In a field trial, Nocita reduced the need for post-op rescue pain treatment with opioids.

Select Important Safety Information
NOCITA is for use in dogs and cats only. See Nocita Package Insert for complete safety information.
Why recovery care should begin with NOCITA™
(bupivacaine liposome injectable suspension)

SEE THE BENEFITS OF ADDRESSING
ACUTE SURGICAL PAIN WITH A
LONG-ACTING LOCAL ANESTHETIC.

THREE REASONS TO MINIMIZE
ACUTE POST-SURGICAL PAIN:¹
• Pain delays healing and return
to function
• Unmanaged acute pain can lead
to chronic maladaptive pain
• Ethical obligation to minimize
pain and suffering

All surgeries result in some degree of
tissue trauma and associated pain.¹

There is a need to provide analgesia for
at least 72 hours postoperative, covering
the critical inflammatory phase of wound
healing. While pain can be controlled in
the clinic, once patients return home,
typically within 24 to 48 hours post-op,
pain control can be more challenging.

Beyond the ethical obligation to minimize
pain and suffering, unmanaged pain
delays healing and return to function and
can lead to chronic maladaptive pain.¹
Additionally, effective pain management
creates a better client experience.

"The benefits are many: smoother
recoveries, less opioid use so less
opioid-related side effects like
gastrointestinal upset and dysphoria,
and even quicker discharge times.
Patients are returning back to 'normal'
quicker, with a willingness to eat, walk
and go ‘potty’ on their own.”

DONNA SISAK, CVT, VTS, ANESTHESIA
SEATTLE VETERINARY SPECIALISTS

Select Important Safety Information
Do not administer concurrently with bupivacaine HCl, lidocaine or other amide local anesthetics.
Local anesthetics (LAs) are one of the most effective means of preventing transduction and transmission of pain signals,1 in part because LAs are the only class of drug that can render complete analgesia. They:

- Block sodium channels on the nerve cell membrane
- Prevent propagation of action potentials (pain signals)
- Are considered safe, with side effects generally limited to very high doses, and do not appear to delay tissue healing1

However, other LA formulations have some limitations:

- Short duration of action (less than eight hours) limits duration of pain relief and may increase the need for additional pain interventions such as opioids
- Lack of technical instructions for effective use
- Complications of indwelling soaker catheters

“One of the most effective classes of analgesics for postoperative pain control.”

— American Animal Hospital Association

“Select Important Safety Information

The safe use of NOCITA in dogs and cats with cardiac disease or with hepatic or renal impairment has not been evaluated.
A long-acting local anesthetic providing up to 72 hours of postoperative pain relief with one dose:

- Provides consistent control after patient is discharged, preventing analgesic gaps
- Pain and dysphoria don’t have to be part of the post-op experience.”

*In a field trial, Nocita reduced the need for post-op rescue pain treatment with opioids

NOCITA™ (bupivacaine liposome injectable suspension) works differently.

Extended-release bupivacaine technology.

NOCITA™ is a sterile aqueous suspension of multivesicular liposomes containing bupivacaine. The liposomes are microscopic structures designed to gradually release bupivacaine from the vesicles:

- Liposomes do not diffuse readily from where they are deposited
- Bupivacaine diffuses locally into surrounding tissues when it is gradually released from individual liposomes

“Game changer. That is probably the most common term used in conjunction with Nocita™. You have 100% compliance because you, as the surgeon, actually give the medication. You know it’s there and it lasts up to 72 hours.”

SHEILAH ROBERTSON, BVMS (HONS), PHD, DACVAA, DECVAA, DACAW, DECAWBM, MRCVS
LAP OF LOVE VETERINARY HOSPICE

Select Important Safety Information

The safe use in dogs or cats younger than 5 months of age, that are pregnant, lactating, or intended for breeding has not been evaluated.
Raising the standard for modern recovery care.

In a recent study, analgesia provided by NOCITA™ (bupivacaine liposome injectable suspension) resulted in a reduction in systemic opioid requirements:

- Total number of rescue opioid doses was significantly lower in the NOCITA™ group
- Total amount of rescue opioids administered was significantly lower in the NOCITA™ group

Benefits of incorporating NOCITA™ into postoperative protocols could include:

- Decreased reliance on systemic opioids to adequately manage post-op pain
- Reduced opioid-associated side effects, including dysphoria
- Earlier discharge from hospital
- Greater client satisfaction

“**We tell owners we are using a product similar to one that is already in widespread use in humans, and it may add some modest expense, but we have seen that it can significantly improve comfort at home and the quality and speed of recovery.**”

MARK EPSTEIN, DVM, DABVP, CVPP
TOTALBOND VETERINARY HOSPITAL

NOCITA™ is the only long-acting local anesthetic that controls post-op pain for up to 72 hours to help dogs undergoing cranial cruciate ligament (CCL) surgery recover comfortably, even after going home.

Select Important Safety Information
The most common adverse reactions in dogs were discharge from incision, incisional inflammation and vomiting.
Single-dose tissue infiltration for dogs.

**DOSING**
- 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
- May be volume-expanded with up to an equal volume (1:1 by volume) of normal sterile saline or Lactated Ringer’s solution to obtain a volume sufficient to infiltrate the entire surgical site
- Use a 25-gauge or larger bore needle for administration

**PROVEN CLINICAL EFFICACY AND DEMONSTRATED SAFETY IN DOGS**
- Proven pain control for up to 72 hours following canine CCL* surgery
- Well-tolerated in dogs following CCL surgery

Long-acting, peripheral nerve block for cats.

**DOSING**
- A dose of 5.3 mg/kg per forelimb (0.4 mL/kg per forelimb) is administered once prior to surgery as a 4-point nerve block prior to onychectomy
- Use a 25-gauge or larger bore needle for administration

**PROVEN CLINICAL EFFICACY AND DEMONSTRATED SAFETY IN CATS**
- Provided up to 72 hours of regional postoperative pain control with just one dose for cats undergoing onychectomy
- Demonstrated safety as a peripheral nerve block in cats undergoing onychectomy

“Nocita™ has added to our clients’ confidence in their pet’s health care. They feel that we are true heroes because we are sending their pet home looking like their pet instead of looking drugged and not ready to come home.”

**DONNA SISAK, CVT, VTS, ANESTHESIA**
SEATTLE VETERINARY SPECIALISTS

Nocita™
- 10 ml vial treats about 55 lb for up to 72 hrs
- 20 ml vial treats about 110 lb for up to 72 hrs

Nocita™

Select Important Safety Information
The most common adverse reactions in cats were elevated body temperature and infection or chewing/licking at the surgical site.

*Cranial cruciate ligament
Available in 10 and 20 mL vials

**Indications**
For single-dose infiltration into the surgical site to provide local postoperative analgesia for cranial cruciate ligament surgery in dogs. For use as a peripheral nerve block to provide regional postoperative analgesia following onychectomy in cats.

**Important Safety Information**
NOCITA is for use in dogs and cats only. Do not administer concurrently with bupivacaine HCL, lidocaine or other amide local anesthetics. The safe use of NOCITA in dogs and cats with cardiac disease or with hepatic or renal impairment has not been evaluated. The safe use in dogs or cats younger than 5 months of age, that are pregnant, lactating or intended for breeding has not been evaluated. The most common adverse reactions in dogs were discharge from incision, incisional inflammation and vomiting. The most common adverse reactions in cats were elevated body temperature and infection or chewing/licking at the surgical site. Please see accompanying product label for full prescribing information.

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

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

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

Adverse Reactions:
Safety was evaluated in 123 NOCITA treated dogs and 59 saline (placebo) treated dogs in a field study in dogs that underwent cranial cruciate ligament stabilization surgery. Dogs enrolled in the study were 1-13 years of age, and weighed 3.4 to 81.3 kg. NOCITA was administered by infiltrative injection at the surgical site at a dose of 5.3 mg/kg (0.4 mL/kg).

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>NOCITA (n = 123)</th>
<th>Saline (n = 59)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discharge from the Incision</td>
<td>4 (3.3%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Incisional Inflammation (erythema and/or edema)</td>
<td>3 (2.4%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3 (2.4%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Abnormalities on Urinalysis (isosthenuria ± proteinuria)</td>
<td>2 (1.6%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Increased ALP</td>
<td>2 (1.6%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Surgical Limb Edema ± Erythema</td>
<td>1 (0.8%)</td>
<td>3 (5.1%)</td>
</tr>
<tr>
<td>Soft Tissue/Diarrhea</td>
<td>1 (0.8%)</td>
<td>1 (1.7%)</td>
</tr>
<tr>
<td>Inappetence</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 events, for technical assistance or to obtain a copy of the Safety Data Sheet (SDS), contact Elanco US Inc. at 1-888-545-5973.

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

Clinical Pharmacology:
Bupivacaine is an amide, non-opioid local anesthetic. It provides local analgesia by deactivating sodium channels on the nerve membrane, preventing the generation and propagation of nerve impulses. It is only present in small concentrations as uncharged molecules at tissue pH as it is a base with pKa of 8. This un-ionized form provides a lipophilicity that permits the drug to traverse across the nerve cell membrane and upon entering the cell, binds to the intracellular sodium channels on the nerve membrane, preventing the generation and propagation of nerve impulses. 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 non-lipid-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.

Pharmacokinetic Parameter:
The pharmacokinetic characterization associated with bupivacaine after subcutaneous NOCITA (bupivacaine liposome injectable suspension) or bupivacaine HCl solution administered to Beagle dogs is provided in Table D-2. 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>NOCITA (mg/kg)</th>
<th>NOCITA (mg/kg)</th>
<th>NOCITA (mg/kg)</th>
<th>bupivacaine HCl (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T ½  (hr)</td>
<td>0.5 (0.5-0.5)</td>
<td>0.5 (0.5-0.5)</td>
<td>60.0 (5.5-7.2)</td>
<td>0.5 (0.5-0.5)</td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>488 (335)</td>
<td>580 (299)</td>
<td>633 (280)</td>
<td>1420 (355)</td>
</tr>
<tr>
<td>T1/2β (hr)</td>
<td>38.2 (12.4)</td>
<td>25.7 (8.15)</td>
<td>43.9 (12.5)</td>
<td>10.1 (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)

+ Reported from steady state concentrations

Following a single subcutaneous dose of 9 mg/kg and 16 mg/kg NOCITA, median time to reach Cmax 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 AUC0-t and T1/2β were comparable. However, due to the slow release mechanism of the NOCITA formulation, the mean Cmax and T1/2β 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-t 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.

PA103060X W1c
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 = 125) or saline (n = 59). The per protocol population for effectiveness was 112 NOCITA treated dogs and 52 saline dogs.

Dogs received an opioid analgesic just prior to general anesthesia and surgery. Surgical repair techniques were at the discretion of the surgeon, and included extra-capular repair, bilateral plate fixation and external (TPLO), or tibial tuberosity advancement (TTA).

Table D-3 shows the number and percent of surgical procedures by treatment group.

Table D-3. Surgical Procedure by Treatment Group

<table>
<thead>
<tr>
<th>Surgical Procedure</th>
<th>NOCITA</th>
<th>Saline</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extra-capular 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 saline was infiltrated into the tissue layers during surgical closure. NOCITA or saline was administered either as is or with the addition of up to 1 mL of sterile saline. Pain was assessed by 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, 24, 30, 36, 48, 56 and 72 hours post-surgery. Dogs with a CMPS-SF score ≥ 6 or were determined to be painful by the investigator received rescue analgesic medication and were classified as treatment failures. No further CMPS-SF pain assessments were recorded for dogs that received rescue analgesic medication. The primary variable for effectiveness was evaluated over the first 24-hour time interval, the percent of treatment success for NOCITA was significantly different from and greater than saline at the first 24-hour time interval (p = 0.0032). The first 24-hour and 48-72 hour time intervals were evaluated as secondary variables and support variable effectiveness of NOCITA for up to 72 hours of anaesthesia.

Table D-4, Number and Percent Effectiveness for NOCITA and Saline (Placebo) at each Time Interval

<table>
<thead>
<tr>
<th>Time Interval</th>
<th>NOCITA</th>
<th>Saline</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain Evaluation</td>
<td>52 (46.4)</td>
<td>24 (46.2)</td>
<td>76 (46.3)</td>
</tr>
<tr>
<td>0-24 hours</td>
<td>77 (68.8%)</td>
<td>19 (36.5%)</td>
<td>96 (61.3%)</td>
</tr>
<tr>
<td>24-48 hours</td>
<td>72 (64.3%)</td>
<td>18 (34.6%)</td>
<td>90 (57.1%)</td>
</tr>
<tr>
<td>48-72 hours</td>
<td>69 (61.6%)</td>
<td>17 (32.7%)</td>
<td>86 (54.1%)</td>
</tr>
</tbody>
</table>

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

Animal Safety:
In a 4-week laboratory study with a 4-week recovery period, 60 healthy dogs aged 5-6 months were administered NOCITA at 8, 16, and 26.6 mg/kg. These doses correspond to 5.3 mg/kg per forelimb (0.4 mL/kg/forelimb volume) and 3.2 mg/kg per hindlimb (0.6 mL/kg/forelimb volume) of bupivacaine liposome injectable suspension, which is equivalent to a 6 mg/kg bupivacaine base dose, 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 and left forelimbs, and then to the right hindlimb noted after only the first dose; abrasions or scabbing noted at the right hindlimb; and one NOCITA treated cat had a motor deficit (unilateral knuckling) which resolved by the end of the 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, urinanalysis, 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 foam cells, syncytiotrophoblasts, plasma cells and/or multinucleated giant cells. The inflammation was often associated with mineralization and/or edema, in the dogs that were maintained for the 4-week recovery period, there were fewer dogs with granulomatous inflammation and mineralization at the injection sites. The inflammation was characterized by a greater number of giant cells. One 9 mg/kg NOCITA group male dog had minimal subcutaneous edema that was not associated with cellular inflammation. These inflammatory changes are associated with administration of the liposomal suspension, and did not occur in the saline and bupivacaine HCl groups.

Storage Conditions:
Unopened vials should be stored refrigerated between 36° F to 46° F (2° C to 8° C). NOCITA must 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 refrigerate. Do Not Freeze.

How Supplied:
13.3 mg/mL bupivacaine liposome injectable suspension in 10 mL or 20 mL single use vial, 10 mL supplied in a 4-vial carton. 20 mL supplied in a single vial carton and 4-vial carton.

Approved by FDA under NADA #141-461

Manufactured for:
Elanco US Inc.
Greenfield, IN 46140 USA

Nocita, Elanco and the diagonal bar logo are trademarks of Elanco or its affiliates.

Rev. date 03/2021

nOCITa™
(bupivacaine liposome injectable suspension)
13.3 mg/mL
For use as a peripheral nerve block in cats 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 particles containing bupivacaine. Each milliliter of NOCITA contains 13.3 mg/mL of bupivacaine. Inactive ingredients and their nominal concentrations are: cholesterol, 4.7 mg/mL; 1,2-dipalmitoyl-sn-glycero-3-phosphatidylcholine (DEPC), 0.9 mg/mL; tricaprylin, 2.0 mg/mL; and 1,2-dieucoryophosphatidylcholine (DEPC), 8.2 mg/mL. Bupivacaine is related chemically and pharmacologically to the amide-type local anesthetics. Chemically, bupivacaine is 1-$\text{d}$-bu$t$y$-N-(2,6-dimethylphenoxy)-2$-$piperidin carbonyl lactic acid with a molecular weight of 286.4. Bupivacaine structural formula is shown in the illustration to the right.

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

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

Pain Grades:
- Wear gloves when handling and administering NOCITA (see WARNINGS).
- NOCITA should not be anticipated. When a topical antiseptic such as povidone iodine or chlorhexidine is applied, the area should be allowed to dry before NOCITA is administered.
- Do not shake vial, Insert the vial multiple times to re-suspend the particles immediately prior to withdrawal of the product from the vial.
- Do not puncture the vial multiple times. Puncture the vial stopper once with a single 25 gauge or larger needle. Use aseptic technique to sequentially aspirate saline. Each syringe should be prepared for single patient use only. Discard the vial after all doses are withdrawn.
- Following withdrawal from the vial into a syringe, NOCITA may be stored at controlled room temperature of 68° F to 77° F (20° C to 25° C) for up to 4 hours. Because the formulation does not contain preservative, the syringe(s) must be discarded after 4 hours.
- Do not dilute NOCITA prior to use as a nerve block in cats.
- Avoid a 25 gauge or larger bore needle for administration.

Dose Administration:
- Aspirate prior to injecting to prevent intravascular administration (see CONTRAINDICATIONS).

Table C-1. Dose Administration for One Forelimb

<table>
<thead>
<tr>
<th>Needle insertion point</th>
<th>Needle withdrawal + drug injection</th>
<th>Drug injection point</th>
</tr>
</thead>
<tbody>
<tr>
<td>to the palmar plane</td>
<td>to the palmar plane</td>
<td>to the palmar plane</td>
</tr>
</tbody>
</table>

Abbreviations:
S - Subcutaneous
Styl - Stylus process of the ulna

Dose Volume per Injection (% of total 0.4 mL/forelimb volume and Description):

A. 0.14 mL/kg (35%) Superficial Branch of the Radial Nerve: At the center of the limb, on the dorsal aspect at the level of the antebrachial carpal joint, insert the needle subcutaneously with the bevel up (•). Advance the needle subcutaneously as depicted by the dotted line and arrow and inject (o) adjacent to the circumference of the accessory cephalic and cephalic veins.

B. 0.08 mL/kg (20%) Dorsal Branch of the Ulnar Nerve: Palpate a groove between the accessory carpal bone (ACb) in the base of the carpal pad and the stylid process of the ulna (Styl). Distal to this groove, insert the needle subcutaneously with the bevel up and advance the needle proximally. Inject once the tip reaches the midpoint of the groove.

C. 0.16 mL/kg (40%) Median Nerve and Superficial Branch of the Palmarch Branch of the Ulnar Nerve: Insert the needle subcutaneously with the bevel up lateral to the distal tip of the accessory carpal pad and advance the needle medially 2/3 the width of the limb, until the tip is located near the base of the first digit. Inject 2/3 of the volume at this point and the remaining volume while withdrawing the needle (solid grey arrow). Gently massage for 5 seconds.

D. 0.02 mL/kg (5%) Deep Branch of the Palmarch Branch of the Ulnar Nerve: Orient the needle perpendicular to the long axis of the limb at the level of the ACb. Insert the needle subcutaneously and advance the needle laterally until it contacts the medial aspect of the ACb. Redirect the needle proximally by rotating the needle 90°, advance it along the medial side of the ACb and the stylid process of the ulna (Styl).
**Contraindications:**
Do not administer by intravenous or intra-arterial injection. If accidental intravascular administration occurs, monitor for cardiovascular (dysrhythmias, hypotension, hypertension) and neurologic (tremors, ataxia, seizures) adverse reactions. Do not use for intra-articular injection. In humans, local anesthetics administered into a joint may cause chondrolysis.

**Warnings:**
NOCITA is an amide local anesthetic. In case of accidental injection or accidental topical exposure, contact a physician and seek medical attention immediately.

Wear gloves when handling vials to prevent accidental topical exposure.

**Precautions:**
Do not administer concurrently with bupivacaine HCl lidocaine or other amide local anesthetics. A safe interval from time of bupivacaine HCl lidocaine or other amide local anesthetic administration to time of NOCITA administration has not been determined. The toxic effects of these drugs and their additive administration are used with caution including monitoring for neurologic and cardiovascular effects related to toxicity.

The safe use of NOCITA in cats with cardiac disease has not been evaluated.
The safe use of NOCITA in cats with renal, hepatic or other impairment has not been evaluated. NOCITA is metabolized by the liver and excreted by the kidneys.
The ability of NOCITA to achieve effective anesthesia has not been evaluated.
The safe use of NOCITA in cats for surgical procedures other than orthoanesthesia has not been evaluated.
The safe use of NOCITA has not been evaluated in cats younger than 5 months old. The safe use of NOCITA has not been evaluated in cats that are pregnant, lactating, or intended for breeding.

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

Table C-2: Adverse Reactions Reported During the Study in the Safety Population (any cat that received treatment)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>NOCITA (n=120)</th>
<th>Saline (n=121)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated body temperature*</td>
<td>5 (4.2%)</td>
<td>5 (4.2%)</td>
</tr>
<tr>
<td>Surgical site infection</td>
<td>3 (2.5%)</td>
<td>2 (1.6%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2 (1.7%)</td>
<td>2 (1.6%)</td>
</tr>
<tr>
<td>Swelling of paw; erythematous digits</td>
<td>1 (0.8%)</td>
<td>1 (0.8%)</td>
</tr>
</tbody>
</table>

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

Elevated body temperature was defined as temperature ≥ 103° F on Day 3 and normal before surgery. One of the NOCITA treated cats had an infection of one surgical site. No other cat with elevated body temperature showed evidence of infection or illness.

Eight cats, 4 in each group, had normal platelet counts before treatment on Day 0 and platelet counts below the reference range (155,000-641,000/mL) on Day 3. The 4 cats treated with NOCITA had platelet counts of 42,000 to 100,000/mL, and the 4 cats in the saline group had platelet counts of 114,000 to 149,000/mL. Decreased platelet counts were not associated with clinical signs.

In a pilot study with 62 cats undergoing orthoanectomy (31 cats treated with NOCITA and 31 with saline), one NOCITA treated cat had a motor deficit (unilateral knuckling) which resolved by the next morning following surgery. Another NOCITA treated cat had bruising at the injection sites. To report suspected adverse events or for assistance in obtaining a copy of the Safety Data Sheet (SDS), contact Elanco US Inc. at 1-888-545-5973.

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

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

Lipid Formulation:
Liposomal encapsulation or incorporation in a lipid complex can substantially affect a drug’s functional properties relative to those of the unencapsulated or nonlipid-associated drug. In addition, different liposomal or lipid-complexed products with a common active ingredient may vary from one another in the chemical composition and physical form of the lipid component.

Such differences may affect functional properties of these drug products. Do not substitute with other bupivacaine formulations.

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

Pharmacokinetics:
The pharmacokinetic characterization associated with bupivacaine after subcutaneous NOCITA (bupivacaine liposome injectable suspension) or bupivacaine HCl solution administered to cats evaluated for 168 hours is provided in Table C-3.

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

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>NOCITA 3 mg/kg</th>
<th>NOCITA 9 mg/kg</th>
<th>NOCITA 15 mg/kg</th>
<th>Bupivacaine HCl 1 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>T max (hr)</td>
<td>12.5 (10-14)</td>
<td>12.1 (10-16)</td>
<td>13.4 (11-16)</td>
<td>12.5 (10-14)</td>
</tr>
<tr>
<td>T max (hr)</td>
<td>10 (8-12)</td>
<td>10 (8-12)</td>
<td>11 (9-13)</td>
<td>10 (8-12)</td>
</tr>
<tr>
<td>C max (mg/mL)</td>
<td>31.4 (28.2-35.6)</td>
<td>260.2 (254-347)</td>
<td>790.8 (692-1098)</td>
<td>263.9 (60.5-506)</td>
</tr>
<tr>
<td>AUC (mg·hr/mL)</td>
<td>11347</td>
<td>32561</td>
<td>19300-47532</td>
<td>38475</td>
</tr>
<tr>
<td>T last (hr)</td>
<td>8 (5-10)</td>
<td>8 (5-10)</td>
<td>10 (7-12)</td>
<td>10 (7-12)</td>
</tr>
<tr>
<td>T last (hr)</td>
<td>120 (112-128)</td>
<td>120 (112-128)</td>
<td>120 (112-128)</td>
<td>120 (112-128)</td>
</tr>
<tr>
<td>C max (mg/mL)</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
</tr>
</tbody>
</table>

NOCITA is for administration only once prior to surgery. Administer 5.3 mg/kg per forelimb (0.4 mL/kg per forelimb) when a topical antiseptic is applied to the periforelimb, for a total dose of 10.6 mg/kg/cat) as a 4-point nerve block (described below) prior to onychectomy in cats.

Approved by FDA under NADA # 141-461
Manufactured for: Elanco US Inc. Greenfield, IN 46140 USA
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References:

W1cPA103060X