CORRECTED FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-455

GALLIPRANT

Grapiprant tablets

dogs

GALLIPRANT (grapiprant tablets) is indicated for the control of pain and inflammation associated with osteoarthritis in dogs

Sponsored by:

Aratana Therapeutics, Inc.

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I.   **GENERAL INFORMATION**

A. File Number

NADA 141-455

B. Sponsor

Aratana Therapeutics, Inc.
11400 Tomahawk Creek Pkwy.
Leawood, KS 66211

Drug Labeler Code: 86026

C. Proprietary Name

GALLIPRANT

D. Established Name

Grapiprant tablets

E. Pharmacological Category

Prostaglandin E_2 EP4 receptor antagonist; a non-steroidal, non-cyclooxygenase inhibitor, anti-inflammatory drug

F. Dosage Form:

Tablets

G. Amount of Active Ingredient

20 mg, 60 mg, or 100 mg

H. How Supplied

GALLIPRANT (grapiprant tablets) is available as 20 mg, 60 mg, and 100 mg tablets.

I. Dispensing Status

Rx

J. Dosage Regimen

The dose of GALLIPRANT (grapiprant tablets) is 0.9 mg/lb (2 mg/kg) once daily.

K. Route of Administration

Oral

L. Species/Class

Dogs

M. Indication

GALLIPRANT (grapiprant tablets) is indicated for the control of pain and inflammation associated with osteoarthritis in dogs.

II. EFFECTIVENESS

A. Dosage Characterization

A dose of 2 mg/kg (0.9 mg/lb) administered orally once daily for the control of pain and inflammation associated with osteoarthritis (OA) was selected based on the following information.

Dose extrapolation, based upon target effective area under the curve (AUC) plasma drug levels from human clinical trials, the ratio of unbound drug fraction in human versus dog serum, and the ratio of EP4 binding affinity in dogs versus humans, resulted in an estimated effective canine dose of 2 mg/kg once daily in a fasted state.

To test the estimated effective canine dose, a masked, randomized, placebo-controlled, multi-centered dose ranging field study was conducted using dogs with naturally occurring osteoarthritis of one or more appendicular joints. Dogs were treated with GALLIPRANT tablets at doses of 2 mg/kg once daily (N=94), 5 mg/kg once daily (N=90), 4 mg/kg twice daily (N=94), or placebo twice daily (N=88). The control of pain and inflammation was assessed by the owner using the Canine Brief Pain Inventory (CBPI) assessment tool. A positive response was seen in all GALLIPRANT tablet treatment groups, with no additional benefit apparent with twice daily dosing. During the study there was no restriction on feeding in relation to dosing. In a previously conducted food effect study, the bioavailability of GALLIPRANT tablets was significantly reduced in the presence of food, with approximately a 4.4-fold and 2.3 fold decrease in Cmax and AUC, respectively, as compared to the fasted condition.

Based on the results of the dose ranging field study, a dose of 2 mg/kg (0.9 mg/lb) given orally once daily was chosen for evaluation in a field study to confirm the effectiveness of GALLIPRANT for the control of pain and inflammation associated with osteoarthritis in dogs.

The anti-inflammatory effect of grapiprant has been demonstrated. Paw swelling, inflammatory biomarkers in the serum, and synovial inflammation were examined in the tarsal joint in adjuvant-induced arthritis (AIA) in rats. Grapiprant exhibited dose dependent anti-inflammatory effects on all parameters tested. The effect of grapiprant on paw swelling was comparable to that seen in rats treated with rofecoxib and piroxicam. In another study, the anti-inflammatory activity of grapiprant on rat carrageenan-induced foot swelling was investigated. Grapiprant inhibited foot swelling in a dose dependent manner compared to controls. Grapiprant shows similar *in vitro* binding affinity (Ki) for the rat and dog EP4 receptor, 20 and 24 nM, respectively.

B. Substantial Evidence

1. Field Study:

   a. Title: A placebo-controlled, pivotal field study to confirm the safety and effectiveness of GALLIPRANT tablets, administered daily as an oral flavored tablet, for the control of pain and inflammation associated with osteoarthritis (OA) in dogs, (Study AT001-CCL-14-005).

   b. Investigators:

Larry Baker, DVM Decatur, IL	Victor Manoharan, DVM West Palm Beach, FL
Jay Butan, DVM Lake Worth, FL	David Menard, DVM Ocala, FL
Carla Case-McCorvey, DVM Savannah, GA	Trent Newcomer, DVM Fort Collins, CO
Peter Davis, DVM Augusta, ME	Michael Petty, DVM Canton, MI
Sam Geller, VMD Quakertown, PA	Howard Robinson, DVM Fort Collins, Co
Brian Harris, DVM Gainesville, FL	Roger Sifferman, DVM Springfield, MO
Susan Hubbard, DVM Rochester, NY	Douglas Stramel Lewisville, TX
David Knaak, DVM Peoria, IL	David Thompson Wyoming, MI

   c. Study Design: This was a multi-center, placebo-controlled, randomized and masked study, which compared a 2 mg/kg once daily dose regimen of GALLIPRANT to a vehicle control for the control of pain and inflammation associated with osteoarthritis in dogs.

      (1) Study Animals: Two hundred and eighty five (285) client-owned dogs were enrolled in the study and included in the evaluation of field safety. There were 148 female and 137 male dogs enrolled in the study. A total of 262 dogs (131 treated and 131 control cases) were included in the per protocol population for effectiveness evaluation.

      GALLIPRANT-treated dogs ranged in age from 2 to 16.75 years old and weighed between 4.1 and 59.6 kilograms (9 – 131 lbs) at the start of treatment.

(2) Treatment Groups: Dogs were randomly assigned into two treatment groups in a 1:1 ratio of GALLIPRANT or vehicle control. Veterinarians and owners were masked to treatment group assignment.

Table 1: Treatment groups.

Treatment group	Dose mg/kg	Number of dogs
GALLIPRANT (grapiprant tablets)	2 mg/kg	141 (69 M, 72F)
Vehicle Control (tablets minus active ingredient)	0 mg/kg	144 (65 M, 79 F)

(3) Drug Administration: Dogs were administered 20 mg, 60 mg, or 100 mg GALLIPRANT tablets at 2 mg/kg or sized matched control tablets once daily for 28 days. Whole or half tablets of the appropriate size tablet of either the GALLIPRANT tablets or control were administered to achieve the daily dose, as indicated in Table 2 below. Actual GALLIPRANT tablet doses administered ranged from 1.54 to 2.92 mg/kg based on the Day 0 body weight.

Table 2. Dosing chart.

Dose	Weight (kgs)	20 mg tablet	60 mg tablet	100 mg Tablet
2 mg/kg daily GALLIPRANT or vehicle control tablets	3.6-6.8	0.5	N/A	N/A
	6.9-13.6	1	N/A	N/A
	13.7-20.4	N/A	0.5	N/A
	20.5-34	N/A	1	N/A
	34.1-68	N/A	N/A	1
	68.1-100	N/A	N/A	2

(4) Inclusion Criteria

- Owner consent
- Bodyweight ≥ 3.6 kg (8 lbs.)
- Clinical signs of osteoarthritis noted by the owner and veterinarian
- Radiographic evidence of osteoarthritis in at least one appendicular joint from radiographs taken within the preceding 60 days
- In general good health or stabilized for chronic conditions as assessed by physical examination, medical history, and clinical pathology evaluations
- Owner assessment of a Pain Severity Score (PSS) of 2 or more and Pain Interference Score (PIS) of 2 or more on the Canine Brief Pain Inventory at Day 0 (to limit bias, owners were unaware of these criteria for inclusion).

(5) Exclusion criteria

- Intended for breeding, or pregnant or lactating female dogs
- Clinical pathology findings considered abnormal and clinically significant, apart from previously identified stable chronic conditions

- Concomitant conditions, such as spinal abnormalities, autoimmune disorders, joint infections, or surgeries that might interfere with treatment assessment
- Use of concomitant medications that might interfere with pain assessment

(6) Measurements and Observations: The primary effectiveness parameter was the owner assessment of pain and overall impression at Day 0 (prior to first dose) compared to Day 28. Owners used the Canine Brief Pain Inventory[1] for assessing OA pain, consisting of the Pain Severity Score (PSS), the owner's assessment of the dog's overall pain; the Pain Interference Score (PIS), the owner's assessment of how the pain interferes with the dog's daily activities; and the Owner's overall impression of their dog's quality of life.

Based on the changes in PSS and PIS, and the Owner's overall impression assessment from baseline (Day 0) to Day 28, each dog was classified as either a treatment success or treatment failure. Dogs were evaluated at screening, Day 0, Day 7, Day 14, Day 21, and Day 28. Dogs removed due to lack of effectiveness or adverse reactions were considered treatment failures.

(7) Statistical analysis: The analyses of the effectiveness variables were conducted on the per protocol population, which comprised of those dogs without significant protocol violations or missing assessments.

The primary effectiveness variable was the percent success rate at Day 28. For a dog to be considered a treatment success, the PSS must have been reduced by 1 or more, and the PIS must have been reduced by 2 or more, and the overall impression must have been the same or better than at Day 0.

The primary effectiveness variable (treatment success or failure) was analyzed using a generalized linear mixed model assuming a binomial distribution and using a logit link. The model included treatment group as a fixed effect, and site and treatment by site interaction as random effects. Pairwise comparisons were assessed comparing active group to control at a 2-sided 0.05 significance level. A 95% confidence interval was calculated for the difference in success rates between active group and control.

Secondary outcome variables included the success rates from Day 0 to Days 7, 14, and 21. The success rates at each time point were presented and analyzed as described for the primary outcome variable.

Secondary outcome variables also included the percent changes from Day 0 to Days 7, 14, 21, and Day 28 in PSS and PIS scores. Analysis of variance modeling was employed to assess possible differences between treatment groups. The model contained terms for treatment, site, and treatment by site interaction.

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[1] http://www.vet.upenn.edu/docs/default-source/VCIC/canine-bpi_userguide.pdf?sfvrsn=0

d. Results: Effectiveness was evaluated in 262 dogs and field safety was assessed in 285 dogs.

(1) Primary Effectiveness Variable: In the 262 dogs evaluated for effectiveness a statistically significant difference (p = 0.0315) was demonstrated between the success rate in the GALLIPRANT tablet group (48.1%) when compared to the control group (31.3%).

Table 3: Success on Day 28 compared to Day 0.

Success	GALLIPRANT (grapiprant tablets) N = 131	Vehicle Control (tablets minus active ingredient) N = 131
% success (n)	48.1 (63)	31.3 (41)
p-value*	0.0315	

*p-value derived by a generalized linear mixed model assuming a binomial distribution and a logit link. The model included treatment group as a fixed effect and site and treatment by site interaction as random effects.

There were 10 control dogs and 1 GALLIPRANT tablet dog removed from the study early due to lack of effectiveness.

(2) Secondary variable

(a) Pain evaluation at Days 7, 14, and 21: The same criteria to classify a dog as a treatment success (a decrease of 1 or more in the Pain Severity Score and a decrease of 2 or more in the Pain Interference Score) was used at Days 7, 14, and 21. Statistically significant differences in success rates were seen in the GALLIPRANT tablet group compared to the control group at each time point.

Table 4: Success on Days 7, 14, and 21 compared to Day 0

Study Day	GALLIPRANT tablets	Control % Success (N)	p-value*
Day 7	30.5 (40)	16 (21)	0.0154
Day 14	41.2 (54)	28.2 (37)	0.0442
Day 21	46.6 (61)	32.8 (43)	0.0443

*p-value derived by a generalized linear mixed model assuming a binomial distribution and a logit link. The model included treatment group as a fixed effect and site and treatment by site interaction as random effects.

(b) Pain Severity Score (PSS) percent change from Day 0 to Days 7, 14, 21, and 28. The Pain Severity Scores in the GALLIPRANT group were statistically significantly different (reduced) compared to control from Day 0 to each of the assessment days; Day 7 p=0.0015, Day 14 p=<0.0001, Day 21 p=0.0480, Day 28 p=0.0034.

(c) Pain Interference Score (PIS) percent change from Day 0 to Days 7, 14, 21, and Day 28. The Pain Interference Scores in the GALLIPRANT tablet group were statistically significantly different (reduced) compared to control from Day 0 to each of the

assessment days; Day 7 p=0.0233, Day 14 p=0.0013, Day 21 p=0.0092, Day 28 p=0.0061.

(3) Adverse reactions: The most commonly reported adverse reactions were anorexia, inappetence, diarrhea, soft stools, and vomiting. The adverse reactions are summarized in Table 5. Some dogs experienced more than one adverse reaction during the study. The majority of cases of anorexia, inappetence, diarrhea, soft stool, and vomiting resolved after a few days.

Table 5. Adverse reactions reported in the field study.

Adverse reaction*	GALLIPRANT (grapiprant tablets) N = 141	Vehicle control (tablets minus grapiprant) N = 144
Vomiting	24	9
Diarrhea, soft stool	17	13
Anorexia, inappetence	9	7
Lethargy	6	2
Buccal ulcer	1	0
Immune mediated hemolytic anemia	1	0

*Dogs may have experienced more than one type or occurrence during the study.

e. Conclusions: Administration of GALLIPRANT tablets at a dose of 2 mg/kg once daily is safe and effective for the control of pain and inflammation associated with osteoarthritis in dogs.

III. TARGET ANIMAL SAFETY:

A. Safety Study (Study 06NG032):

1. Title: A 9-Month Oral Toxicity Study of CJ-023423 (grapiprant) in dogs with a 4-week recovery

2. Type of Study: Laboratory safety study

3. Location: Pfizer Global Research & Development
          Nagoya Laboratories (now RaQualia)
          Taketoyo, Aichi
          Japan

4. General Design:

   a. Purpose: To evaluate the potential toxicity and systemic exposure of grapiprant when administered orally, once daily, for 9 consecutive months to Beagles and assess the reversibility of any toxic changes.

   b. Test Animals: Nine-month old, healthy Beagles ranging in weight from 5.56 – 9.75 kgs were used in the study.

   c. Control: Control dogs received the vehicle, a methylcellulose 0.5% (w/v) suspension.

   Treatment Groups: Grapiprant was dosed via oral gavage in a 0.5% methylcellulose suspension (vehicle). Each day food was offered once daily in the afternoon and time of actual food consumption was not recorded. The grapiprant dose was administered on average 2 hours (range 1.18 h to 2.5 h) after the food bowl was removed in the morning of dosing and toxicokinetic sampling. The dose levels noted in Table 6 represent the corresponding dose level based on the results of the PK bridging study of the grapiprant suspension to the final market formulation tablets (see detailed description below). The dose levels are based on the dose of 3 mg/kg (the target dose is 2 mg/kg but there is an inherent dose band of up to 3 mg/kg when using the 3 tablet sizes).

Table 6. Dosing groups

Tx Group	Dose mg/kg* (fed exposure – fasted exposure)	Number and Gender of Animals
1 (Control)	0 mg/kg /0.5% methylcellulose	4 male/4 female
2	1 mg/kg (0.12X - 0.25X)	4 male/4 female
3	6 mg/kg (0.72X - 1.48X)	4 male/4 female
4a	50 mg/kg (4.88X - 10.16X)	4 male/4 female
4b	50 mg/kg with 1 month recovery (4.88X - 10.16X)	2 male/2 female

Dose levels based on a pharmacokinetic bridging study (Study AT001-CPK-13-010; see summary below) to link the 0.5% methylcellulose suspension of grapiprant to the final market formulation tablets. The methylcellulose formulation is less bioavailable than GALLIPRANT tablets.

   d. Study Duration: All dogs were dosed once daily for 9 consecutive months. Two dogs/sex in the 50 mg/kg treatment group were allowed a one-month recovery phase before necropsy.

   e. Variables Measured: Clinical observations and food consumption were assessed daily and body weights were measured weekly. Ophthalmic exams were performed pre-study, twice during dosing, and once during the recovery phase. Electrocardiograms were recorded pre-study, three times during dosing, and once during the recovery phase. Hematology, clinical

chemistries and coagulation samples were evaluated pre-study, three times during dosing, and once during recovery. Urinalyses were done pre-study, once during dosing, and once during the recovery phase. Serum drug concentrations were measured at 0.5, 1, 2, 4, 8, and 24 hours post-dose on Day 1 and during Week 38. Gross pathology, histopathology, and organ weights were evaluated at study conclusion.

5. Results: All dogs survived to study conclusion.

   a. Clinical Observations: Adverse gastrointestinal (GI) events of vomiting, and loose, bloody and/or mucous stools were observed in all groups including control; however, the incidence was higher in dogs administered grapiprant compared with that in control animals. The GI events decreased in the recovery group once grapiprant was discontinued.

   b. Clinical chemistry evaluations showed a significant decrease in mean serum albumin at Weeks 26 and 39 (14% decrease in grapiprant-treated vs control value) at the 50 mg/kg dose (4.88X – 10.16X) and in mean A/G ratio at Week 39 (decrease of 16%) at the 6 mg/kg dose (0.72X – 1.48X).

   Individually, there was a dose related trend of decreasing albumin, total protein, and/or calcium. Calcium decreases were considered secondary to decreased albumin levels. These changes returned to normal range at the end of the recovery period after the drug was discontinued.

   Three treated and one control dog had elevated alkaline phosphatase values $\geq$ 400-550 IU/L range.

   c. Drug concentrations: Serum drug concentrations were approximately dose proportional from 1 to 6 mg/kg and more than dose proportional from 6 to 50 mg/kg.

   d. Pathology: One dog in the 50 mg/kg group (4.88X – 10.16X) had mild regeneration of the mucosal epithelium of the ileum. This dog also vomited twice and had numerous episodes of abnormal stools and albumin at the low end of the reference range. One dog in the 1mg/kg group (0.12X – 0.25X) and three dogs in the 50 mg/kg group (4.88X – 10.16X) had esophageal submucosal cell infiltration. Three dogs in the 6 mg/kg group (0.72X – 1.48X) had minimal-mild muscular esophageal degeneration/necrosis. Additionally, one dog in the 6mg/kg group (0.72X – 1.48X) had minimal atrophy of the esophageal gland.

6. Conclusion: This study supports the safety of grapriprant when administered to dogs at a dose of 2 mg/kg once daily. Grapiprant at doses up to 50 mg/kg (4.88X - 10.16X dose level of tablets) for 9 months was associated with mild gastrointestinal signs such as soft or watery stools with mucus and/or blood. Vomiting and mild, reversible decreases in total protein and albumin were also associated with grapiprant, with the incidence increasing with increased doses.

B. Pharmacokinetic Study (Study AT001-CPK-13-010):

1. Title: Pharmacokinetic Comparison of Two Formulations in a Cross-over Design in Beagle Dogs for Two Dose Levels

2. Type of Study: Laboratory study

3. Location: Ricerca Biosciences, LLC
   Concord, OH

4. General Design:

   a. Purpose: To determine and compare the pharmacokinetic parameters of grapiprant in Beagle dogs after single oral administration of a tablet formulation and a methylcellulose suspension formulation at a dose of 6 mg/kg or 50 mg/kg.

   b. Test Animals: Sixteen healthy Beagles were divided into two groups.

   c. Treatment Groups: The 9 month oral toxicity study (Study 06NG032) was conducted using a methylcellulose suspension of grapiprant. Therefore, this pharmacokinetic (PK) study included two dosing groups to compare the methylcellulose suspension used in the toxicity study to the final market formulation, GALLIPRANT tablets, using the 60 mg and 100 mg tablets. Dogs received a single dose of each formulation with a 15-day washout period between dose administrations.

Table 7. Grapiprant dosing groups

Group	Dose	GALLIPRANT tablets (strength and quantity)	Methylcellulose suspension* (concentration and volume)	Number and Gender of Dogs
(A and B)	6 mg/kg	One 60 mg tablet	1.2 mg/mL 50 mL/dog	2 male/ 2 female
(A and B)	50 mg/kg	Five 100 mg tablets	10 mg/mL 50 mL/dog	2 male/ 2 female

* Formulation used in the 9 month toxicity study

   d. Route of administration: oral for tablets and oral gavage for the suspension

   e. Study duration: Seventeen days

   f. Variables Measured: Serum grapiprant concentrations were measured and clinical observations and body weights were observed. Blood samples were collected at 0 (second dose only), 0.5, 1, 2, 4, 5, 8, 12, 24, and 36 hours after dosing.

5. Results: Vomiting was noted in a few dogs at the 500 mg dose. Two dogs vomited soon after receiving five 100 mg tablets. Another 500 mg-dosed dog vomited on Day 0 (suspension) and Day 15 (tablets). Liquid feces were noted in two dogs receiving 60 mg. Fecal abnormalities of loose, mucoid, or liquid

feces were more prevalent at 500 mg (6 incidences) than 60 mg (2 incidences).

Table 8: Relative bioavailability of grapiprant at Nominal Dose of 6 mg/kg

Parameter	Unit	GALLIPRANT tablets	Methyl-cellulose Suspension	Geometric Ratio	LCL	UCL
AUC_{0}-last	ng*hr/mL	17596	13165	1.34	1.10	1.62
C_{max}	ng/mL	5020	3713	1.35	1.09	1.68
T_{max}	hr	1.297	1.000	1.30	1.00	1.68

LCL=lower confidence limit
UCL=upper confidence limit
T_{max}=time to maximum plasma concentration (C_{max})

Table 9: Relative bioavailability of grapiprant at Nominal Dose of 50 mg/kg

Parameter	Unit	GALLIPRANT tablets	Methyl-cellulose Suspension	Geometric Ratio	LCL	UCL
AUC_{0}-last	ng*hr/mL	436219	265774	1.64	1.26	2.14
C_{max}	ng/mL	97724	83550	1.17	0.94	1.45
T_{max}	hr	1.834	1.122	1.63	1.09	2.45

LCL=lower confidence limit
UCL=upper confidence limit
T_{max}=time to maximum plasma concentration (C_{max})

The results of this study were used to determine the corresponding dose levels of grapiprant administered to the dogs in the toxicity study if the study had included the GALLIPRANT tablet formulation. In a separate study, effect of food was evaluated for both the tablet and suspension formulations. The results suggested that food reduced the Cmax and AUC significantly. The reduction in the Area under the Curve (AUC) concentration in the fed state compared to the fasted state for the suspension formulation was slightly lower (0.48) than for the tablet formulation (0.37). The margin of safety evaluated in the toxicity study should be calculated based upon differences in bioavailability seen between suspension and tablet and differences in bioavailability of suspension in fed and fasted conditions. The calculations are shown below and exposures are listed for fed and fasted conditions.

Table 10: Dose levels administered in the 9 month toxicity study based on bridging methylcellulose suspension to GALLIPRANT tablets.

Target animal Study Dose (mg/kg/day) of Methylcellulose Suspension	Exposure of grapiprant compared to 3 mg/kg/day Dose of Grapiprant Methylcellulose Suspension[1]	Exposure of GALLIPRANT tablet Equivalent (mg/kg/day) Based on AUC[2] Ratios[3] (Based upon relative bioavailability if the TAS conducted under fasted conditions)	Exposure of GALLIPRANT tablet Equivalent (mg/kg/day) Based on AUC[2] Ratios[4] (Based upon relative bioavailability if the TAS study was conducted under fed conditions but the tablet is administered under fasted conditions)
0	0	0X	0X
1.0	0.33X	0.25X	0.12X
6.0	2.00X	1.48X	0.72X
50.0	16.67X	10.16X	4.88X

[1]Dose administered in target animal safety study (Study 06NG032) divided by 3 (1X mg/kg/day dose where X is defined as the maximum dose a dog could receive (i.e. 3 mg/kg/day) when dose with the whole or half tablets at the labeled dose of 2 mg/kg).

[2]AUC= Area under the grapiprant versus time curve

[3]The tablet equivalents are estimated by dividing the grapiprant methylcellulose suspension doses in the target animal safety study (Study 06NG032), assuming that it was administered under fasted conditions, by the mean relative bioavailability ratio of GALLIPRANT tablet/suspension (Study AT001-CPK-13-010) when compared in the fasted state. The mean ratio for the 1 and 6 mg/kg dose is 1.34 (the corresponding upper and lower 90% confidence limits about the ratio of treatment means =1.10 and 1.62, respectively). The mean ratio for the 50 mg/kg dose is 1.64 (the corresponding upper and lower 90% confidence limits about the ratio of treatment means =1.26 and 2.14, respectively).

[4]The tablet equivalents are estimated by dividing the grapiprant methylcellulose suspension doses in the target animal safety study (Study 06NG032), assuming that it was administered under fed conditions. The mean relative bioavailability ratio of GALLIPRANT tablet/suspension (Study AT001-CPK-13-010) when compared in the fasted state, was corrected for the mean relative bioavailability ratio of fed/fasted grapiprant methylcellulose suspension (Study AT001-CPK-12-009). The ratio of GALLIPRANT suspension administered fed/fasted at 2 mg/kg suspension dose is 0.48 (the corresponding upper and lower 90% confidence limits about the ratio of treatment means =0.30 and 0.76, respectively)

6. Estimation of the multiples of the 1X dose (tablet fasted state) is based upon the following relationships (using the 50 mg/kg suspension as an example):

   a. Establish a bridge between Suspension (Fed) vs Tablet (Fasted)

      (1) Consider Tablet (fasted)/Suspension (fasted) = 1.64;

      (2) To account for differences in bioavailability under fed conditions, the ratio would be Tablet (fasted)*0.37/Suspension (fasted)*0.48. Since Tablet (fasted)/Suspension (fasted) = 1.64, this equation can be recalculated as (0.37/0.48)*1.64 = 1.26.

      (3) If the tablets are to be administered with food, the observed margin of safety would be divided by 1.26. However, as dogs in the safety study may have been in the fed state and the tablet can be given in the fasted state, the ratio can be expressed as Tablet (fasted)/suspension (fasted)*0.48. The corresponding relationship can be written as 1.64/0.48 = 3.42.

(4) Determine the multiples of the 1X dose relative to a fasted tablet using the highest mg/kg dose in the dose band: If the 50 mg dose provides a 16.7-fold exposure (relative to suspension fed, 3 mg dose), then the fasted tablet would be 16.7/3.42 = 4.88.

7. Conclusions: Administration of grapiprant as GALLIPRANT tablets to dogs resulted in exposure to grapiprant that was 1.34-1.64 fold higher than the levels of exposure observed when grapiprant was administered as a methylcellulose suspension.

C. Field Safety and other safety studies:

To test the estimated effective canine dose, a masked, randomized, placebo-controlled, multi-centered dose ranging field study was conducted using dogs with naturally occurring osteoarthritis of one or more appendicular joints. Dogs received GALLIPRANT tablets at doses of 2 mg/kg once daily (N=94), 5 mg/kg once daily (N=90), 4 mg/kg twice daily (N=94), or placebo twice daily (N=88) for 28 days. The most common adverse reactions related to treatment were diarrhea, vomiting and inappetence, with increasing incidence in the 5 mg/kg once daily and 4 mg/kg twice daily groups. The 2 mg/kg once daily dose group and the placebo group had similar incidence rates for these adverse events. Changes in clinical pathology included concurrent elevations of alkaline phosphatase and alanine aminotransferase values on Day 28, and dose-dependent decreases in total protein values. There was no clinical impact related to these clinical pathology changes.

In Study AT001-CL-003, a dose ranging study, one dog receiving 2 mg/kg twice daily of grapiprant developed mild ulcers on the upper lip. In a one month toxicity study, vomiting, mucous and loose stools and/or bloody stools and diarrhea were seen at 30 mg/kg dosing. One dog in the 30 mg/kg dose group had focal inflammation in the jejunal and ileal mucosa.

IV.   HUMAN FOOD SAFETY:

This drug is intended for use in dogs, which are non-food animals. 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 GALLIPRANT tablets.

"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. To report suspected adverse drug events and/or obtain a copy of the Safety Data Sheet (SDS) or for technical assistance call Aratana Therapeutics at 1-844-640-5500."

VI.   AGENCY CONCLUSIONS

The data submitted in support of this NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and 21 CFR part 514. The data

demonstrate that GALLIPRANT, when used according to the label, is safe and effective for the control of pain and inflammation associated with osteoarthritis in dogs.

A. Marketing Status

The drug is restricted to use by or on the order of, a licensed veterinarian because professional expertise is needed to diagnose and provide guidance in the control of osteoarthritis pain. Furthermore, the veterinarian monitors patients for possible adverse effects of the drug.

B. Exclusivity

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

C. Patent Information:

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