

# NOCITA®

(bupivacaine liposome injectable suspension)

13.3 mg/mL

For local infiltration injection in dogs only

Local anesthetic

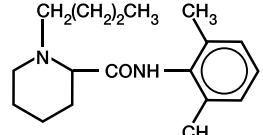
Single use vial

Caution:

Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

Description:

NOCITA® (bupivacaine liposome injectable suspension) is a sterile, non-pyrogenic, white to off-white, preservative-free, aqueous suspension of multivesicular lipid-based particles containing bupivacaine, intended for local infiltration at the surgical site in dogs. Each milliliter of NOCITA contains 13.3 mg of bupivacaine. Inactive ingredients and their nominal concentrations are: cholesterol, 4.7 mg/mL; 1, 2-dipalmitoyl-sn-glycero-3 phospho-rac-(1-glycerol) (DPPG), 0.9 mg/mL; tricaprilyn, 2.0 mg/mL; and 1, 2-dierucoylphosphatidylcholine (DEPC), 8.2 mg/mL. Bupivacaine is related chemically and pharmacologically to the amide-type local anesthetics. Chemically, bupivacaine is 1-butyl-N-(2, 6-dimethylphenyl)-2-piperidinecarboxamide with a molecular weight of 288.4. Bupivacaine structural formula is shown in the illustration to the right.



Indication:

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

Dosage and Administration:

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.

Dosing Instructions:

- **Wear gloves** when handling and administering NOCITA (see **WARNINGS**).
- NOCITA should not be allowed to come into contact with topical antiseptics. When a topical antiseptic such as povidone iodine or chlorhexidine is applied, the area should be allowed to dry before NOCITA is administered into the surgical site.
- **Do not shake vial.** Invert the vial multiple times to re-suspend the particles immediately prior to withdrawal of the product from the vial.
- Do not puncture the vial multiple times. Once the vial stopper has been punctured with a sterile needle, draw out the dose into a sterile syringe. Each syringe should be prepared for single patient use only. Discard the vial after the entire dose is withdrawn.
- Following withdrawal from the vial into a syringe, NOCITA may be stored at controlled room temperature of 68° F to 77° F (20° C to 25° C) for up to 4 hours. After 4 hours, the syringe must be discarded.
- NOCITA may be administered diluted or undiluted. NOCITA may be diluted with up to an equal volume (1:1 by volume) of normal (0.9%) sterile saline or Lactated Ringer's solution to obtain a volume sufficient to cover the surgical site.  
Do not dilute with water or other hypotonic solutions as it will result in disruption of the liposomal particles (see **CLINICAL PHARMACOLOGY**).  
Do not mix NOCITA with other local anesthetics or other drugs prior to administration (see **PRECAUTIONS**).
- Administer with a 25 gauge or larger bore needle.
- Administer by infiltration injection: Inject slowly into the tissues using an infiltration injection technique. To obtain adequate coverage, infiltrate all of the tissues in each surgical closure layer. Aspirate frequently to prevent intravascular administration (see **CONTRAINDICATIONS**).

Contraindications:

Do not administer by intravenous or intra-arterial injection. If accidental intravascular administration occurs, monitor for cardiovascular (dysrhythmias, hypotension, hypertension) and neurologic (tremors, ataxia, seizures) adverse reactions.

Do not use for intra-articular injection. In humans, local anesthetics administered into a joint may cause chondrolysis.

Warnings:

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.

Precautions:

Do not administer concurrently with bupivacaine HCl, lidocaine or other amide local anesthetics. A safe interval from time of bupivacaine HCl, lidocaine or other amide local anesthetic administration to time of NOCITA administration has not been determined.

The safe use of NOCITA for surgical procedures other than cranial cruciate ligament surgery has not been evaluated (see **ANIMAL SAFETY** and **ADVERSE REACTIONS**).

The safe use of NOCITA has not been evaluated in dogs younger than 5 months old.

The safe use of NOCITA has not been evaluated in dogs that are intended for breeding, or are pregnant or lactating.

The safe use of NOCITA in dogs with hepatic or renal impairment has not been evaluated. NOCITA is metabolized by the liver and excreted by the kidneys.

The safe use of NOCITA in dogs with cardiac disease has not been evaluated.

The ability of NOCITA to achieve effective anesthesia has not been studied. Therefore, NOCITA is not indicated for pre-incisional or pre-procedural loco-regional anesthetic techniques that require deep and complete sensory block in the area of administration.

Adverse Reactions:

Safety was evaluated in 123 NOCITA treated dogs and 59 placebo treated dogs in a field study in dogs that underwent cranial cruciate ligament stabilization surgery. Dogs enrolled in the study were 1-13 years of age, and weighed 3.4 to 61.3 kg. NOCITA was administered by infiltrative injection at the surgical site at a dose of 5.3 mg/kg (0.4 mL/kg).

Table 1. 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%)
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%)
Fever	1 (0.8%)	0 (0.0%)

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

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

For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or online at <http://www.fda.gov/AnimalVeterinary/SafetyHealth>

Clinical Pharmacology:

Bupivacaine is an amide, non-opioid local anesthetic. It provides local analgesia by deactivating sodium channels on the nerve membrane, preventing the generation and propagation of nerve impulses. It is only present in small concentrations as uncharged molecules at tissue pH as it is a base with pKa of 8. This un-ionized form provides a lipophilicity that permits the drug to traverse across the nerve cell membrane and upon entering the cell, binds to the intracellular portion of voltage-gated sodium channels and blocks sodium influx into nerve cells, which prevents depolarization. Without depolarization, no initiation or conduction of a pain signal can occur.

Lipid Formulation

Liposomal encapsulation or incorporation in a lipid complex can substantially affect a drug's functional properties relative to those of

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the unencapsulated or nonlipid-associated drug. In addition, different liposomal or lipid-complexed products with a common active ingredient may vary from one another in the chemical composition and physical form of the lipid component. Such differences may affect functional properties of these drug products. Do not substitute with other bupivacaine formulations.

After injection of NOCITA into the soft tissue, bupivacaine is released from the multivesicular liposomes over a period of time.

### Pharmacokinetics

The pharmacokinetic characterization associated with bupivacaine after subcutaneous NOCITA (bupivacaine liposome injectable suspension) or bupivacaine HCl solution administered to Beagle dogs is provided in Table 2.

Table 2. Mean (± SD) Plasma Pharmacokinetic Parameters for bupivacaine after single subcutaneous administration of NOCITA and bupivacaine HCl solution in male and female Beagle dogs in a laboratory study

PK Parameter	NOCITA <sup>a</sup> 9 mg/kg	NOCITA <sup>a</sup> 18 mg/kg	NOCITA <sup>a</sup> 30 mg/kg	bupivacaine HCl 9 mg/kg
N, sex	6, (3M/3F)	6, (3M/3F)	6, (3M/3F)	6, (3M/3F)
T <sub>max</sub> <sup>b</sup> (hr)	0.5 (0.5-0.5)	0.5 (0.5-0.5)	60.0 (0.5-72)	0.5 (0.5-0.5)
C <sub>max</sub> <sup>c</sup> (ng/mL)	488 (335)	560 (299)	633 (280)	1420 (355)
AUC <sub>(0-72)</sub> <sup>c</sup> (ng*hr/mL)	9100 (4460)	12800 (2020)	25600 (8160)	9720 (1860)
T <sub>1/2</sub> <sup>c</sup> (hr)	36.2 (12.4)	25.7 (8.15)	43.9 (12.5)	10.1 (8.54)

<sup>a</sup> 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.

<sup>b</sup> Median (Range)

<sup>c</sup> Reported from steady state concentrations

Following a single subcutaneous dose of 9 mg/kg and 18 mg/kg NOCITA, median time to reach C<sub>max</sub> was rapid (0.5 hr) but it was delayed significantly at a high dose of 30 mg/kg (60 hr). Following equivalent doses (9 mg/kg) of NOCITA and bupivacaine HCl solution, the mean bupivacaine AUC<sub>(0-72)</sub> and T<sub>max</sub> were comparable. However, due to the slow release mechanism of the NOCITA formulation, the mean C<sub>max</sub> and T<sub>1/2</sub> were approximately 3-fold lower and 3.5-fold higher, respectively. Following an increase in dose of NOCITA, the bupivacaine pharmacokinetics was nonlinear with high variability in exposure parameters. Both C<sub>max</sub> and AUC<sub>(0-72)</sub> increase with dose but the increases were less than dose proportional. Further, the non-linear bupivacaine pharmacokinetics was made evident by an increase in the terminal phase half-life with the increase in dose.

### Effectiveness:

Effectiveness was demonstrated in a multi-center, placebo-controlled, randomized and masked field study in client-owned dogs undergoing cranial cruciate ligament stabilization surgery. In this study, 182 dogs were enrolled in the study and randomized to treatment with NOCITA (n = 123) or placebo (sterile saline, n = 59). The per protocol population for effectiveness was 112 NOCITA treated dogs and 52 placebo dogs.

Dogs received an opioid analgesic just prior to general anesthesia and surgery. Surgical repair technique was at the discretion of the surgeon, and included extra-capsular repair, tibial plateau leveling osteotomy (TPLO), or tibial tuberosity advancement (TTA). Table 3 shows the number and percent of surgical procedure by treatment group.

Table 3. Surgical Procedure by Treatment Group

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	50 (44.6)	22 (42.3)	72 (43.9)
TTA	10 (8.9)	6 (11.5)	16 (9.8)

Using an infiltration injection technique, a single dose of NOCITA or placebo was infiltrated into the tissue layers during surgical closure. NOCITA or placebo was administered undiluted or diluted up to two-fold (1:1) with sterile saline. Pain was assessed by trained observers using the Glasgow Composite Measure Pain Scale-Short Form (CMPS-SF) for up to 72 hours following surgical closure. Pain assessments were conducted prior to surgery, and at 0.5, 1, 2, 4, 8, 12, 24, 30, 36, 48, 56 and 72 hours post-surgery. Dogs with a CMPS-SF score ≥ 6 or that were determined to be painful by the investigator received rescue analgesic medication and were classified as treatment failures. No further CMPS-SF pain assessments were recorded for dogs that received rescue analgesic medication. The primary variable for effectiveness was evaluated over the first 24-hour time interval. The percent of treatment success for NOCITA was significantly different from and greater than placebo at the first 24-hour time interval (p = 0.0322). The 24-48 hour and 48-72 hour time intervals were evaluated as secondary variables and support effective use of NOCITA for up to 72 hours of analgesia.

Table 4. Number and % Effectiveness for NOCITA and Placebo at each Time Interval

Time Interval for Pain Evaluation	NOCITA (n = 112)	Placebo (n = 52)
0-24 hours	77 (68.8%)	19 (36.5%)
24-48 hours	72 (64.3%)	18 (34.6%)
48-72 hours	69 (61.6%)	17 (32.7%)

### Animal Safety:

In a 4-week laboratory study with a 4-week recovery period, 60 healthy dogs aged 5-6 months were administered NOCITA at 8, 16 and 26.6 mg/kg. These doses correspond to 1.5, 3 and 5 times the maximum labeled dose of 5.3 mg/kg bupivacaine base. The active control group was administered 9 mg/kg bupivacaine HCl (equivalent to 8 mg/kg bupivacaine base), and the placebo group was administered 1.2 mL/kg saline. All dogs were dosed by subcutaneous injection twice weekly for 4 weeks. Doses alternated between two injection sites to the right or left of dorsal midline near the scapula. There were 6 dogs/sex/group for the first 4 weeks, and then 3 dogs/sex/group were maintained and monitored during a 4-week recovery period.

All dogs survived the study, and there were no clinically relevant treatment-related effects on clinical observations, physical examination, body weight, electrocardiograms (ECG), hematology, serum chemistry, urinalysis, coagulation, and organ weights. Injection site reactions on histopathology included minimal to moderate edema, granulomatous inflammation and mineralization in the subcutaneous tissue in some dogs that received NOCITA. In dogs that were evaluated immediately after the 4-week treatment period, granulomatous inflammation was characterized by numerous vacuolated macrophages and fewer lymphocytes, plasma cells and/or multinucleated giant cells. The inflammation was often associated with mineralization and/or edema. In the dogs that were maintained for the 4-week recovery period, there were fewer dogs with granulomatous inflammation and mineralization at the injection sites. The inflammation was characterized by a greater number of giant cells. One 9 mg/kg NOCITA group male dog had minimal subcutaneous edema that was not associated with cellular inflammation. These inflammatory changes are associated with administration of the liposomal suspension, and did not occur in the saline and bupivacaine HCl groups.

### Storage Conditions:

Unopened vials should be stored refrigerated between 36° F to 46° F (2° C to 8° C)

NOCITA may be held at a controlled room temperature of 68° F to 77° F (20° C to 25° C) for up to 30 days in sealed, intact (unopened) vials. **Do Not Freeze.**

### How Supplied:

13.3 mg/mL bupivacaine liposome injectable suspension in 20 mL single use vial, in a single vial carton and 4-vial cartons.

NADA 141-461, Approved by the FDA

US Patent: 8,182,835

US Patent: 8,834,921

US Patent: 9,205,052



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Additional Information is available at [www.aratana.com](http://www.aratana.com) or by calling Aratana Therapeutics at 1-844-272-8262.

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