



nocita™
(bupivacaine liposome injectable suspension)

TECHNICAL MONOGRAPH

SEE THE DIFFERENCE

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.

Elanco

TM

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 **nocita™**
(bupivacaine liposome injectable suspension)



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1. Introduction

How long should analgesia last?

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

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 at least 72 hours; consequently, 72 hours is the recommended minimum amount of time analgesics should be provided following surgery.²

Therefore, 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.¹

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.

THREE REASONS TO MINIMIZE ACUTE POSTSURGICAL PAIN:¹

- 1 Pain delays healing and return to function.
- 2 Unmanaged acute pain can lead to chronic maladaptive pain.
- 3 Ethical obligation to minimize pain and suffering.



Select Important Safety Information

Do not administer concurrently with bupivacaine HCl, lidocaine or other amide local anesthetics.

1. Introduction

Optimizing postoperative pain management

There are four central tenets to optimizing postoperative analgesia:

- 1 Provide preemptive analgesia.
- 2 Use multimodal pain management.
- 3 Deliver overlapping/continuous analgesia.
- 4 Match the analgesic plan to the severity of surgical pain.²

The use of analgesics with complementary modes of action can be employed to target these various points along the pain pathway.

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 (LAs), alpha-2 agonists, and/or N-methyl-D-aspartate receptor antagonists.¹

The most effective means of preventing the transduction and transmission of pain is through the use of LAs¹. Current methods of providing LAs include wound/tissue infiltration, lidocaine strips, topical creams, regional nerve blocks, epidurals and the placement of soaker catheters.



"The task force supports 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."

AMERICAN ANIMAL HOSPITAL ASSOCIATION

Local anesthetics 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 healing.¹

The use of LAs as part of multimodal analgesia for postoperative pain is the standard of care recommended by the WSAVA² and the 2015 Pain Management Guidelines from the AAHA and AAFP.¹ Bupivacaine HCl is 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 eight hours.³

Most 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

TRANSDUCTION^{4,5}

- NSAIDs
- Local anesthetics
- Opioids
- Corticosteroids

TRANSMISSION^{4,5}

- Local anesthetics
- Alpha-2 agonists
- Corticosteroids

MODULATION^{4,5}

- NSAIDs
- Local anesthetics
- Opioids
- Alpha-2 agonists
- Tricyclic antidepressants
- Cholinesterase inhibitors
- N-methyl-D-aspartate antagonists
- Anticonvulsants

PERCEPTION^{4,5}

- General anesthetics
- Opioids
- Alpha-2 agonists



Scan the code to learn more about addressing pain at different levels of the pain pathway

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.

1. Introduction

Nocita™ (bupivacaine liposome injectable suspension) is **the only long-acting local anesthetic that provides up to 72 hours of pain relief** when administered via tissue infiltration in cranial cruciate ligament (CCL) surgery in dogs or as a peripheral nerve block prior to forelimb onychectomy in cats.

An extended-release formulation of bupivacaine was approved:



**OCTOBER
2011**

By the Center for Drug Evaluation and Research (CDER)-FDA

For administration into the surgical site to produce postsurgical analgesia in humans

**AUGUST
2016**

By the Center for Veterinary Medicine (CVM)-FDA

To provide local postoperative analgesia via tissue infiltration following cranial cruciate ligament surgery in **dogs**

**AUGUST
2018**

By the CVM-FDA

To provide regional post-operative analgesia via peripheral nerve block administered prior to onychectomy in **cats**

2. How it works

What makes Nocita™ different?

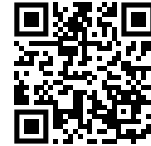
Extended-release bupivacaine technology

Nocita is a sterile aqueous suspension of multivesicular liposomes containing bupivacaine (**Figure 1**).

The liposomes are microscopic structures designed to gradually release bupivacaine from the vesicles:

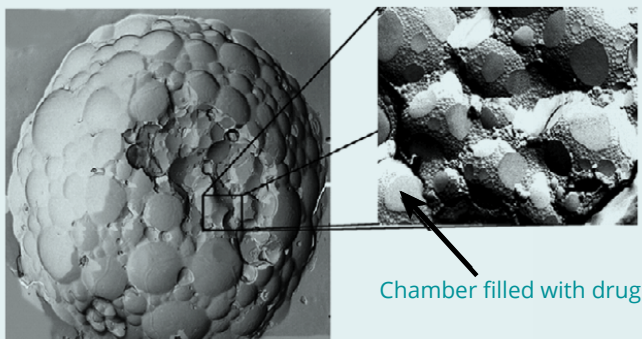
- Liposomes do not diffuse readily from where they are deposited.
- Bupivacaine diffuses locally into surrounding tissues when it is gradually released from individual liposomes.

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



Scan to learn more about what makes Nocita different

Figure 1. Multivesicular Liposome



Select Important Safety Information

The most common adverse reactions in dogs were discharge from incision, incisional inflammation and vomiting.

Administration in dogs

In dogs, the technique for instilling bupivacaine liposome injectable suspension into a surgical site differs slightly from that used for traditional bupivacaine formulation because the liposomes do not diffuse freely from where they are deposited, as bupivacaine solution does. Therefore, a moving-

needle tissue infiltration injection technique is used to inject the suspension into all tissue layers surrounding the surgical field (**Figure 2**).

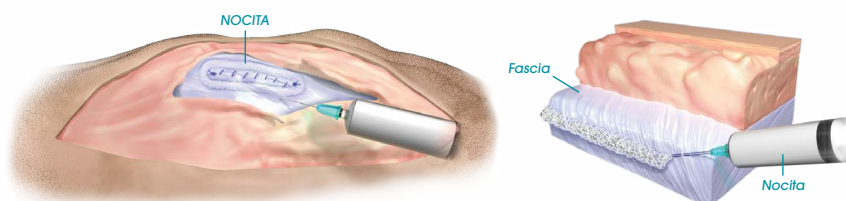
As bupivacaine is gradually released from individual liposomes, it will diffuse locally into the surrounding tissues.

Figure 2. Surgical Site Infiltration With Bupivacaine Liposome Injectable Suspension Using a Moving-Needle Technique in Dogs

A. Incision



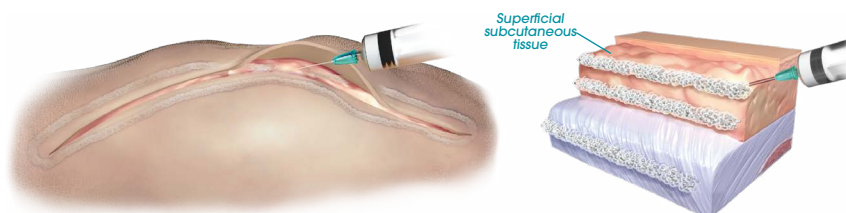
B. Fascia Layer Infiltration (after joint capsule closure)



C. Deep Subcutaneous Tissue Infiltration (post retinacular fascia closure)

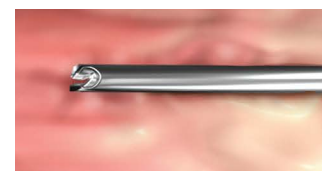


D. Superficial Subcutaneous Tissue Infiltration (prior to subcuticular closure)



Moving Needle Injection Technique

Introduce tip of the needle into the tissue.



Gradually withdraw needle while injecting.



Dose: 5.3mg/kg (0.4ml/kg)

- Volume expand up to 1:1 with sterile saline or lactated Ringers solution
- Use a 25-gauge needle or larger to avoid disrupting liposomes
- Administer Nocita™ (bupivacaine liposome injectable suspension) in all tissue layers affected by surgery
- Administer Nocita along the entire length of the incision, including the proximal and distal ends
- Not for intra-articular use

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.

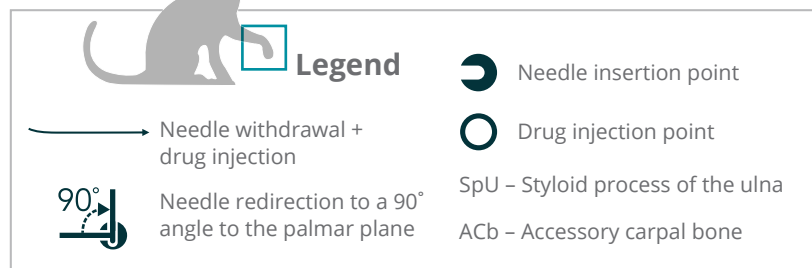


Scan to see how
Nocita is administered

Administration in cats

Figure 3. Administration of Bupivacaine Liposome Injectable Suspension as a 4-point Peripheral Nerve Block in Cats

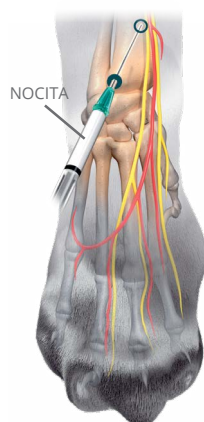
Administer 5.3 mg/kg per forelimb (0.4 mL/kg per forelimb, for a total dose of 10.6 mg/kg/cat) as a 4-point nerve block prior to onychectomy.



A.

0.14 mL/kg (35%) Superficial Branch of the Radial Nerve

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



Dorsal

B.

0.08 mL/kg (20%) Dorsal Branch of the Ulnar Nerve

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

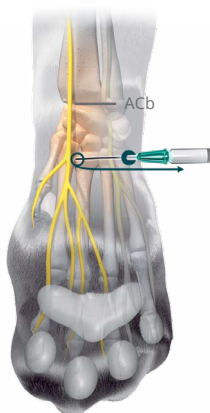


Lateral

C.

0.16 mL/kg (40%) Median Nerve and Superficial Branch of the Palmar Branch of the Ulnar Nerve

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

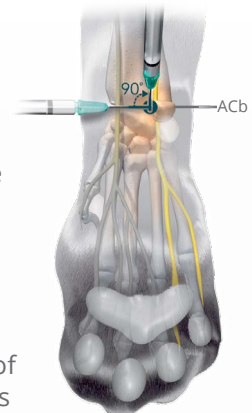


Palmar

D.

0.02 mL/kg (5%) Deep Branch of the Palmar Branch of the Ulnar Nerve

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



Palmar

Do not administer concurrently with bupivacaine HCl, lidocaine or other amide local anesthetics.

3. Pharmacology

Bupivacaine provides local analgesia by reversibly deactivating sodium channels on neuronal cell membranes, preventing the generation and propagation of nerve impulses.

Once bupivacaine is released from the liposome, its distribution, metabolism and excretion are expected to follow the same kinetics as bupivacaine HCl.⁶

- The rate of systemic absorption of bupivacaine is dependent on the total dose of drug administered, the route of administration and the vascularity of the administration site.
- Nocita™ (bupivacaine liposome injectable suspension) is a suspension of multivesicular liposomes containing bupivacaine in 0.9% sodium chloride solution along with a small amount (less than 8%) of free (unencapsulated) bupivacaine.
- Do not mix Nocita with other local anesthetics or other drugs prior to administration.



Select Important Safety Information

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

4. Efficacy and Safety

Clinical efficacy in dogs

Field Study

The effectiveness of Nocita in providing prolonged postsurgical analgesia was evaluated in a randomized, prospective, blinded, placebo-controlled, multicenter field study in client-owned dogs undergoing CCL stabilization surgery.⁷

Study Design:

- 182 client-owned dogs undergoing stifle surgery to stabilize torn CCL
- Anesthesia and surgery methods:
 - Premedication: hydromorphone and acepromazine
 - Induction and maintenance of anesthesia: propofol, isoflurane and IV fluids
 - Surgical procedures: 46.3% extra-capsular, 43.9% TPLO, 9.8% TTA

- 5.3 mg/kg Nocita or placebo (0.4 mL/kg volume equivalent) in a single dose by moving needle infiltration injection technique during surgical closure

- Option to volume expand with normal sterile saline or LRS; used at up to 1:1 by volume

Test article distribution:

- ~25% around joint capsule incisions
- ~50% around fascial/subcutaneous tissue and hardware or suture insertions
- ~25% in subcuticular tissue

Pain Assessments:⁸

- Postoperative pain assessed at multiple time points through 72 hours following administration
- Success defined as no pain intervention*



Primary Endpoint

Percent treatment successes from 0-24 hours, Nocita vs. placebo ($p < 0.05$)

Secondary Endpoints

Percent treatment successes from 0-48 hours and 0-72 hours, Nocita vs. placebo ($p < 0.05$)



EFFECTIVENESS RESULTS IN DOGS	Nocita	Saline	P-value
Primary endpoint 0-24 hours	68.8%	36.5%	0.0322
Secondary endpoint** 0-48 hours	64.3%	34.6%	0.0402
Secondary endpoint** 0-72 hours	61.6%	32.7%	0.0432

Conclusion

Nocita was proven to provide pain control for up to 72 hours following canine CCL surgery:⁸

- Percent of treatment success for the Nocita-treated group was statistically significantly greater than the placebo-treated group over 0-24 hours
- Greater percent successes through 48 and 72 hours support effective use of Nocita for up to 72 hours of analgesia

*Pain intervention = rescue analgesia or score of ≥ 6 on Modified UNESP-Botucatu Multidimensional Composite Pain (Brondani) Scale

**Failures carried forward from each previous interval

4. Efficacy and Safety

Safety in dogs

Nocita™ (bupivacaine liposome injectable suspension) demonstrated safety and was well tolerated in dogs following cranial cruciate ligament surgery⁸

Field Study Design:

- 182 client-owned dogs undergoing knee surgery
- 5.3 mg/kg by infiltration injection during surgical closure

ADVERSE REACTION IN DOGS	Nocita=123	Saline placebo N=59
Discharge from the incision	4 (3.3%)	0 (0.0%)
Incisional inflammation (erythema or edema)	3 (2.4%)	0 (0.0%)
Vomiting	3 (2.4%)	0 (0.0%)
Abnormalities on urinalysis (isosthenuria ± proteinuria)	2 (1.6%)	0 (0.0%)
Increased ALP	2 (1.6%)	0 (0.0%)
Surgical limb edema ± erythema	1 (0.8%)	3 (5.1%)
Soft stool/Diarrhea	1 (0.8%)	1 (1.7%)
Inappetence	1 (0.8%)	1 (1.7%)
Fever	1 (0.8%)	0 (0.0%)

Target animal safety study in healthy beagles⁸

Design

- Twice weekly subcutaneous injections for a total of eight injections of bupivacaine liposome injectable suspension at 9, 18 or 30 mg/kg/dose (1.5x, 3x or 5x the recommended dose) or bupivacaine HCl at 9 mg/kg/dose
- Alternating SQ sites (right and left of dorsal midline)

Results

Nocita did not produce systemic toxicity and had a high margin of safety.

- Local granulomatous inflammation occurred at injection sites of dogs from Nocita groups, and some had grossly visible redness, thickening or inflammation at injection sites
- Results are consistent with local exposure to the liposome component of Nocita
- No effects were seen on body weights, food consumption, clinical signs, ECGs hematology, coagulation, clinical chemistries or urinalysis
- The study supports safe use of Nocita at label dose

Clinical efficacy in cats

The effectiveness of Nocita in providing prolonged regional postoperative analgesia was evaluated in a randomized, prospective, blinded, placebo-controlled, multicenter field study in client-owned cats undergoing feline onychectomy.⁹

Study design:

- 241 client-owned cats undergoing forelimb onychectomy
- 5.3 mg/kg/forelimb administered once prior to surgery as a 4-point nerve block

Pain Assessments:*

- Post-operative pain assessed at multiple time points through 72 hours following administration
- Success defined as no pain intervention



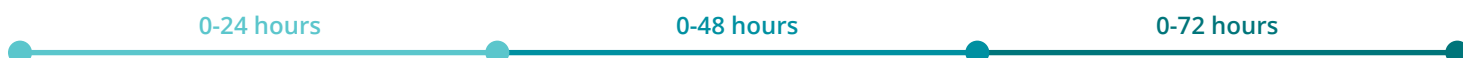
Scan to learn more about identifying and addressing pain in cats

Primary Endpoint

Percent treatment successes from 0-24 hours, Nocita vs. placebo ($P < 0.05$)

Secondary Endpoints

Percent treatment successes from 0-48 hours and 0-72 hours, Nocita vs. placebo ($P < 0.05$)



EFFECTIVENESS RESULTS IN CATS	0-24 hours		
	Nocita	Saline	P-value
Primary endpoint 0-24 hours	75.2%	40.3%	0.0252
Secondary endpoint 0-48 hours	68.7%	34.7%	0.0395
Secondary endpoint 0-72 hours	68.4%	35.3%	0.0452

Conclusion

Nocita was proven to provide up to 72 hours of regional postoperative analgesia following feline onychectomy:⁹

- Percent of treatment success for the Nocita-treated group was statistically significantly greater than the placebo-treated group over 0-24 hours
- Greater percent successes through 48 and 72 hours support effective use of Nocita for up to 72 hours of analgesia

*Pain intervention = rescue analgesia or score of ≥ 6 on Modified UNESP-Botucatu Multidimensional Composite Pain (Brondani) Scale

4.Efficacy and Safety



Safety in cats
Nocita™ (bupivacaine liposome injectable suspension) demonstrated safety as a peripheral nerve block in cats undergoing onychectomy⁹

ADVERSE REACTION IN CATS	Nocita=120	Saline placebo N=121
Elevated body temperature	8 (6.7%)	5 (4.1%)
Surgical site infection	4 (3.3%)	1 (0.8%)
Chewing/Licking of surgical site	3 (2.5%)	2 (1.7%)
Diarrhea	2 (1.7%)	1 (0.8%)
Injection site erythema	1 (0.8%)	0 (0.0%)
Swelling of paw; erythematous digits	1 (0.8%)	0 (0.0%)

NOTE: Surgical site is NOT injection site.

5.Toxicity

Local anesthetic toxicities affect the neurologic or cardiovascular systems, manifest from high plasma levels of the local anesthetic and commonly are a result of accidental intravascular injection of the drug or administration of an overdose.

The pharmacokinetic values for bupivacaine after a single subcutaneous administration of Nocita or bupivacaine HCl solution relative to the bupivacaine

levels that have been associated with seizure onset in dogs are shown in **Figure 4**.¹⁰

The pharmacokinetic values for bupivacaine after a single subcutaneous administration of NOCITA or bupivacaine HCl solution relative to the bupivacaine levels that have been associated with seizure onset in cats are shown in **Figure 5**.¹¹

5.Toxicity

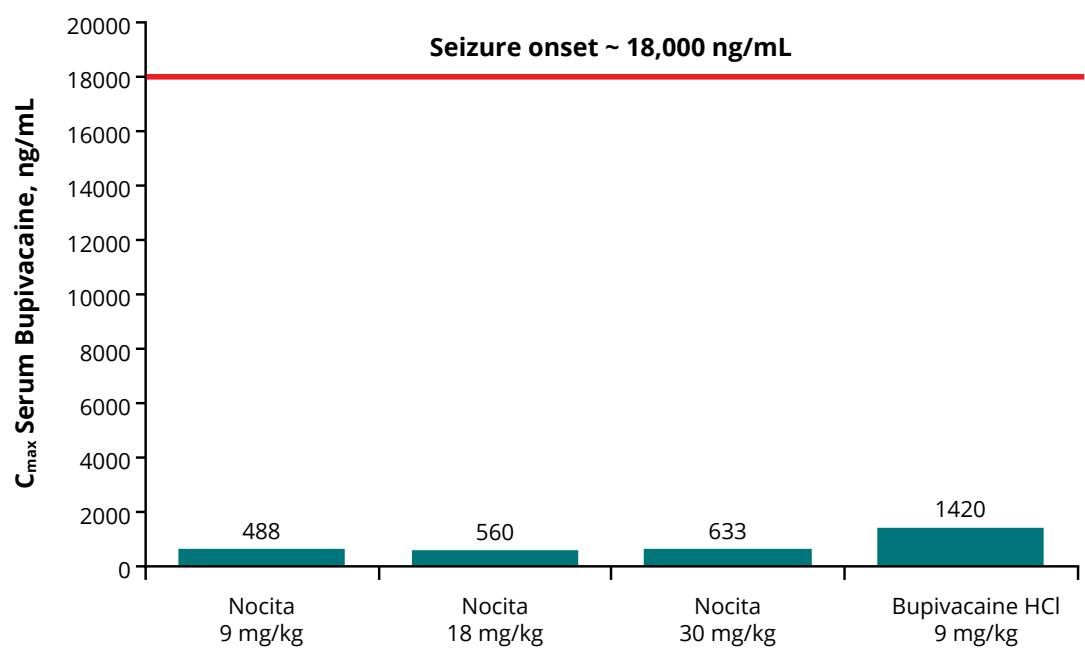


Figure 4. Pharmacokinetic Values for Bupivacaine After a Single Subcutaneous Administration of Nocita or Bupivacaine HCL Solution in Beagle Dogs

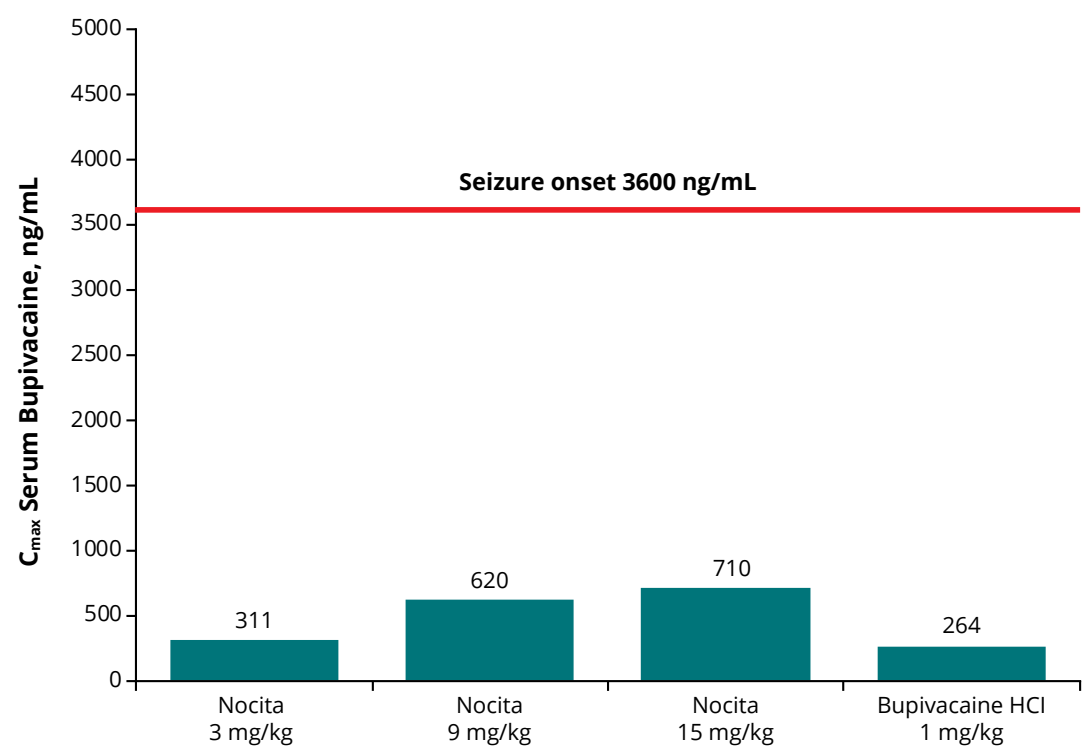


Figure 5. Pharmacokinetic Values for Bupivacaine After a Single Subcutaneous Administration of Nocita or Bupivacaine HCL Solution in Cats

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.

6. See the Difference

Nocita™ (bupivacaine liposome injectable suspension) is the only FDA-approved, long-acting local anesthetic that controls post-op pain for up to 72 hours in one dose to help pets recover comfortably, even after going home.

The benefits of incorporating Nocita into postoperative protocols could include:

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



Controls pain to help post-op return to function



Less opioid use¹²



Discharge patients sooner, possibly equalizing or reducing cost of care



Recovery care begins with Nocita

Select Important Safety Information

Do not administer concurrently with bupivacaine HCl, lidocaine or other amide local anesthetics.

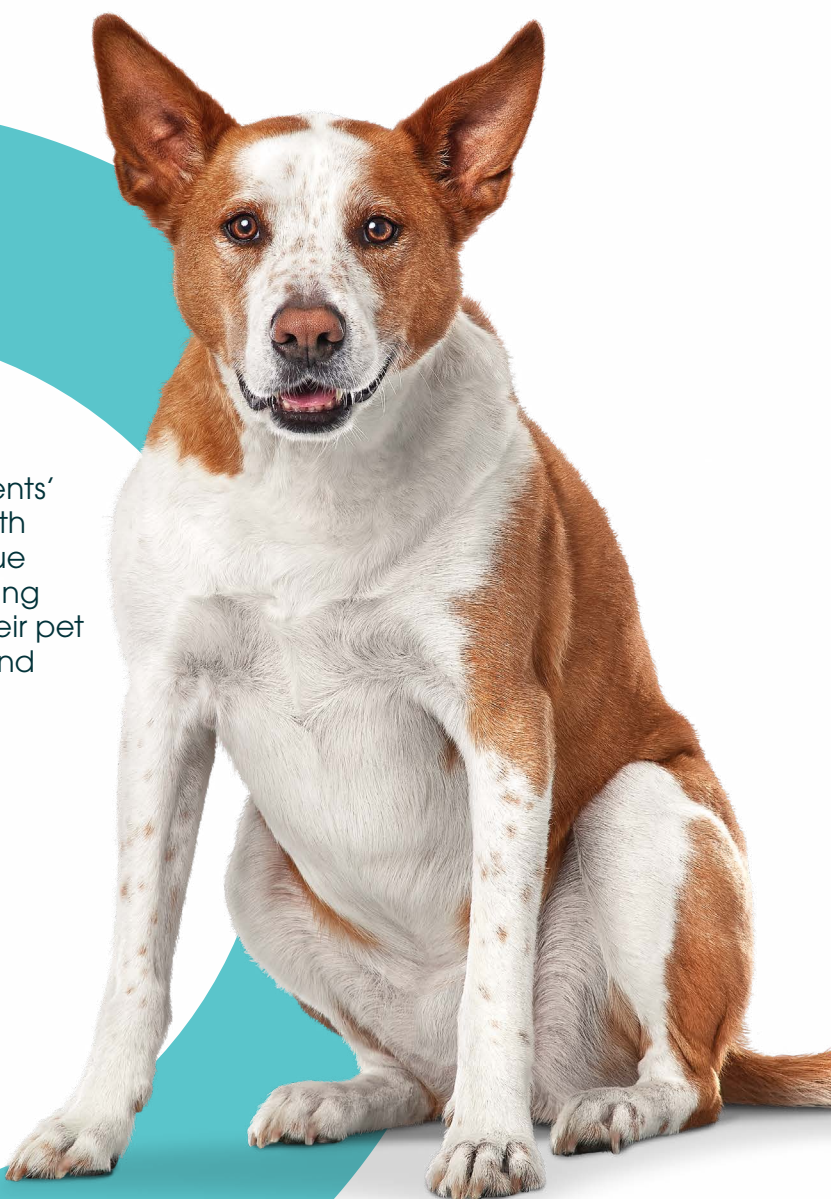
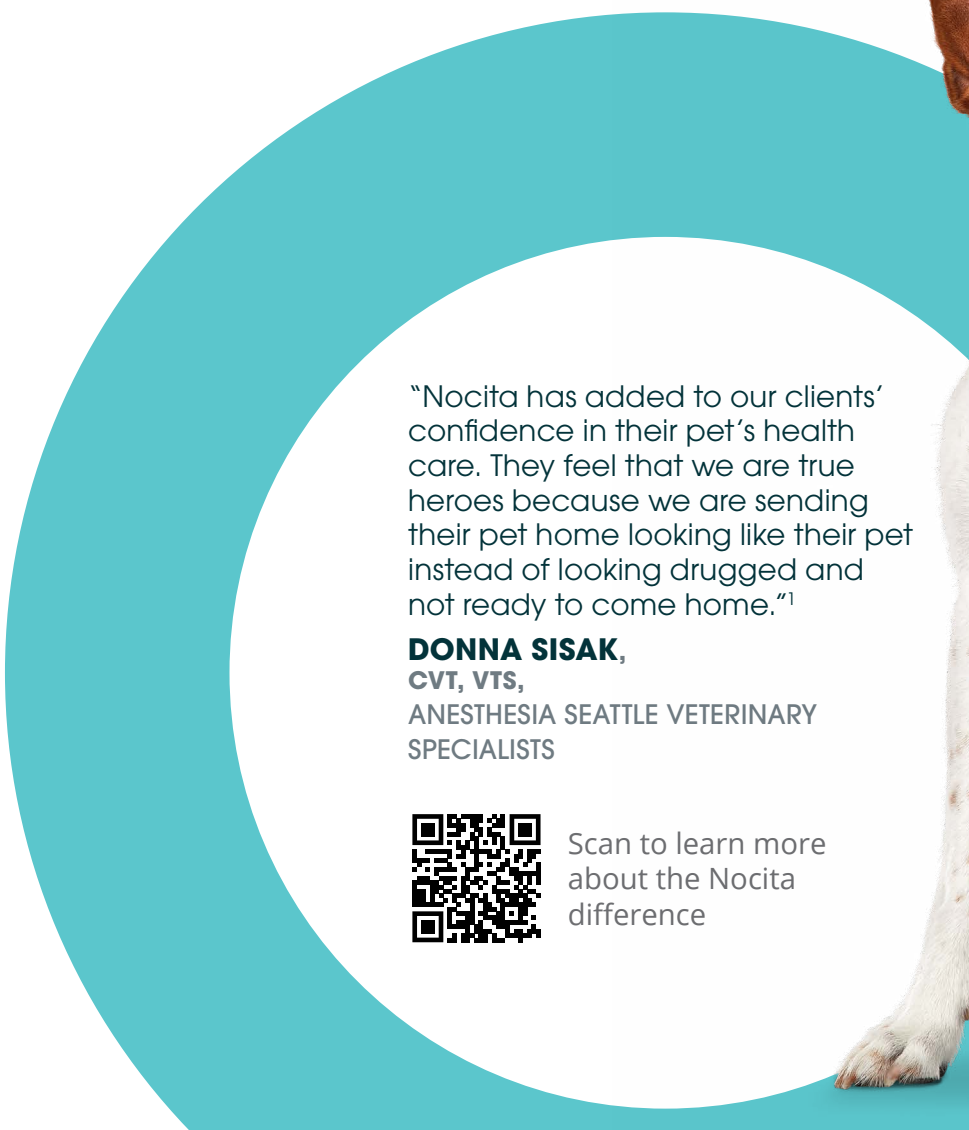
Comparison of liposomal bupivacaine and 0.5% bupivacaine hydrochloride for control of postoperative pain in dogs undergoing tibial plateau leveling osteotomy¹²

Study Design:

- Prospective, blinded, randomized clinical trial
- 33 client-owned dogs undergoing TPLO for treatment of cranial cruciate ligament rupture
- Two treatment groups
 - Nocita: liposomal-encapsulated bupivacaine (LEB)
 - Sensorcaine: 0.5% bupivacaine HCL (0.5BH)

Results:

- Nocita provided adequate analgesia after TPLO surgery with a reduction in systemic opioid requirements¹²
- The Nocita group required significantly lower:
 - Total number of rescue opioid doses
 - Total amount of rescue opioids administered



“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.”¹

DONNA SISAK,
CVT, VTS,
ANESTHESIA SEATTLE VETERINARY
SPECIALISTS



Scan to learn more
about the Nocita
difference

7. References

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 **nocita™**
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 **nocita™**
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Recovery care begins with Nocita



Controls Pain to Help Post-Op Return to Function

Single-Dose Administration

Long-Acting Local Anesthetic

FDA-Approved

Up to 72-Hour Analgesia



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.](#)

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