NOCITA® (bupivacaine liposome injectable suspension) is a sterile, non-pyrogenic, white to slightly yellow, opalescent suspension containing bupivacaine. Each 1 mL of NOCITA contains 13.3 mg of bupivacaine as the hydrochloride (hydrochloric acid) and its nominal concentrations are: chloride, 4.7 mg/mL; 1.13 mg/mL of bupivacaine HCl (hydrochloric acid); 0.25% (w/v) of polysorbate 20; 0.25% (w/v) of polysorbate 80; 0.125% (w/v) of disodium hydrogen phosphate (DIP); 0.125% (w/v) of sodium hydroxide; and 0.125% (w/v) of sodium dihydrogen phosphate (DSP) with a molecular weight of 2884. Bupivacaine structural formula is shown in the Illustration to the right.

Indication and Administration:
NOCITA is for single dose injection only. A dose of 5.3 mg/kg (0.4 mL/kg) is administered by infiltration injection into the tissues of the area of interest at the time of incisional closure. A single dose administered during surgical closure may provide up to 12 hours of pain control.

Usage 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 is used, NOCITA may be stored at controlled room temperature of 68° F to 77° F (20° C to 25° C) for up to 30 days in sealed, intact (unopened) vials. Do not re-refrigerate. Do Not Freeze.
• NOCITA may be held at a controlled room temperature of 68° F to 77° F (20° C to 25° C) for up to 30 days in sealed, intact (unopened) vials. Do not re-refrigerate.
• If the dose volume of NOCITA (0.4 mL/kg) is not sufficient to cover the surgical site, add up to an equal volume of normal (0.9%) sterile saline or Lactated Ringer’s solution. If saline or Lactated Ringer’s is added to the NOCITA dose, administer the entire volume by tissue infiltration into the tissues of the area of interest. NOCITA may be stored at controlled room temperature of 68° F to 77° F (20° C to 25° C) for up to 30 days in sealed, intact (unopened) vials. Do not re-refrigerate.
• 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 shake vial.
• Invert the vial multiple times to resuspend the particles immediately prior to withdrawal of the product from the vial.
• Do not puncture the vial multiple times. Puncture the vial stopper once with a 25 gauge or larger needle. Use an aseptic technique to prevent accidental topical exposure.

Warning:

NOCITA is an amide local anesthetic. In cases of accidental injection or topical 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 last dose of other amide local anesthetic to time of administration of NOCITA has not been determined. The toxic effects of these drugs are additive and their administration should be used with caution including monitoring for neurologic and cardiovascular effects related to both drugs.

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

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

The safety of NOCITA in dogs with impaired renal function has not been studied. Therefore, NOCITA is not indicated for pre-intracardial or pre-procedural i/o regional anesthetic techniques that require deep and complete sensory block in the area of administration.

The safety of NOCITA for surgical procedures other than cranial cruciate ligament surgery has not been evaluated (see ANIMAL SAFETY and Clinical Pharmacology). The safety of NOCITA has not been evaluated in dogs younger than 5 months old.

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

Adverse Reactions:
Data from a study evaluating 123 NOCITA treated dogs and 50 saline (placebo) treated dogs in a field study in dogs undergoing cranial cruciate ligament stabilization surgery. Dogs enrolled in the study were 5 - 13 years of age, and weighed 34 - 63.5 kg. NOCITA was administered by infiltration 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>No. of Dogs (N)</th>
<th>Nocita (n = 123)</th>
<th>Saline (n = 50)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intestinal inflammation</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>3 (2.5%)</td>
<td>0 (0.0%)</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain and/or ileus</td>
<td>2 (1.6%)</td>
<td>0 (0.0%)</td>
<td></td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>1 (0.8%)</td>
<td>1 (2.0%)</td>
<td></td>
</tr>
<tr>
<td>Urinary retention</td>
<td>1 (0.8%)</td>
<td>0 (0.0%)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>2 (1.6%)</td>
<td>0 (0.0%)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>11 (8.9%)</td>
<td>3 (6.0%)</td>
<td></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) for technical assistance, contact Aratana Therapeutics at 1-844-640-5500.

Adverse Reactions:
- **Intestinal Inflammation and/or Ileus**: 0 (0.0%) vs. 0 (0.0%)
- **Vomiting**: 3 (2.5%) vs. 0 (0.0%)
- **Abdominal Pain and/or Ileus**: 2 (1.6%) vs. 0 (0.0%)
- **Hemorrhage**: 1 (0.8%) vs. 1 (2.0%)
- **Urinary Retention**: 1 (0.8%) vs. 0 (0.0%)
- **Others**: 2 (1.6%) vs. 0 (0.0%)
- **Total**: 11 (8.9%) vs. 3 (6.0%)

No statistically significant differences were observed between the groups.

CLINICAL PHARMACOLOGY
Liposomal encapsulation or incorporation in a lipidic matrix can substantially affect a drug's functional properties relative to those of the unencapsulated or nanoparticulate-associated drug. In addition, different liposomal or lipid complexed products contain one or more active ingredients that vary with one another in the chemical composition and physical form of the lipids employed. 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.

Hematotoxicity
The pharmacokinetics associated with bupivacaine after subcutaneous NOCITA (bupivacaine liposome injectable suspension) or bupivacaine HCl solution administered to Beagle dogs is provided in Table D-2.

Table D-2: Mean (± SD) Plasma Pharmacokinetic Parameters for bupivacaine after subcutaneous administration of NOCITA and bupivacaine HCl solution in female Beagle dogs in a laboratory study

<table>
<thead>
<tr>
<th>Parameter</th>
<th>NOCITA</th>
<th>Bupivacaine HCl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tmax (hr)</td>
<td>0.5 (0.5)</td>
<td>0.5 (0.5)</td>
</tr>
<tr>
<td>Cmax (mcg/mL)</td>
<td>62 (28)</td>
<td>25 (16)</td>
</tr>
<tr>
<td>AUC (mcgXhr/mL)</td>
<td>556 (391)</td>
<td>295 (180)</td>
</tr>
<tr>
<td>CL (mL/hr/kg)</td>
<td>31 (17)</td>
<td>30 (14)</td>
</tr>
</tbody>
</table>

* * * 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)

* 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.

Adipocytokines:
In a 4-week laboratory study with a 4-week recovery period, 60 healthy dogs aged 6-5 months were administered NOCITA at 8, 16 and 26.5 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 the same amount of bupivacaine liposome injectable suspension as NOCITA (0.4 mL/kg) bupivacaine base, and the placebo group was administered 1.2 mL/kg saline. All dogs were dosed by subcutaneous injection twice weekly for 4 weeks. Doses alternated between two injection sites to the right or left of dorsal midline near the scapula. There were 10 dogs/group for the first 4 weeks, and then 3 dogs/group were maintained and monitored for 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 and system function tests. In the 4-week treatment and recovery period, there were no statistically significant changes in either the treatment or placebo groups.

Table D-3: Number and Percent of Dogs with PAIN (Saline (Placebo) x Time Interval)*

<table>
<thead>
<tr>
<th>Time Interval for Evaluation</th>
<th>NOCITA</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-0.5 hours</td>
<td>58 (46.4)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>0.5-24 hours</td>
<td>57 (45.9)</td>
<td>56 (47.6)</td>
</tr>
<tr>
<td>24-48 hours</td>
<td>59 (47.8)</td>
<td>54 (46.8)</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.

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

Manufactured for Aratana Therapeutics, Inc., Leawood, KS 66211
Additional information is available at www.atarata.com or by calling Aratana Therapeutics at 1-844-272-8362.
NOCITA is a registered trademark of Aratana Therapeutics, Inc, Aratana Therapeutics, Inc.
13.3 mg/mL

For use as a peripheral nerve block in cats only

Local Anesthetic

Single use vial

Caution:

NOCITA® (bupivacaine liposome injectable suspension) is a sterile, nonpyrogenic white or off-white, preservative-free, aqueous suspension of multivesicular lipid-based particles containing bupivacaine. Each milliliter of NOCITA contains 13.3 mg/mL of bupivacaine.

Description:

NOCITA® is a sterile, nonpyrogenic white or off-white, preservative-free, aqueous suspension of multivesicular lipid-based particles containing bupivacaine. Each milliliter of NOCITA contains 13.3 mg/mL of bupivacaine.

Contraindications:

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 established.

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 established.

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 an opioid-like local anesthetic which acts as a local anesthetic and a partial agonist at opioid receptors.

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

<table>
<thead>
<tr>
<th>Dose Volume per Injection</th>
<th>Local Anesthetic Volume (nL) - NOCITA (bupivacaine liposome injectable suspension)</th>
<th>Local Anesthetic Volume (nL) - bupivacaine HCl</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.06 mL/kg (15%)</td>
<td>320</td>
<td>384</td>
<td>0.1 mL/kg (10.6 mg/kg bupivacaine base) = 2 mL/kg bupivacaine HCl</td>
</tr>
<tr>
<td>0.12 mL/kg (30%)</td>
<td>640</td>
<td>768</td>
<td>0.2 mL/kg (21.2 mg/kg bupivacaine base) = 2.5 mL/kg bupivacaine HCl</td>
</tr>
<tr>
<td>0.18 mL/kg (45%)</td>
<td>960</td>
<td>1,152</td>
<td>0.3 mL/kg (31.6 mg/kg bupivacaine base) = 3 mL/kg bupivacaine HCl</td>
</tr>
</tbody>
</table>

Additional Precautions:

Do not mix NOCITA with other local anesthetics or other drugs prior to administration (see PHARMACOLOGY).

Dose Administration:

• Infiltrate aseptically with 10-20 mL of saline after injection in a closed syringe system (see CONTRAINDICATIONS). Saline should not be used to dilute NOCITA.

• Do not administer intramuscularly.

• Use a needle of appropriate gauge for the intended site of administration. Use a syringe of sufficient capacity to accommodate the dose volume per injection.

• Do not administer intrathecally. Intrathecal administration of NOCITA can cause severe local and systemic reactions.

• Do not use for intrathecal injection. In humans, local anesthetics administered into a joint may cause chondrolysis.

Administering in the absence of a closed syringe system may increase the risk of infection.

Adverse Reactions:

In a 22-d laboratory study, 40 healthy cats weighing 4-5.6 kg and 6-8 months of age were treated with either 1 mg/kg NOCITA (n = 40) or saline (n = 18) on 2 consecutive days. The cats were randomly assigned to each treatment group.

• NOCITA was well tolerated in the 40 cats that received it. Two cats developed a suppurative, open, necrotic wound over the region of the right stifle after the second dose administration. For the cats which survived the study, there were no clinically relevant treatment-related effects on electrocardiograms, hematology, or serum chemistry findings included subacute or chronic inflammation, mineralization, myofiber degeneration and myofiber necrosis. Injection site reactions associated with NOCITA were sites of inflammation, erythema, and swelling.

• Spontaneous clinical observations and histopathology findings throughout both negative and active control groups and NOCITA groups included no evidence of adverse effects attributable to injection. Adverse effects related to NOCITA administration were not identified.

Storage Conditions:

Unsealed vials should be stored refrigerated between 39°F to 46°F (4°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 containers. After opening for use, vials are not recommended for use after 30 days.

Manufactured for: Aratana Therapeutics, Inc., Leawood, KS 66211

Additional Information is available at www.aratana.com or by calling Aratana Therapeutics at 1-844-272-8662.

At 13 years of age or older (see CONTRAINDICATIONS).

Additional Precautions:

Do not use for intrathecal injection. In humans, local anesthetics administered into a joint may cause chondrolysis.

Adverse Reactions:

In a 22-d laboratory study, 40 healthy cats weighing 4-5.6 kg and 6-8 months of age were treated with either 1 mg/kg NOCITA (n = 40) or saline (n = 18) on 2 consecutive days. The cats were randomly assigned to each treatment group.

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