nocita®

(bupivacaine liposome injectable suspension)

Technical Monograph

ARATANA THERAPEUTICS®

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1 Introduction

Overview of Postoperative Pain Management

Many surgical patients experience pain of moderate to extreme intensity during the first few days of postsurgical recovery.[1] Provision of adequate perioperative pain control is important for an expedient and successful patient recovery, in addition to being an ethical obligation of all veterinarians. Unlike some chronic pain conditions, most acute, perioperative pain is predictable and is directly related to the type and degree of tissue injury. Insufficiently managed acute pain can lead to central sensitization, possibly culminating in chronic, maladaptive pain through the process of neuroplasticity, or remodeling of the pain pathways.[2] Chronic, maladaptive pain is very difficult to manage, whereas a number of techniques, both pharmaceutical and nonpharmaceutical, have been proven to minimize acute, postsurgical pain.

Postsurgical pain can typically be well controlled in hospitalized patients using a multimodal analgesic regimen that involves an appropriate combination of opioids, cyclooxygenase (COX)-inhibiting nonsteroidal anti-inflammatory drugs (NSAIDs), local anesthetics, alpha$_2$ agonists, and/or N-methyl-D-aspartate receptor antagonists.[3] However, most veterinary patients that undergo soft-tissue or orthopedic surgery are discharged from the veterinary hospital within 24 to 48 hours postoperatively. Therefore, analgesics that provide continued pain relief must be prescribed and/or delivered in the home environment. Currently, there are limited US Food and Drug Administration (FDA)–approved options available for the treatment of postoperative pain in dogs and cats (**Table 1**).

Table 1. FDA-Approved Therapeutics for the Management of Surgical Pain in Dogs and Cats

Dogs	Cats
▪ Oral COX-inhibiting NSAIDs ▪ Injectable carprofen ▪ Injectable dexmedetomidine ▪ Injectable robenacoxib ▪ Oral robenacoxib	▪ Injectable meloxicam ▪ Injectable buprenorphine ▪ Injectable butorphanol tartrate ▪ Injectable dexmedetomidine ▪ Injectable robenacoxib ▪ Oral robenacoxib

Limitations of these analgesics include, but are not limited to, the need for repeat oral or injectable administration (which places patients at risk for analgesic gaps and consumes valuable technician time), and concerns over untoward side effects (eg, sedation, gastrointestinal upset) of varying severity, even at clinically recommended dosages.

The most effective means of preventing the transduction and transmission of pain is through the use of local anesthetics. Current methods of providing local anesthetics include wound/tissue infiltration, lidocaine strips, topical creams, regional nerve blocks, epidurals, and the placement of soaker catheters. Although the use of local anesthetics perioperatively is supported by the American Animal Hospital Association (AAHA)/American Association of Feline Practitioners (AAFP)[3] and World

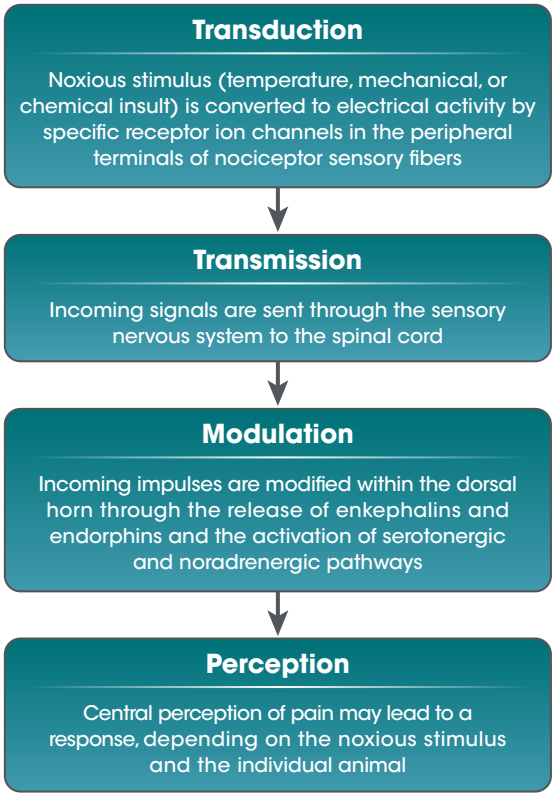
Small Animal Veterinary Association (WSAVA) Pain Guidelines,[4] there are limitations that function as barriers to their use. These limitations include the technical difficulty associated with epidural blocks, potential complications of the indwelling soaker catheter, and the short duration of action (< 8 hours) of the available formulations of local anesthetics.

There are numerous local anesthetics with well-established safety and efficacy profiles available for clinical use in the perioperative period.[4] Bupivacaine HCl was introduced into clinical practice in the early 1960s and is now one of the most commonly used and longest-acting local anesthetics, but its clinical benefit is limited by a duration of action that rarely exceeds 8 hours.[5]

Science of Nociception

Nociception, the process that leads to the conscious perception of pain, has been called the alarm system that announces the presence of a potentially damaging noxious stimulus, such as heat, cold, intense mechanical force, or a chemical irritant.[2] The nociceptive system serves a valuable protective function to prevent tissue damage, destruction of joints, loss of digits or appendages, and pressure ulcers. Nociceptive pain is a vital physiological sensation for preservation of health and prevention of injury, a concept exemplified by the repeated injuries, often leading to a reduced life expectancy, in people with congenital insensitivity to pain.[6] While the ability to feel pain is important to one's health, so too is the need to alleviate extreme or chronic pain. The nociceptive system can be broken down into 4 steps: transduction, transmission, modulation, and perception (**Figure 1**).[6,7] An individual animal's response to pain varies with many factors, including age, sex, health status, species, and interspecies variation.[8]

Figure 1. Processes Involved in Nociception



Sensory neurons express transducing ion-channel receptors that have a high threshold of activation to external stimuli. The ion-channel receptors are nonselective cation or sodium channels that are not gated by voltage but by temperature, chemical ligands, and mechanical shearing forces. During activation the channels open, allowing Na^+ and Ca^{2+} to flow into the nociceptor peripheral terminal, which generates an inward current, resulting in membrane depolarization. If the initial depolarization is sufficient, voltage-gated Na^+ channels will open, leading to further depolarization and initiation of action potentials. The frequency and duration of the action potentials reflect the intensity and duration of the noxious stimulus.[6,9]

Injury and inflammation of tissues causes changes to the chemical environment of the peripheral terminal of nociceptors, leading to peripheral sensitization. Damaged cells release their intracellular contents, such as adenosine triphosphatase and K^+ ions, while inflammatory cells recruited to the site of injury produce cytokines, chemokines, and growth factors. Some of these local mediators act directly on the nociceptor terminal to produce pain (nociceptor activators), while others lead to sensitization of the nociceptor terminal and result in hypersensitization to subsequent stimuli (nociceptor sensitizers). For example, adenosine triphosphatase released by damaged cells activates ligand-gated P-purinoceptors on nociceptors, resulting in immediate detection of tissue damage. In contrast, the build-up of protons at the site of injury causes a decrease in tissue pH and acts on acid-sensitive ion channels and transient receptor potential V1 channels on nociceptors, leading to delayed pain perception. The peptide hormone bradykinin both activates and sensitizes the nociceptor terminal through the constitutively expressed B2 receptor.[6,9]

Prostanoids are key mediators of pain following tissue injury. Arachidonic acid released from damaged cell membranes is converted to inflammatory prostanoids through the action of phospholipase A_2 (PLA_2). PLA_2 and the downstream enzymes responsible for the production of inflammatory prostanoids, including COX-2 and prostaglandin E (PGE) synthases, are induced during inflammation and are not constitutively expressed. COX-1 and COX-2 convert arachidonic acid into prostaglandin H_2, which is subsequently converted into PGE_2. PGE_2 and nerve growth factor bind to G-protein-coupled PGE and tyrosine kinase A receptors to alter the sensitivity of the nociceptor terminal. This sensitization occurs several hours after initiation of inflammation. Downstream activation of protein kinase C and A lead to phosphorylation of amino acids/proteins, further altering the activity of receptors and ion channels.[6,9]

How Long Is Long Enough?

There are limited data as to how long postsurgical pain persists, and this time period will vary with the type of surgical procedure performed. The perception of pain occurs during the inflammatory phase of wound healing, which lasts approximately 72 hours; consequently, 72 hours is the recommended minimum amount of time analgesics should be provided following surgery.[5] In humans, acute postoperative pain is followed by persistent pain in 10% to 50% of patients, and 2% to 10% of these patients experience severe chronic pain. Such discomfort may last for more than 3 to 6 months after surgery. Persistent postoperative pain (PPOP) is the consequence of ongoing inflammation and/or neuropathic pain from injury to peripheral nerves and represents a major, largely underdiagnosed clinical problem.[10]

A key difference between pain management in animals compared with humans is how pain is reported and recorded. While humans can verbalize the pain they feel, it is up to veterinarians and pet owners to observe and perceive the signs of pain in pets. Postsurgical pain in pets can typically be well controlled in hospitalized patients when pain assessment and pain intervention are part of postoperative protocols. However, most veterinary patients that undergo soft-tissue or orthopedic surgery are discharged from the veterinary hospital within 12 to 48 hours postoperatively. Therefore, analgesics must be delivered and/or prescribed that bridge pain relief in the home environment.[5] Adequate postoperative pain control during the early postoperative window is key to preventing PPOP.

Optimizing Postoperative Pain Management

There are 4 central tenets to optimizing postoperative analgesia: (1) provide preemptive analgesia, (2) use multimodal pain management, (3) deliver overlapping/continuous analgesia, and (4) match the analgesic plan to the severity of surgical pain.[4] In order to follow these guidelines, veterinarians must consider methods of minimizing the transduction and transmission of pain in peripheral tissue, attenuating modulation of pain in the spinal cord, and reducing the conscious perception of pain. The use of analgesics with complementary modes of action can be employed to target these various points along the pain pathway (**Table 2**).

Table 2. Options for Postoperative Pain Management

Local/Regional Anesthetics
▪ Render complete analgesia
▪ Considered safe, with side effects generally limited to very high doses or due to inadvertent intravascular administration, and do not appear to delay tissue healing[3]
▪ The duration of action of standard formulations is limited to hours; therefore, they do not provide extended pain relief
Opioids
▪ Oral formulations have limited usefulness in dogs compared with humans, but pharmacokinetic studies demonstrate possible efficacy of codeine and hydrocodone in dogs[11,12]; however, they are not FDA approved in animals
▪ Opioids are scheduled drugs and require Drug Enforcement Administration licenses, recordkeeping, and secure storage
COX-Inhibiting NSAIDs
▪ Commonly used perioperative analgesics that can be continued in the home environment ▪ Longer-term use requires monitoring of serum chemistry and complete blood counts and may have side effects that limit use in some dogs
Other Analgesics (eg, gabapentin, pregabalin, amitriptyline, tramadol, amantadine)
▪ Focused on managing maladaptive pain in humans, but not FDA approved for use in animals, and side effects can be a concern ▪ Studies showing effectiveness for post-surgical analgesia in dogs and cats are limited

The use of local anesthetics as part of multimodal analgesia for postoperative pain is the standard of care recommended by the WSAVA[4] and the 2015 Pain Management Guidelines from the AAHA and AAFP[3]. Furthermore, analgesia needs to be continued for at least 72 hours postoperatively, during which time most dogs and cats have been discharged from the hospital. NOCITA® (bupivacaine liposome injectable suspension) is a long-acting local anesthetic that provides up to 72 hours of pain relief when administered via tissue infiltration in cranial cruciate ligament (CCL) surgery in dogs or as a peripheral nerve block prior to forelimb onychectomy in cats.

2 Local Anesthetics

Use in Dogs and Cats

Local anesthetics are widely available in companion-animal practice and have been shown to provide analgesia with little risk for untoward effects. The 2015 Pain Management Guidelines from the AAHA support the International Veterinary Academy of Pain Management position that "because of their safety and significant benefit, local anesthetics should be utilized, insofar as possible, with every surgical procedure."[3]

Mechanism of Action

Local anesthetics block cell-membrane sodium channels on neurons, thereby preventing the propagation of action potentials and transmission of pain signals. Local anesthetics differ in their chemical structures and can broadly be categorized into amides (eg, lidocaine, bupivacaine, mepivacaine, ropivacaine) and esters (eg, procaine, tetracaine). The chemical structure influences the solubility and metabolism of the drug. The 2 most commonly used local anesthetics in veterinary medicine are lidocaine (rapid onset to maximum effect; 1 to 2 hours' duration of action) and bupivacaine (slower time to maximum effect; up to 8 hours' duration of action unless formulated for extended release). Both lidocaine and bupivacaine are metabolized by the liver.[5]

Effects on Tissue

The effects of local anesthetics on wound healing have been investigated in many in vitro and in vivo models. While there is some evidence that these drugs alter the cellular events of early tissue healing, there does not appear to be a clinically significant impact on wound healing or mechanical wound strength in animals or humans.[13] In addition, the clinical use of local anesthetics has not been associated with increased risk of surgical site infection.[14] Local anesthetics as a class have been shown to have antimicrobial properties in vitro. Several studies have found that concentrations of bupivacaine HCl between 0.125% and 0.75% are able to inhibit the growth of pathogenic bacteria and fungi, including *Escherichia coli, Staphylococcus aureus, Staphylococcus epidermidis, Candida albicans,* and others.[15]

However, bupivacaine and other local anesthetics have demonstrated chondrotoxicity, particularly when delivered in high concentration or with extended duration of exposure to compromised cartilage. The implication of a single intra-articular injection of a local anesthetic, as may be performed at the time of orthopedic surgery, is currently unclear. Therefore, high doses of intra-articular local anesthetics should be avoided.[16]

Incisional block, either preoperatively or at the time of wound closure, has been advocated as a means of enhancing multimodal perioperative pain management.[17] This technique may use lidocaine, bupivacaine, or a combination of both, although the clinical benefits for combination remain unclear. Bupivacaine can be instilled through a needle into the subcutaneous tissue along the incisional line and is expected to provide several hours of analgesia postoperatively. If extended duration of analgesia is desired, a wound soaker catheter may be placed. Repeated administration of a local anesthetic through this catheter can provide extended analgesia throughout the hospitalization or pain management period. However, soaker catheters can pose their own challenges as they are at risk for accidental, premature removal and/or may contribute to increased surgical-site infection rate.

Local anesthetics are also used for regional nerve blocks, and these techniques have demonstrated a significant enhancement of postoperative analgesia in pets. However, the duration of analgesia using these techniques is limited due to the duration of action of current formulations, and the transient motor dysfunction that some animals experience may provide additional challenges in the early postoperative period.

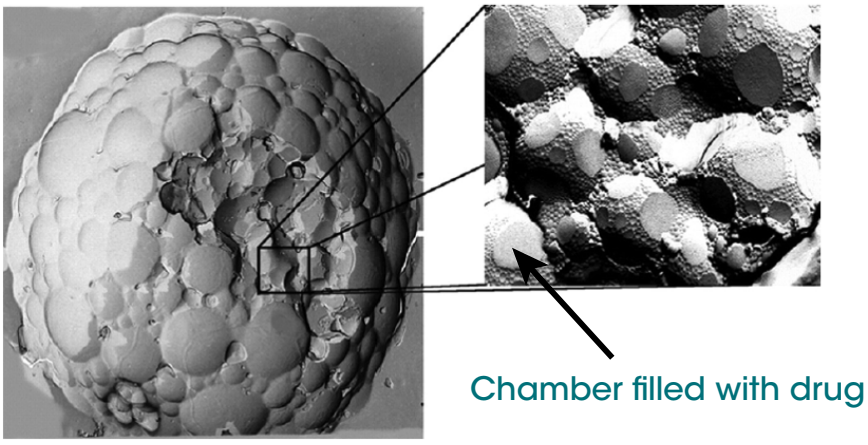
While local anesthetics have demonstrated a beneficial role in companion-animal pain management in the immediate postoperative period, these drugs do not provide effective prolonged analgesia in their traditional single-dose administration formulation for patients discharged from the hospital soon after surgery or for patients requiring extended hospitalization.

3 NOCITA At a Glance

Modern multimodal analgesia regimens should incorporate local anesthetics as advocated by industry leaders[3,4] due to their established efficacy. The local anesthetic class is the only class of analgesics that can completely block pain signals. In addition, local anesthetics are safe if administered at clinically recommended doses. Despite these efficacy and safety profiles, clinical use of local anesthetics as part of a multimodal analgesic regimen remains uncommon.[18] Explanations for this infrequent use include the technical difficulty associated with some nerve and epidural blocks, potential complications of an indwelling soaker catheter, and the short duration of action (< 8 hours) of the available local anesthetic solutions.

An extended-release formulation of bupivacaine was developed for use as a single-dose surgical site infiltration to provide postsurgical analgesia in human patients, and this product subsequently received FDA approval in October 2011. The extended-release bupivacaine technology used in this product consists of multivesicular liposomes composed of hundreds to thousands of chambers per particle, encapsulating aqueous bupivacaine.[19] The liposomes are microscopic structures made of nonconcentric lipid bilayers that resemble a honeycomb matrix and are designed such that bupivacaine is gradually released from vesicles over a period of approximately 96 hours (**Figure 2**).

Figure 2. Multivesicular Liposome

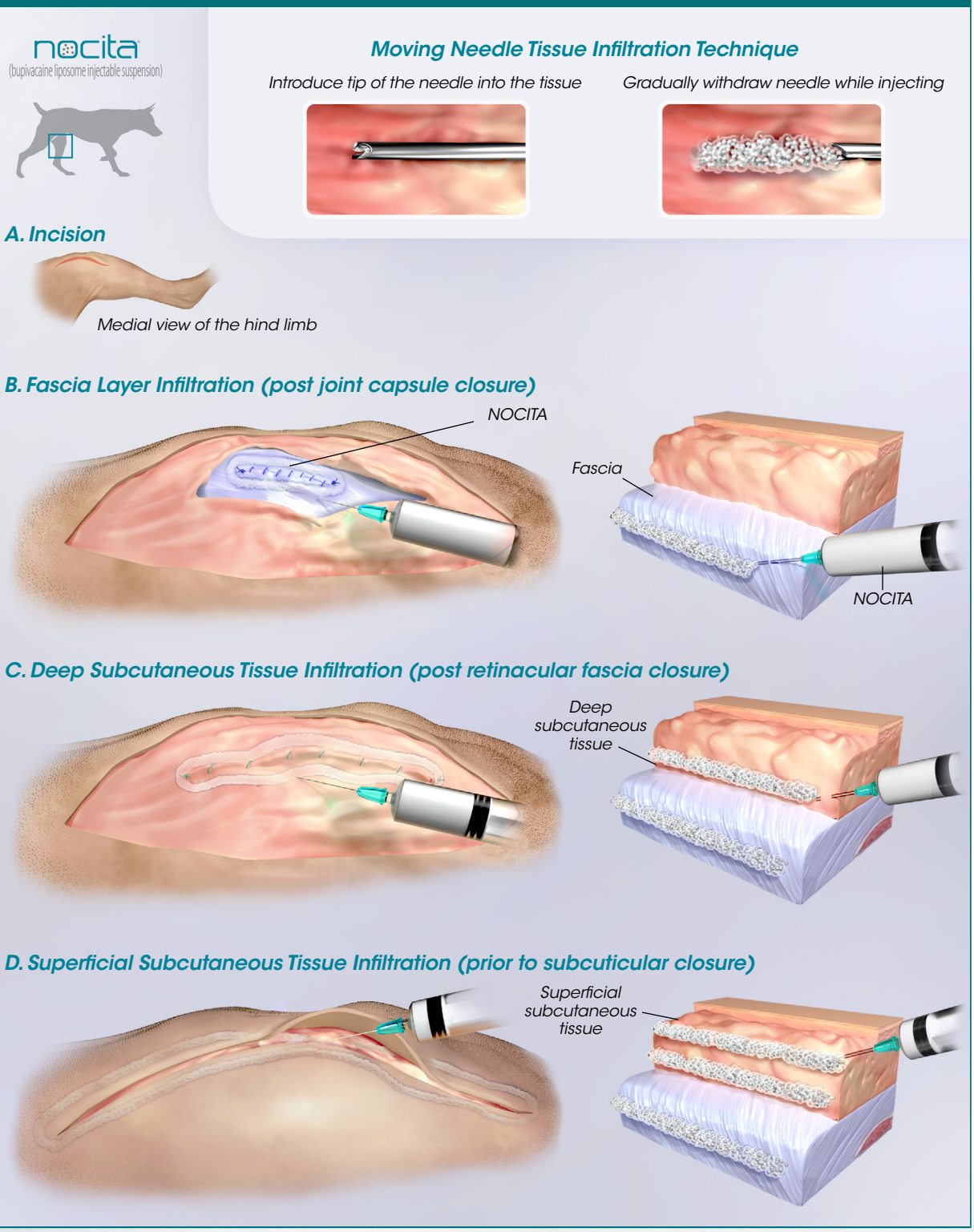


Using identical technology, NOCITA (bupivacaine liposome injectable suspension), a nonpyrogenic, preservative-free, bupivacaine liposome injectable suspension was developed for clinical use in dogs and cats. This sustained-release formulation limits analgesic gaps, which are periods of inadequate pain control that can compromise a patient's recovery from surgery.

In dogs, the technique for instilling bupivacaine liposome injectable suspension into a surgical site differs slightly from that used for traditional bupivacaine formulation because the liposomes do not diffuse freely from where they are deposited as bupivacaine solution does. Therefore, a moving-needle tissue infiltration injection technique is used to inject the suspension into all tissue layers surrounding the surgical field (**Figure 3**). As bupivacaine is gradually released from individual liposomes, it will diffuse locally into the surrounding tissues. In cats, bupivacaine liposome injectable suspension is administered as a 4-point peripheral nerve block to provide regional analgesia prior to forelimb onychectomy (**Figure 4**). Bupivacaine liposome injectable suspension should not be coadministered with other local anesthetics, such as lidocaine, as these can cause premature release of bupivacaine from the liposomal vesicles.

For further information on administration of bupivacaine liposome injectable suspension, please visit https://nocita.aratana.com/.

Figure 3. Surgical Site Infiltration With Bupivacaine Liposome Injectable Suspension Using a Moving-Needle Technique in Dogs



NOCITA received FDA approval in 2016 for single-dose infiltration into the surgical site to provide local postoperative analgesia for cranial cruciate ligament surgery in dogs.

Figure 4. Administration of Bupivacaine Liposome Injectable Suspension as a Peripheral Nerve Block in Cats

nocita
(bupivacaine liposome injectable suspension)

Legend

- Needle insertion point
- Drug injection point
- Needle withdrawal + drug injection
- Needle redirection to a 90˚ angle to the palmar plane

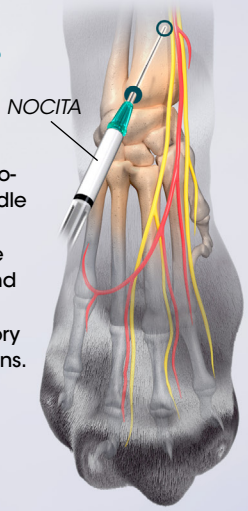
Abbreviations

SpU, styloid process of the ulna
ACb, accessory carpal bone

A. 0.14 mL/kg (35%)

Superficial Branch of the Radial Nerve:

At the center of the limb, on the dorsal aspect at the level of the antebrachio-carpal joint, insert the needle subcutaneously with the bevel up (●). Advance the needle subcutaneously and inject (○) adjacent to the confluence of the accessory cephalic and cephalic veins.

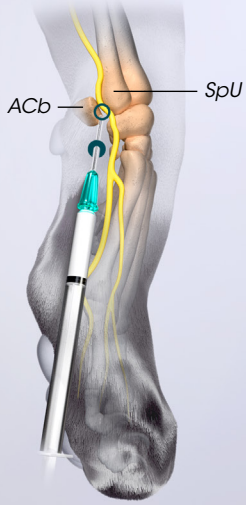


Dorsal

B. 0.08 mL/kg (20%)

Dorsal Branch of the Ulnar Nerve:

Palpate a groove between the accessory carpal bone (ACb, in the base of the carpal pad) and the styloid process of the ulna (SpU). Distal to this groove, insert the needle subcutaneously with the bevel up and advance the needle proximally. Inject once the tip reaches the midpoint of the groove.

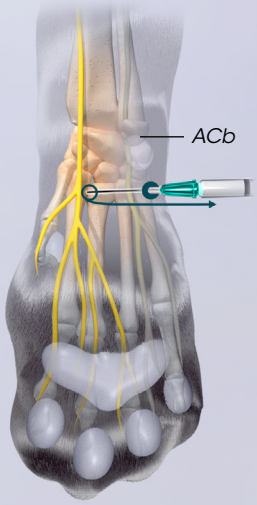


Lateral

C. 0.16 mL/kg (40%)

Median Nerve and Superficial Branch of the Palmar Branch of the Ulnar Nerve:

Insert the needle subcutaneously with the bevel up lateral to the distal tip of the accessory carpal pad and advance the needle medially 2/3 the width of the limb, until the tip is located near the base of the first digit. Inject 2/3 of the volume at this point and the remaining volume while withdrawing the needle (solid teal arrow). Gently massage for 5 seconds.

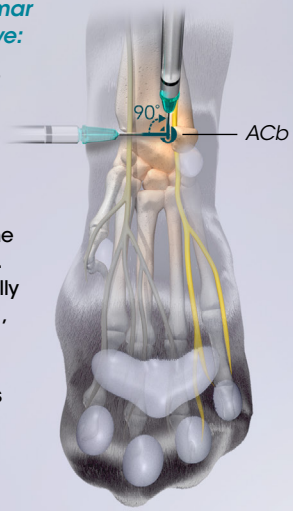


Palmar

D. 0.02 mL/kg (5%)

Deep Branch of the Palmar Branch of the Ulnar Nerve:

Orient the needle perpendicular to the long axis of the limb at the level of the ACb. Insert the needle subcutaneously and advance the needle laterally until it contacts the medial aspect of the ACb. Redirect the needle dorsally by rotating the needle 90˚, advance it along the medial side of the ACb 2-3 mm until it penetrates the flexor retinaculum, and inject.



Palmar

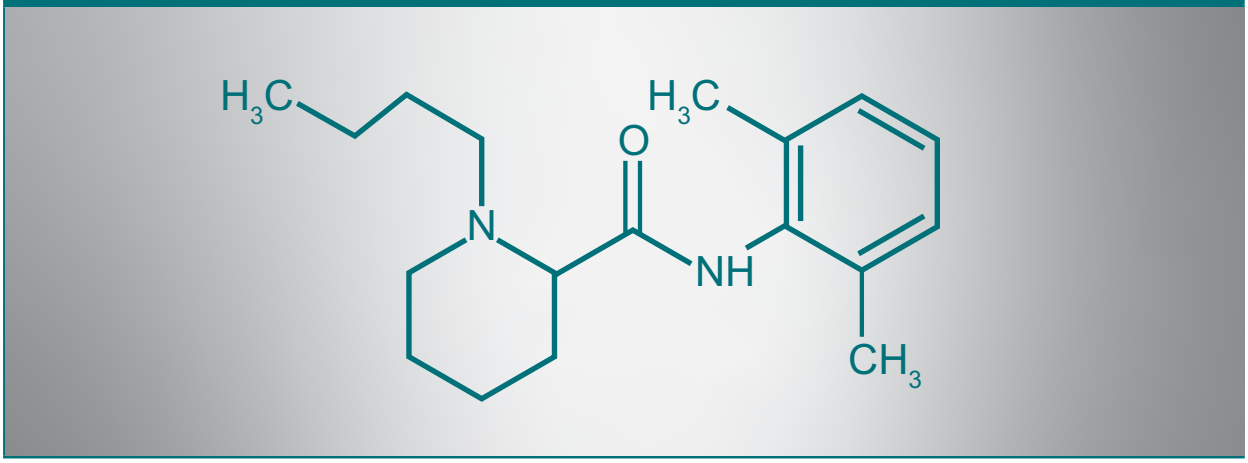
NOCITA received FDA approval in 2018 for use as a peripheral nerve block to provide regional postoperative analgesia following onychectomy in cats.

4 NOCITA Pharmacology

Chemical Composition

Bupivacaine is an aminoamide local anesthetic. The chemical structure and nomenclature for bupivacaine is shown in **Figure 5**. The empirical formula for bupivacaine is **$C_{18}H_{28}N_2O$,** and the molecular weight is 288.43 Daltons.[20]

Figure 5. Chemical Structure and Chemical Nomenclature of Bupivacaine



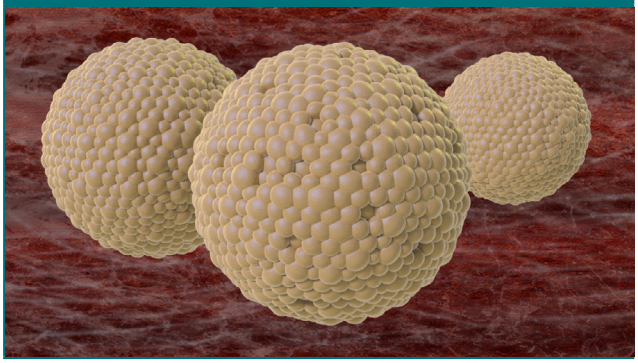
1-butyl-N-(2, 6-dimethylphenyl)-2-piperidinecarboxamide

NOCITA Mechanism of Action

Bupivacaine provides local analgesia by reversibly deactivating sodium channels on neuronal cell membranes, preventing the generation and propagation of nerve impulses. Because it is a weak base (pKa = 8), bupivacaine is present in only small concentrations as uncharged molecules at tissue pH. This un-ionized form provides a lipophilicity that permits the drug to traverse the cell membrane. Upon entering the cell, bupivacaine binds to the intracellular portion of voltage-gated sodium channels and blocks sodium influx into nerve cells, preventing depolarization. Without depolarization, no initiation or conduction of a pain signal can occur. Small nociceptive fibers, specifically unmyelinated C fibers and myelinated Aδ fibers, are blocked before larger sensory Aβ and motor Aα fibers.[21]

To provide a longer duration of analgesia than bupivacaine HCl or other local anesthetics, NOCITA (bupivacaine liposome injectable suspension) is in an encapsulated liposomal formulation. The multivesicular liposome particles in NOCITA are made up of a honeycomb-like structure consisting of many nonconcentric compartments that contain bupivacaine for gradual, local release (**Figure 6**). In vivo, NOCITA releases drug over an extended period by erosion of the exterior surface and reorganization of the particles' lipid membranes.[22]

Figure 6. Multivesicular Liposome Particles for Extended Bupivacaine Release



For further information on the mechanism of action of NOCITA, please visit https://nocita.aratana.com/.

Pharmacokinetic Profile in Dogs

NOCITA is administered as a single treatment by tissue infiltration during surgical closure into the tissues to control postoperative pain in CCL surgery in dogs. The pharmacokinetic characterization associated with bupivacaine after subcutaneous NOCITA (bupivacaine liposome injectable suspension) or bupivacaine HCl solution was administered to beagle dogs is provided in **Table 3**.[20]

Table 3. Plasma Pharmacokinetic Parameters for Bupivacaine After Single Subcutaneous Administration of NOCITA or Bupivacaine HCl Solution in Beagle Dogs

PK Parameter	NOCITA[a] 9 mg/kg n = 6 (3 M, 3F)	NOCITA[a] 18 mg/kg n = 6 (3 M, 3F)	NOCITA[a] 30 mg/kg n = 6 (3 M, 3F)	Bupivacaine HCl 9 mg/kg n = 6 (3 M, 3F)
T_{max}[b] (hr)	0.5 (0.5-0.5)	0.5 (0.5-0.5)	60 (0.5-72)	0.5 (0.5-0.5)
C_{max} (ng/mL)	488 (335)	560 (299)	633 (280)	1420 (355)
$AUC_{(0-72)}$ (ng•hr/mL)	9100 (4460)	12800 (2020)	25600 (8160)	9720 (1860)
$T_{1/2}$[c] (hr)	36.2 (12.4)	25.7 (8.15)	43.9 (12.5)	10.1 (8.54)

AUC, area under the curve; C_{max}, maximum plasma concentration; F, female; M, male; PK, pharmacokinetic; $T_{1/2}$, half-life.

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

[b] Median (range)

[c] Reported from steady-state concentrations.

Absorption in Dogs

Following single subcutaneous doses of 9 mg/kg and 18 mg/kg NOCITA (bupivacaine liposome injectable suspension), the median time to reach C_{max} was rapid (0.5 hr), but it was delayed significantly at a high dose of 30 mg/kg (60 hr).[21] Following equivalent doses (9 mg/kg) of NOCITA and bupivacaine HCl solution, the mean bupivacaine $AUC_{(0-72)}$ and T_{max} were comparable. However, due to the slow release mechanism of NOCITA, the mean C_{max} and $T_{1/2}$ on day 1 were approximately 3-fold lower and 3.5-fold higher, respectively, compared with those of bupivacaine HCl. Following an increase in dose of NOCITA, the bupivacaine pharmacokinetics were nonlinear, with high variability in exposure parameters. Both C_{max} and $AUC_{(0-72)}$ increased with dose, but the increases were less than dose proportional. Furthermore, the nonlinear bupivacaine pharmacokinetics was made evident by an increase in the terminal-phase half-life with the increase in dose.[21] Of note, NOCITA can result in measurable systemic bupivacaine in plasma for up to 96 hours, but the systemic plasma levels do not necessarily correlate with local efficacy.[23]

Pharmacokinetic Profile in Cats

NOCITA is administered as a peripheral nerve block to provide regional postoperative analgesia following onychectomy in cats. The pharmacokinetic characterization associated with bupivacaine after subcutaneous NOCITA (bupivacaine liposome injectable suspension) or bupivacaine HCl solution administered to cats evaluated for 168 hours is provided in **Table 4**.[21]

Table 4. Plasma Pharmacokinetic Parameters for Bupivacaine After Single Subcutaneous Administration of NOCITA or Bupivacaine HCl Solution in Cats

PK Parameter	NOCITA[a] 3 mg/kg n = 6	NOCITA[a] 9 mg/kg n = 6	NOCITA[a] 15 mg/kg n = 6	Bupivacaine HCl 1 mg/kg n = 6
T_{max}[b] (hr)	12.5 (1-48)	10 (1-24)	1.5 (1-24)	1 (1-4)
T_{last}[b] (hr)	108 (72-144)	120 (72-168)	144 (120-168)	18 (12-24)
C_{max}[c] (ng/mL)	311.4 (82.2-565)	620.2 (374-892)	709.7 (462-1090)	263.9 (60.5-506)
$AUC_{(last)}$[c] (ng•hr/mL)	11347 (5176-15767)	32561 (19390-47532)	38475 (26460-48252)	1608 (314-2363)

AUC_{last}, area under the curve from the time of dosing to the last quantifiable plasma concentration; C_{max}, maximum plasma concentration; T_{last}, time to last quantifiable plasma concentration; T_{max}, time to maximum plasma concentration.

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

[b] Median (range).

[c] Mean (range).

Absorption in Cats

Following single subcutaneous doses of NOCITA (bupivacaine liposome injectable suspension), there was a less than dose proportional increase in C_{max} and AUC_{last} across the dose range tested (3-15 mg/kg) and a high variability in all reported parameters. Half-life is not reported for NOCITA in cats because the prolonged absorption confounds the estimation of the terminal elimination phase. Therefore, T_{last} is included as a more appropriate measure of the duration of quantifiable plasma concentrations.

Distribution, Metabolism, and Excretion

Once bupivacaine is released from the liposome, its distribution, metabolism, and excretion are expected to follow the same kinetics as bupivacaine HCl.[24] The rate of systemic absorption of bupivacaine is dependent on the total dose of drug administered, the route of administration, and the vascularity of the administration site. To some extent, local anesthetics such as bupivacaine are distributed to all body tissues, with high concentrations found in highly perfused organs, such as the liver, lungs, heart, and brain. Elimination of bupivacaine depends largely on the reversible binding to plasma proteins and red blood cells in the systemic circulation to transport bupivacaine to the liver, where it is metabolized; bupivacaine has a high protein-binding capacity of 95%. The kidney is the main excretory organ for bupivacaine and its metabolites. Patients with hepatic disease, especially those with severe hepatic disease, may be more susceptible to the potential toxicities of aminoamide local anesthetics such as bupivacaine.[24] NOCITA is intended for single-dose administration; therefore, accumulation of bupivacaine or its metabolites is not expected, even in patients with impaired hepatic or renal function.

NOCITA is a suspension of multivesicular liposomes containing bupivacaine in 0.9% sodium chloride solution along with a small amount (< 8%) of free (unencapsulated) bupivacaine. Liposomal encapsulation or incorporation in a lipid complex can substantially affect a drug's functional properties relative to those of the unencapsulated or non–lipid-associated drug. In addition, different liposomal or lipid-complexed products with a common active ingredient may vary in the chemical composition and physical form of the lipid component. Such differences may affect functional properties of these drug products. Do not mix NOCITA with other local anesthetics or other drugs prior to administration.

5 NOCITA Safety

Local anesthetic toxicities affect the neurological or cardiovascular systems, manifest from high plasma levels of the local anesthetic, and commonly are a result of accidental intravascular injection of the drug or administration of an overdose. Extended-release bupivacaine has been studied in dog models as part of its development for human use.

Pilot Dose-Finding and Expanded Studies in Dogs[25]

In a pilot study to determine the maximum tolerated doses of intravascular administration of bupivacaine liposome injectable suspension (liposome bupivacaine) vs bupivacaine HCl, maximum doses at which no meaningful adverse events were observed were higher with liposome bupivacaine than with bupivacaine HCl after both intravenous and intra-arterial administration (**Table 5**). In a subsequent expanded study of systemic adverse effects and pharmacokinetics following intravascular administration of liposome bupivacaine at 9.0 mg/kg intravenous and 4.5 mg/kg intra-arterial, there were no observed changes in pathology and no mortality; adverse clinical signs included convulsions, lying on side, and decreased muscle tone, all of which were transient.

Table 5. Maximum Dosages of Study Drug That Were Associated With No Meaningful Adverse Events

Route of Administration	Bupivacaine HCl, mg/kg	Liposome Bupivacaine, mg/kg
Intravenous	0.75	4.5
Intra-arterial	0.1	1.5

Local Toxicity Studies in Dogs

Additional studies have centered on the local safety and tolerability of liposome bupivacaine following tissue infiltration.

Study of Effects on Wound Healing[23]

In a study evaluating liposome bupivacaine in a dog model of inguinal hernia repair, dogs given 9, 18, or 25 mg/kg liposome bupivacaine experienced similar incidence and severity of histological changes at day 15 compared with controls who received bupivacaine HCl or saline, and there were no observed differences in local toxicity or delays in wound healing between the study groups. The authors concluded that there were no significant adverse effects on wound healing using liposome bupivacaine at higher doses than expected with clinical use.

Single-Dose Toxicity Study[26]

A single-dose toxicity study using liposome bupivacaine (9, 18, and 30 mg/kg), bupivacaine HCl (9 mg/kg), or saline, administered around the brachial plexus of dogs, found similar pathology and histology at days 3 and 15 between dogs treated with liposome bupivacaine and controls. The only liposome bupivacaine–related adverse effect was minimal to mild granulomatous inflammation of the adipose tissue at the injection site observed in a few dogs at days 3 and 15; this inflammation was considered to be a normal reaction to liposomes. No cardiovascular- or central nervous system–related adverse events were observed. The results of this study demonstrated that liposome bupivacaine did not cause severe local irritation or tissue damage even when injected at high doses around the brachial plexus.

Target Animal Safety Study[27]

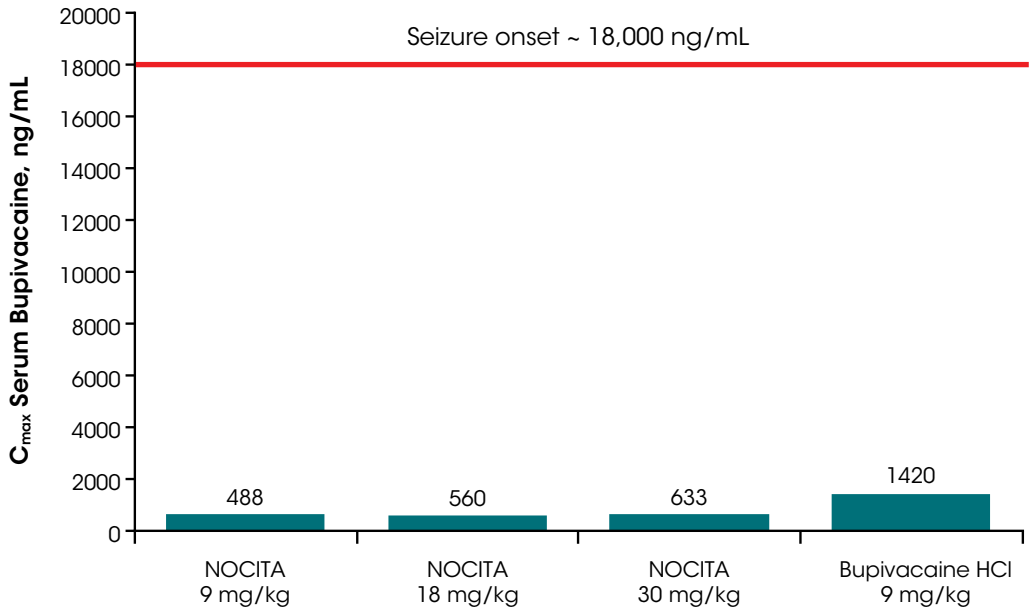
In a 4-week laboratory repeat-dose toxicity study, 60 healthy dogs aged 5 to 6 months were administered NOCITA at 8, 16, and 26.6 mg/kg bupivacaine base (corresponding to 1.5, 3, and 5 times the maximum label dose, respectively, of 5.3 mg/kg bupivacaine base). The active control group was administered 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, for a total of 8 injections. Doses alternated between 2 injection sites to the right or left of dorsal midline near the scapula. There were 6 dogs of each sex per group for the first 4 weeks, and then 3 dogs of each sex per group were maintained and monitored during a treatment-free 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, hematology, serum chemistry, urinalysis, coagulation, or organ weights. Injection-site reactions upon histopathologic examination included minimal to moderate edema, granulomatous inflammation, and mineralization in the subcutaneous tissues 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, fewer dogs had granulomatous inflammation and mineralization at the injection sites. The inflammation was characterized by a greater number of giant cells compared with the number observed immediately after the 4-week treatment period. One male dog in the 9-mg/kg NOCITA group had minimal subcutaneous edema that was not associated with cellular inflammation. These inflammatory changes, which were considered a normal response to the administration of liposomes, did not occur in the saline or bupivacaine HCl groups.

Pharmacokinetic Values of Liposomal Bupivacaine in Relation to Levels Causing Seizure Onset in Dogs

The pharmacokinetic values for bupivacaine after a single subcutaneous administration of NOCITA or bupivacaine HCl solution relative to the bupivacaine levels that have been associated with seizure onset in dogs are shown in **Figure 7**.[20, 28]

Figure 7. Pharmacokinetic Values for Bupivacaine After a Single Subcutaneous Administration of NOCITA or Bupivacaine HCl Solution in Beagle Dogs



Safety in Cats

Target Animal Safety Study[30]

In a 22-day laboratory study, 40 healthy cats (4 cats/sex/group) aged 5 to 6 months were administered NOCITA 10.6, 21.2, or 31.8 mg/kg; active control (bupivacaine HCl 5.3 mg/kg); or negative control (2.37 mL/kg saline) by injection using a suprainguinal approach for a femoral nerve block of the right hindlimb on Days 0, 9, and 18. These NOCITA doses correspond to 1, 2, and 3 times the maximum labeled total dose of 10.6 mg/kg/cat (representing 2, 4, and 6 times the maximum labeled dose of 5.3 mg/kg/forelimb).

Two cats died during the study. One male in the active control group died during recovery from anesthesia after the second dose despite resuscitation efforts, and no definitive cause of death was determined. One female in the NOCITA 31.8 mg/kg group was euthanized on Day 15 due to progression of and discomfort associated with an open and necrotic wound near the right stifle. This cat developed hindlimb motor impairment, as well as a suppurative, open, necrotic wound over the region of the right stifle after the second dose administration. 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. Histopathology findings at the stifle wound included inflammation, ulcer, cavitation, necrosis, and fibrosis. Histopathology findings of inflammation at the injection site and femoral nerve were similar to those in other NOCITA-treated cats.

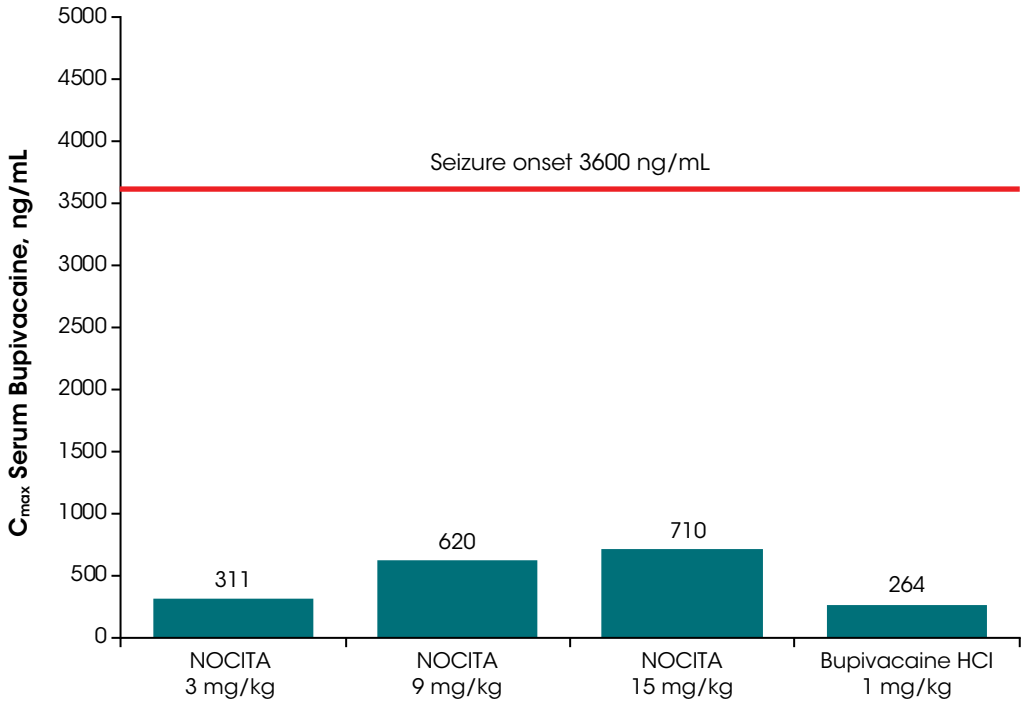
In the 38 cats that survived the study, there were no clinically relevant treatment-related effects on electrocardiograms, hematology, serum chemistry, urinalysis, coagulation, or organ weights. Right hindlimb impairment was expected because the entire dose was administered as a femoral nerve block. Right hindlimb impairment occurred in 23 of the 24 cats administered NOCITA, which persisted for 1 to 5 days; 2 cats administered negative control, which persisted for 1 day; and none of the cats administered active control. Left hindlimb impairment was observed the day after the first dose in 1 cat administered NOCITA 21.2 mg/kg. NOCITA treatment-related effects were observed on histopathological examination of soft tissue and the femoral nerve at the injection sites. Injection-site histopathology findings in the soft tissue included subacute or chronic inflammation, mineralization, myofiber degeneration, and myofiber necrosis. Injection-site histopathology findings in the femoral nerve included subacute or chronic inflammation.

Among the NOCITA, active control, and negative control groups, sporadic clinical observations included soft or watery or mucoid stool, inguinal swelling on the right hindlimb after only the first dose, and abrasions or scabbing at the right abdominal and inguinal regions as well as on the right hindlimb and at the right stifle; histopathology findings at or near the injection site or right stifle included ulceration and suppurative crusts on the skin; and histopathology findings at the injection site included subcutaneous foreign material and fibrosis, and myofiber regeneration.

Pharmacokinetic Values of Liposomal Bupivacaine in Relation to Levels Causing Seizure Onset in Cats

The pharmacokinetic values for bupivacaine after a single subcutaneous administration of NOCITA or bupivacaine HCl solution relative to the bupivacaine levels that have been associated with seizure onset in cats are shown in **Figure 8**.[20, 31]

Figure 8. Pharmacokinetic Values for Bupivacaine After a Single Subcutaneous Administration of NOCITA or Bupivacaine HCl Solution in Cats



The aforementioned studies were all performed in healthy dogs and cats. Patient factors, such as cardiac, renal, or hepatic disease, may increase the incidence of adverse events. No known long-term safety issues associated with liposome bupivacaine have been identified to date.

6 NOCITA Efficacy

Canine Pilot Field Study[32]

A masked, randomized, placebo-controlled, multicenter pilot field study was conducted to evaluate the efficacy of NOCITA at a dose of up to 5.3 mg/kg for postoperative analgesia following CCL surgery in dogs.

Study Design

Dogs were randomly assigned to receive either NOCITA up to 5.3 mg/kg or saline (placebo) after CCL surgery. NOCITA or placebo was administered by the surgeon completing the CCL surgery prior to wound closure and was injected slowly into the tissues using a moving-needle tissue infiltration technique. Approximately 25%, 50%, and 25% of NOCITA or placebo was injected into the tissues around the joint capsule, the fascial tissue, and the subcuticular tissue, respectively. Control of pain was assessed using the Glasgow Composite Measure Pain Scale-Short Form (CMPS-SF). The pain assessors were trained on the use of the CMPS-SF and assessed pain prior to surgery and at 2, 4, 8, 12, 24, 30, 36, 48, 54, 60, and 72 hours after NOCITA or placebo injection unless the dog was withdrawn from the study prior to 72 hours. After the CMPS-SF assessment was completed, a Surgical Site Manipulation Score was assessed by manipulation of the stifle joint on which CCL surgery had been performed. Dogs were removed from the study and given rescue analgesia if the CMPS-SF score was > 8 or if the veterinarian felt that additional analgesia was needed. An exploratory analysis evaluated treatment success, defined as no pain intervention, over intervals of 0 to 24 hours, 24 to 48 hours, and 48 to 72 hours. Treatment failures from previous intervals were carried forward to the next interval.

Results

A total of 49 dogs were screened, 46 of which were enrolled in the study; 3 dogs (all from a single site) were classified as screen failures and removed from the study prior to treatment. All 46 dogs enrolled in the study were included in the safety and per-protocol populations.

Dogs who received NOCITA had consistently lower CMPS-SF pain scores over 72 hours following dosing compared with those who received saline placebo, with a statistically significant treatment effect favoring NOCITA ($P = 0.0027$). The Surgical Site Manipulation scores also demonstrated the prolonged analgesic effect of NOCITA; however, these scores were less consistent throughout the study, resulting in an overall treatment effect that was statistically significant only when exploratory analysis included site interaction in the model.

Dogs that received NOCITA were more likely to remain in the study following the surgical procedure compared with dogs who received saline. This was observed through study completion; 9 of 24 dogs in the NOCITA group and 2 of 22 dogs in the saline group remained in the study 72 hours after dosing. Similar results were seen in the exploratory analysis of treatment success. For each time interval, more dogs remained in the NOCITA treatment group compared with the saline group, and this effect was statistically significant for each time interval (**Table 6**).

Table 6. Treatment Success Over Time

Time Interval for Pain Evaluation	Treatment Success, n (%)		*P* Value
	NOCITA n = 24	Saline n = 22	
0-24 hours	19 (79.2)	5 (22.7)	0.0001
24-48 hours	10 (41.7)	3 (13.6)	0.0349
48-72 hours	9 (37.5)	2 (9.1)	0.0240

Results of the safety testing showed that NOCITA was well tolerated. Two adverse events were reported in the saline group, and 3 were reported in the NOCITA group. One dog in the NOCITA group was found to have mild bradycardia on the end-of-study physical examination 4 hours after surgery. It was unknown if this was related to treatment, and it resolved without intervention. No other significant changes were observed in the physical examination findings. The 2 other adverse events observed in the NOCITA group included vomiting and nose rubbing, neither of which was considered related to treatment. Both events were considered mild in severity and resolved completely.

Conclusions

The results of this pilot field study showed that NOCITA provided safe and prolonged postsurgical analgesia when administered as a single dose of up to 5.3 mg/kg via tissue infiltration at the surgical site in dogs undergoing CCL surgery.

Canine Pivotal Field Study[29]

The effectiveness of NOCITA in providing prolonged postsurgical analgesia was evaluated in a multicenter, placebo-controlled, randomized, masked field study in client-owned dogs undergoing CCL stabilization surgery.

Study Design

In this study, 182 dogs were enrolled and randomized to treatment with NOCITA (n = 123) or saline (placebo, n = 59). The per-protocol population included 112 dogs treated with NOCITA and 52 dogs that received saline.

Dogs received an opioid analgesic just prior to general anesthesia and surgery. Surgical technique was at the discretion of the surgeon and included extracapsular repair, tibial plateau–leveling osteotomy (TPLO), or tibial tuberosity advancement (TTA). **Table 7** shows the surgical procedures by treatment group.

Table 7. Surgical Procedures by Treatment Group

Surgical Procedure, n (%)	NOCITA n = 112	Saline n = 52	Total n = 164
Extracapsular 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)

TPLO, tibial plateau–leveling osteotomy; TTA, tibial tuberosity advancement.

Using a moving-needle injection technique, a single dose of NOCITA or saline was infiltrated into the tissue layers during surgical closure. NOCITA or saline was administered either as is or with the addition of an equal volume of sterile saline or Lactated Ringer's solution. Pain was assessed by trained observers using the 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 after surgery. Dogs with a CMPS-SF score ≥ 6 or that were determined by the investigator to be in pain received rescue analgesic medication and were classified as treatment failures. No further CMPS-SF pain assessments were recorded for dogs that received rescue analgesia medication. The primary variable for effectiveness was evaluated over the first 24-hour time interval.

Results

The percentage of treatment success with NOCITA was statistically significantly greater than that with saline at the first 24-hour time interval (*P* = 0.0322). The 24- to 48-hour and 48- to 72-hour time intervals were evaluated as secondary variables and support effective use of NOCITA for up to 72 hours of analgesia (**Table 8**).

Table 8: Treatment Success Over Time[a]

Time Interval for Pain Evaluation	Treatment Success, n (%)		*P* Value
	NOCITA n = 112	Saline n = 52	
0-24 hours	77 (68.8)	19 (36.5)	0.0322
24-48 hours	72 (64.3)	18 (34.6)	0.0402
48-72 hours	69 (61.6)	17 (32.7)	0.0432

[a] For dogs that were deemed treatment failures over any time interval, the failure was carried forward to all subsequent time intervals. Therefore, the time intervals for evaluating treatment success are equivalent to 0-24 hours, 0-48 hours, and 0-72 hours.

Conclusions

The results of this study demonstrated that NOCITA administered at a dose of 5.3 mg/kg provided effective postoperative analgesia for up to 72 hours following CCL surgery in dogs.

Feline Pivotal Field Study[30]

The effectiveness of NOCITA in providing prolonged postsurgical analgesia was evaluated in a multicenter, placebo-controlled, randomized, masked field study in client-owned cats undergoing bilateral forelimb onychectomy.

Study Design

In this study, 241 cats were enrolled and randomized to treatment with NOCITA (n = 120) or saline (placebo, n = 121). Cats received an opioid analgesic just prior to general anesthesia and surgery. The nerve block injection sites were shaved and a standard surgical preparation with chlorhexidine or povidone iodine was used. Prior to onychectomy, NOCITA or saline was administered as a 4-point nerve block (**Figure 4**).

Pain was assessed by trained observers using a modified version of the UNESP-Botucatu Multidimensional Composite Pain Scale for up to 72 hours following extubation. 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. Cats with a composite pain score ≥ 6 or that were determined by the assessor to be in pain received rescue analgesic medication and were classified as treatment failures. After receiving rescue analgesia, cats did not have further pain assessments performed. The primary variable for effectiveness was evaluated over the first 24-hour time interval.

Results

The percentage of treatment success with NOCITA was statistically significantly greater than that with saline for the first 24-hour time interval ($P = 0.0252$). The 0- to 48-hour and 0- to 72-hour time intervals were evaluated as secondary variables and support effective use of NOCITA for up to 72 hours of analgesia (**Table 9**).

Table 9. Treatment Success Over Time

Time Interval for Pain Evaluation	Treatment Success, n/N (%)		*P* Value
	NOCITA	Saline	
0-24 hours	88/117 (75.2)	48/119 (40.3)	0.0252
0-48 hours	79/115 (68.7)	41/118 (34.7)	0.0395
0-72 hours	78/114 (68.4)	42/119 (35.3)	0.0452

The per-protocol populations for effectiveness varied for each pain assessment time interval because of protocol deviations affecting only 1 of the 3 time intervals for some cats.

Conclusions

The results of this study confirm that NOCITA at a dose of 5.3 mg/kg/forelimb (10.6 mg/kg/cat) administered as a peripheral nerve block provides safe and effective postoperative analgesia for up to 72 hours following onychectomy in cats.

7 The NOCITA Difference

NOCITA is an amide local anesthetic in an encapsulated liposomal formulation that was developed with the goal of providing a longer duration of postoperative analgesia compared with its nonliposomal counterpart bupivacaine HCl or other local anesthetic solutions. The use of NOCITA contributes significantly to a modern multimodal analgesia plan. Its extended duration of action assists in preventing analgesia gaps during the first 72 hours following CCL surgery in dogs and onychectomy in cats. NOCITA provides a bridge between an in-hospital analgesia plan and postsurgical pain relief in the home environment. Additionally, NOCITA is administered at the time of closure by the surgeon in dogs and prior to onychectomy in cats and does not require repeat or continuous administration postoperatively, saving valuable technician time.

For further information, please visit https://nocita.aratana.com/

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10 Package Insert

In Dogs

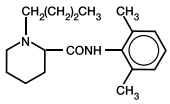
NOCITA®

(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. 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; tricaprylin, 2.0 mg/mL; and 1,2 dierucocylphosphatidylcholine (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.** Puncture the vial stopper once with a single 25 gauge or larger needle. Use aseptic technique to sequentially attach and fill sterile syringes for dosing. Each syringe should be prepared for single patient use only. Discard the vial after all doses are 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. Because the formulation does not contain preservative, the syringe(s) must be discarded after 4 hours.
- If the dose volume of NOCITA (0.4 mL/kg) is not sufficient to cover the surgical site, add up to an equal volume of normal (0.9%) sterile saline or Lactated Ringer's solution. If saline or Lactated Ringer's is added to the NOCITA dose, administer the entire volume by tissue infiltration into the surgical site. Do not mix 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**).
- Use a 25 gauge or larger bore needle for administration.
- 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 toxic effects of these drugs are additive and their administration should be used with caution including monitoring for neurologic and cardiovascular effects related to toxicity.

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

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 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.

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 pregnant, lactating, or intended for breeding.

Adverse Reactions:
Safety was evaluated in 123 NOCITA treated dogs and 59 saline (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 D-1. Adverse Reactions Reported During the Study in the Safety Population (any dog that received treatment)

Adverse Reaction	NOCITA (n = 123)	Saline (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 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 D-2.

Table D-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[a] 9 mg/kg	NOCITA[a] 18 mg/kg	NOCITA[a] 30 mg/kg	bupivacaine HCl 9 mg/kg
N, sex	6, (3M/3F)	6, (3M/3F)	6, (3M/3F)	6, (3M/3F)
T_{max}[b] (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_{max} (ng/mL)	488 (335)	560 (299)	633 (280)	1420 (355)
$AUC_{(0-72)}$ (ng*hr/mL)	9100 (4460)	12800 (2020)	25600 (8160)	9720 (1860)
$T_{1/2}$[c] (hr)	36.2 (12.4)	25.7 (8.15)	43.9 (12.5)	10.1 (8.54)

[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.
[b] Median (Range)
[c] Reported from steady state concentrations

Following a single subcutaneous dose of 9 mg/kg and 18 mg/kg NOCITA, median time to reach C_{max} 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 $AUC_{(0-72)}$ and T_{max} were comparable. However, due to the slow release mechanism of the NOCITA formulation, the mean C_{max} and $T_{½}$ 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_{max} and $AUC_{(0-72)}$ 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.

In Dogs (continued)

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 saline (placebo, n = 59). The per protocol population for effectiveness was 112 NOCITA treated dogs and 52 saline 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 D-3 shows the number and percent of surgical procedures by treatment group.

Table D-3. Surgical Procedure by Treatment Group

Surgical Procedure	NOCITA (n = 112) n (%)	Saline (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 saline was infiltrated into the tissue layers during surgical closure. NOCITA or saline was administered either as is or with the addition of up to an equal volume of 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 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 saline 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 D-4. Number and Percent Effectiveness for NOCITA and Saline (Placebo) at each Time Interval*

Time Interval for Pain Evaluation	NOCITA (n = 112)	Saline (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%)

*For dogs that were deemed treatment failures over any time interval, the failure was carried forward to all subsequent time intervals. Therefore, the time intervals for evaluating treatment success are equivalent to 0-24 hours, 0-48 hours, and 0-72 hours.

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 re-refrigerate. **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

ARATANA THERAPEUTICS

Manufactured for: Aratana Therapeutics, Inc., Leawood, KS 66211
Additional Information is available at www.aratana.com or by calling Aratana Therapeutics at 1-844-272-8262.

AT3-015-17 May 2018

In Cats

NOCITA®

(bupivacaine liposome injectable suspension)

13.3 mg/mL

For use as a peripheral nerve block in cats only

Local Anesthetic

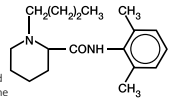
Single use vial

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. Each milliliter of NOCITA contains 13.3 mg/mL 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; tricaprylin, 2.0 mg/mL; and 1,2 dierucocylphosphatidylcholine (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 use as a peripheral nerve block to provide regional postoperative analgesia following onychectomy in cats.

Dosage and Administration:

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/cat) as a 4-point nerve block (described below) prior to onychectomy. Administration prior to surgery may provide up to 72 hours of pain control.

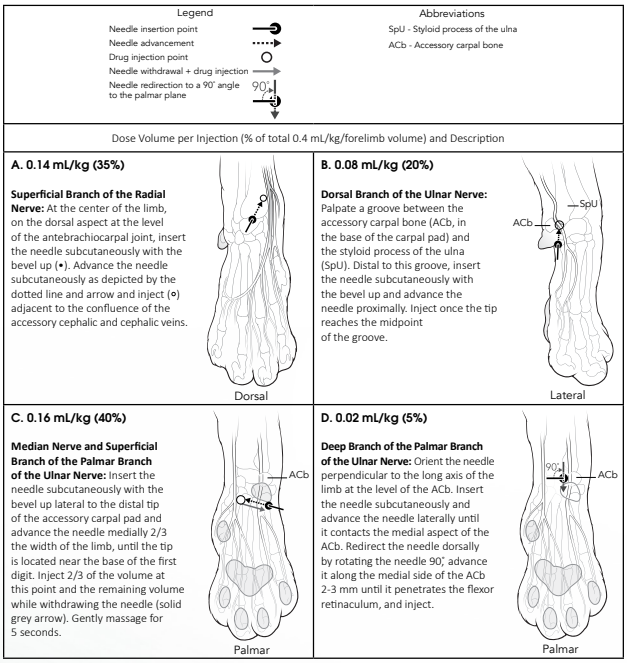
Prepare Dose(s):

- **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.
- **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.** Puncture the vial stopper once with a single 25 gauge or larger needle. Use aseptic technique to sequentially attach and fill sterile syringes. Each syringe should be prepared for single patient use only. Discard the vial after all doses are 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. Because the formulation does not contain preservative, the syringe(s) must be discarded after 4 hours.
- Do not dilute NOCITA prior to use as a nerve block in cats.
  Do not mix 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**).
- Use a 25 gauge or larger bore needle for administration.

Dose Administration:

- Aspirate prior to injecting to prevent intravascular administration (see **CONTRAINDICATIONS**).

Table C-1. Dose Administration for One Forelimb.[1]



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 toxic effects of these drugs are additive and their administration should be used with caution including monitoring for neurologic and cardiovascular effects related to toxicity.

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

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

The ability of NOCITA to achieve effective anesthesia has not been evaluated.

The safe use of NOCITA in cats for surgical procedures other than onychectomy has not been evaluated.

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

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

Adverse Reactions:

Safety was evaluated in 120 NOCITA treated cats and 121 saline (placebo) treated cats in a field study in cats undergoing onychectomy. Cats enrolled in the study were 5 months to 10 years of age, and weighed 2.0 to 9.3 kg. NOCITA was administered as a 4-point peripheral nerve block at a dose of 5.3 mg/kg per forelimb (0.4 mL/kg per forelimb).

Table C-2: 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° F on Day 3 and normal before surgery. One of the NOCITA treated cats had an infection of one surgical site. No other cat with elevated body temperature showed evidence of infection or illness.

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 of 42,000 to 100,000/µL, and the 4 cats in the saline group had platelet counts of 114,000 to 149,000/µL. Decreased platelet counts were not associated with clinical signs.

In a pilot study with 62 cats undergoing onychectomy (31 cats treated with NOCITA and 31 with saline), one NOCITA treated cat had a motor deficit (unilateral knuckling) which resolved by the next morning following surgery. Another NOCITA treated cat had bruising at the injection sites.

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 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, 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 cats evaluated for 168 hours is provided in Table C-3.

Table C-3. Plasma pharmacokinetic parameters for bupivacaine after single subcutaneous administration of NOCITA and bupivacaine HCl solution in male and female cats in a laboratory study.

PK Parameter	NOCITA[a] 3 mg/kg	NOCITA[a] 9 mg/kg	NOCITA[a] 15 mg/kg	bupivacaine HCl 1 mg/kg
N	6	6	6	6
T_{max}[b] (hr)	12.5 (1-48)	10 (1-24)	1.5 (1-24)	1 (1-4)
T_{last}[b] (hr)	108 (72-144)	120 (72-168)	144 (120-168)	18 (12-24)
C_{max}[c] (ng/mL)	311.4 (82.2-565)	620.2 (374-892)	709.7 (462-1090)	263.9 (60.5-506)
$AUC_{(last)}$[c] (ng*hr/mL)	11347 (5176-15767)	32561 (19390-47532)	38475 (26460-48252)	1608 (314-2363)

[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.
[b] Median (range)
[c] Mean (range)
T_{max} = time to maximum plasma concentration
T_{last} = time to last quantifiable plasma concentration
C_{max} = maximum plasma concentration
AUC_{last} = area under the curve from the time of dosing to the last quantifiable plasma concentration

Following a single subcutaneous dose of NOCITA, there was a less than dose proportional increase in C_{max} and AUC_{last} across the dose range tested (3-15 mg/kg). There was a high variability in all reported parameters. Half-life is not reported for NOCITA in cats because the prolonged absorption confounds the estimation of the terminal elimination phase. Therefore, T_{last} is included as a more appropriate measure of the duration of quantifiable plasma concentrations.

In Cats (continued)

Effectiveness:

Effectiveness was demonstrated in a multi-center, placebo-controlled, randomized and masked field study in client-owned cats undergoing bilateral forelimb onychectomy. In this study, 241 cats were enrolled in the study and randomized to treatment with NOCITA (n = 120) or saline (placebo, n = 121).

Cats received an opioid analgesic just prior to general anesthesia and surgery. The nerve block injection sites were shaved and a standard surgical preparation with chlorhexidine or povidone iodine was used. Prior to onychectomy, NOCITA or saline was administered as a 4-point nerve block (see **DOSING INSTRUCTIONS**).

Pain was assessed by trained observers using a modified version of the UNESP-Botucatu Multidimensional Composite Pain Scale for up to 72 hours following extubation. 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. Cats with a composite pain score ≥ 6 or that were determined to be painful by the assessor received rescue analgesic medication and were classified as treatment failures. After receiving rescue analgesia, cats did not have further pain assessments performed. The primary variable for effectiveness was evaluated over the first 24-hour time interval. The percent of treatment success for NOCITA was significantly greater than saline for the 0-24 hour time interval ($p = 0.0252$). The 0-48 hour and 0-72 hour time intervals were evaluated as secondary variables and support effective use of NOCITA for up to 72 hours of analgesia.

Table C-4. Number and Percent Effectiveness for NOCITA and Saline (Placebo) Groups at each Time Interval

Time Interval for Pain Evaluation	NOCITA	Saline
0-24 hours	88/117 (75.2%)	48/119 (40.3%)
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.

Animal Safety:

In a 22 day laboratory study, 40 healthy cats (4 cats/sex/group) aged 5-6 months were administered negative control (2.37 mL/kg saline), active control (5.3 mg/kg bupivacaine HCl), or NOCITA at 10.6, 21.2, or 31.8 mg/kg via injection using a suprainguinal approach for a femoral nerve block of the right hindlimb on Days 0, 9 and 18. These NOCITA doses correspond to 1, 2 and 3 times the maximum labeled total dose of 10.6 mg/kg/cat (representing 2, 4 and 6 times the maximum labeled dose of 5.3 mg/kg/forelimb).

Two cats died during the study. One male in the active control group died during recovery from anesthesia after the second dose and no definitive cause of death was determined. One female in the 31.8 mg/kg group was euthanized on Day 15. This cat developed a suppurative, open, necrotic wound over the region of the right stifle after the second dose administration.

For the cats who survived the study, there were no clinically relevant treatment-related effects on electrocardiograms, hematology, serum chemistry, urinalysis, coagulation, and organ weights. Right hindlimb impairment was expected because the entire dose was administered as a femoral nerve block. Right hindlimb impairment occurred in 23 of the 24 NOCITA 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. NOCITA treatment-related findings were observed on histopathology of soft tissue and the femoral nerve at the injection sites. Injection site soft tissue histopathology findings included subacute or chronic inflammation, mineralization, myofiber degeneration and myofiber necrosis. Injection site femoral nerve histopathology findings included subacute or chronic inflammation.

Sporadic clinical observations and histopathology findings throughout both negative and active control groups and NOCITA groups included: soft or watery or mucoid stool; inguinal swelling on the right hindlimb noted after only the first dose; abrasions or scabbing noted at the right abdominal and inguinal regions as well as on the right hindlimb and at the right stifle; histopathology findings at or near the injection site or right stifle included ulceration and suppurative crusts on the skin, histopathology findings at the injection site of subcutaneous foreign material and fibrosis, and myofiber regeneration.

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 re-refrigerate. **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.

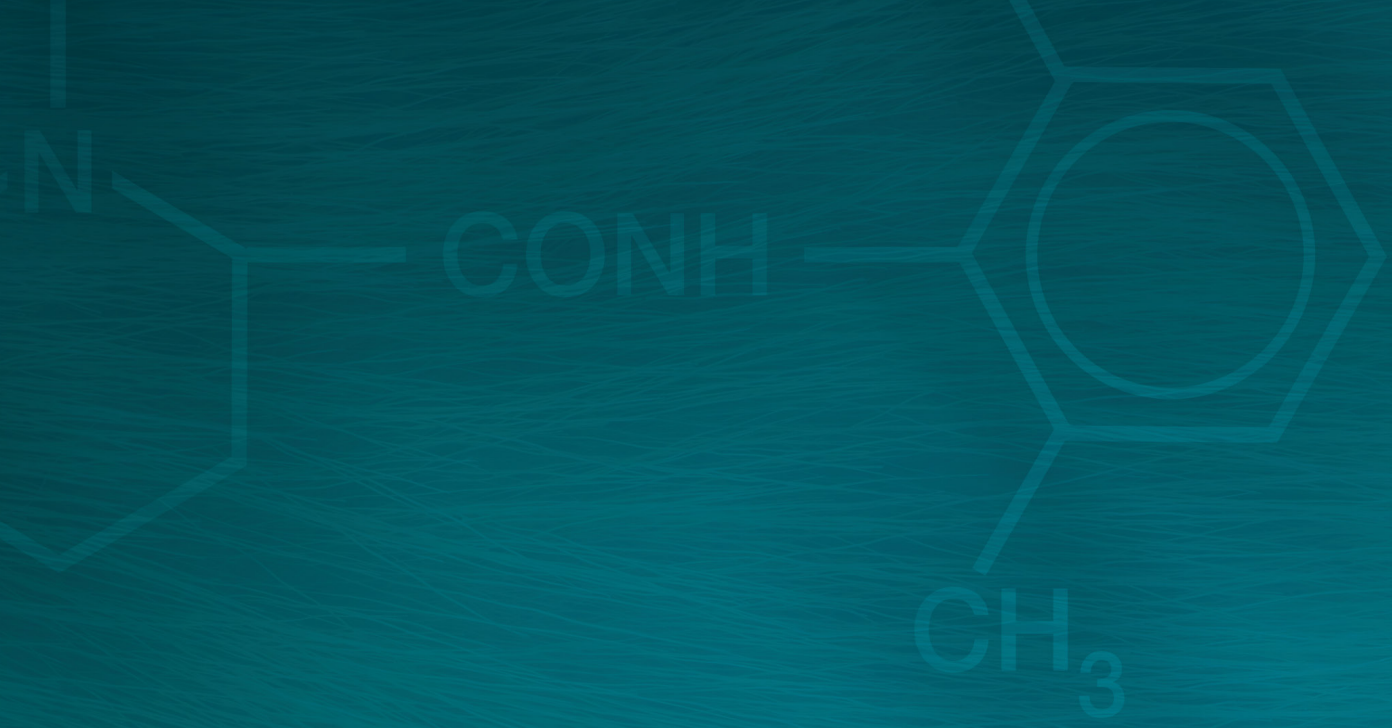
NADA 141-461, Approved by the FDA

US Patent: 8,182,835
US Patent: 8,834,921
US Patent: 9,205,052

Manufactured for: Aratana Therapeutics, Inc., Leawood, KS 66211
Additional Information is available at www.aratana.com or by calling Aratana Therapeutics at 1-844-272-8262.

Reference:
1. Location and relative volumes 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.

AT3-016-01 May 2018



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(bupivacaine liposome injectable suspension)

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