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Nubratori Statement of Information

1. Nubratori RX is a Federally Registered FDA Outsourcing Facility in good standing under Section 503B of the FD&C Act. Copies of any and all licenses and registrations are available upon request.

2. Nubratori RX Products are produced and lawfully sold in the USA, under the FDA Structured Product Listing Marketing Category #C181659 "Outsourcing Facility Compounded Human Drug Product" **(Exempt From Approval Requirements)**

3. Under the Drug Quality and Security Act of 2013 enacted by Congress human drug products compounded by an outsourcing facility, such as Nubratori RX, are exempt from the following three sections of the FD&C Act: section 505 (21 U.S.C. 355)

    a. Concerning the approval of drugs under new drug applications or abbreviated new drug applications); section 502(f)(1) (21 U.S.C. 352(f)(1).
    b. Concerning the labeling of drugs with adequate directions for use.
    c. Concerning Drug Supply Chain Security Requirements: section 582 (21 U.S.C. 360eee-1)

4. Nubratori RX follows cGMP (current Good Manufacturing Practice) as promulgated by the FDA.

5. Nubratori RX products are sold nationally, listed in national drug databases, such as First Data Bank, Redbook and Medispan, and are reimbursed by most insurance payers. Nubratori RX is assigned a specific labeler code by the FDA.

6. Outsourcing Facility products must be administered, prescribed and dispensed only to patients whereby the healthcare provider believes there to be a significant clinical difference over other commercially available products on the market.

Surgical Procedures

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ENDURA-KT™ Injectable

(Tetracaine 0.2%, Lidocaine 0.4%, Epinephrine 1:250,000)

• Endura-KT contains two components, that when combined, reconstitute into a preservative-free, patented local anesthetic compound. Endura-kit consists of one pre-loaded Luer-Lock syringe containing 0.2ml of Epinephrine 1:1000 and one vial containing 50ml of Tetracaine and Lidocaine. Combining these two components results in a solution of 0.2% Tetracaine / 0.4% Lidocaine with Epinephrine 1:250,000. Maximum recommended dose is 1.5ml/kg IBW.[1]

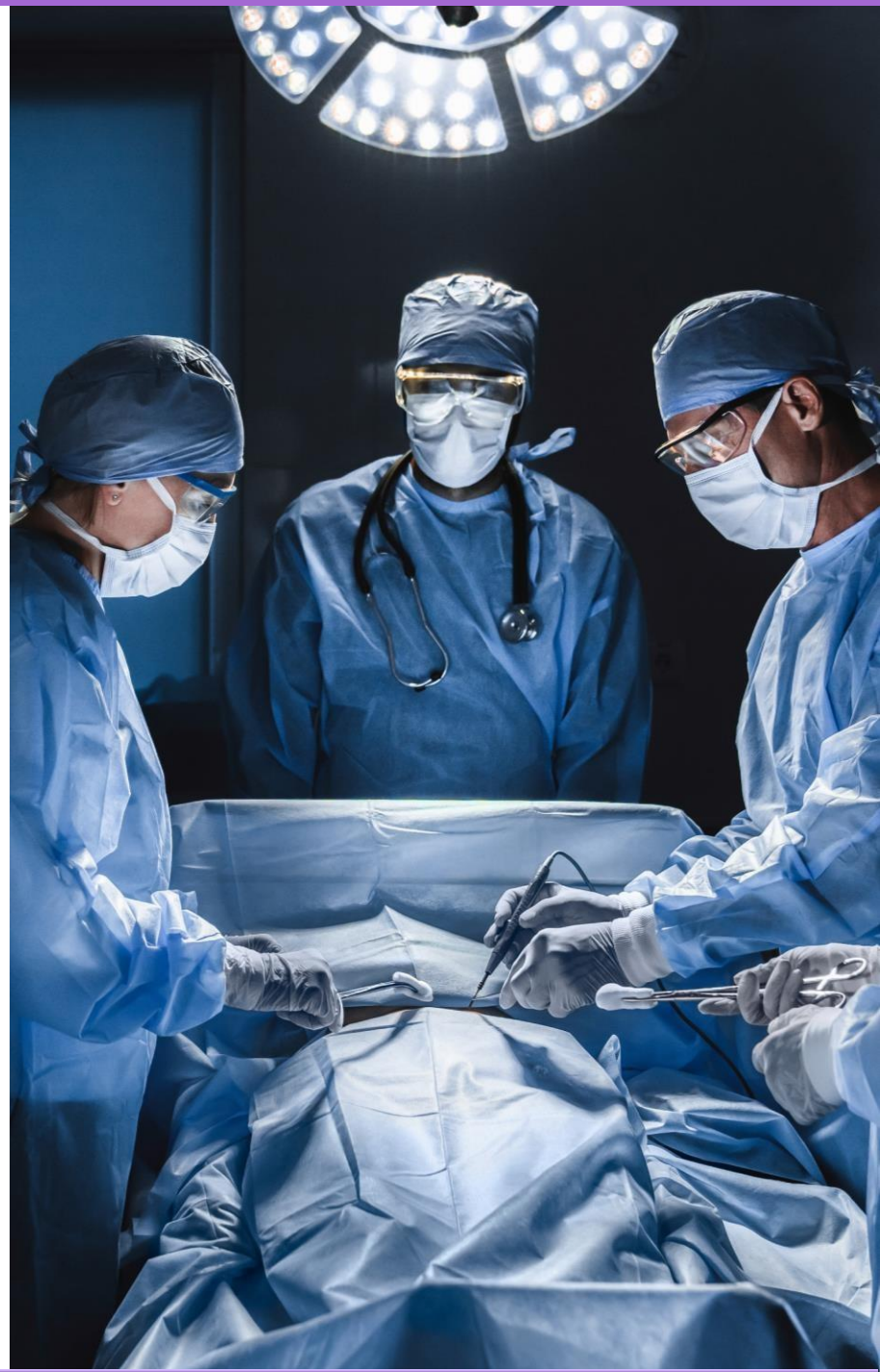
• Endura-KT may be suitable for a variety of surgical procedures for longer acting local incisional infiltration as well as for longer acting regional anesthesia with peripheral nerve blocks and fascial plane blocks. The low toxicity of this combination, due to the dilute concentration of the components, allows for higher volume dosing for volume/plane blocks to ensure full coverage of affected nerves.[2,3]

About Endura-KT™

Tetracaine is an amino-ester class local anesthetic. Clinicians have used it for a variety of purposes in the US since the early 1930s. A 0.2% concentration of Tetracaine is not neurotoxic and produces minimal motor blockade, allowing longer and more complete sensory blockade, which is ideal for post-operative analgesia. Tetracaine is immediately metabolized in contact with blood, ameliorating risks associated with unintentional intravascular injection and therefore carrying minimal risk.[3]

Lidocaine is an amino-amide and was approved as a local anesthetic in the U.S. in 1948. It has a long record of safety and efficacy and is administered millions of times each year in the U.S. It is often administered in formulations combined with Epinephrine. It is both common and effective to combine local anesthetic with different onset times and durations to achieve better performance for patients.[2,8,9]

Epinephrine, at the 1:250,000 level, has greater direct alpha-2 effects than traditionally understood vasoconstrictive effects, with similar pharmacodynamics in terms of K+ channel gating effects and trans-compartmental movement of local anesthetic within the neuron. All of this contributes to the observed extended duration of sensory blockade by the combination product.



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Surgical Procedures

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ENDURA-KT™ Injectable

(Tetracaine 0.2%, Lidocaine 0.4%, Epinephrine 1:250,000)

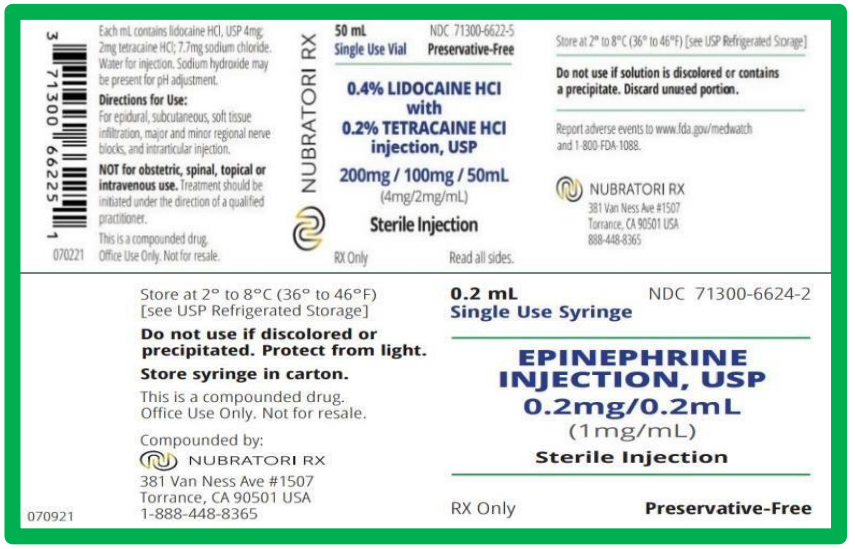
- **There is a demand for non-opioid pain control after surgery.**[4,5]

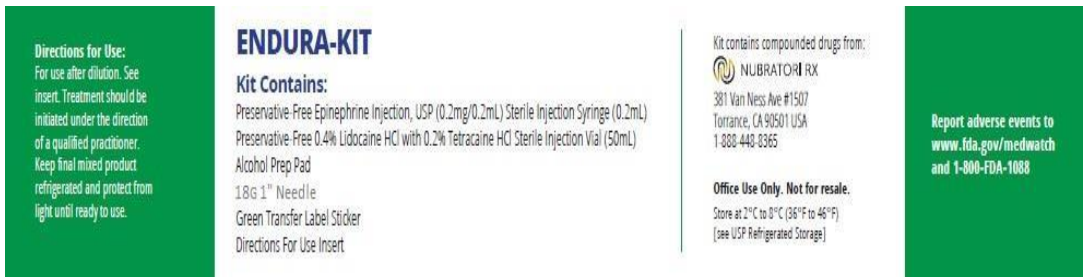
- The primary goal for adequate pain relief after surgery is to increase the patient's level of comfort with the least amount of side effects. This approach will allow for completion of important tasks such as **early ambulation** and **range of motion**, and will subsequently result in **decreased postoperative complications.**[6,7]

- The benefits of receiving opioid-free pain relief may lead to patients **experiencing little to no risk of developing opioid tolerance** or addiction as well as avoiding opioid related side effects. Minimizing opioid use, particularly in the setting of an Enhanced Recovery After Surgery, has been shown to **decrease hospital length of stay** after numerous procedures.[5,7]

Endura-KT is not recommended for topical use or for spinal anesthesia.
This product is an off-label use of two long available and very safe anesthetics.

"Medications can only be ordered by healthcare providers when it is determined the product is clinically significant over other commercially available products"





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ENDURA-KIT

Tetracaine, Lidocaine, and Epinephrine Solution Characteristics

It has long been known that the addition of epinephrine to local anesthetics increases both the duration of local anesthetic effects as well as enhancing the quality of the sensory blockade. This was initially attributed to the vasoconstrictive properties of epinephrine and was thought to be intuitively obvious as the promoter of longer duration. It is now known that there are multiple effects of epinephrine on neural gating activity, particularly on K+ channels; on trans-compartmental local anesthetic transfer within neurons; and a demonstrable direct enhancement of sensory blockade by alpha-2 agonism from the drug. This type of enhancement has been demonstrated apart from epinephrine by alpha-2 agonist drugs such as dexmedetomidine and clonidine, when used as local anesthetic promoters.

Historically, increasing the concentration of epinephrine was also thought obvious, therefore, to provide even greater promotion of local anesthetic effect. In practice, this was not the case. Some dental anesthetic solutions were developed containing as much as 1:10,000 epinephrine, with 1:50,000 solutions being common. These massively increased concentrations are notable for increasing post-operative pain by generating hyperemia of injected tissues as the epinephrine levels recede. Unfortunately, “obvious” explanations of pharmacological effects typically are not all that obvious.

The anesthesia literature suggests that the optimum concentration of epinephrine for optimum enhancement of duration of local anesthetic effect is only 1:250,000, eliminating fears of injection into digits, the penis, etc.; preventing rebound hyperemia pain generation; and providing enhanced length and quality of local anesthetic effect. This is the reason that the resultant concentration of epinephrine in Endura-Kit/Enduracaine™ PAT is not higher than it is. Formulation of the combination has relied on the minimal effective dose to provide maximal clinical effect, thus maximal therapeutic safety. At the 1:250,000 level, direct alpha-2 effects are greater than overall vasoconstrictive effects, with similar pharmacodynamics in terms of K+ channel gating effects and trans-compartmental movement of local anesthetic within the neuron, all contributing to the observed extended duration of sensory blockade by the combination product.

The Pharmacological Safety Profile of Tetracaine

A USP Formulation of Lidocaine 0.4%, Tetracaine 0.2% and Epinephrine 1:250,000

Question: Is Tetracaine more neurotoxic and/or cardiotoxic than bupivacaine?
Answer: NO
Question: Is the first metabolite of Tetracaine, para-aminobenzoic acid (PABA), a major allergen?
Answer: NO

All local anesthetics are neurotoxic in some concentration. For instance, the most popular current local anesthetic, lidocaine, is neurotoxic in concentrations of 5%. This illustrates the basic maxim of toxicology and pharmacology, that "the dose makes the poison". 1% tetracaine is similar in neurotoxicity to 5% lidocaine or 1% bupivacaine. Bupivacaine, however, is the most cardiotoxic amide local anesthetic. Cardiac conduction suppression remains the hallmark of bupivacaine, not tetracaine. Therefore bupivacaine 0.75% was removed from the market by FDA. Tetracaine has been used intrathecally for nearly 90 years worldwide, in a concentration of 0.5%, with no evidence of neurotoxicity on spinal nerve roots. 2% lidocaine is safe as well for intrathecal use. 5% lidocaine has been associated with Transient Neuropathic Syndrome.

Neither tetracaine nor lidocaine has been associated with cardiac toxicity at normal doses, even if unintentionally injected intravenously. Ergo, if 0.5% tetracaine is not toxic intrathecally on naked spinal nerve roots, it is not possible to be toxic to myelinated peripheral nerves in an even lower concentration. As regards PABA, the primary metabolite of tetracaine, this is also not toxic in low doses. Indeed, PABA is a degradation product of several medications as well as a substance which occurs naturally in the living human body. Even a cursory inspection of the relevant literature confirms this.

There are several newer and longer-acting local anesthetic products becoming available but nearly all of them share the same issue: their base component is some concentration of the highly cardiotoxic amide local anesthetic, bupivacaine. They vary with assorted methods used in the delivery system. There are liposomes, acetate gels, etc., but unfortunately, all these preparations share the issues associated with the well-known and potentially lethal cardiac conduction system toxicity of the underlying agent. Despite recent advances in therapy for bupivacaine cardiac toxicity with the use of intralipid therapy, the rescue agent is neither universally effective nor unassociated with inpatient hospitalization. Endura-Kit, a patented and trademarked, novel iteration of the USP components lidocaine, tetracaine, and epinephrine, forming the patented and trademarked drug, Enduracaine, offers very long-acting, very low toxicity local anesthesia, whether by local infiltration or nerve block, with substantially less motor block than its long-lasting sensory block. Further, because of the very slow decrease in analgesic effect, Endura-Kit™ version of Enduracaine$^{PAT\ TM}$ does not typically show a rebound pain effect as the local anesthetic recedes.

In our research, and among early adopters (over 8,000 uses), we have not found the drug to be implicated in Local Anesthetic Systemic Toxicity (LAST). LAST is thus essentially a phenomenon of the use of bupivacaine The consideration is irrelevant for tetracaine, which hydrolyzes on contact with either RBC or plasma pseudocholinesterases. Thus, the long-acting component of tetracaine exists but moments in the circulation, as it is immediately hydrolyzed by plasma and RBC pseudocholinesterases. With even a large volume (contents of vial), unintentional intravascular injection is not associated with lethal consequences. As well, since there is no liposome involved, the drug diffuses as injected locally, thus allowing surgeons to use their normal and customary local infiltration techniques. When used for nerve block in a relatively avascular tissue plane, such as with adductor canal, fascia iliaca, or interscalene type blocks, duration is extended by the drugs' slow movement into the circulation.

Endura-Kit™ is a cost-effective long-acting local anesthetic. It is provided in a 50ml vial, at an average cost per ml that is 60% less than liposomal bupivacaine. There is no minimum purchase. We are happy to provide sample drug to trial on request. As well, with use of the drug, our national sales and marketing partner, InfuseSystem, provides a real time text application which allows the user to check patient analgesia status, supplemental analgesic usage, etc., online. And the maximal recommended dose is 1.5ml/kg patient weight, allowing adequate volume for any volume-dependent block or infiltration. For additional information or for free trial samples, please visit: ***www.intermedtn.com***