Date of Approval: August 12, 2016

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-461

NOCITA

bupivacaine liposome injectable suspension

Dog

For single-dose infiltration into the surgical site to produce local postoperative analgesia for cranial cruciate ligament surgery in dogs

Sponsored by:

Aratana Therapeutics, Inc.

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I. GENERAL INFORMATION

A. File Number

NADA 141-461

B. Sponsor

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

Drug Labeler Code: 086026

C. Proprietary Name

NOCITA

D. Product Established Name

Bupivacaine liposome injectable suspension

E. Pharmacological Category

Local anesthetic

F. Dosage Form

Injectable suspension

G. Amount of Active Ingredient

13.3 mg/mL

H. How Supplied

20 mL vial

I. Dispensing Status

Rx

J. Dosage Regimen

NOCITA is for single dose administration only. A dose of 5.3 mg/kg (0.4 mL/kg) is administered by infiltration injection into the tissue layers at the time of incisional closure. A single dose administered during surgical closure may provide up to 72 hours of pain control.

K. Route of Administration

Infiltration injection

L. Species

Dog

M. Indication

For single-dose infiltration into the surgical site to produce local postoperative analgesia for cranial cruciate ligament surgery in dogs.

II. EFFECTIVENESS

A. Dosage Characterization

Pilot Field Study
Forty-six client-owned dogs were enrolled in a masked, randomized, placebo-controlled pilot field study to evaluate a dose of 5.3 mg/kg of NOCITA (bupivacaine liposome injectable suspension) for post-operative analgesia following cranial cruciate ligament surgery. Dogs were randomly assigned to receive NOCITA or saline. Treatment was administered during surgical closure into the surgical tissue layers using an infiltrative injection technique. NOCITA was administered undiluted or diluted up to 1:1 with sterile saline. Post-operative pain was assessed using the Glasgow Composite Measure Pain Scale (CMPS-SF) for up to 72 hours post-surgery. Fewer dogs treated with NOCITA required rescue analgesia compared to the saline placebo group for each pain assessment time point. Based on the results of this study, a dose of 5.3 mg/kg was chosen for evaluation in a field study to confirm the effectiveness of NOCITA.

B. Substantial Evidence

Title: A Placebo-Controlled Pivotal Clinical Field Study to Confirm the Safety and Effectiveness of AT-003 to Provide Local Post-Surgical Analgesia in Dogs. Study No. AT003-CCL-14-003.

Study Dates: December 2014-May 2015

Study Locations:
Quakertown, PA
Williston, VT
Fort Collins, CO
Coral Springs, FL
Springfield, MO

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

Objective: To determine the safety and effectiveness of NOCITA for local post-surgical analgesia in dogs undergoing cranial cruciate ligament (CCL) surgery.

Study Animals: Dogs with a cranial cruciate ligament injury that were otherwise healthy based on physical examination and clinical pathology. There were 82 spayed females, 80 neutered males, and 2 intact males enrolled. The most commonly enrolled breed classification was large sized mixed breeds (38.1%), Labrador Retrievers (9.8%), and then small sized mixed breeds (6.7%). Dogs

ranged in age from 1 to 13 years, and weighed 3.4 to 61.3 kg, at the time of surgery and treatment. Surgical procedures conducted during the study included tibial plateau leveling osteotomy (TPLO), lateral suture stabilization (extra-capsular repair), and tibial tuberosity advancement (TTA).

Treatment Groups:

Table 1. Treatment Groups

Treatment Group	**Dose**	**Number of Dogs Enrolled**	**Per Protocol Population**
NOCITA	5.3 mg/kg	123	112
Placebo (saline)	0.4 mL/kg	59	52

Housing: Dogs were hospitalized for 3 days following surgery.

Randomization and Masking: Personnel that performed pain assessments were masked to treatment group assignment. The surgeon was not masked to treatment group assignment and did not participate in pain assessments.

Inclusion Criteria: Signed owner consent; dog was at least 5 months old, and diagnosed within the last 4 months with a cranial cruciate ligament (CCL) injury.

Exclusion Criteria: Bilateral CCL injury; chronic pain in the surgical joint or other concurrent painful condition; uncontrolled endocrine or systemic disease; invasive surgical procedure within 14 days or orthopedic surgery within 60 days prior to enrollment; treatment with topical or systemic anti-inflammatory products, NSAIDs, analgesics, or other pain modulating drugs within 48 hours of surgery; treatment with tramadol within 24 hours of surgery; behavioral issues that would interfere with the pain assessments; or intolerance to general anesthesia and opioid analgesics.

General Anesthesia and Surgical Procedure: All dogs received preanesthetic medications and analgesia (phenothiazine and opioid class drug) by intravenous (IV) or intramuscular (IM) injection. Propofol was administered for anesthesia induction, and isoflurane with or without nitrous oxide gas was used for anesthetic maintenance. All dogs received IV fluids during general anesthesia and surgery. Use of additional systemic, local, or regional anesthesia (epidural, nerve block, intra-articular, skin patches, etc.) was not permitted. Concomitant medications such as antibiotics and anti-emetics were allowed during the peri-operative period.

All dogs underwent a CCL stabilization surgery. See Table 2 below for the number and percent of dogs that received each type of CCL stabilization.

Table 2. Surgical Procedure by Treatment Group in the Per Protocol Population

Surgical Procedure	**NOCITA N=112 n (%)**	**Placebo N=52 n (%)**	**Total N=164 n (%)**
Extra-capsular repair	52 (46.4)	24 (46.2)	76 (46.3)
TPLO[a]	50 (44.6)	22 (42.3)	72 (43.9)
TTA[b]	10 (8.9)	6 (11.5)	16 (9.8)

[a] Tibial plateau leveling osteotomy
[b] Tibial tuberosity advancement

Dose Administration: NOCITA (bupivacaine liposome injectable suspension) was administered at 5.3 mg/kg (0.4 mL/kg) and could be diluted up to 1:1 with sterile saline to create a volume that was adequate to cover the surgical site. Placebo group dogs were administered 0.4 mL/kg sterile saline; placebo doses were not diluted. NOCITA or sterile saline was administered into the tissue layers during surgical closure by use of infiltration injection.

Measurements and Observations: Prior to anesthesia and surgery, baseline physical examination (including heart rate, respiratory rate, body weight, and body temperature), hematology, serum chemistry, urinalysis, and pain assessments were performed. These were also assessed again at study end or at time of removal from the study.

Safety was monitored during the study by clinical observations and documentation of adverse events.

Pain assessments: Pain was assessed using the validated Glasgow Composite Measure Pain Scale-Short Form (CMPS-SF) by trained veterinarians and technicians. No more than three assessors evaluated each individual dog over the 3-day study schedule. Pain assessments were conducted prior to surgery (baseline), and at 0.5, 1, 2, 4, 8, 12, 24, 30, 36, 48, 56, and 72 hours post-surgery. Pain assessments were discontinued if a dog required rescue analgesia. Rescue analgesia was administered if the CMPS-SF score was ≥6, or if the Investigator determined the dog required additional analgesia regardless of the CMPS-SF score.

Statistical Methods: The analyses of the effectiveness variables were conducted on per protocol population, which comprised those dogs without significant protocol violations.

The effectiveness variable was the % successes over each time interval (0-24, 24-48, and 48-72 hours). Success was defined as no pain intervention. Conversely, a treatment failure was defined as having received pain intervention. The primary effectiveness variable was the % successes for the time interval from 0-24 hours. It was analyzed using a generalized linear mixed model as described below. If this variable achieved statistical significance, the tests of the following two secondary effectiveness variables were to be performed at alpha = 0.05, 2-sided in a sequential hierarchical manner based on a closed testing procedure. The secondary effectiveness endpoints were ranked in sequence according to the hierarchical order specified below:

- % successes from 24-48 hours
- % successes from 48-72 hours

Failures during the 0-24 hour interval were carried forward to the 24-48 hour interval. Similarly, failures during the 0-24 and 24-48 hour intervals were carried forward to the 48-72 hour interval.

The effectiveness variables (treatment success or failure) were 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. A 95% confidence interval was calculated for the difference in success rates between treatment groups.

Criteria for Success/Failure: Success was defined as a statistically significantly greater proportion of treatment successes in the NOCITA group compared to the placebo group.

Results:

Effectiveness: Effectiveness was evaluated in 164 dogs that underwent CCL surgery (112 dogs in the NOCITA group and 52 in the placebo group). Treatment success was defined for each dog as no pain intervention over the interval of 0-24 hours post-surgery.

The observed success rates for the 0-24 hour interval are summarized in Table 3 below.

Table 3. Number and Percent Effectiveness for NOCITA and Placebo at the 0-24 Hour Time Interval

Time Interval for Pain Assessment	NOCITA (n=112)	Placebo (n=52)
0-24 hours	77 (68.8%)	19 (36.5%)

Based on the statistical model, the estimated success rates are 68.3% and 36.1% for the NOCITA group and the placebo group, respectively. The difference in success rates is significant at P=0.0322.

Pain assessments for 24-72 hours: For dogs that were treatment successes during the 0-24 hour time interval, pain assessments were evaluated for up to 72 hours. For dogs that were deemed treatment failures over the interval of 0-24 hours, the failure was carried forward to all subsequent time intervals. Treatment failures from 24-48 hour interval were carried forward to the 48-72 hour interval.

The observed success rates for the 24-48 and 48-72 hour intervals are summarized in Table 4 below.

Table 4. Number and Percent Effectiveness for NOCITA and Placebo at the 24-48 Hour and 48-72 Hour Time Intervals

Time Interval for Pain Assessment	**NOCITA (n=112)**	**Placebo (n=52)**
24-48 hours	72 (64.3%)	18 (34.6%)
48-72 hours	69 (61.6%)	17 (32.7%)

For the 24-48 hour interval, based on the statistical model, the estimated success rates are 65.4% and 35.8% for the NOCITA group and the placebo groups, respectively. The difference in success rates is significant at P=0.0402. For the 48-72 hour interval, based on the statistical model, the estimated success rates are 61.6% and 32.7% for the NOCITA group and the placebo groups, respectively. The difference in success rates is significant at P=0.0432.

Group Mean Glasgow Pain Scale Short Form (CMPS-SF) Scores: The mean total CMPS-SF scores at baseline (pre-surgical) evaluation were 1.90 for the NOCITA group and 1.35 for the placebo group. The mean scores for the NOCITA group were less than those of the placebo group at each time point on Day 0. By the 24-hour assessment, 31 dogs in the placebo group had already received rescue pain intervention, and no further scores were obtained for these dogs.

Physical Examination: There were no new abnormalities noted during physical examination at early removal or study end, except for those related to the surgical procedure and incision. These findings were reported as adverse reactions (see below).

Clinical Pathology: There were no clinically significant changes in clinical pathology values (hematology, serum chemistry, and urinalysis) between groups during the study. If a clinical pathology value was normal at baseline and abnormal at the follow-up evaluation, the abnormality was reported as an adverse reaction.

Adverse Reactions: Adverse reactions were recording using VeDDRA terms by the Investigators. Field safety was evaluated in all 182 dogs (123 dogs in the NOCITA group and 59 dogs in the placebo group). The following adverse reactions were reported during the study.

Table 5: Adverse Reactions Reported During the Study in the Safety Population (any dog that received treatment)

Adverse Reaction	**NOCITA (N=123)**	**Placebo (N=59)**
Discharge from the Incision	4 (3.3%)	0 (0.0%)
Incisional Inflammation (erythema and/or edema)	3 (2.4%)	0 (0.0%)
Vomiting	3 (2.4%)	0 (0.0%)
Abnormalities on Urinalysis (isosthenuria ± proteinuria)	2 (1.6%)	0 (0.0%)
Increased ALP	2 (1.6%)	0 (0.0%)
Fever	1 (0.8%)	0 (0.0%)
Surgical Limb Edema ±Erythema	1 (0.8%)	3 (5.1%)
Soft Stool/Diarrhea	1 (0.8%)	1 (1.7%)
Inappetence	1 (0.8%)	1 (1.7%)

Note: If an animal experienced the same event more than once, only the first occurrence was tabulated

Conclusions: Treatment with NOCITA dosed at 5.3 mg/kg by infiltration injection into the tissues layers during surgical closure following cranial cruciate ligament (CCL) surgery was safe and provided post-operative analgesia for up to 72 hours in dogs.

III. TARGET ANIMAL SAFETY

Title: SKY0402: A Subcutaneous Toxicity Study with Twice weekly Dosing for Four Weeks in Dogs, Study No. 947-037.

Type of Study: Laboratory study conducted according to Good Laboratory Practices (GLP)

Study Dates: September 10, 2007 to November 2, 2007

Study Location: Mattawan, MI

Study Design:

Objective: To evaluate the local and systemic toxicity of twice-weekly subcutaneous injections with NOCITA (bupivacaine liposome injectable suspension) for 4 weeks, and to evaluate the reversibility, progression, or delayed appearance of any observed changes during a 4-week post-treatment observation period.

Study Animals: Sixty Beagle dogs (30 males, 30 females), aged 5-6 months old at receipt, determined as healthy based on physical examination, clinical pathology, and fecal parasitology.

Treatment Groups and Drug Administration: Dogs were randomized to saline (0.9% sodium chloride, USP), bupivacaine HCl, or NOCITA (bupivacaine liposome injectable suspension).

Table 6. Treatment Groups and Dosages

Treatment Group	**Dose (mg/kg)**	**Volume (mL/kg)**	**Dose Multiple**	**Number of Dogs**
Saline	1.2	1.2	0X	6 male 6 female
Bupivacaine HCl, 7.5 mg/mL	9	1.2	n/a	6 male 6 female
NOCITA[a], 15 mg/mL	9	0.6	1.5X	6 male 6 female
NOCITA[a], 15 mg/mL	18	1.2	3X	6 male 6 female
NOCITA[a], 25 mg/mL	30	1.2	5X	6 male 6 female

[a] 5.3 mg/kg NOCITA bupivacaine base is equal to 6 mg/kg bupivacaine HCl. NOCITA doses in this table are in the bupivacaine HCl equivalent.

Dose Administration: Doses were administered by subcutaneous injection, twice weekly for 4 weeks. Injection administration was to the left or right of dorsal midline, and alternated between injection Site 1 and Site 2. The coat was shaved prior to dose administration and the sites marked and numbered. The dose was administered at Site 1 on Days 1, 8, 15, and 22, and at Site 2 on Days 4, 11, 18, and 25.

Study Schedule: All dogs were administered drug twice-weekly for 4 weeks. Three dogs/sex/group were then evaluated at necropsy (terminal group) one day after the last dose was administered. The remaining dogs were observed for an additional 4-week recovery period before evaluation at necropsy (recovery group).

Variables Measured: Observations for mortality, morbidity, and injury were conducted twice daily, and food consumption was measured daily for all animals. Detailed clinical observations were conducted weekly. Body weights were measured and recorded pretest and weekly. Food consumption was measured and recorded daily. Electrocardiographic examinations were conducted pretest, pre-dose, and at 1 hour post dose (± 15 min) on Day 22 (Terminal), and on Day 50 (Recovery). Blood and urine samples for clinical pathology evaluations were collected from all animals pretest and prior to terminal and recovery necropsies. Blood samples for determination of the plasma concentrations of bupivacaine were collected from the three animals/sex/group designated for recovery at designated time points on Days 1 and 25. The toxicokinetic parameters were determined for bupivacaine from plasma concentration-time data. At the end of terminal and recovery periods, necropsy

examinations were performed, organ weights were recorded, and selected tissues were microscopically examined.

Statistical Methods: Analysis of variance was used to evaluate all continuous variables. Models included treatment, sex and the treatment-by-sex interaction as fixed effects. For variables measured more than once throughout the study, the following fixed effects were also included: time and the interactions treatment-by-time, sex-by-time and treatment-by-sex-by-time. If pre-treatment values existed, the value closest to the first treatment administration was included as a covariate.

Results:
Clinical Observations and Examinations: There were no clinically relevant findings in the NOCITA and bupivacaine HCl groups compared to the saline group.

Electrocardiogram (ECG): There were no clinically relevant effects on ECG for any of the groups during the study. The ECG variables remained within the normal intervals and durations for dogs.

Body weight: There were no clinically relevant effects on body weight for any of the groups during the study.

Food Consumption: There were no clinically relevant effects on food consumption for any of the groups during the study.

Clinical Pathology: There were no clinically relevant findings for hematology, serum chemistry, and urinalysis variables in any of the treatment groups. There were no test-article effects on prothrombin time (PT) and activated partial thromboplastin time (APTT).

Necropsy Examination: Swollen or thickened injection sites were noted in one male and one female dog in the NOCITA 30 mg/kg terminal group. The swollen or thickened injection sites corresponded with granulomatous inflammation and/or edema and were considered treatment-related.

Red discoloration at injection sites was noted in one male dog in the NOCITA 9 mg/kg recovery group, one female dog in the NOCITA 18 mg/kg terminal group, and one male and one female dog in the NOCITA 30 mg/kg terminal group. Red discoloration at injection sites was only seen in one male dog in the bupivacaine HCl terminal group, and was not seen in any dogs in the saline group. Often there was no microscopic correlate to the red discoloration at the injection sites. In these cases the toxicological significance of the macroscopic finding was unknown. Rarely the red discoloration corresponded with hemorrhage, edema, and/or subacute subcutaneous inflammation.

Organ Weights: There were no clinically relevant treatment-related effects on organ weights.

Histopathology: Treatment-related microscopic findings were present in the injection sites of male and female terminal and recovery dogs receiving NOCITA. Minimal to moderate granulomatous inflammation was observed in the subcutaneous tissue of male and female terminal and recovery dogs receiving NOCITA. In the terminal dogs, granulomatous inflammation was characterized by numerous vacuolated

macrophages and fewer lymphocytes, plasma cells, and/or multinucleated giant cells. The inflammation was often associated with edema and/or mineralization. Giant cells were primarily observed when mineralization was present. The mineral deposits may be related to small amounts of foreign matter (i.e. liposome particles) in the loose connective tissues of the subcutaneous space. The mineral deposits were usually surrounded by multinucleated giant cells.

In recovery dogs, the granulomatous inflammation was observed in a fewer number of animals and was characterized by a greater number of giant cells sometimes often associated with mineralization but not edema. In one male recovery dog in the NOCITA 9 mg/kg group, minimal subcutaneous edema not associated with inflammation was noted.

Subcutaneous granulomatous inflammation was not observed in terminal or recovery dogs receiving saline or bupivacaine HCl. The subcutaneous granulomatous inflammation associated with NOCITA was observed in the recovery dogs at four weeks after the last injection. The granulomatous inflammation associated with NOCITA was considered a tissue response to the presence of liposomes.

Table 7. NOCITA Related Injection Site Histopathology in Terminal Group Dogs

Injection Site Findings		**NOCITA[a] 9 mg/kg (n=6)**	**NOCITA[a] 18 mg/kg (n=6)**	**NOCITA[a] 30 mg/kg (n=6)**
Injection Site 1	Edema	1/6	2/6	N/A
	Granulomatous Inflammation	3/6	4/6	3/6
	Mineralization	1/6	3/6	1/6
Injection Site 2	Edema	1/6	3/6	4/6
	Granulomatous Inflammation	3/6	5/6	5/6
	Mineralization	2/6	2/6	2/6

[a] 5.3 mg/kg NOCITA bupivacaine base is equal to 6 mg/kg bupivacaine HCl. NOCITA doses in this table are in the bupivacaine HCl equivalent.

Table 8. NOCITA Related Injection Site Microscopic Findings in Recovery Group Dogs

Injection Site Findings		**NOCITA[a] 9 mg/kg (n=6)**	**NOCITA[a] 18 mg/kg (n=6)**	**NOCITA[a] 30 mg/kg (n=6)**
Injection Site 1	Edema	1/6	N/A	N/A
	Granulomatous Inflammation	none	1/6	2/6
	Mineralization	none	1/6	2/6
Injection Site 2	Edema	none	none	none
	Granulomatous Inflammation	2/6	none	1/6
	Mineralization	2/6	1/6	none

[a] 5.3 mg/kg NOCITA bupivacaine base is equal to 6 mg/kg bupivacaine HCl. NOCITA doses in this table are in the bupivacaine HCl equivalent.

Plasma Pharmacokinetic Analysis: Blood samples were collected from three dogs/sex/group designated for recovery for determination of the plasma concentrations of bupivacaine for toxicokinetic assessments. The blood samples were collected prior to dosing and at 0.5, 1, 2, 4, 8, 12, 24, 48, and 72 hours post-dose on Days 1 and 25. $AUC_{0\text{-tlast}}$ was estimated using the linear trapezoidal rule from pre-dose (Days 1 and 25) to the last time associated with quantifiable concentration. The pharmacokinetic (PK) parameters are provided table 9.

Table 9. Mean (± SD) Pharmacokinetic Parameters for Bupivacaine After Subcutaneous Administration of NOCITA or Bupivacaine HCl

Dosing Day	Treatment	Bupivacaine (mg/kg)	$AUC_{0\text{-tlast}}$ (hour·ng/mL)	$AUC_{0\text{-tlast}}$/Dose (hour·ng/mL)	C_{max} (ng/mL)	C_{max}/Dose (ng/mL)	$t_{1/2}$[a] (hour)	t_{max} (hour)
1	Bupiv. HCl	9	9,720 ± 1,860	1,080 ± 207	1,420 ± 355	158 ± 39.5	16.9 ± 6.05	0.5 ± 0.0
1	NOCITA[b]	9	9,100 ± 4,460	1,010 ± 495	488 ± 335	54.2 ± 37.2	59.5 ± 49.1[a]	0.5 ± 0.0
1	NOCITA[b]	18	12,800 ± 2,020	711 ± 112	560 ± 299	31.1 ± 16.6	104 ± 105	0.5 ± 0.0
1	NOCITA[b]	30	25,600 ± 8,160	853 ± 272	633 ± 280	21.1 ± 9.34	31.8[a]	48.1± 30.2
25	Bupiv. HCl	9	9,120 ± 4,090	1,010 ± 455	1,990 ± 304	221 ± 33.8	10.1 ± 8.54	0.5 ± 0.0
25	NOCITA[b]	9	17,300 ± 8,710	1,920 ± 968	1,200 ± 301	133 ± 33.4	36.2 ± 12.4	0.5 ± 0.0
25	NOCITA[b]	18	24,300 ± 8,960	1,350 ± 498	1,310 ± 521	72.6 ± 28.9	25.7 ± 8.15	0.75 ± 0.61
25	NOCITA[b]	30	43,800 ± 23,300	1,460 ± 777	910 ± 433	30.3 ± 14.4	43.9 ± 12.5[a]	12.8 ± 18.0

[a] Parameter not calculated in dog 118 (9 mg/kg, Day 1), dog 140, 141, 142 and 147 (30 mg/kg, Day 1), and 141 (30 mg/kg, Day 25) due to insufficient number of data points during the terminal phase to estimate a reliable plasma half-life.

[b] 5.3 mg/kg NOCITA bupivacaine base is equal to 6 mg/kg bupivacaine HCl. NOCITA doses in this table are in the bupivacaine HCl equivalent.

On Day 1, the bupivacaine PK parameters (T_{max}, and $AUC_{0\text{-}t}$) were comparable following both bupivacaine HCl and NOCITA. The $t_{1/2}$ was longer for NOCITA as compared to that of bupivacaine HCl. The difference in $t_{1/2}$ was consistent following repeat dose and probably reflects a stabilization of terminal concentration at steady state. The time to reach maximum concentration was rapid and occurred at the first time point (0.5 hr) for the 9 and 18 mg/kg doses. For the 30 mg/kg dose group, the T_{max} occurred at 48.1 and 12.8 hours on Day 1 and Day 25, respectively. The mean C_{max} and AUC0-t both increase with dose but the increases were less than dose proportional. The repeated dose of bupivacaine HCl did not result in any accumulation. The repeated dose of NOCITA resulted in moderate accumulation with AUC0-t ratio on Day 25 versus Day 1 of approximately 2 across the dose levels. There were no gender differences in the PK of bupivacaine.

Conclusions: NOCITA administered as a subcutaneous injection, twice-weekly for 4 weeks, at 9, 18, and 30 mg/kg (bupivacaine base equivalent of 5.3, 16, and 26.6 mg/kg) did not produce systemic toxicity and had a high margin of safety. Local granulomatous inflammation occurred at the injection sites of dogs from all NOCITA groups, and some dogs had grossly visible redness, thickening, or inflammation at the injection sites. This finding is consistent with local exposure to the liposome component of NOCITA. This study supports the safe use of NOCITA, administered at 5.3 mg/kg by infiltration injection into the surgical site, in dogs.

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 NOCITA:

Not for use in humans. Keep out of reach of children.

NOCITA is an amide local anesthetic. In case of accidental injection or accidental topical exposure, contact a physician and seek medical attention immediately.

Wear gloves when handling vials to prevent accidental topical exposure.

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 NOCITA, when used according to the label, is safe and effective for single-dose infiltration into the surgical site to produce local postoperative analgesia for cranial cruciate ligament surgery in dogs.

A. Marketing Status

This product may be dispensed only by or on the lawful order of a licensed veterinarian (Rx marketing status). Adequate directions for lay use cannot be written because professional expertise is required to properly administer the injection during surgery and monitor the safe use of the product, including management of any adverse reactions.

B. Exclusivity

NOCITA, 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.