

Statistical Methods: No statistical analysis was conducted.

Results: All dogs survived until scheduled necropsy.

Clinical Observations and Physical Examinations: Abnormal feces (mainly black and rust mucoid feces and diarrhea) were observed at higher incidences in the 175 and 600 mg/kg/day groups and at lower incidences in the 50 mg/kg/day group. Abnormal excreta began as soon as 1 day after the first dose and persisted throughout the study. There was no progression of severity of abnormal feces, but the abnormal feces persisted throughout the study. Higher incidences of emesis (mainly containing tablets, food, and/or rust colored material) was seen in the 600 mg/kg/day group compared to the other groups. Four dogs in the 600 mg/kg/day group were reported with pale gums corresponding to anemia seen in these dogs.

Body Weights and Food Consumption: Dogs in the 600 mg/kg/day group did not gain weight at the same rate as the other groups. Dogs in the 600 mg/kg/day group had decreased food consumption compared to the other groups.

Clinical Pathology: The clinical pathology results are based on group mean values. The results of the hematology indicate a drug effect in the 600 mg/kg/day group only, consisting of microcytic, hypochromic anemia with mild regeneration (inadequate) and thrombocytosis. Dogs in the 600 mg/kg/day group had decreases in hemoglobin, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC) at Week 19 and Week 38 compared to the other groups. Dogs in the 600 mg/kg/day group had increases in platelets, percent reticulocytes, and absolute reticulocytes at Week 19 and Week 38 compared to the other groups. Females in the 175 mg/kg/day and 600 mg/kg/day groups had increases in absolute neutrophils at Week 38 compared to the other groups. Females in the 600 mg/kg/day group had increases in absolute neutrophils at Week 19 compared to the other groups. Females in the 175 mg/kg/day and 600 mg/kg/day groups had decreases in absolute lymphocytes at Week 38 compared to the other groups. Females in the 600 mg/kg/day group had decreases in absolute lymphocytes at Week 19 compared to the other groups.

The results of the serum chemistry indicate a drug effect in the 600 mg/kg/day group and to a lesser extent the 175 mg/kg/day group and include lower albumin, total protein, cholesterol, calcium, and sodium levels and increased potassium levels. Males in the 175 mg/kg/day and 600 mg/kg/day groups had a decreased serum albumin and total protein at Week 19 compared to the other groups. Males in the 600 mg/kg/day group had a decreased serum albumin and total protein at Week 38 compared to the other groups. Sodium was decreased in the males in the 600 mg/kg/day group at Week 19 and all test article treated dogs at Week 38 compared to the males in the 0 mg/kg/day group. Cholesterol and calcium were decreased in the males in the 600 mg/kg/day group at Weeks 19 and 38 compared to the other groups. Potassium was increased in the males in the 600 mg/kg/day group at Weeks 19 and 38 compared to the other groups. Females in the 600 mg/kg/day group had a decreased serum albumin, total

protein, calcium, and sodium at Weeks 19 and 38 compared to the other groups. Cholesterol was decreased in the females in the 600 mg/kg/day group at Weeks 19 and 38 and to a lesser extent in the females in the 175 mg/kg/day group at Weeks 19 and 38 compared to the 0 and 50 mg/kg/day groups. Potassium was increased in the females in the 600 mg/kg/day group at Weeks 19 and 38, and to a lesser extent in the females in the 175 mg/kg/day group at Week 38 compared to the 0 and 50 mg/kg/day groups.

There were no clinically relevant urinalysis abnormalities between groups.

Gross Pathology and Histopathological Findings: Gross lesions including localized irritation of the gastrointestinal tract (reddened areas, erosion, and red streaks) and discoloration of the gastrointestinal tract (dark red areas and gray areas) and lymph nodes (red, gray, and green) were observed in all groups administered crofelemer. Gross lesions occurred in a dose-dependent manner where the higher doses had higher incidences. There were no clinically relevant differences in organ weights between groups. On histopathology, inflammation and pigmentation of the gastrointestinal tract and pigmentation in the liver was observed in the groups administered crofelemer. Histiocytosis, erythrocytosis, basophilic bodies, and pigmentation of the lymph nodes was observed in the groups administered crofelemer. Splenic macrophage infiltration was observed in several dogs administered crofelemer. Histopathologic lesions occurred in a dose-dependent manner where the higher doses had higher incidences.

There were no ophthalmic examination or ECG findings related to drug administration.

Conclusions: The study supports the safety of CANALEVIA™-CA1 for the treatment of chemotherapy-induced diarrhea in dogs when administered orally according to the dosing instructions in the labeling. Crofelemer-related findings included gastrointestinal effects and were observed during the study (abnormal feces, vomiting, decreased food consumption, and decreased weight gain) and on necropsy (irritation and discoloration of the gastrointestinal tract). Gastrointestinal effects were generally dose-dependent where the higher doses had higher incidences. Crofelemer-related hematology findings in the 600 mg/kg/day group included decreases in hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration; and increases in platelets, percent reticulocytes, and absolute reticulocytes. The hematology findings in the 600 mg/kg/day group were consistent with a microcytic, hypochromic anemia with mild regeneration (inadequate), and thrombocytosis. Increases in absolute neutrophils were seen in females in the 175 and 600 mg/kg/day groups. Crofelemer-related serum chemistry findings in the 600 mg/kg/day group and to a lesser extent the 175 mg/kg/day group included decreased albumin, total protein, cholesterol, calcium, and sodium levels and increased potassium compared to the other groups.

C. A 30-Day Target Animal Safety Study

Title: A 30-Day Oral Toxicity Study of Enteric Coated SP-303 in Dogs. (Study No. WIL-288006)

Study Dates: June 1997 to July 1997

Study Location: Ashland, OH

Study Design:

Objective: To evaluate the toxicity potential of enteric-coated SP-303 (crofelemer) tablets when administered orally to dogs for 30 days.

Study Animals: Thirty-two healthy Beagle dogs (16 male and 16 female Beagle dogs), aged approximately six months old at first dose administration, weighing 7.0 kg to 9.3 kg for the males and 5.7 kg to 7.9 kg for the females at randomization (Study Day -3).

Experimental Design: The study was a randomized laboratory study conducted in accordance with GLP regulations. The study was not masked.

Drug Administration: Dogs were dosed by oral administration once a day for 30 or 31 days. The study utilized SP-303 tablets containing 125 mg of crofelemer. Individual doses were prepared by counting out the number of tablets required and placing them into gelatin capsules. For the test article-treated groups, the appropriate number of test article tablets was dispensed into 1 or 2 gelatin capsules (size 12) for each dog. For fractional amounts (e.g., 21.3 tablets), the number of tablets was rounded up (e.g., 22 tablets). The placebo tablets used to dose the control group animals were prepared in a similar manner. All control group animals received the placebo tablets at a number equivalent to that used for the 600 mg/kg/day group.

Table III.4 Treatment Groups

Treatment Group	Treatment	Dosage Level (mg/kg) Once a Day	Number and Sex of Animals
1	Placebo	0	4M, 4F
2	SP-303	50	4M, 4F
3	SP-303	175	4M, 4F
4	SP-303	600	4M, 4F

Measurements and Observations: Clinical observations were performed during drug administration and approximately 2-3 hours following treatment throughout the study. Detailed physical examinations were performed on all animals weekly, beginning one week prior to treatment and until study termination. Individual body weights were recorded pre-study, Study Day 0, and weekly until study termination. Individual food consumption was recorded daily beginning one week prior to treatment and until study termination. Ophthalmological examinations and ECGs were performed pre-treatment and during the last week of the study (Week 4). Blood and urine were collected for clinical pathology (hematology, clinical chemistry, coagulation parameters, and urinalysis) pre-study and on Study Day 26 (Week 3). Blood samples for pharmacokinetic (PK) analysis were collected prior to dosing on the first and last complete days of dosing (Study Days 0 and 29) and at 2, 6, 12, 18, and 24 hours post-dosing. The plasma samples were analyzed for SP-303 using a High Performance Liquid

Chromatography (HPLC) method validated for dog plasma with a lower limit of quantification of 100 ng/mL. At the end of the study, dogs were euthanized and select organ weights were recorded and tissues were collected for gross pathology and histopathology.

Statistical Methods: No statistical analysis was conducted.

Results: All dogs survived until scheduled necropsy.

Clinical Observations and Physical Examinations: Abnormal feces (mainly black and rust mucoid feces and diarrhea) were observed at higher incidences in the 175 and 600 mg/kg/day groups and at lower incidences in the 50 mg/kg/day group. Abnormal excreta began as soon as 1 day after the first dose and persisted throughout the study. There was no progression of severity of abnormal feces, but the abnormal feces persisted throughout the study.

Body Weights and Food Consumption: Dogs in the 600 mg/kg/day group failed to gain weight at the same rate as the other groups. Dogs in the 600 mg/kg/day group had decreased food consumption compared to the other groups.

Clinical Pathology: The clinical pathology results presented below are based on group mean values. The results of the hematology indicated a drug effect in the 600 mg/kg/day females, and consisted of decreases in red blood cells, hemoglobin, and hematocrit and increases in percent reticulocytes and absolute reticulocytes at Week 3 compared to the other groups. Dogs in the 600 mg/kg/day groups had increases in absolute neutrophils at Week 3 compared to the other groups. Females in the 600 mg/kg/day group had decreases in serum albumin, total protein, and calcium at Week 3 compared to the other groups. There were no clinically relevant abnormalities between groups.

Gross Pathology and Histopathological Findings: Gross lesions including localized irritation of the gastrointestinal tract (reddened mucosa) and mesenteric lymph nodes (reddened) were observed in the 175 and 600 mg/kg/day groups with the dogs in the 600 mg/kg/day having higher incidences. There were no clinically relevant differences in organ weights between groups. On histopathology, minimal to mild congestion in varying segments of the small and large intestines, and congestion in the mesenteric and suprapharyngeal lymph nodes was seen in the groups administered crofelemer in a dose-dependent manner where the higher doses had higher incidences.

Pharmacokinetics: There was systemic drug exposure at 50, 175, and 600 mg/kg when administered orally once daily for 30 days. Crofelemer is a water soluble large molecular weight drug and its absorption from the gastrointestinal tract is limited by its permeability. The systemic drug exposure could be a result of a disruption of intestinal permeability at high doses. On Day 0, there were no quantifiable plasma concentrations before 6 hours in any of the groups. The use of gelatin capsules may have caused a delay in the dissolution and absorption of the drug until the test article reached the colon (based on the gastrointestinal transit rate in dogs).

There was a less than dose proportional increase in drug exposure for the 175 and 600 mg/kg groups. The accumulation index on Day 29 for the 50, 175, and 600 mg/kg groups was 2.3, 1.9, and 1.5 respectively.

There were no ophthalmic examination or ECG findings related to drug administration.

Conclusions: The study supports the safety of CANALEVIA™-CA1 for the treatment of chemotherapy-induced diarrhea in dogs when administered orally according to the dosing instructions in the labeling. Crofelemer-related findings included gastrointestinal effects and were observed during the study (abnormal feces) and on necropsy (irritation and congestion). Gastrointestinal effects were generally dose-dependent where the higher doses had higher incidences. Crofelemer-related hematology findings were limited to the 600 mg/kg/day group females and consisted of decreases in red blood cell parameters. Increases in absolute neutrophils were seen in the 600 mg/kg/day group. Crofelemer-related serum chemistry findings in the 600 mg/kg/day group females included decreases in albumin, total protein, and calcium compared to the other groups.

D. Cardiovascular Study

Title: Potential Cardiovascular Effects of Orally-Administered Crofelemer in the Beagle Dog. (Study No. MPI 1310-012)

Study Dates: October 2009 to November 2009

Study Location: Mattawan, MI

Study Design:

Objective: To evaluate the potential cardiovascular effects of the test article in Beagle Dogs.

Study Animals: Four healthy Beagle dogs, aged approximately one to one and a half years, weighing 9.8 to 12.9 kg on Study Day -1.

Experimental Design: The study was a randomized laboratory study conducted in accordance with GLP regulations. The study was not masked.

Drug Administration: All doses were administered to all dogs one time, according to a modified Latin square design, with one dog/sex/treatment dosing each week with at least a 7 day washout period between administrations until each dog received all treatments. The same 4 dogs were administered placebo tablets (0 mg/kg) and crofelemer at doses of 60, 200, and 600 mg/kg. Doses were administered orally in a gelatin capsule. Because the 125 and 250 mg tablets had to be administered whole, the dose each dog received was approximate.

Measurements and Observations: Observations for morbidity, mortality, injury, and the availability of food and water were performed twice daily throughout the study. A detailed clinical examination of each animal was performed prior to dosing and following completion of the cardiovascular monitoring periods (approximately 20 hours post-dose). Body weights for all animals were measured and recorded the day of transfer, prior to selection for study, and the day prior to

each dose administration during the study. Systolic, diastolic, and mean arterial blood pressures, heart rate (derived from blood pressure and ECG), and ECG were monitored continuously by telemetry for at least 22 hours nine days prior to the first dosing and from at least two hours predose until at least 20 hours post-dose for each dosing. Body temperature was measured and collected by radiotelemetry at the same intervals as the cardiovascular data.

Statistical Methods: No statistical analysis was conducted.

Results: All dogs survived until study termination.

Observations and Detailed Clinical Examinations: Soft, watery, mucoid, or discolored (brown, red, black) feces were reported in all dogs after the 200 mg/kg and 600 mg/kg dosing.

Cardiovascular Evaluations: There was no effect on systolic, diastolic, and mean arterial blood pressures related to treatment during the study. There was no effect on heart rate and ECG related to treatment during the study.

There was no effect on body weight or body temperature related to treatment during the study.

Conclusions: There were no crofelemer-related effects on the cardiovascular parameters at doses of 60, 200, and 600 mg/kg. Following single doses of 200 and 600 mg/kg, crofelemer produced soft, watery, mucoid, or discolored (brown, red, black) feces.

E. Field Safety

1. A Masked, Randomized, Placebo-Controlled, Multi-Site Pilot Effectiveness Study to Evaluate Crofelemer for the Treatment of Acute Diarrhea in the Dog. (Study No. CANA-003)

   Title: Clinical Field Study to Evaluate the Safety and Effectiveness of Crofelemer (SP-303) for the Treatment of Acute Diarrhea in Dogs. (Study No. CANA-003)

   Study Dates: January 2016 to March 2019.

   Study Locations:

Austin, TX	Haute, IN
Bartonville, IL	Largo, FL
Bend, OR*	Lincoln, NE
Blue Ash, OH	Media, PA
Boulder, CO	Pittsburgh, PA
Brunswick, ME	Quakertown, PA
Cheyenne, WY	Reno, NV
Daytona Beach, FL	Springfield, MO
Fort Collins, CO	Terre Haute, IN
Fort Worth, TX	Zanesville, OH

*Two study locations.

Study Design:

Objective: The objective was to determine the clinical safety and effectiveness of crofelemer in alleviating clinical signs of acute diarrhea in dogs.

Study Animals: Dogs were aged 8 weeks to 15.9 years of age, of various breeds, intact or altered, and weighing 5.5 pounds to 143.2 pounds. The dogs were housed in the shelter or veterinary hospital during the study. The evaluation of stools was scored using the Purina Fecal Scoring Chart[1]. Data was captured via video camera in the event that study personnel were not present to witness stools and record fecal score.

Experimental Design: This study was a masked, placebo-controlled, multi-center field study conducted according to Good Clinical Practices (GCP). Dogs were included if at least two months old, at least five pounds in body weight, and had at least 1 watery bowel movement occurring within the previous 12 hours with a Purina Fecal Score (PFS) of 6 or 7. Dogs were excluded if had a screening PFS of 6 or 7, but followed by PFS of 1, 2, 3, 4, or 5 within the 12 hours prior to first study treatment; were positive for parvovirus; had hemorrhagic diarrhea; received prohibited medication within 72 hours of first dose administration; were pregnant, lactating, or intended for breeding; fed a therapeutic diet for the purpose of managing diarrhea within seven days prior to first dose administration; were NPO (nothing per os) for the purpose of managing diarrhea; had vomited within the previous 12 hours; and/or had intestinal parasites.

Treatment success (resolution of diarrhea) was defined as any dog that developed formed stool (PFS of 1, 2, 3, 4, or 5) or had no stool, and maintained formed stool or no stool (no PFS of 6 or 7) for a 16 hour period during the Treatment Period (T0hr – T72hr). A treatment failure was defined as any dog that did not develop formed stool (a PFS of 1, 2, 3, 4 or 5), or had not maintained the absence of stool for 16 hours during the Treatment Period (T0hr– T72hr). Dogs withdrawn due to perceived lack of effectiveness or who had an adverse event preventing continued participation in the study were also considered treatment failures.

Drug Administration: The dogs were administered doses every 12 hours for three days. Initially, the study utilized tablets containing 20 mg and 80 mg of crofelemer. These tablets were administered to dogs from January 2016 to March 2016 during the study. The tablets were administered at a dose of 20 mg twice a day for dogs 5 to 20 pounds; 80 mg twice a day for dogs > 20 pounds to 90 pounds; and 160 mg twice a day (2 of the 80 mg tablets) twice a day for dogs > 90 pounds. The protocol was amended in March 2016 to change to the commercial formulation of CANALEVIA™-CA1 tablets, containing 125 mg of crofelemer per tablet. Dogs weighing between 5 and 137 pounds were administered one tablet every 12 hours for 6 doses. The 125 mg tablets were administered whole, resulting in a dose range of 2 to 46.3 mg/kg per dose. Only one dog weighed over 137 pounds and was administered two tablets every 12 hours. Control dogs were administered placebo tablets.

Dogs randomized to receive crofelemer included 21 dogs administered the 80 mg tablets, one dog administered the 20 mg tablets, and 112 dogs administered the CANALEVIA™-CA1 tablets containing 125 mg of crofelemer.

Table III.5. Treatment Groups

Treatment Group	Dosage Level (mg/kg)	Number of Dogs
Crofelemer	2 to 46.3	134
Placebo	0	66

Measurements and Observations: Dogs had fecal scores assessed every four hours. Dogs had physical examination and clinical pathology performed at study start and study end. Dogs were monitored for 24 hours after the final dose for a total study duration of 96 hours.

Results: A preliminary analysis revealed a numerically higher, but not statistically significantly different, success rate in the group treated with crofelemer when compared to placebo. Both treatment groups had high success rates. Due to limitations in the effectiveness data, a complete evaluation of the effectiveness results was not performed.

There were no crofelemer-related treatment findings on physical examinations.

Adverse Reactions: Table III.6 shows adverse reactions during the study.

Table III.6. Adverse Reactions

Adverse Reaction	Crofelemer N = 134	Placebo N = 66
Vomiting	11 (8.2%)	1 (1.5%)
Decreased blood glucose[1]	10 (7.5%)	3 (4.5%)
Urinary system abnormality[2]	10 (7.5%)	2 (3%)
Upper respiratory signs[3]	7 (5.2%)	0 (0%)
Decreased serum calcium[4]	5 (3.7%)	0 (0%)

[1]Dogs with decreased blood glucose at study end had normal blood glucose (reference range 74-145 mg/dL) prior to dosing. None of the dogs were reported to be clinically affected by the decreased blood glucose. The low blood glucose values ranged from 34 to 71 mg/dL.
[2]Urinary system abnormalities were documented as development of a urinary tract infection, cystitis, or a worsening pyuria in the urine.
[3]Upper respiratory signs included coughing, nasal discharge, sneezing, and congestion.

[4]Dogs with decreased serum calcium (reference range 8.7-12 mg/dL) at study end had normal calcium at screening. The decreased calcium values were not associated with decreased albumin values. None of the dogs were reported to be clinically affected by the decreased serum calcium. The lowest reported calcium was 5.8 mg/dL.

Five dogs administered crofelemer and one control dog were removed from the study for no improvement in stools. One additional dog administered crofelemer was removed for hemorrhagic stool.

Conclusion: This clinical field study supports the safe use of CANALEVIA™-CA1 when administered orally according to the dosing instructions in the labeling for dogs. The endpoint for the study did not define resolution of diarrhea the same as the pilot study used to support reasonable expectation of effectiveness, and a complete evaluation of the effectiveness results was not performed.

2. An Open-label Pilot Study to Assess the Safety of SP-303 (crofelemer) in Alleviating the Clinical Signs associated with Secretory Diarrhea in the Dog. (Study No. CANA-001b)

   The safety of crofelemer (not commercial formulation) was evaluated in an open-label pilot study in shelter-housed and client-owned dogs, ages two months to 10 years old, with diarrhea. The study included 48 dogs administered crofelemer. Dogs were administered crofelemer orally approximately every 12 hours for three days at a dose range of 1.3 to 13.3 mg/kg. Dogs were between the ages of 2 months and 10 years with a fecal score of 3, 4, or 5 (viscous liquid with some particular matter, watery or liquid stools with little or no particulate matter, or severe watery diarrhea with no particulate matter visible). A baseline physical examination was obtained, and daily assessments included body temperature; fecal scores; and a scored assessment of general attitude, hydration status, appetite, and reaction to abdominal palpation. Fecal scores were obtained every four hours. The adverse reactions included decreased appetite in 16/48 (33%) dogs, vomiting in 3 (6%) dogs, decreased activity in 3 dogs (6%), abdominal pain in 1 (2%) dog, and 1 (2%) dog had blood in feces.

3. An Open-label Pilot Study to Evaluate the Safety of SP-303 in an Enteric-Coated Tablet Administered to Dogs with Chemotherapy-Induced Diarrhea (CID). (Study No. CANA-002)

   The safety of CANALEVIA™-CA1 (commercial formulation) was evaluated in an open-label pilot study in eight client-owned dogs, ages 7 to 12 years old, with various cancers receiving various oral and injectable chemotherapy regimens. Eight dogs (4 male and 4 female) were administered CANALEVIA™-CA1 orally approximately every 12 hours for three days at a dose range of 2.8 to 4.1 mg/kg. The study did not include a control group so effectiveness comparisons could not be made. Hematological, serum chemistry, and clinical observations noted during the study could be attributable to underlying neoplasia or the chemotherapy the dogs received and included thrombocytopenia, thrombocytosis, anemia, increased MCV, decreased MCHC, increased nucleated red blood cells (NRBC), neutropenia, lymphopenia,

monocytopenia, increased alkaline phosphatase, increased creatinine, firm mandibular lymph nodes, soft amorphous stool, lethargy, and anorexia. Other hematological, serum chemistry, and clinical observations included one incidence each of increased platelets, increased globulin, increased magnesium, increased hematocrit, increased lactate dehydrogenase, a subcutaneous mass on the right thorax, and decreased diameter of stool.

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

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

Not for use in humans. Keep this and all medications out of reach of children. Consult a physician in case of accidental ingestion by humans.

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 CANALEVIA™-CA1, when used according to the label, is safe and has a reasonable expectation of effectiveness for the treatment of chemotherapy-induced diarrhea in dogs.

A. Conditional Approval Eligibility

Conditional approval is an option for animal drugs intended for use in minor species (all animals other than major species, which are horses, cattle, pigs, chickens, turkeys, dogs, and cats) or for minor uses (diseases or conditions in major species that occur infrequently or in limited geographical areas). A product's eligibility for conditional approval under minor use status requires a sponsor to justify that the disease or condition for which the proposed product is intended afflicts a "small number of animals" of that species in the U.S. annually. The "small number" for each major species is established by regulation (21 CFR § 516.3). At the time of this approval, FDA's "small number of animals" threshold for dogs was 70,000.

FDA conducted a minor use assessment and determined that the occurrence of chemotherapy-induced diarrhea in dogs in the U.S. annually is below the published "small number" of 70,000 dogs. As part of this assessment, FDA reviewed multiple sources of data, including the scientific literature, a sponsor-conducted survey of veterinarians, and Brakke Consulting Inc.'s 2009 Report on Cancer in Dogs and Cats,[2] which included data from Brakke's 2009 survey of general veterinary practitioners, the Veterinary Cancer Registry, and Banfield Pet Hospital's medical records. FDA estimated that the rate of occurrence of malignant neoplasia in dogs in the U.S. annually is approximately 1% of the canine population (with 90% certainty). FDA's estimate was derived from

weighted averages of the incidence of cancer in dogs from published studies and reports, as well as weighted averages of ratios of rates of occurrence of malignant neoplasia (0.31) to total neoplasia (1.00) in dogs,[2,3,4,5,6] because some estimates of cancer in dogs included benign neoplasms. This amounts to approximately 721,000 dogs with malignant neoplasia in the U.S. annually (utilizing a canine population of 72.1 million).[7]

In the 2009 Brakke Consulting survey, 53% of canine "cancer patients" were treated by general veterinary practitioners and 45% were referred to veterinary oncologists (2% other).[2] Of the 53% treated by general practitioners, 26% (i.e., 14% of all dogs with malignant neoplasia) received chemotherapy from those practitioners. Of those canine cancer patients referred to oncologists (45%), Brakke estimated that 58% (i.e., 26% of all dogs with malignant neoplasia) received chemotherapy from those veterinary oncologists.[2] Using the 1% canine malignant neoplasia rate and the Brakke survey results, FDA estimated that approximately 101,000 dogs are treated with chemotherapy by general practitioners (72.1 million x 0.01 x 0.14) and approximately 187,000 dogs are treated with chemotherapy by oncologists (72.1 million x 0.01 x 0.26) for a total of 288,000 (or approximately 317,000 dogs with 90% certainty) that are treated with chemotherapy in the U.S. on an annual basis.

Using the estimate above as part of a weighted average along with a more direct estimate of dogs and cats treated with chemotherapy on an annual basis from Brakke,[2] adjusted by FDA for dogs only (250,000 dogs with 90% certainty), as well as an estimate based on a survey of veterinarians that the sponsor provided, FDA concluded that approximately 282,000 dogs are treated with chemotherapy in the U.S. on an annual basis.

The sponsor provided two estimates of the rate of occurrence of diarrhea associated with chemotherapy in dogs, one from the survey of veterinarians that they conducted (20.7%) and one from a retrospective analysis of canine cases seen by a Veterinary Medical Teaching Hospital Oncology Service in 2012 (17.4%). A weighted average of these two estimates is approximately 18%. FDA estimated that, if 282,000 dogs receive chemotherapy on an annual basis and 18% of those dogs experience diarrhea as a result, then 50,760 dogs (or 57,200 dogs with 90% certainty) are eligible for treatment for chemotherapy-induced diarrhea on an annual basis.

Using the above estimates, FDA determined that the number of dogs with chemotherapy-induced diarrhea in the U.S. on an annual basis is lower than 70,000 dogs. Therefore, the Agency concluded that the use of CANALEVIA™-CA1 (crofelemer delayed-release tablets) for the treatment of chemotherapy-induced diarrhea in dogs in the U.S. constitutes a minor use, and the product is eligible for conditional approval.

B. Marketing Status

CANALEVIA™-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 order of a licensed veterinarian (Rx marketing status). Adequate directions for lay use cannot be written because professional expertise is required to properly diagnosis the cause of diarrhea and monitor dogs receiving chemotherapy.

C. Exclusivity

CANALEVIA™-CA1, as approved in our 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 FD&C Act. Except as provided in section 573(c)(2) of the FD&C Act, we may not approve or conditionally approve another application submitted for such new animal drug with the same intended use as CANALEVIA™-CA1.

D. Patent Information

For current information on patents, see the Green Book Reports in the Animal Drugs @ FDA database.

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