nocita®
(bupivacaine liposome injectable suspension)
Technical Monograph
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Introduction

Overview of Postoperative Pain Management

Many surgical patients experience pain of moderate to extreme intensity during the first few days of postsurgical recovery. 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. 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. 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 (Table 1).

<table>
<thead>
<tr>
<th>Dogs</th>
<th>Cats</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral COX-inhibiting NSAIDs</td>
<td>Injectable meloxicam</td>
</tr>
<tr>
<td>Injectable carprofen</td>
<td>Oral robenacoxib</td>
</tr>
<tr>
<td>Fentanyl transdermal solution</td>
<td>Injectable buprenorphine</td>
</tr>
<tr>
<td></td>
<td>Injectable butorphanol tartrate</td>
</tr>
</tbody>
</table>

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), the need for advanced equipment to administer a constant rate infusion, and concerns over untoward side effects (eg, sedation, gastrointestinal upset) of varying severity, even at clinically recommended dosages.

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

There are numerous local anesthetics available for clinical use in the perioperative period, with well-established safety and efficacy profiles. 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. Altogether, the limitations of currently available postoperative analgesics indicate a clear unmet need for better postsurgical pain management. A long-acting local anesthetic that provides pain management for veterinary patients for up to 72 hours and can be added to the multimodal analgesic arsenal would satisfy this unmet need.

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. 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 physiologic 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. 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). An individual animal’s response to pain varies with many factors, including age, sex, health status, species, and interspecies variation.

Figure 1. Processes Involved in Nociception

- **Transduction**: Noxious stimulus (temperature, mechanical, or chemical insult) is converted to electrical activity by specific receptor ion channels in the peripheral terminals of nociceptor sensory fibers.
- **Transmission**: Incoming signals are sent through the sensory nervous system to the spinal cord.
- **Modulation**: Incoming impulses are modified within the dorsal horn through the release of enkephalins and endorphins and the activation of serotonergic and noradrenergic pathways.
- **Perception**: Central perception of pain may lead to a response, depending on the noxious stimulus and the individual animal.
Introduction (continued)

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 Ca²⁺ 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 A₂ (PLA₂). PLA₂ 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 H₂, which is subsequently converted into PGE₂. PGE₂ 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
Introduction  (continued)

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. 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.

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. 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. 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

<table>
<thead>
<tr>
<th>Local/Regional Anesthetics</th>
<th>Render complete analgesia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Considered safe, with side effects generally limited to very high doses, and do not appear to delay tissue healing3</td>
</tr>
<tr>
<td></td>
<td>The duration of action of standard formulations is limited to hours; therefore, they do not provide extended pain relief</td>
</tr>
<tr>
<td>Opioids</td>
<td>Oral formulations have limited usefulness in dogs compared with humans, but pharmacokinetic studies demonstrate possible efficacy of codeine and hydrocodone in dogs11,12; however, they are not FDA approved in animals</td>
</tr>
<tr>
<td></td>
<td>Recuvyr (fentanyl) transdermal solution provides 4 days of postoperative pain control when applied to the dorsal scapular area of a dog prior to surgery; however, isolation from children for 72 hours is recommended13</td>
</tr>
<tr>
<td></td>
<td>Opioids are scheduled drugs and require Drug Enforcement Administration licenses, recordkeeping, and secure storage</td>
</tr>
<tr>
<td>COX-Inhibiting NSAIDs</td>
<td>Commonly used perioperative analgesics that can be continued in the home environment</td>
</tr>
<tr>
<td></td>
<td>Longer-term use requires monitoring of serum chemistry and complete blood counts and may have side effects that limit use in some dogs</td>
</tr>
<tr>
<td>Other Analgesics (eg, gabapentin, pregabalin, amitriptyline, tramadol, amantadine)</td>
<td>Focused on managing maladaptive pain in humans, but not FDA approved for use in animals, and side effects can be a concern</td>
</tr>
<tr>
<td>Nonpharmacological Modalities</td>
<td>Acupuncture, laser therapy, and pulsed electromagnetic field technology therapy: minimally invasive and complement a pain treatment protocol</td>
</tr>
<tr>
<td></td>
<td>Physical therapy: advantageous after certain surgeries and helps with muscle rehabilitation</td>
</tr>
<tr>
<td></td>
<td>Thermal modification: heat or cold applications can be useful techniques for localized pain management</td>
</tr>
<tr>
<td></td>
<td>Chiropractic care: no evidence for use in dogs, but well defined in human applications5</td>
</tr>
<tr>
<td></td>
<td>Gentle handling techniques: proper handling of patients should be a top consideration with all pain management protocols</td>
</tr>
</tbody>
</table>

There is a clear unmet need for a long-acting local anesthetic that can be added to the multimodal analgesic arsenal to provide pain management for veterinary patients for extended periods. 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.
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.”

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 unless formulated for extended release). Both lidocaine and bupivacaine are metabolized by the liver.

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.14 In addition, the clinical use of local anesthetics has not been associated with increased risk of surgical site infection.15 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.16

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.17

Incisional block, either preoperatively or at the time of wound closure, has been advocated as a means of enhancing multimodal perioperative pain management.18 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 those patients requiring extended hospitalization.
Modern multimodal analgesia regimens should incorporate local anesthetics as advocated by industry leaders\textsuperscript{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 very 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.\textsuperscript{19} 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.

In response to an unmet need for a long-acting local anesthetic, 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.\textsuperscript{20} 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 $\approx$ 96 hours (Figure 2).

The technique for instilling bupivacaine liposome injectable suspension into a surgical site differs slightly from the use of a 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. 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 using a moving-needle tissue infiltration technique, please visit http://www.aratana.com/therapeutics/post-operative-pain/.
Using identical technology, NOCITA, a nonpyrogenic, preservative-free, bupivacaine liposome injectable suspension was developed for clinical use in dogs and received FDA approval in 2016. This sustained-release formulation limits analgesic gaps, which are periods of inadequate pain control that can compromise a patient’s recovery from surgery.
### NOCITA Pharmacology

#### Chemical Composition

Bupivacaine is an aminoamide local anesthetic. The chemical structure and nomenclature for bupivacaine is shown in Figure 4. The empirical formula for bupivacaine is C\textsubscript{28}H\textsubscript{26}N\textsubscript{2}O, and the molecular weight is 288.43 Daltons.\(^{21}\)

![Figure 4. Chemical Structure and Chemical Nomenclature of Bupivacaine](image)

(RS)-1-buty-N(2,6-dimethylphenyl)piperidine-2-carboxamide

#### 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 A\(\delta\) fibers, are blocked before larger sensory A\(\beta\) and motor A\(\alpha\) fibers.\(^{22}\)
NOCITA Pharmacology (continued)

To provide a longer duration of anesthesia than bupivacaine HCl or other local anesthetics, NOCITA (bupivacaine liposomal 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 5). In vivo, NOCITA releases drug over an extended period by erosion of the exterior surface and reorganization of the particles’ lipid membranes.23

Figure 5. Multivesicular Liposome Particles for Extended Bupivacaine Release

For further information on the mechanism of action of NOCITA, please visit http://www.aratana.com/therapeutics/post-operative-pain/.

Pharmacokinetic Profile

NOCITA is a single treatment administered by tissue infiltration during surgical closure into the tissues to control postoperative pain in CCL surgery. 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 3.21

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

<table>
<thead>
<tr>
<th>PK Parameter, mean (SD)</th>
<th>NOCITAb</th>
<th>Bupivacaine HCl 9 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median $T_{\text{max}}$ (range), hr</td>
<td>0.5 (0.5-0.5)</td>
<td>0.5 (0.5-0.5)</td>
</tr>
<tr>
<td>$C_{\text{max}}$, ng/mL</td>
<td>488 (335)</td>
<td>560 (299)</td>
</tr>
<tr>
<td>AUC$_{(0-72)}$, ng·hr/mL</td>
<td>9100 (4460)</td>
<td>12800 (2020)</td>
</tr>
<tr>
<td>$T_{1/2}$, hr</td>
<td>36.2 (12.4)</td>
<td>25.7 (8.2)</td>
</tr>
</tbody>
</table>

AUC, area under the curve; PK, pharmacokinetics.

a $N = 6$ dogs (3 males and 3 females) per dosing group.
b NOCITA bupivacaine base is equal to 6 mg/kg bupivacaine HCl. NOCITA doses in this table are the bupivacaine HCl equivalent.
c Reported from steady state concentrations.
Absorption

Following single subcutaneous doses of 9 mg/kg and 18 mg/kg 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).\textsuperscript{21} Following equivalent doses (9 mg/kg) of bupivacaine liposome injectable suspension and bupivacaine HCl solution, the mean bupivacaine AUC_{(0-72)} and T_{max} were comparable. However, due to the slow release mechanism of the bupivacaine liposome injectable suspension, the mean C_{max} and T_{1/2} on day 1 were approximately 3-fold lower and 3.5-fold higher, respectively, compared with bupivacaine HCl. Following an increase in dose of bupivacaine liposome injectable suspension, 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.\textsuperscript{21} Of note, bupivacaine liposome injectable suspension 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.\textsuperscript{24}

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.\textsuperscript{25} The rate of systemic absorption of bupivacaine is dependent upon 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 the aminoamide local anesthetics such as bupivacaine.\textsuperscript{25} 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 substitute NOCITA with other bupivacaine formulations.
Local anesthetic toxicities affect the neurologic or cardiovascular systems, manifest from high plasma levels of the local anesthetic, and commonly are a result of the accidental intravascular injection of the drug or the administration of an overdose. Extended-release bupivacaine has been studied in dog models as part of the development for human use.

**Pilot Dose-Finding and Expanded Studies**

In a pilot study to determine the maximum tolerated doses after 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 4). 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 4: Maximum Dosages of Study Drug That Were Associated With No Meaningful Adverse Events**

<table>
<thead>
<tr>
<th>Route of Administration</th>
<th>Bupivacaine HCl, mg/kg</th>
<th>Liposome Bupivacaine, mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenous</td>
<td>0.75</td>
<td>4.5</td>
</tr>
<tr>
<td>Intra-arterial</td>
<td>0.1</td>
<td>1.5</td>
</tr>
</tbody>
</table>

**Local Toxicity Studies**

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

**Study of Effects on Wound Healing**

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 doses higher than expected with clinical use.

**Single-Dose Toxicity Study**

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. There were no cardiovascular- or central nervous system–related adverse events observed in these study animals. 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.
Repeat-Dose Local Toxicity Study

In a 4-week laboratory repeat-dose toxicity study, 60 healthy dogs aged 5 to 6 months were given liposome bupivacaine 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 for NOCITA). 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 histopathology included minimal to moderate edema, granulomatous inflammation, and mineralization in the subcutaneous tissues in some dogs that received liposome bupivacaine. 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 compared with the number observed immediately after the 4-week treatment period. One male dog in the 9-mg/kg liposome bupivacaine 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.

The aforementioned studies were all performed in healthy animals. 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.
NOCITA Efficacy

Canine Pilot Field Study

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. The 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 additional analgesia was needed. An exploratory analysis evaluated treatment success, defined as no pain intervention, over the 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 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 only statistically significant when exploratory analysis included site interaction in the model.

Results of the safety testing showed that NOCITA was well tolerated. Two adverse events were reported in the placebo 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.

Table 5: Treatment Success Over Time

<table>
<thead>
<tr>
<th>Time Interval for Pain Evaluation</th>
<th>Treatment Success, n (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NOCITA (n = 24)</td>
<td>Placebo (n = 22)</td>
</tr>
<tr>
<td>0-24 hours</td>
<td>19 (79.2)</td>
<td>5 (22.7)</td>
</tr>
<tr>
<td>24-48 hours</td>
<td>10 (41.7)</td>
<td>3 (13.6)</td>
</tr>
<tr>
<td>48-72 hours</td>
<td>9 (37.5)</td>
<td>2 (9.1)</td>
</tr>
</tbody>
</table>
NOCITA Efficacy (continued)

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
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 at a dose of up to 5.3 mg/kg (n = 123) or placebo (sterile saline, n = 59). The per-protocol population included 112 dogs treated with NOCITA and 52 dogs that received placebo.

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 6 shows the number and percentage of surgical procedures by treatment group.

Using a moving-needle 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 2-fold (1:1) with sterile saline. 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 to be in pain 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 analgesia medication. The primary variable for effectiveness was evaluated over the first 24-hour time interval.

<table>
<thead>
<tr>
<th>Surgical Procedure, n (%)</th>
<th>NOCITA (n = 112)</th>
<th>Placebo (n = 52)</th>
<th>Total (n = 164)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extracapsular repair</td>
<td>52 (46.4)</td>
<td>24 (46.2)</td>
<td>76 (46.3)</td>
</tr>
<tr>
<td>TPLO</td>
<td>50 (44.6)</td>
<td>22 (42.3)</td>
<td>72 (43.9)</td>
</tr>
<tr>
<td>TTA</td>
<td>10 (8.9)</td>
<td>6 (11.5)</td>
<td>16 (9.8)</td>
</tr>
</tbody>
</table>

TPLO, tibial plateau–leveling osteotomy; TTA, tibial tuberosity advancement.
NOCITA Efficacy (continued)

Results
The percentage of treatment success for NOCITA was statistically significantly greater than placebo 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 7).

Table 7: Treatment Success Over Time

<table>
<thead>
<tr>
<th>Time Interval for Pain Evaluation</th>
<th>Treatment Success, $n$ (%)</th>
<th>$P$ Value$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NOCITA (n = 112)</td>
<td>Placebo (n = 52)</td>
</tr>
<tr>
<td>0-24 hours</td>
<td>77 (68.8)</td>
<td>19 (36.5)</td>
</tr>
<tr>
<td>24-48 hours$^b$</td>
<td>72 (64.3)</td>
<td>18 (34.6)</td>
</tr>
<tr>
<td>48-72 hours$^b$</td>
<td>69 (61.6)</td>
<td>17 (32.7)</td>
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</table>

$^a$ Site and treatment-by-site interactions were included as random effects in the analysis.

$^b$ Treatment failures from the previous interval were carried forward.

Conclusions
The results of this study demonstrated that NOCITA administered at a dose of up to 5.3 mg/kg, provided effective postoperative analgesia for up to 72 hours following CCL surgery in dogs.
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 anesthetics. 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 provides a bridge between an in-hospital analgesia plan and a strategy instituted in the home environment. Additionally, NOCITA is administered at the time of closure by the surgeon and does not require repeat or continuous administration postoperatively, saving valuable technician time.

**NOCITA Prescribing Information**

NOCITA (bupivacaine liposome injectable suspension), NADA 141-461, is indicated for single-dose infiltration into the surgical site to produce local postoperative analgesia following CCL surgery in dogs.

NOCITA is a sterile, nonpyrogenic, 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 mL of NOCITA contains 13.3 mg of bupivacaine in 20-mL, single-use vials, in 1-vial or 4-vial cartons.

**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.
- 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 resuspend 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 the 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.
  - **Please note:** Do not dilute NOCITA with water or other hypotonic solutions as it will result in disruption of the liposomal particles.
  - Do not mix NOCITA with other local anesthetics or other drugs prior to administration.
- 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.
**NOCITA Prescribing Information** (continued)

**Contraindications**
Do not administer by intravenous or intra-arterial injection. If accidental intravascular administration occurs, monitor for cardiovascular (dysrhythmia, 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 chondralysis.

**Warnings**

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.

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 preincisional or preprocedural loco-regional anesthetic techniques that require deep and complete sensory block in the area of administration.

Please refer to the NOCITA **package insert** for additional information.
References


Rausch-Derra LC, Huebner M, Wolford JA. A placebo-controlled pivotal clinical field study to confirm the safety and efficacy of AF-003 (bupivacaine liposome injectable suspension) in providing local postoperative analgesia in dogs. Vet Anesth Analgesia. 2016;In review.


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 anesthetics. When a topical anesthetic such as lidocaine or chloroprocaine 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 (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) or more of 0.9% sterile saline or lactated Ringer’s solution to obtain a volume sufficient to cover the surgical site.

Adverse Reactions:

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 multilamellar 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) Pharmacokinetic Parameters for bupivacaine after single subcutaneous administration of NOCITA® and bupivacaine HCl solution in male and female Beagle dogs in a laboratory study

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>NOCITA®</th>
<th>Placebo</th>
<th>NOCITA®</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_{1/2}$ (hr)</td>
<td>44.0 (6.5)</td>
<td>56.5 (5.3)</td>
<td>50.5 (6.2)</td>
<td>56.1 (5.3)</td>
</tr>
<tr>
<td>$C_{max}$ (ng/mL)</td>
<td>50.1 (12.4)</td>
<td>25.7 (8.15)</td>
<td>25.7 (8.15)</td>
<td>25.7 (8.15)</td>
</tr>
</tbody>
</table>

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 $C_{max}$ were comparable. However, due to the slow release mechanism of the NOCITA® formulation, the mean bupivacaine $C_{max}$ was significantly lower and $T_{1/2}$ longer than that for the solution. 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.
Package Insert (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 = 112) or placebo (sterile saline, n = 52). The per protocol population for effectiveness was 111 NOCITA treated dogs and 52 placebo dogs.

Dogs received an epidural 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

<table>
<thead>
<tr>
<th>Surgical Procedure</th>
<th>NOCITA (n = 112)</th>
<th>Placebo (n = 52)</th>
<th>Total (n = 164)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extra-capsular repair</td>
<td>52 (46.4%)</td>
<td>24 (48.1%)</td>
<td>76 (46.3%)</td>
</tr>
<tr>
<td>TPLO</td>
<td>50 (44.6%)</td>
<td>22 (42.3%)</td>
<td>72 (43.9%)</td>
</tr>
<tr>
<td>TTA</td>
<td>10 (8.9%)</td>
<td>6 (11.5%)</td>
<td>16 (9.8%)</td>
</tr>
</tbody>
</table>

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, 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 = 0.032). 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

<table>
<thead>
<tr>
<th>Time Interval for Pain Evaluation</th>
<th>NOCITA (n = 112)</th>
<th>Placebo (n = 52)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.24 hours</td>
<td>77 (68.0%)</td>
<td>44 (84.6%)</td>
</tr>
<tr>
<td>0.5-0.5</td>
<td>6 (5.4%)</td>
<td>5 (9.6%)</td>
</tr>
<tr>
<td>0-72 hours</td>
<td>72 (64.3%)</td>
<td>18 (34.6%)</td>
</tr>
<tr>
<td>48-72 hours</td>
<td>69 (61.6%)</td>
<td>17 (32.7%)</td>
</tr>
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</table>

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 were 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 mineralisation 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 a 20 mL single use vial, in a single vial carton and 4-vial cartons. NDA 814-141. Approved by the FDA
US Patent: 8,182,835
US Patent: 8,834,021
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
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