Date of Approval: August 3, 2018

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-461

NOCITA®

bupivacaine liposome injectable suspension

Cats

This supplement provides for use as a peripheral nerve block to provide regional postoperative analgesia following onychectomy in cats.

Sponsored by:

Aratana Therapeutics, Inc.

Table of Contents

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 vials

I. Dispensing Status

Rx

J. Dosage Regimen

NOCITA® is for administration only once prior to surgery. Administer 5.3 mg/kg per forelimb (0.4 mL/kg per forelimb, for a total dose of 10.6 mg/kg per cat) as a 4-point nerve block prior to onychectomy. Administration prior to surgery may provide up to 72 hours of pain control.

K. Route of Administration

Perineural

L. Species

Cats

M. Indication

For use as a peripheral nerve block to provide regional postoperative analgesia following onychectomy in cats.

N. Effect of Supplement

This supplement provides the addition of the indication for use as a peripheral nerve block to provide regional postoperative analgesia following onychectomy in cats.

II. EFFECTIVENESS

A. Dosage Characterization

Pilot Field Study
Sixty-two client-owned cats were presented for elective surgery and enrolled in a masked, randomized, placebo-controlled pilot field study to evaluate a total dose of 5.3 mg/kg per forelimb (total dose of 10.6 mg/kg per cat) of NOCITA® (bupivacaine liposome injectable suspension) for post-operative analgesia following bilateral forelimb onychectomy. All cats received a short-acting opioid analgesic prior to surgery and were randomly assigned to receive NOCITA® or saline (placebo). Treatment was administered after anesthesia induction and prior to surgery, as a 4-point nerve block. Post-operative pain was assessed using a modified version of the UNESP-Botucatu Multidimensional Composite Pain Scale for up to 72 hours post-surgery. See the Effectiveness clinical field study design below for a description of the pain scale. Cats considered painful based on the score using the pain scale or based on the investigator's assessment were administered additional pain medication (rescue analgesia). Fewer cats treated with NOCITA® required rescue analgesia compared to the saline group. Adverse reactions included swelling, discharge, infection at the surgical site, injection site bruising, lameness, and a motor deficit (unilateral knuckling). Based on the results of this study, a dose of 5.3 mg/kg per forelimb (total dose of 10.6 mg/kg per cat) was chosen for evaluation in a field study to confirm the effectiveness of NOCITA® to provide regional post-operative analgesia for onychectomy in cats.

B. Substantial Evidence

The effectiveness of NOCITA® was demonstrated in the clinical field study described below. Two hundred and forty-one client-owned cats were presented for elective surgery. All cats received a short-acting opioid analgesic prior to surgery and were randomly assigned to receive NOCITA® or saline (placebo). One hundred and twenty cats were administered NOCITA® at 5.3 mg/kg per forelimb as a 4-point peripheral nerve block. Post-operative pain was assessed using a modified version of the UNESP-Botucatu Multidimensional Composite Pain Scale for up to 72 hours post-surgery. Cats considered painful based on the score using the pain scale or based on the investigator's assessment were administered additional pain medication (rescue analgesia). Fewer cats treated with NOCITA® required rescue analgesia compared to the saline group. NOCITA® was found to be safe and effective for regional postoperative analgesia for up to 72 hours following

onychectomy in cats. Adverse reactions observed in the field study were infrequent, and included elevated body temperature, surgical site infection, chewing and licking of the surgical site, diarrhea, injection site erythema, and swelling of paw with erythematous digits. CVM concluded that NOCITA® is safe and effective when used according to prescribing instructions.

Title: A placebo-controlled pivotal clinical field study to confirm the safety and effectiveness of AT 003 to provide post-surgical analgesia when used as a nerve block for onychectomy in cats. Study number AT003-FCL-008

Study Dates: June 2016 – October 2017

Study Locations:
Bartonville, IL
Decatur, IL
Battle Creek, MI
Grand Rapids, MI
Springfield, MO
Harrisburg, PA
Quakertown, PA
Wichita Falls, TX

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

Objective: To determine the safety and effectiveness of NOCITA® for use as a peripheral nerve block to provide regional postoperative analgesia in cats undergoing bilateral forelimb onychectomy. Conducted in accordance with Good Clinical Practice.

Study Animals: The study enrolled 241 cats presented for elective bilateral forelimb onychectomy surgery that were healthy based on physical examination and clinical pathology. Cats ranged in age from 5 months to 10 years, and in weight from 2.0 to 9.3 kg, at the time of surgery and treatment. Most cats, 200/241 (82.9%), were under 2 years of age at the time of surgery on Day 0. There were 90 neutered males, 69 spayed females, 42 intact males, and 40 intact females enrolled. The most commonly enrolled breed classifications were domestic short-hair (77.2%), domestic long-hair (7.5%), domestic medium-hair (7.1%), and Siamese (4.6%).

Experimental Design:

Treatment Groups:

Table II.1. Treatment Groups

Treatment Group*	Dose	Number of Cats Enrolled
NOCITA®	5.3 mg/kg	120
Saline (placebo)	0.4 mL/kg	121

*All cats in both treatment groups received an opioid analgesic prior to surgery.

Housing: Cats were hospitalized for 3 days following surgery.

Randomization and Masking: Cases were randomized as they were deemed eligible for enrollment. The electronic data capture system (EDCS) automatically randomized cases using site-specific randomization tables. 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; cat was at least 5 months old, healthy and presented for bilateral forelimb onychectomy.

Exclusion Criteria: Cats undergoing concurrent surgical procedure(s); invasive surgical procedure within 14 days; concurrent painful condition; uncontrolled systemic disorders such as diabetes mellitus, hyperthyroidism, etc.; heart murmurs, unless previously established or heard only at elevated heart rate; treatment with topical or systemic anti-inflammatory products such as steroids, aspirin, or non-steroidal anti-inflammatory drugs (NSAIDs), analgesics, or other pain modulating drugs within 48 hours of surgery; treatment with long-acting glucocorticoids within 14 days of surgery; treatment with sustained-release buprenorphine or other opioid within 7 days of surgery; vaccination within 3 days of surgery; behavioral issues that would interfere with the pain assessments; or intolerance to general anesthesia and opioid analgesics.

General Anesthesia: All cats received short acting preanesthetic analgesia (opioid class drug) by intravenous (IV) or intramuscular (IM) injection; use of an alpha-2 agonist at a low dose was optional. Anesthesia was induced with propofol, alfaxalone, or isoflurane and general anesthesia was maintained with isoflurane or sevoflurane. Cats received parenteral fluids during general anesthesia and surgery as needed. Use of additional systemic, local, or regional anesthesia (epidural, nerve block, intra-articular, transdermal, etc.) was not permitted, except for lidocaine on the arytenoids to aid endotracheal intubation. Concomitant medications such as antibiotics and anti-emetics were allowed during the peri-operative period.

Drug administration and surgery: The injection sites were shaved and a standard surgical preparation with chlorhexidine or povidone-iodine performed, based on standard practice at each hospital. NOCITA® vials are intended for single use. If multiple doses were needed from one vial, a single needle was inserted into the vial one time and, using aseptic technique, the drug was withdrawn into syringes by sequentially attaching and filling syringes as needed.

Prior to onychectomy, NOCITA® or saline (placebo) was administered as a 4-point nerve block using a 25 or 22 gauge needle as follows:

Table II.2. Locations of 4-point Nerve Block[1]

Nerve(s)	Dose (5.3 mg/kg per forelimb NOCITA® or 0.4 mL/kg per forelimb saline)	Percent of Total Volume Per Forelimb
(A) Superficial branch of the radial nerve	0.14 mL/kg	35%
(B) Dorsal branch of the ulnar nerve	0.08 mL/kg	20%
(C) Median nerve and superficial branch of the palmar branch of the ulnar nerve	0.16 mL/kg	40%
(D) Deep branch of the palmar branch of the ulnar nerve	0.02 mL/kg	5%

Following administration of NOCITA® or saline, cats underwent onychectomy using laser, scalpel, or guillotine nail trimmer, depending on the standard practice at each hospital. Surgical sites were closed using suture or tissue glue; one surgeon did not close the surgical sites. Use of bandaging was permitted and was standardized for each site.

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.

Safety was monitored during the study by clinical observations, clinical pathology, physical examinations, and documentation of adverse events.

Pain assessments: Pain was assessed by trained veterinarians and technicians using a modified version of the UNESP-Botucatu Multidimensional Composite Pain

[1] Location and relative volumes for the nerve blocks were based on: Enomoto M, Lascelles BDX, and Gerard MP. Defining the local nerve blocks for feline distal thoracic limb surgery: a cadaveric study. Journal of Feline Medicine and Surgery. 2016 18 (10): 838-845.

Scale. The full UNESP-Botucatu Multidimensional Composite Pain Scale[2] was validated in English with three subscales: 1) Pain Expression, 2) Psychomotor Change, and 3) Physiological Variables using cats undergoing ovariohysterectomy. The scale was modified for use in the field study to allow pain assessments following onychectomy. The modified scale used two subscales: 1) Pain Expression and 2) Psychomotor Change. Subscale 1 was modified by removing reference to reaction to palpation of the abdomen/flank. The final modified scale used in the field study had a total possible score of 21, with 9 points possible in subscale 1 and 12 points possible in subscale 2.

No more than three assessors evaluated each individual cat 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 cat required rescue analgesia. Rescue analgesia was administered if the composite pain score was ≥6, or if the assessor determined the cat required analgesia regardless of the pain score.

Statistical Methods:
The analyses of the effectiveness variables were conducted on per protocol populations, which comprised those cats without significant protocol deviations.

The effectiveness variable was the percent successes over each time interval (0-24, 0-48, and 0-72 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 percent successes for the time interval 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 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:

- Percent successes for 0-48 hours
- Percent successes for 0-72 hours

Failures during the 0-24 hour interval were carried forward and remained failures for the 0-48 hour and 0-72 hour intervals. Failures during the 0-48 hour interval were carried forward and remained failures for the 0-72 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.

[2] Brondani JT, Mama KR, Luna SP, Wright BD, Niyom S, Ambrosio J, Vogel PR, Padovani CR. Validation of the English version of the UNESP-Botucatu multidimensional composite pain scale for assessing postoperative pain in cats. BMC Vet Res 2013 Jul 17;9:143.

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

Results:
Effectiveness: Effectiveness was evaluated in 236 cats that underwent onychectomy (117 cats in the NOCITA® group and 119 in the saline group).

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

Table II.3. Number of Cats and Percent Effectiveness for NOCITA® and Saline at the 0-24 Hour Time Interval

Time Interval for Pain Assessment	NOCITA® (n=117)	Saline (n=119)
0-24 hours	88 (75.2%)	48 (40.3%)

The difference in success rates for the 0-24 hour interval is significant at p=0.0252.

The observed success rates for the 0-48 and 0-72 hour intervals are summarized in Table II.4 below.

Table II.4. Number of Cats and Percent Effectiveness for NOCITA® and Saline at the 0-48 Hour and 0-72 Hour Time Intervals

Time Interval for Pain Assessment	NOCITA®	Saline
0-48 hours	79/115 (68.7%)	41/118 (34.7%)
0-72 hours	78/114 (68.4%)	42/119 (35.3%)

The per protocol populations for effectiveness varied for each pain assessment time interval because of protocol deviations affecting only one of the three time intervals for some cats.

The difference in success rates for the 0-48 hour interval is significant at p=0.0395. The difference in success rates for the 0-72 hour interval is significant at p=0.0452.

Physical Examination: There were no new abnormalities noted during physical examination at study end except for those related to the forelimbs, including surgical sites. 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. Eight cats, 4 in each group, had normal platelet counts before treatment on

Day 0 and platelet counts below the reference range (155,000-641,000/µL) on Day 3. The 4 cats treated with NOCITA® had platelet counts ranging from 42,000 to 100,000/µL, and the 4 cats in the saline group had platelet counts ranging from 114,000 to 149,000/µL. Decreased platelet counts were not associated with clinical signs.

Adverse Reactions: Adverse reactions were recorded by the investigators. Field safety was evaluated in all 241 cats (120 cats in the NOCITA® group and 121 cats in the saline placebo group). The following adverse reactions were reported during the study.

Table II.5. Adverse Reactions Reported During the Study in the Safety Population (any cat that received treatment)

Adverse Reaction	NOCITA® (n=120)	Saline (n=121)
Elevated body temperature*	8 (6.7%)	5 (4.1%)
Surgical site infection	4 (3.3%)	1 (0.8%)
Chewing/licking of surgical site	3 (2.5%)	2 (1.7%)
Diarrhea	2 (1.7%)	1 (0.8%)
Injection site erythema	1 (0.8%)	0 (0.0%)
Swelling of paw; erythematous digits	1 (0.8%)	0 (0.0%)

Note: If an animal experienced the same event more than once, only the first occurrence was tabulated.
*Elevated body temperature was defined as temperature ≥ 103 ºF on Day 3 and normal before surgery. One of the NOCITA® treated cats had infection of one surgical site. No other cat with fever showed evidence of infection or illness.

Conclusions: Administration of NOCITA® at 5.3 mg/kg per forelimb as a 4-point peripheral nerve block is safe and effective for regional postoperative analgesia for up to 72 hours following onychectomy in cats.

III. TARGET ANIMAL SAFETY

The safety of NOCITA® administered as an injection for peripheral nerve block was evaluated in a laboratory study. The use of the femoral nerve injection site in the safety study allowed for administration of greater dose volumes than would have been possible at a more distal site of perineural administration. The higher doses allowed for the evaluation of systemic effects, as well as local effects on peripheral nerves and surrounding tissue, of NOCITA® in cats. Eight cats in each group were administered either NOCITA® at 10.6, 21.2, or 31.8 mg/kg; saline as a negative control; or bupivacaine HCl as an active control at 5.3 mg/kg, every 9 days for 3 doses. Impaired hindlimb function was observed in most cats administered NOCITA®. Bupivacaine produces local analgesia by deactivating sodium channels on the nerve membrane, preventing the generation and propagation of nerve impulses. Therefore, the observed impaired limb function was related to altered signal conduction in the femoral nerve due to the amount of drug administered at one site adjacent to the

nerve. One cat in the highest NOCITA® dose group (31.8 mg/kg) developed right hindlimb impairment and an open wound consistent with self-trauma near the stifle. The cat was euthanized due to progression of the wound. Chewing/licking at the surgical site was an adverse reaction observed in a small percentage of cats in the field study, but did not necessitate treatment beyond routine post-operative monitoring of the cat and the surgical and injection sites. Subacute or chronic inflammation was observed at the femoral nerve and at the injection site (in the skin, subcutis, or muscle) in most cats administered NOCITA®. This study supports the safe use of NOCITA® when administered as instructed as a peripheral nerve block with a total exposure of 10.6 mg/kg in cats.

A. Multi-dose Safety Study

Title: AT-003: Peripheral Nerve Block Target Animal Safety Study in Cats, Study No. 2175-007.

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

Study Dates: August 3, 2016 to June 8, 2017

Study Location: Mattawan, MI

Study Design:

Objective: To evaluate the safety of NOCITA®. The maximum labeled dose is 5.3 mg/kg for each forelimb. The study design resulted in administration of 10.6 mg/kg, 21.2 mg/kg, and 31.8 mg/kg NOCITA® per cat as a single injection for a femoral nerve block (which corresponds to 2X, 4X, and 6X the labeled dose per forelimb.)

Study Animals: Forty domestic short-haired cats (20 males, 20 females), approximately 5 months old, with a bodyweight range of 2.00 – 3.75 kg, determined as healthy based on physical examination, clinical pathology, electrocardiogram, and fecal parasitology.

Experimental Design: Cats were randomized to saline (0.9% sodium chloride, USP), bupivacaine HCl, or NOCITA®.

Table III.1. Treatment Groups and Dosages

Treatment Group	Dose (mg/kg)	Volume (mL/kg)	Number of Cats
Saline (negative control)	0	2.37	4 male 4 female
Bupivacaine HCl, (5 mg/mL, active control)	5.3	1.0	4 male 4 female
NOCITA®	10.6	0.79	4 male 4 female

Treatment Group	Dose (mg/kg)	Volume (mL/kg)	Number of Cats
NOCITA®	21.2	1.58	4 male 4 female
NOCITA®	31.8	2.37	4 male 4 female

Drug Administration: Doses were administered once on Days 0, 9, and 18 via injection for a femoral nerve block in the right hindlimb, using a suprainguinal approach. Cats were sedated with ketamine and acepromazine and maintained under general anesthesia using isoflurane in oxygen. The cats were positioned in left lateral recumbency with the right hindlimb abducted 90 degrees and extended caudally, and the sartorius, iliopsoas, and pectineus muscles were located as landmarks. A 22-gauge insulated needle with a nerve stimulator was advanced to the location of the femoral nerve in the inguinal region. After confirmation of location using the nerve stimulator and after ensuring avoidance of a vein or artery via aspiration, the dose contained within a pre-filled syringe was administered.

Study Schedule: All cats were administered doses on Days 0, 9, and 18, with the dosing schedule staggered for two cohorts (2 cats/sex/group/cohort). All cats were euthanized and evaluated at necropsy on Day 21.

Measurements and Observations: Observations for mortality, morbidity, and injury were conducted twice daily. Detailed clinical observations were conducted once daily. Physical examinations were conducted pre-study, prior to each dose, 24 hours (±1 hour) after each dose, and prior to necropsy on Day 21. Body weights were measured and recorded pre-study, prior to each dose, and prior to necropsy on Day 21. Electrocardiographic examinations were performed pre-study and prior to and after dosing (2 hours ±30 minutes post-dose) on Days 0 and 18. Blood and urine samples for clinical pathology evaluations were collected from all animals pre-study and prior to necropsy on Day 21. On Day 21, necropsy examinations were performed, organ weights were recorded, and selected tissues were examined microscopically.

Statistical Methods:
Statistical comparisons were performed for each treatment group including the bupivacaine treated active control group compared to the negative control group who received saline. Statistical comparisons were also performed for each NOCITA® group compared to the bupivacaine treated positive control.
Endpoints measured once post-treatment (organ weights) were analyzed using analysis of variance with 'treatment', 'sex', and 'treatment by sex' as fixed effects, and cohort as a random effect. Endpoints measured once post-treatment (clinical chemistry, hematology, coagulation, and urinalysis) that include a pre-treatment measurement were analyzed using analysis of covariance with 'treatment', 'sex', and 'treatment by sex' and a covariate all as fixed effects, and cohort as a random effect. The pre-treatment value closest to dosing was used as the covariate. Endpoints measured multiple times post-treatment that include a pre-treatment measurement (body weights and ECG parameters) were analyzed using repeated measures analysis of covariance with 'treatment', 'time', and 'sex'; the two-way

interactions 'treatment by time', 'treatment by sex', and 'sex by time'; the three-way interaction 'treatment by time by sex' and a covariate all as fixed effects, and cohort as a random effect. The pre-treatment value closest to dosing was used as the covariate.

Results:

Mortality and Morbidity: There were two unscheduled deaths during the study.

One active control male died after the second dose was administered. This cat died during recovery from anesthesia despite resuscitation efforts. The definitive cause of death was not determined.

The other cat, a female in the 31.8 mg/kg group, was euthanized on Day 15 due to progression and discomfort associated with an open and necrotic wound near the right stifle. This cat developed right hindlimb motor impairment as well as sparse and wet fur with small punctures (consistent with self-trauma) and erythema noted at the level of the right stifle after administration of the second dose. Pain medication, antibiotics, subcutaneous fluids, and wound care were provided. However, the area with the punctures progressed to discoloration and edema ultimately resulting in sloughing of the affected area such that the joint capsule was visible. This cat had clinical pathology findings consistent with inflammation. The histopathology findings of inflammation at the injection site and femoral nerve were similar to other NOCITA® treated cats. Histopathology findings at the stifle wound included inflammation, ulcer, cavitation, necrosis, and fibrosis.

Clinical observations and examinations: Right hindlimb impairment occurred in 23 of the 24 NOCITA® treated cats which persisted for 1-5 days; 2 negative control cats which persisted for 1 day; and none of the active control cats. Left hindlimb impairment was observed the day after the first dose in one cat in the 21.2 mg/kg group. All of the control and NOCITA® treated groups had observations of occasional soft, watery, or mucoid stool; inguinal swelling on the right hindlimb noted only after the first dose; and observations of scabbing or abrasion located on the right hindlimb, right inguinal area, and right abdominal region.

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

Electrocardiograms (ECG): There were no clinically relevant effects on ECG 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. One cat in the bupivacaine active control group, one cat in the 10.6 mg/kg group and one cat in the 21.2 mg/kg group had normal platelet counts prior to study start but decreased platelets at study termination (52,000, 83,000 and 50,000 platelets respectively, normal range 106,000-721,000/µL). There were no test-article effects on prothrombin time (PT), activated partial thromboplastin time (APTT), or fibrinogen.

Necropsy Examination: The Day 21 gross pathology findings were consistent with the reported clinical observation and examination findings. In addition, scabbing and abrasions were located at the right hindlimb, right inguinal area, and right

abdominal region for cats in both control groups and the 21.2 and 31.8 mg/kg treatment groups.

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

Histopathology: Treatment-related microscopic findings at the femoral nerve were subacute or chronic inflammation. Treatment-related microscopic findings at the injection site were subacute or chronic inflammation, mineralization, myofiber degeneration, and necrosis at the skin, subcutis, or muscle. Sporadic microscopic findings were axonal degeneration of the femoral nerve and the following findings at the skin, subcutis, or muscle: suppurative crust, ulcer, foreign material, fibrosis, and myofiber regeneration. The findings are represented below in Tables III.2a and III.2b.

Table III.2a Number of Cats and Percent with Histopathology Findings at the Femoral Nerve Injection Site

Finding	Negative Control (N=8)	Active Control (N=8)	NOCITA® 10.6 mg/kg (N=8)	NOCITA® 21.2 mg/kg (N=8)	NOCITA® 31.8 mg/kg (N=8)
Axonal degeneration	1 (12.5%)	1 (12.5%)	1 (12.5%)	1 (12.5%)	0 (0%)
Inflammation	1 (12.5%)	0 (0%)	7 (87.5%)	8 (100%)	8 (100%)

Table III.2b Number of Cats and Percent with Histopathology Findings at the Skin, Subcutis, or Muscle Injection Site

Finding	Negative Control (N=8)	Active Control (N=8)	NOCITA® 10.6 mg/kg (N=8)	NOCITA® 21.2 mg/kg (N=8)	NOCITA® 31.8 mg/kg (N=8)
Suppurative crust	1 (12.5%)	0 (0%)	1 (12.5%)	1 (12.5%)	1(12.5%)
Inflammation	3 (37.5 %)	5 (62.5%)	8 (100%)	7 (87.5%)	8 (100%)
Mineralization	0 (0%)	1 (12.5%)	7 (87.5%)	6 (75%)	6 (75%)
Myofiber degeneration or necrosis	2 (25%)	2 (25%)	3 (37.5%)	6 (75%)	6 (75%)
Myofiber regeneration	2 (25%)	4 (50%)	2 (25%)	2 (25%)	3 (37.5%)
Fibrosis	2 (25%)	1 (12.5%)	0 (0%)	1 (12.5%)	2 (25%)
Ulcer	1 (12.5%)	0 (0%)	1 (12.5%)	0 (0%)	2 (25%)
Foreign material (hair, keratin)	2 (25%)	3 (37.5%)	1 (12.5%)	0 (0%)	0 (0%)

Findings at the skin near the injection site on the right hindlimb were similar to injection site findings and included suppurative crust, ulceration, inflammation, minimal foreign material, and perivascular mononuclear cell infiltration.

Conclusion: NOCITA® administered as an injection for femoral nerve block, every 9 days for 3 doses, at 10.6, 21.2, and 31.8 mg/kg did not produce systemic toxicity and had an acceptable margin of safety. Impaired hindlimb function was

observed in most cats treated with NOCITA®. Subacute or chronic inflammation was observed at the femoral nerve and at the injection site (in the skin, subcutis, or muscle) in most cats administered NOCITA®. This study supports the safe use of NOCITA® when administered, according to the dosing instructions in the labeling, as a peripheral nerve block with a total exposure of 10.6 mg/kg in cats.

IV. HUMAN FOOD SAFETY

This drug is intended for use in cats. Because this new animal drug is not intended for use in food producing animals, CVM did not require data pertaining to drug residues in food (i.e., human food safety) for approval of this NADA.

V. USER SAFETY

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to 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 use as a peripheral nerve block to provide regional postoperative analgesia following onychectomy in cats.

A. Marketing Status

This product may be dispensed only by or on the lawful order of a licensed veterinarian (Rx marketing status). Adequate directions for lay use cannot be written because professional expertise is required for safe use and proper administration of the product. Furthermore, professional expertise is required to monitor for and respond to any adverse reactions.

B. Exclusivity

This supplemental approval for NOCITA® qualifies for THREE years of marketing exclusivity under section 512(c)(2)(F)(iii) of the FD&C Act because the supplemental application included safety and effectiveness studies. This exclusivity begins as of the date of our approval letter and only applies to the use as a peripheral nerve block to provide regional postoperative analgesia following onychectomy in cats.

C. Supplemental Applications

This supplemental NADA did not require a reevaluation of the safety and effectiveness data in the original NADA (21 CFR 514.106(b)(1)).

D. Patent Information:

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