Overview of Post-Operative 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.

Controlling Post-Operative Pain with a Multi-Modal Analgesic Regimen

Post-operative pain can typically be well-controlled in hospitalized patients. Most veterinary patients that undergo soft-tissue or orthopedic surgery are discharged from the veterinary hospital within 24 to 48 hours post-operatively. Therefore, analgesics that provide continued pain relief must be prescribed and/or delivered in the home environment.


Continuing Education by Aratana Therapeutics®

Controlling Post-Operative Pain with a Multi-Modal Analgesic Regimen Continued

using a multi-modal analgesic regimen that involves an appropriate combination of opioids, cyclooxygenase (COX)-inhibiting nonsteroidal anti-inflammatory drugs (NSAIDs), local anesthetics, alpha2 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 post-operatively. Therefore, analgesics that provide continued pain relief must be prescribed and/or delivered in the home environment. Currently, there are limited U.S. Food and Drug Administration (FDA)–approved options available for the treatment of post-operative pain in dogs (Table 1).

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.
• Concerns over untoward side effects (e.g., 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

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

<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 and injectable robenacoxib</td>
<td>• Oral and injectable robenacoxib</td>
</tr>
<tr>
<td>• Fentanyl transdermal solution (discontinued)</td>
<td>• Injectable buprenorphine</td>
</tr>
<tr>
<td></td>
<td>• Injectable butorphanol tartrate</td>
</tr>
</tbody>
</table>

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 (https://www.wsava.org/sites/default/files/jsap_0.pdf)\(^4\) there are limitations that function as barriers to their use.

**These limitations include:**

- Technical difficulty associated with some nerve and epidural blocks.
- Potential complications of the indwelling soaker catheter.
- Short duration of action (< 8 hours) of the available formulations of local anesthetics.

There are numerous local anesthetics available for clinical use in the perioperative period with established safety and efficacy profiles, though none are approved for use in dogs.\(^4\) 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.\(^5\)

Altogether, the limitations of currently available post-operative analgesics indicate an unmet need for better post-operative 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 multi-modal analgesic arsenal could satisfy this unmet need.

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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.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

How Long Is Long Enough?

There is limited data as to how long post-operative 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 post-operative 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 post-operative 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 Bridge in Pain Relief

A key difference between pain management in animals compared to 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. Post-operative pain in pets can typically be well-controlled in hospitalized patients when pain assessment and pain intervention are part of post-operative protocols. However, most veterinary patients that undergo soft-tissue or orthopedic surgery are discharged from the veterinary hospital within 12 to 48 hours post-operatively.

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.

A Bridge in Pain Relief Continued

Therefore, analgesics must be delivered and/or prescribed that bridge pain relief in the home environment.\(^5\) Adequate post-operative pain control during the early post-operative window is key to preventing PPOP.

Optimizing Post-Operative Pain Management

There are 4 central tenets to optimizing post-operative analgesia: (1) provide preemptive analgesia, (2) use multi-modal 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 - On Next Page).

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

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Local Anesthetics

Use in Dogs and Cats

Local anesthetics are widely available in companion animal practice and have been shown to

Use in Dogs and Cats Continued

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 Link to Pain Guidelines: https://www.aaha.org/public_documents/professional/guidelines/2015_aaha_aafp_pain_management_guidelines_for_dogs_and_cats.pdf

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 (e.g., lidocaine, bupivacaine, mepivacaine, ropivacaine) and esters (e.g., 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.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

Effects on Tissue Continued

mechanical wound strength in animals or humans.\textsuperscript{14} In addition, the clinical use of local anesthetics has not been associated with increased risk of surgical site infection.\textsuperscript{15} Local anesthetics as a class have been shown to have antimicrobial properties \textit{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 \textit{Escherichia coli}, \textit{Staphylococcus aureus}, \textit{Staphylococcus epidermidis}, \textit{Candida albicans}, and others.\textsuperscript{16, 17}

Incisional block, either preoperatively or at the time of wound closure, has been advocated as a means of enhancing multi-modal perioperative pain management.\textsuperscript{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 post-operatively.

Challenges in the Early Post-Operative Period

Local anesthetics are also used for regional nerve blocks, and these techniques have demonstrated a significant enhancement of post-operative analgesia in pets. However, the duration of analgesia using these


Challenges in the Early Post-Operative Period Continued

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 post-operative period.

While local anesthetics have demonstrated a beneficial role in companion animal pain management in the immediate post-operative period, these drugs do not provide effective prolonged analgesia in their traditional single-dose administration formulation.

The Need for a Long-Acting Local Anesthetic

Thought leaders have advocated that modern multi-modal analgesia regimens should incorporate local anesthetics 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 multi-modal analgesic regimen remains uncommon. Explanations for the 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 previously available local anesthetic solutions.

An Extended-Release Formula

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 injection to provide post-operative analgesia in human patients, and received FDA-approval in October 2011. In August 2016, the Center for Veterinary Medicine (CVM) FDA-approved an extended-release formulation of bupivacaine to provide local post-operative analgesia.

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An Extended-Release Formula Continued

for cranial cruciate ligament surgery in dogs. 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. 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 ≈ 96 hours (Figure 2).

The Technique for Instilling Bupivacaine Liposome Injectable Suspension into a Surgical Site

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.

The Technique for Instilling Bupivacaine Liposome Injectable Suspension into a Surgical Site Continued

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.

**Figure 3. Surgical Site Infiltration with Bupivacaine Liposome Injectable Suspension Using a Moving-Needle Technique**

![Diagram of surgical site infiltration](image)

**FDA-Approved NOCITA® (bupivacaine liposome injectable solution)**

**Chemical Composition**

Bupivacaine is an aminoamide local anesthetic. The chemical structure and nomenclature for bupivacaine is shown in Figure 4 (On the Next Page). The empirical formula for bupivacaine is $C_{28}H_{26}N_{2}O$, and the molecular weight is 288.43 Daltons.21

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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.22

To provide a longer duration of anesthesia than bupivacaine HCl or other local anesthetics, NOCITA 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

Pharmacokinetic Profile

NOCITA is a single dose administered by tissue infiltration injection during surgical closure into the tissues to control post-operative pain in cranial cruciate ligament (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 3.21

<table>
<thead>
<tr>
<th>PK Parameter, mean (SD)</th>
<th>NOCITA®</th>
<th>Bupivacaine HCl</th>
<th>9 mg/kg</th>
<th>18 mg/kg</th>
<th>30 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>
<td>60 (0.5 - 72)</td>
<td>0.5 (0.5 - 0.5)</td>
<td></td>
</tr>
<tr>
<td>$C_{\text{max}}$, ng/mL</td>
<td>488 (335)</td>
<td>560 (299)</td>
<td>633 (280)</td>
<td>1420 (355)</td>
<td></td>
</tr>
<tr>
<td>AUC$_{0-152}$, ng • hr/mL</td>
<td>9100 (4460)</td>
<td>12800 (2020)</td>
<td>25600 (8160)</td>
<td>9720 (1860)</td>
<td></td>
</tr>
<tr>
<td>$T_{1/2}$, hr$^c$</td>
<td>36.2 (12.4)</td>
<td>25.7 (8.2)</td>
<td>43.9 (12.5)</td>
<td>10.1 (8.5)</td>
<td></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 doses are given in bupivacaine HCl equivalents. (A NOCITA) or (A liposomal bupivacaine) dose of 5.3 mg/kg is equal to 6 mg/kg bupivacaine HCl.
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 Cmax was rapid (0.5 hr), but it was delayed significantly


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Due to the slow release mechanism of the bupivacaine liposome injectable suspension, the mean Cmax and T1/2 on day 1 were approximately 3 times lower and 3.5 times higher, respectively, compared with bupivacaine HCl.

Absorption Continued

at a high dose of 30 mg/kg (60 hr). Following equivalent doses (9 mg/kg) of bupivacaine liposome injectable suspension and bupivacaine HCl solution, the mean bupivacaine AUC(0-72) and Tmax were comparable. However, due to the slow release mechanism of the bupivacaine liposome injectable suspension, the mean Cmax and T1/2 on day 1 were approximately 3 times lower and 3.5 times higher, respectively, compared with bupivacaine HCl. 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.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.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.

Distribution, Metabolism, and Excretion Continued

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 aminoamidine 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. \textit{Do not substitute NOCITA with other bupivacaine formulations.}

NOCITA Safety Studies

NOCITA – Extended-Release Bupivacaine Safety

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. Bupivacaine liposome injectable suspension has been studied in dog models as part of the development for human use.

\textsuperscript{25} Marcaine\textsuperscript{TM} [package insert]. Lake Forest, IL: Hospira, Inc.; 2014.
Dose-Finding and Expanded Studies

In a study to determine the maximum tolerated doses after intravascular administration of bupivacaine liposome injectable suspension vs bupivacaine HCl, maximum doses at which no meaningful adverse events were observed were higher with bupivacaine liposome injectable suspension 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. suspension has been studied in dog models as part of the development for human use.

![Table 4: Maximum Dosages of Study Drug That Were Associated with No Meaningful Adverse Events](image)

<table>
<thead>
<tr>
<th>Route of Administration</th>
<th>Bupivacaine HCl, mg/kg</th>
<th>Bupivacaine Liposome Injectable Suspension, 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 bupivacaine liposome injectable suspension following tissue infiltration.

Study of Effects on Wound Healing

In a study evaluating bupivacaine liposome injectable suspension in a dog model of inguinal hernia repair, dogs given 9, 18, or 25 mg/kg bupivacaine liposome injectable suspension 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 bupivacaine liposome injectable suspension at doses higher than expected with clinical use.24

Repeat-Dose Local Toxicity Study

In a 4-week laboratory repeat-dose toxicity study, 60 healthy dogs aged 5 to 6 months were given bupivacaine liposome injectable suspension 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).28 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.28

All dogs survived the study, and there were no clinically relevant treatment-related effects on clinical observations, physical examination, body weight, electrocardiograms, hematology, serum


Repeat-Dose Local Toxicity Study Continued

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 bupivacaine liposome injectable suspension.28

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 bupivacaine liposome injectable suspension have been identified to date.

NOCITA Efficacy Study

Clinical Effectiveness Study 30

The effectiveness of NOCITA in providing prolonged post-operative 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),

30. NOCITA Freedom of Information Summary, NADA 141-461

IMPORTANT SAFETY INFORMATION: NOCITA® (bupivacaine liposome injectable suspension) is for use in dogs only. Do not use in dogs younger than 5 months of age, dogs used for breeding, or in pregnant or lactating dogs. Do not administer by intravenous or intra-arterial injection. Adverse reactions in dogs may include discharge from incision, incisional inflammation and vomiting. Avoid concurrent use with bupivacaine HCl, lidocaine or other amide local anesthetics. Please see the full Prescribing Information for more detail.
**Study Design Continued**

or tibial tuberosity advancement (TTA). **Table 5** shows the number and percentage of surgical procedures by treatment group.

<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.

Using a moving-needle 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 2-fold (1:1) with sterile saline. Pain was assessed by trained observers using the short form composite measure pain score (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.
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 6).

Table 6: Treatment Success over Time

<table>
<thead>
<tr>
<th>Time Interval for Pain Evaluation</th>
<th>Treatment Success, n (%)</th>
<th>PValue&lt;sup&gt;a&lt;/sup&gt;</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&lt;sup&gt;b&lt;/sup&gt;</td>
<td>72 (64.3)</td>
<td>18 (34.6)</td>
</tr>
<tr>
<td>48-72 hours&lt;sup&gt;b&lt;/sup&gt;</td>
<td>69 (61.6)</td>
<td>17 (32.7)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Site and treatment-by-site interactions were included as random effects in the analysis.

<sup>b</sup> 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 post-operative analgesia for up to 72 hours following CCL surgery in dogs.

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Summary

NOCITA is an amide local anesthetic in an encapsulated liposomal formulation that was developed with the goal of providing a longer duration of post-operative analgesia compared with its nonliposomal counterpart bupivacaine HCl or other local anesthetics. The use of NOCITA contributes to a modern multi-modal 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 post-operatively, saving valuable technician time.

Please see full Prescribing Information at the end of the document for more detail.

Are You Ready to Take the Quiz?

Congratulations, you have finished the course content for this CE course. Click the button below to launch the quiz.

Launch Quiz
NOCITA®

(bupivacaine liposome injectable suspension)

13.3 mg/mL

For local infiltration injection in dogs only

Local anesthetic

Single use vial

Cautions:

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

Description:

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

Indication:

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

Dosage and Administration:

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

Dosing Instructions:

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

Contraindications:

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

Use in animals with cardiac disease has not been evaluated. NOCITA is metabolized by the liver and excreted by the kidneys.

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

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

Adverse Reactions:

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

Table 1. Adverse Reactions Reported During the Study in the Safety Population (any dog that received treatment)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>NOCITA (n = 123)</th>
<th>Placebo (n = 59)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased Incision</td>
<td>4 (3.3%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Discharge from the Incision</td>
<td>3 (2.4%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Discharge from the Incision</td>
<td>1 (0.8%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Soft Tissue/Ehara</td>
<td>1 (0.8%)</td>
<td>1 (1.7%)</td>
</tr>
<tr>
<td>Nycthaemia</td>
<td>1 (0.8%)</td>
<td>1 (1.7%)</td>
</tr>
<tr>
<td>Fever</td>
<td>1 (0.8%)</td>
<td>0 (0.0%)</td>
</tr>
</tbody>
</table>

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/vets or at the website of the American Animal Hospital Association.

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 unchanged 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 2.

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

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>NOCITAa 9 mg/kg</th>
<th>NOCITAa 18 mg/kg</th>
<th>NOCITAa 30 mg/kg</th>
<th>bupivacaine HCl 9 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1/2 (h)</td>
<td>0.5 (0.5-0.5)</td>
<td>0.5 (0.5-0.5)</td>
<td>0.5 (0.5-0.5)</td>
<td>0.5 (0.5-0.5)</td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>1860 (335)</td>
<td>560 (299)</td>
<td>633 (330)</td>
<td>1420 (335)</td>
</tr>
<tr>
<td>AUC0–infinity (ng*h/mL)</td>
<td>9100 (4460)</td>
<td>22800 (20200)</td>
<td>25660 (8160)</td>
<td>9720 (1860)</td>
</tr>
<tr>
<td>T1/2 (h)</td>
<td>36.2 (12.4)</td>
<td>25.7 (8.15)</td>
<td>43.9 (12.5)</td>
<td>16.1 (8.54)</td>
</tr>
</tbody>
</table>

* 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.
* Median (Range)

The pharmacokinetics was nonlinear with high variability in exposure parameters. Both Cmax and T1/2 were comparable. However, due to the slow release mechanism of the NOCITA formulation, the mean Cmax and T1/2 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 Cmax and AUC0–infinity increase with dose but the increases were less than dose proportional. Further, the non-linear bupivacaine pharmacokinetics was made evident by an increase in the terminal phase half-life with the increase in dose.

**Effectiveness:**

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

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

### Table 3. Surgical Procedure by Treatment Group

<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 (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>

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 (CMPSF-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 post-surgery hours. Dogs with a CMPSF-SF score > 2 or that were determined to be painful by the investigator received rescue analgesic medication and were classified as treatment failures. No further CMPSF-SF pain assessments were recorded for dogs that received rescue analgesic medication. The primary variable for effectiveness was evaluated over the first 24-hour time interval. The percent of treatment success for NOCITA was significantly different from and greater than placebo at the first 24-hour time interval (p = 0.0322). The 24-48 hour and 48-72 hour time intervals were evaluated as secondary variables and support effective use of NOCITA for up to 72 hours of analgesia.

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

<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 (68.3%)</td>
<td>19 (36.5%)</td>
</tr>
<tr>
<td>24-48 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>
</tbody>
</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 26.1 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 or near the scapula. There were 6 dogs/dosing group for the first 4 weeks, and then 3 dogs/dosing group were monitored 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 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 9-9 mg/kg NOCITA group male dog had minimal subcutaneous edema that was not associated with cellular inflammation. These inflammatory changes are associated with administration of the liposomal suspension, and did not occur in the saline and bupivacaine HCl groups.

**Storage Conditions:**

Unopened vials should be stored refrigerated between 36° F to 46° F (2° C to 8° C). NOCITA may be held at a controlled room temperature of 68° F to 77° F (20° C to 25° C) for up to 30 days in sealed, intact (unopened) vials. Do Not Freeze.

### How Supplied:

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

NADA 141-461, Approved by the FDA
US Patent: 8,182,835
US Patent: 8,834,921
US Patent: 9,205,052

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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