Naropin™

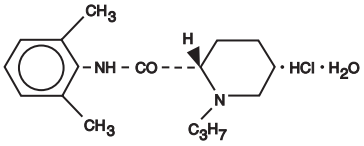
021683R01

(ropivacaine HCl Injection)

DESCRIPTION

Naropin™ (ropivacaine HCl Injection) is a member of the amino amide class of local anesthetics. Naropin injections are sterile, isotonic solutions that contain the enantiomerically pure drug substance, sodium chloride for isotonicity and Water for Injection. Sodium hydroxide and/or hydrochloric acid may be used for pH adjustment. These solutions are administered parenterally.

Naropin contains ropivacaine HCl which is chemically described as S-(-)-1-propyl-2',6'-pipecoloxylidide hydrochloride monohydrate. The drug substance is a white crystalline powder, with a chemical formula of $C_{17}H_{26}N_2O \cdot HCl \cdot H_2O$, molecular weight of 328.89 and the following structural formula:



At 25°C ropivacaine HCl has a solubility of 53.8 mg/mL in water, a distribution ratio between n-octanol and phosphate buffer at pH 7.4 of 141 and a pKa of 8.07 in 0.1 M KCl solution. The pKa of ropivacaine is approximately the same as bupivacaine (8.1) and is similar to that of mepivacaine (7.7). However, ropivacaine has an intermediate degree of lipid solubility compared to bupivacaine and mepivacaine.

Naropin is preservative free and is available in single dose containers in 2.0, 5.0, 7.5 and 10.0 mg/mL concentrations. The specific gravity of Naropin solutions range from 1.002 to 1.005 at 25°C.

CLINICAL PHARMACOLOGY

Mechanism of Action

Ropivacaine is a member of the amino amide class of local anesthetics and is supplied as the pure S-(-)-enantiomer. Local anesthetics block the generation and the conduction of nerve impulses, presumably by increasing the threshold for electrical excitation in the nerve, by slowing the propagation of the nerve impulse, and by reducing the rate of rise of the action potential. In general, the progression of anesthesia is related to the diameter, myelination and conduction velocity of affected nerve fibers. Clinically, the order of loss of nerve function is as follows: (1) pain, (2) temperature, (3) touch, (4) proprioception, and (5) skeletal muscle tone.

PHARMACOKINETICS

Absorption

The systemic concentration of ropivacaine is dependent on the total dose and concentration of drug administered, the route of administration, the patient's hemodynamic/circulatory condition and the vascularity of the administration site.

From the epidural space, ropivacaine shows complete and biphasic absorption. The half-lives of the two phases, (mean ± SD) are 14 ± 7 minutes and 4.2 ± 0.9 h, respectively. The slow absorption is the rate limiting factor in the elimination of ropivacaine which explains why the terminal half-life is longer after epidural than after intravenous administration. Ropivacaine shows dose-proportionality up to the highest intravenous dose studied, 80 mg, corresponding to a mean ± SD peak plasma concentration of 1.9 ±0.3 μg/mL.

Distribution

After intravascular infusion, ropivacaine has a steady state volume of distribution of 41 ± 7 liters. Ropivacaine is 94% protein bound, mainly to α_1-acid glycoprotein. An increase in total plasma concentrations during continuous epidural infusion has been observed, related to a postoperative increase of α_1-acid glycoprotein. Variations in unbound, i.e. pharmacologically active, concentrations have been less than in total plasma concentration. Ropivacaine readily crosses the placenta and equilibrium in regard to unbound concentration will be rapidly reached (see PRECAUTIONS, Labor and Delivery).

Metabolism

Ropivacaine is extensively metabolized in the liver, predominantly by aromatic hydroxylation mediated by cytochrome P4501A to 3-hydroxy ropivacaine. Approximately 37% of the total dose is excreted in the urine as both free and conjugated 3-hydroxy ropivacaine. Low concentrations of 3-hydroxy ropivacaine have been found in the plasma. Urinary excretion of the 4-hydroxy and both the 3-hydroxy and 4-hydroxy N-dealkylated metabolites accounts for less than 3% of dose. An additional metabolite, 2-hydroxy-methyl-ropivacaine, has been identified but not quantified in the urine. Both 3-hydroxy and 4-hydroxy ropivacaine have a local anesthetic activity in animal models less than that of ropivacaine. There is no evidence of *in vivo* racemization in urine of S-(-)-ropivacaine to R-(+)-ropivacaine.

Elimination

The kidney is the main excretory organ for most local anesthetic metabolites. In total, 86% of the ropivacaine dose is excreted in the urine after intravenous administration of which only 1% relates to unchanged drug. Ropivacaine has a mean ± SD total plasma clearance of 387 ± 107 mL/min, an unbound plasma clearance of 7.2 ± 1.6 L/min, and a renal clearance of 1 mL/min. The mean ± SD terminal half-life is 1.8 ± 0.7 h after intravascular administration and 4.2 ± 1.0 h after epidural administration (see Absorption).

Pharmacodynamics

Studies in humans have demonstrated that, unlike most other local anesthetics, the presence of epinephrine has no major effect on either the time of onset or the duration of action of ropivacaine. Likewise, addition of epinephrine to ropivacaine has no effect on limiting systemic absorption of ropivacaine.

Systemic absorption of local anesthetics can produce effects on the central nervous and cardiovascular systems. At blood concentrations achieved with therapeutic doses, changes in cardiac conduction, excitability, refractoriness, contractility, and peripheral vascular resistance are minimal. However, toxic blood concentrations depress cardiac conduction and excitability, which may lead to atrioventricular block, ventricular arrhythmias and to cardiac arrest, sometimes resulting in fatalities. In addition, myocardial contractility is depressed and peripheral vasodilation occurs, leading to decreased cardiac output and arterial blood pressure.

Following systemic absorption, local anesthetics can produce central nervous system stimulation, depression or both. Apparent central stimulation is usually manifested as restlessness, tremors and shivering, progressing to convulsions, followed by depression and coma, progressing ultimately to respiratory arrest. However, the local anesthetics have a primary depressant effect on the medulla and on higher centers. The depressed stage may occur without a prior excited stage.

In two clinical pharmacology studies (total n=24) ropivacaine and bupivacaine were infused (10 mg/min) in human volunteers until the appearance of CNS symptoms, e.g., visual or hearing disturbances, perioral numbness, tingling and others. Similar symptoms were seen with both drugs. In one study, the mean ± SD maximum tolerated intravenous dose of ropivacaine infused (124 ± 38 mg) was significantly higher than that of bupivacaine (99 ± 30 mg) while in the other study the doses were not different (115 ± 29 mg of ropivacaine and 103 ± 30 mg of bupivacaine). In the latter study, the number of subjects reporting each symptom was similar for both drugs with the exception of muscle twitching which was reported by more subjects with bupivacaine than ropivacaine at comparable intravenous doses. At the end of the infusion, ropivacaine in both studies caused significantly less depression of cardiac conductivity (less QRS widening) than bupivacaine. Ropivacaine and bupivacaine caused evidence of depression of cardiac contractility, but there were no changes in cardiac output.

In nonclinical pharmacology studies comparing ropivacaine and bupivacaine in several animal species, the cardiac toxicity of ropivacaine was less than that of bupivacaine, although both were considerably more toxic than lidocaine. Arrhythmogenic and cardiodepressant effects were seen in animals at significantly higher doses of ropivacaine than bupivacaine. The incidence of successful resuscitation was not significantly different between the ropivacaine and bupivacaine groups.

Clinical Trials

Ropivacaine was studied as a local anesthetic both for surgical anesthesia and for acute pain management. (See DOSAGE and ADMINISTRATION.)

The onset, depth and duration of sensory block are, in general, similar to bupivacaine. However, the depth and duration of motor block, in general, are less than that with bupivacaine.

Epidural Administration In Surgery

There were 25 clinical studies performed in 900 patients to evaluate Naropin epidural injection for general surgery. Naropin was used in doses ranging from 75 to 250 mg. In doses of 100-200 mg, the median (1st-3rd quartile) onset time to achieve a T10 sensory block was 10 (5-13) minutes and the median (1st-3rd quartile) duration at the T10 level was 4 (3-5) hours. (See DOSAGEAND ADMINISTRATION.)

Higher doses produced a more profound block with a greater duration of effect.

Epidural Administration In Cesarean Section

There were 8 studies performed in 218 patients to evaluate Naropin for cesarean section. 5 mg/mL (0.5%) Naropin was used in doses up to 150 mg. Median onset measured at T6 ranged from 11 to 26 minutes. Median duration of sensory block at T6 ranged from 1.7 to 3.2 h, and duration of motor block ranged from 1.4 to 2.9 h. Naropin provided adequate muscle relaxation for surgery in all cases.

Epidural Administration In Labor And Delivery

There were 10 double-blind clinical studies performed to evaluate Naropin versus bupivacaine for epidural block for management of labor pain (Naropin, n=258; bupivacaine, n=231). When administered in doses up to 278 mg as intermittent injections or as a continuous infusion, Naropin produced adequate pain relief.

A prospective meta-analysis on 6 of these studies provided detailed evaluation of the delivered newborns and showed no difference in clinical outcomes compared to bupivacaine. There were significantly fewer instrumental deliveries in mothers receiving ropivacaine as compared to bupivacaine.

LABOR AND DELIVERY META-ANALYSIS: MODE OF DELIVERY

Delivery Mode	Naropin n=199		Bupivacaine n=188	
	n	%	n	%
Spontaneous Vertex	116	58	92	49
Vacuum Extractor	26	}27*	33	}40
Forceps	28		42	
Cesarean Section	29	15	21	11

*p=0.004 versus bupivacaine

Epidural Administration In Postoperative Pain Management

There were 8 clinical studies performed in 382 patients to evaluate Naropin for postoperative pain management after upper and lower abdominal surgery and after orthopedic surgery. The studies utilized intravascular morphine via PCA as a rescue medication and as an efficacy variable. Epidural anesthesia with Naropin was used intraoperatively for each of these procedures prior to initiation of postoperative Naropin. The incidence and intensity of the motor block were dependent on the dose rate of Naropin and the site of injection. Cumulative doses of up to 770 mg of ropivacaine were administered over 24 hours (intraoperative block plus postoperative continuous infusion). The overall quality of pain relief, as judged by the patients, in the ropivacaine groups was rated as good or excellent (73% to 100%). The frequency of motor block was greatest at 4 hours and decreased during the infusion period in all groups. At least 80% of patients in the upper and lower abdominal studies and 42% in the orthopedic studies had no motor block at the end of the 21-hour infusion period. Sensory block was also dose rate-dependent and a decrease in spread was observed during the infusion period. Clinical studies with 2 mg/mL (0.2%) Naropin have demonstrated that infusion rates of 6-10 mL (12-20 mg) per hour provide adequate analgesia with only slight and non-progressive motor block in cases of moderate to severe postoperative pain. In these studies, this technique resulted in a significant reduction in patients' morphine rescue dose-requirement. Clinical experience supports the use of Naropin epidural infusions for up to 24 hours.

Epidural infusion of Naropin has, in some cases, been associated with transient increases intemperature to > 38.5°C. This occurred more frequently at doses >16 mg/h.

Peripheral Nerve Block

Naropin, 5 mg/mL, (0.5%), was evaluated for its ability to provide anesthesia for surgery using the techniques of Peripheral Nerve Block. There were 13 studies performed including a series of 4 pharmacodynamic and pharmacokinetic studies performed on minor nerve blocks. From these, 235 Naropin treated patients were evaluable for efficacy. Naropin was used in doses up to 275 mg. When used for brachial plexus block, onset depended on technique used. Supraclavicular blocks were consistently more successful than axillary blocks. The median onset of sensory block (anesthesia) produced by ropivacaine 0.5% via axillary block ranged from 10 minutes (medial brachial cutaneous nerve) to 45 minutes (musculocutaneous nerve). Median duration ranged from 3.7 hours (medial brachial cutaneous nerve) to 8.7 hours (ulnar nerve). The 5 mg/mL (0.5%) Naropin solution gave success rates from 56% to 86% for axillary blocks, compared with 92% for supraclavicular blocks.

Local Infiltration

There were 7 clinical studies performed to evaluate the local infiltration of Naropin to produce anesthesia for surgery and analgesia in postoperative pain management. In these studies, 297 patients who received Naropin in doses up to 200 mg were evaluable for efficacy. With infiltration of 100-200 mg Naropin, the time to first request for analgesic was 2-6 hours. When compared to placebo, Naropin produced lower pain scores and a reduction of analgesic consumption.

INDICATIONS AND USAGE

Naropin is indicated for the production of local or regional anesthesia for surgery, for postoperative pain management and for obstetrical procedures.

Surgical Anesthesia:	epidural block for surgery including cesarean section; major nerve block; local infiltration
Acute Pain Management:	epidural continuous infusion or intermittent bolus e.g., postoperative or labor; local infiltration

Standard current textbooks should be consulted to determine the accepted procedures and techniques for the administration of local anesthetic agents.

CONTRAINDICATIONS

Naropin is contraindicated in patients with a known hypersensitivity to Naropin or to any local anesthetic agent of the amide type.

WARNINGS

FOR CESAREAN SECTION, THE 5 MG/ML (0.5%) NAROPIN SOLUTION IN DOSES UP TO 150 MG IS RECOMMENDED. AS WITH ALL LOCAL ANESTHETICS, NAROPIN SHOULD BE ADMINISTERED IN INCREMENTAL DOSES. SINCE NAROPIN SHOULD NOT BE INJECTED RAPIDLY IN LARGE DOSES, IT IS NOT RECOMMENDED FOR EMERGENCY SITUATIONS, WHERE A FAST ONSET OF SURGICAL ANESTHESIA IS NECESSARY. HISTORICALLY, PREGNANT PATIENTS WERE REPORTED TO HAVE A HIGH RISK FOR CARDIAC

ARRHYTHMIAS,CARDIAC/ CIRCULATORY ARREST AND DEATH WHEN BUPIVACAINE WAS INADVERTENTLY RAPIDLY INJECTED INTRAVENOUSLY.

LOCAL ANESTHETICS SHOULD ONLY BE EMPLOYED BY CLINCIANS WHO ARE WELL VERSED IN THE DIAGNOSIS AND MANAGEMENT OF DOSE RELATED TOXICITY AND OTHER ACUTE EMERGENCIES WHICH MIGHT ARISE FROM THE BLOCK TO BE EMPLOYED, AND THEN ONLY AFTER INSURING THE **IMMEDIATE (WITHOUT DELAY)** AVAILABILITY OF OXYGEN, OTHER RESUSCITATIVE DRUGS, CARDIOPULMONARY RESUSCITATIVE EQUIPMENT, AND THE PERSONNEL RESOURCES NEEDED FOR PROPER MANAGEMENT OF TOXIC REACTIONS AND RELATED EMERGENCIES (See also ADVERSE REACTIONS and PRECAUTIONS). DELAY IN PROPER MANAGEMENT OF DOSE RELATED TOXICITY, UNDERVENTILATION FROM ANY CAUSE AND/OR ALTERED SENSITIVITY MAY LEAD TO THE DEVELOPMENT OF ACIDOSIS, CARDIAC ARREST AND, POSSIBLY, DEATH.

SOLUTIONS OF NAROPIN SHOULD NOT BE USED FOR THE PRODUCTION OF OBSTETRICAL PARACERVICAL BLOCK ANESTHESIA, RETROBULBAR BLOCK OR SPINAL ANESTHESIA (SUBARACHNOID BLOCK) DUE TO INSUFFICIENT DATA TO SUPPORT SUCH USE. INTRAVENOUS REGIONAL ANESTHESIA (BIER BLOCK) SHOULD NOT BE PERFORMED DUE TO A LACK OF CLINICAL EXPERIENCE AND THE RISK OF ATTAINING TOXIC BLOOD LEVELS OF NAROPIN.

It is essential that aspiration for blood, or cerebrospinal fluid (where applicable), be done prior to injecting any local anesthetic, both the original dose and all subsequent doses, to avoid intravascular or subarachnoid injection. However, a negative aspiration does *not* ensure against an intravascular or subarachnoid injection.

A well-known risk of epidural anesthesia may be an unintentional subarachnoid injection of local anesthetic. Two clinical studies have been performed to verify the safety of Naropin at a volume of 3 mL injected into the subarachnoid space since this dose represents an incremental epidural volume that could be unintentionally injected. The 15 and 22.5 mg doses injected resulted in sensory levels as high as T5 and T4, respectively. Sensory analgesia started in the sacral dermatomes in 2-3 minutes, extended to the T10 level in 10-13 minutes and lasted for approximately 2 hours. The results of these two clinical studies showed that a 3 mL dose did not produce any serious adverse events when spinal anesthesia blockade was achieved.

Naropin should be used with caution in patients receiving other local anesthetics or agents structurally related to amide-type local anesthetics, since the toxic effects of these drugs are additive.

PRECAUTIONS

General

The safe and effective use of local anesthetics depends on proper dosage, correct technique, adequate precautions and readiness for emergencies.

Resuscitative equipment, oxygen and other resuscitative drugs should be available for immediate use (see WARNINGS and ADVERSE REACTIONS). The lowest dosage that results in effective anesthesia should be used to avoid high plasma levels and serious adverse effects. Injections should be made slowly and incrementally, with frequent aspirations before and during the injection to avoid intravascular injection. When a continuous catheter technique is used, syringe aspirations should also be performed before and during each supplemental injection. During the administration of epidural anesthesia, it is recommended that a test dose of a local anesthetic with a fast onset be administered initially and that the patient be monitored for central nervous system and cardiovascular toxicity, as well as for signs of unintended intrathecal administration before proceeding. When clinical conditions permit, consideration should be given to employing local anesthetic solutions which contain epinephrine for the test dose because circulatory changes compatible with epinephrine may also serve as a warning sign of unintended intravascular injection. An intravascular injection is still possible even if aspirations for blood are negative. Administration of higher than recommended doses of Naropin to achieve greater motor blockade or increased duration of sensory blockade may negate the advantages of Naropin's favorable cardiovascular depression profile in the event that an inadvertent intravascular injection occurs.

Injection of repeated doses of local anesthetics may cause significant increases in plasma levels with each repeated dose due to slow accumulation of the drug or its metabolites or to slow metabolic degradation. Tolerance to elevated blood levels varies with the physical condition of the patient. Debilitated, elderly patients, and acutely ill patients and children should be given reduced doses commensurate with their age and physical condition. Local anesthetics should also be used with caution in patients with hypotension, hypovolemia or heart block.

Careful and constant monitoring of cardiovascular and respiratory vital signs (adequacy of ventilation) and the patient's state of consciousness should be performed after each local anesthetic injection. It should be kept in mind at such times that restlessness, anxiety, incoherent speech, light-headedness, numbness and tingling of the mouth and lips, metallic taste, tinnitus, dizziness, blurred vision, tremors, twitching, depression, or drowsiness may be early warning signs of central nervous system toxicity.

Because amide-type local anesthetics such as Naropin are metabolized by the liver, these drugs, especially repeat doses, should be used cautiously in patients with hepatic disease. Patients with severe hepatic disease, because of their inability to metabolize local anesthetics normally, are at a greater risk of developing toxic plasma concentrations. Local anesthetics should also be used with caution in patients with impaired cardiovascular function because they may be less able to compensate for functional changes associated with the prolongation of A-V conduction produced by these drugs.

Many drugs used during the conduct of anesthesia are considered potential triggering agents for malignant hyperthermia. Amide-type local anesthetics are not known to trigger this reaction. However, since the need for supplemental general anesthesia cannot be predicted in advance, it is suggested that a standard protocol for management should be available.

Epidural Anesthesia

During epidural administration, Naropin should be administered in incremental doses of 3 to 5 mL with sufficient time between doses to detect toxic manifestations of unintentional intravascular or intrathecal injection. Syringe aspirations should also be performed before and during each supplemental injection in continuous (intermittent) catheter techniques. An intravascular injection is still possible even if aspirations for blood are negative. During the administration of epidural anesthesia, it is recommended that a test dose be administered initially and the effects monitored before the full dose is given. When clinical conditions permit, the test dose should contain epinephrine (10 to 15 μg have been suggested) to serve as a warning of unintentional intravascular injection. If injected into a blood vessel, this amount of epinephrine is likely to produce a transient "epinephrine response" within 45 seconds, consisting of an increase in heart rate and systolic blood pressure, circumoral pallor, palpitations and nervousness in the unsedated patient. The sedated patient may exhibit only a pulse rate increase of 20 or more beats per minute for 15 or more seconds. Therefore, following the test dose, the heart should be continuously monitored for a heart rate increase. Patients on beta-blockers may not manifest changes in heart rate, but blood pressure monitoring can detect a rise in systolic blood pressure. A test dose of a short-acting amide anesthetic such as 30 to 40 mg of lidocaine is recommended to detect an unintentional intrathecal administration. This will be manifested within a few minutes by signs of spinal block (e.g., decreased sensation of the buttocks, paresis of the legs, or, in the sedated patient, absent knee jerk). An intravascular or subarachnoid injection is still possible even if results of the test dose are negative. The test dose itself may produce a systemic toxic reaction, high spinal or epinephrine-induced cardiovascular effects.

Use in Head and Neck Area

Small doses of local anesthetics injected into the head and neck area may produce adverse reactions similar to systemic toxicity seen with unintentional intravascular injections of larger doses. The injection procedures require the utmost care. Confusion, convulsions, respiratory depression, and/or respiratory arrest, and cardiovascular stimulation or depression have been reported. These reactions may be due to intra-arterial injection of the local anesthetic with retrograde flow to the cerebral circulation. Patients receiving these blocks should have their circulation and respiration monitored and be constantly observed. Resuscitative equipment and personnel for treating adverse reactions should be immediately available. Dosage recommendations should not be

exceeded (see DOSAGE AND ADMINISTRATION).

Use in Ophthalmic Surgery

The use of Naropin in retrobulbar blocks for ophthalmic surgery has not been studied. Until appropriate experience is gained, the use of Naropin for such surgery is not recommended.

Information for Patients

When appropriate, patients should be informed in advance that they may experience temporary loss of sensation and motor activity in the anesthetized part of the body following proper administration of lumbar epidural anesthesia. Also, when appropriate, the physician should discuss other information including adverse reactions in the Naropin package insert.

Clinically Significant Drug-Drug Interactions

Naropin should be used with caution in patients receiving other local anesthetics or agents structurally related to amide-type local anesthetics, since the toxic effects of these drugs are additive.

In vitro studies indicate that cytochrome P4501A is involved in the formation of 3-hydroxy ropivacaine, the major metabolite. Thus agents likely to be administered concomitantly with Naropin, which are metabolized by this isozyme family may potentially interact with Naropin. Such interaction might be a possibility with drugs known to be metabolized by P4501A2 via competitive inhibition such as theophylline, imipramine and with potent inhibitors such as fluvoxamine and verapamil.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long term studies in animals of most local anesthetics, including Naropin, to evaluate the carcinogenic potential have not been conducted.

Weak mutagenic activity was seen in the mouse lymphoma test. Mutagenicity was not noted in the other assays, demonstrating that the weak signs of *in vitro* activity in the mouse lymphoma test were not manifest under diverse *in vivo* conditions.

Studies performed with ropivacaine in rats did not demonstrate an effect on fertility or general reproductive performance over two generations.

Pregnancy Category B

Teratogenicity studies in rats and rabbits did not show evidence of any adverse effects on organogenesis or early fetal development in rats or rabbits. The doses used were approximately equal to 5 and 2.5 times, respectively, the maximum recommended human dose (250 mg) based on body weight. There were no treatment related effects on late fetal development, parturition, lactation, neonatal viability or growth of the offspring in 2 perinatal and postnatal studies in rats, at dose levels up to approximately 5 times the maximum recommended human dose based on body weight. In another study with a higher dose, 23 mg/kg, an increased pup loss was seen during the first 3 days postpartum, which was considered secondary to impaired maternal care due to maternal toxicity.

There are no adequate and well-controlled studies in pregnant women of the effects of Naropin on the developing fetus. Naropin should be used during pregnancy only if clearly needed. This does not preclude the use of Naropin after fetal organogenesis is completed or for obstetrical anesthesia or analgesia. (See Labor and Delivery).

Labor and Delivery

Local anesthetics, including Naropin, rapidly cross the placenta, and when used for epidural block can cause varying degrees of maternal, fetal and neonatal toxicity (see CLINICAL PHARMACOLOGY, PHARMACOKINETICS). The incidence and degree of toxicity depend upon the procedure performed, the type and amount of drug used, and the technique of drug administration. Adverse reactions in the parturient, fetus and neonate involve alterations of the central nervous system, peripheral vascular tone and cardiac function.

Maternal hypotension has resulted from regional anesthesia with Naropin for obstetrical pain relief. Local anesthetics produce vasodilation by blocking sympathetic nerves. Elevating the patient's legs and positioning her on her left side will help prevent decreases in blood pressure. The fetal heart rate also should be monitored continuously, and electronic fetal monitoring is highly advisable.

Epidural anesthesia has been reported to prolong the second stage of labor by removing the parturient's reflex urge to bear down or by interfering with motor function. Spontaneous vertex delivery occurred more frequently in patients receiving Naropin than in those receiving bupivacaine.

Nursing Mothers

Some local anesthetic drugs are excreted in human milk and caution should be exercised when they are administered to a nursing woman. The excretion of ropivacaine or its metabolites in human milk has not been studied. Based on the milk/plasma concentration ratio in rats, the estimated daily dose to a pup will be about 4% of the dose given to the mother. Assuming that the milk/plasma concentration in humans is of the same order, the total Naropin dose to which the baby is exposed by breast feeding is far lower than by exposure in utero in pregnant women at term (see PRECAUTIONS).

Pediatric Use

No special studies were conducted in pediatrics. Until further experience is gained in children younger than 12 years, administration of Naropin in this age group is not recommended.

ADVERSE REACTIONS

Reactions to Naropin are characteristic of those associated with other amide-type local anesthetics. A major cause of adverse reactions to this group of drugs may be associated with excessive plasma levels, which may be due to overdosage, unintentional intravascular injection or slow metabolic degradation.

The reported adverse events are derived from controlled clinical trials in the U.S. and other countries. The reference drug was usually bupivacaine. The studies were conducted using a variety of premedications, sedatives, and surgical procedures of varying length. Most adverse events reported were mild and transient, and may reflect the surgical procedures, patient characteristics (including disease) and/or medications administered.

Of the 3558 patients enrolled in the clinical trials, 2404 were exposed to Naropin. Each patient was counted once for each type of adverse event.

Incidence >5%

hypotension, fetal bradycardia, nausea, bradycardia, vomiting, paresthesia, back pain

Incidence 1-5%

fever, headache, pain, postoperative complications, urinary retention, dizziness, pruritus, rigors, anemia, hypertension, tachycardia, anxiety, oliguria, hypoesthesia, chest pain, fetal disorders including tachycardia and fetal distress, and neonatal disorders including jaundice, tachypnea, fever, respiratory disorder and vomiting

A comparison has been made between Naropin and bupivacaine for events with a frequency of 1% or greater. Tables 1a and 1b show adverse events (number and percentage) in patients exposed to *similar doses* in double-blind controlled clinical trials. In the trials, Naropin was administered as an epidural anesthetic/analgesic for surgery, labor, or cesarean section. In addition, patients that received Naropin for peripheral nerve block or local infiltration are included.

Table 1a.
Adverse Events Reported in ≥1% of Adult Patients Receiving Regional Or Local Anesthesia (Surgery, Labor, Cesarean Section, Peripheral Nerve Block and Local Infiltration)

Adverse Reaction	Naropin total N = 742		Bupivacaine total N = 737	
	N	(%)	N	(%)
hypotension	237	(31.9)	225	(30.5)
nausea	92	(12.4)	96	(13.0)
paresthesia	51	(6.9)	44	(6.0)
vomiting	48	(6.5)	38	(5.2)
back pain	36	(4.9)	47	(6.4)
pain	39	(5.3)	40	(5.4)
bradycardia	32	(4.3)	38	(5.2)
headache	23	(3.1)	26	(3.5)
fever	25	(3.4)	20	(2.7)
chills	16	(2.2)	14	(1.9)
dizziness	18	(2.4)	10	(1.4)
pruritus	16	(2.2)	11	(1.5)
urinary retention	10	(1.3)	12	(1.6)
hypoesthesia	8	(1.1)	10	(1.4)

Table 1b.
Adverse Events Reported in ≥1% of Fetuses or Neonates of Mothers Who Received Regional Anesthesia (Cesarean Section and Labor Studies)

Adverse Reaction	Naropin total N = 337		Bupivacaine total N = 317	
	N	(%)	N	(%)
fetal bradycardia	58	(17.2)	53	(16.7)
neonatal jaundice	12	(3.6)	12	(3.8)
neonatal tachypnea	8	(2.4)	11	(3.5)
fetal tachycardia	7	(2.1)	8	(2.5)
neonatal fever	6	(1.8)	8	(2.5)
fetal distress	4	(1.2)	8	(2.5)
neonatal respiratory distress	5	(1.5)	4	(1.3)
neonatal vomiting	5	(1.5)	1	(0.3)

Incidence <1%

The following list includes all adverse and intercurrent events which were recorded in more than one patient, but occurred at an overall rate of less than one percent, and were considered clinically relevant.

Application Site Reactions – injection site pain

Cardiovascular System – vasovagal reaction, syncope, postural hypotension, non-specific ECG abnormalities

Female Reproductive – poor progression of labor, uterine atony

Gastrointestinal System – fecal incontinence, tenesmus

General and Other Disorders – hypothermia, malaise, asthenia, accident and/or injury

Hearing and Vestibular – tinnitus, hearing abnormalities

Heart Rate and Rhythm – extrasystoles, non-specific arrhythmias, atrial fibrillation

Liver and Biliary System – jaundice

Metabolic Disorders – hypokalemia, hypomagnesemia

Musculoskeletal System – myalgia, cramps

Myo/Endo/Pericardium – ST segment changes, myocardial infarction

Nervous System – tremor, Horner's syndrome, paresis, dyskinesia, neuropathy, vertigo, coma, convulsion, hypokinesia, hypotonia, ptosis, stupor

Psychiatric Disorders – agitation, confusion, somnolence, nervousness, amnesia, hallucination, emotional lability, insomnia, nightmares

Respiratory System – dyspnea, bronchospasm, coughing

Skin Disorders – rash, urticaria

Urinary System Disorders – urinary incontinence, urinary tract infection, micturition disorder

Vascular – deep vein thrombosis, phlebitis, pulmonary embolism

Vision – vision abnormalities

For the indication epidural anesthesia for surgery, the 15 most common adverse events were compared between different concentrations of Naropin and bupivacaine. Table 2 is based on data from trials in the U.S. and other countries where Naropin was administered as an epidural anesthetic for surgery.

Table 2. Common Events (Epidural Administration)

Adverse Reaction	Naropin						Bupivacaine			
	5 mg/mL total N=256		7.5 mg/mL total N=297		10 mg/mL total N=207		5 mg/mL total N=236		7.5 mg/mL total N=174	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
hypotension	99	(38.7)	146	(49.2)	113	(54.6)	91	(38.6)	89	(51.1)
nausea	34	(13.3)	68	(22.9)			41	(17.4)	36	(20.7)
bradycardia	29	(11.3)	58	(19.5)	40	(19.3)	32	(13.6)	25	(14.4)
back pain	18	(7.0)	23	(7.7)	34	(16.4)	21	(8.9)	23	(13.2)
vomiting	18	(7.0)	33	(11.1)	23	(11.1)	19	(8.1)	14	(8.0)
headache	12	(4.7)	20	(6.7)	16	(7.7)	13	(5.5)	9	(5.2)
fever	8	(3.1)	5	(1.7)	18	(8.7)	11	(4.7)		
chills	6	(2.3)	7	(2.4)	6	(2.9)	4	(1.7)	3	(1.7)
urinary retention	5	(2.0)	8	(2.7)	10	(4.8)	10	(4.2)		
paresthesia	5	(2.0)	10	(3.4)	5	(2.4)	7	(3.0)		
pruritus			14	(4.7)	3	(1.4)			7	(4.0)

Using data from the same studies, the number (%) of patients experiencing hypotension is displayed by patient age, drug and concentration in Table 4. In Table 3, the adverse events for Naropin are broken down by gender.

Naropin™ (ropivacaine HCl Injection)

Table 3.
Most Common Adverse Events by Gender (Epidural Administration)
Total N: Females = 405, Males = 355

Adverse Reaction	Female		Male	
	N	(%)	N	(%)
hypotension	220	(54.3)	138	(38.9)
nausea	119	(29.4)	23	(6.5)
bradycardia	65	(16.0)	56	(15.8)
vomiting	59	(14.6)	8	(2.3)
back pain	41	(10.1)	23	(6.5)
headache	33	(8.1)	17	(4.8)
chills	18	(4.4)	5	(1.4)
fever	16	(4.0)	3	(0.8)
pruritus	16	(4.0)	1	(0.3)
pain	12	(3.0)	4	(1.1)
urinary retention	11	(2.7)	7	(2.0)
dizziness	9	(2.2)	4	(1.1)
hypoesthesia	8	(2.0)	2	(0.6)
paresthesia	8	(2.0)	10	(2.8)

Table 4.
Effects of Age on Hypotension (Epidural Administration)
Total N: Naropin = 760, bupivacaine = 410

	Naropin						Bupivacaine			
AGE	5 mg/mL		7.5 mg/mL		10 mg/mL		5 mg/mL		7.5 mg/mL	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
<65	68	(32.2)	99	(43.2)	87	(51.5)	64	(33.5)	73	(48.3)
≥65	31	(68.9)	47	(69.1)	26	(68.4)	27	(60.0)	16	(69.6)

Systemic Reactions

The most commonly encountered acute adverse experiences that demand immediate countermeasures are related to the central nervous system and the cardiovascular system. These adverse experiences are generally dose-related and due to high plasma levels which may result from overdosage, rapid absorption from the injection site, diminished tolerance or from unintentional intravascular injection of the local anesthetic solution. In addition to systemic dose-related toxicity, unintentional subarachnoid injection of drug during the intended performance of lumbar epidural block or nerve blocks near the vertebral column (especially in the head and neck region) may result in underventilation or apnea ("Total or High Spinal"). Also, hypotension due to loss of sympathetic tone and respiratory paralysis or underventilation due to cephalad extension of the motor level of anesthesia may occur. This may lead to secondary cardiac arrest if untreated. Factors influencing plasma protein binding, such as acidosis, systemic diseases that alter protein production or competition with other drugs for protein binding sites, may diminish individual tolerance.

Central Nervous System Reactions

These are characterized by excitation and/or depression. Restlessness, anxiety, dizziness, tinnitus, blurred vision or tremors may occur, possibly proceeding to convulsions. However, excitement may be transient or absent, with depression being the first manifestation of an adverse reaction. This may quickly be followed by drowsiness merging into unconsciousness and respiratory arrest. Other central nervous system effects may be nausea, vomiting, chills, and constriction of the pupils.

The incidence of convulsions associated with the use of local anesthetics varies with the route of administration and the total dose administered. In a survey of studies of epidural anesthesia, overt toxicity progressing to convulsions occurred in approximately 0.1 % of local anesthetic administrations.

Cardiovascular System Reactions

High doses or unintentional intravascular injection may lead to high plasma levels and related depression of the myocardium, decreased cardiac output, heart block, hypotension, bradycardia, ventricular arrhythmias, including ventricular tachycardia and ventricular fibrillation, and possibly cardiac arrest. (See WARNINGS, PRECAUTIONS, and OVERDOSAGE sections.)

Allergic Reactions

Allergic type reactions are rare and may occur as a result of sensitivity to the local anesthetic (see WARNINGS). These reactions are characterized by signs such as urticaria, pruritus, erythema, angioneurotic edema (including laryngeal edema), tachycardia, sneezing, nausea, vomiting, dizziness, syncope, excessive sweating, elevated temperature, and possibly, anaphylactoid symptomatology (including severe hypotension). Cross sensitivity among members of the amide-type local anesthetic group has been reported. The usefulness of screening for sensitivity has not been definitively established.

Neurologic Reactions

The incidence of adverse neurologic reactions associated with the use of local anesthetics may be related to the total dose and concentration of local anesthetic administered and are also dependent upon the particular drug used, the route of administration and the physical status of the patient. Many of these observations may be related to local anesthetic techniques, with or without a contribution from the drug.

During lumbar epidural block, occasional unintentional penetration of the subarachnoid space by the catheter or needle may occur. Subsequent adverse effects may depend partially on the amount of drug administered intrathecally and the physiological and physical effects of a dural puncture. These observations may include spinal block of varying magnitude (including high or total spinal block), hypotension secondary to spinal block, urinary retention, loss of bladder and bowel control (fecal and urinary incontinence), and loss of perineal sensation and sexual function. Signs and symptoms of subarachnoid block typically start within 2-3 minutes of injection. Doses of 15 and 22.5 mg of Naropin resulted in sensory levels as high as T5 and T4, respectively. Sensory analgesia started in the sacral dermatomes in 2-3 minutes and extended to the T10 level in 10-13 minutes and lasted for approximately 2 hours. Other neurological effects following unintentional subarachnoid administration during epidural anesthesia may include persistent anesthesia, paresthesia, weakness, paralysis of the lower extremities and loss of sphincter control, all of which may have slow, incomplete or no recovery. Headache, septic meningitis, meningismus, slowing of labor, increased incidence of forceps delivery, or cranial nerve palsies due to traction on nerves from loss of cerebrospinal fluid have been reported (see DOSAGE AND ADMINISTRATION discussion of Lumbar Epidural Block). A high spinal is characterized by paralysis of the arms, loss of consciousness, respiratory paralysis and bradycardia.

OVERDOSAGE

Acute emergencies from local anesthetics are generally related to high plasma levels encountered during therapeutic use of local anesthetics or to unintended subarachnoid or intravascular injection of local anesthetic solution. (See ADVERSE REACTIONS, WARNINGS, and PRECAUTIONS.)

Management of Local Anesthetic Emergencies

The practitioner should be familiar with standard contemporary textbooks that address the management of local anesthetic emergencies. No specific information is available on the treatment of overdosage with Naropin; treatment should be symptomatic and supportive. Therapy with Naropin should be discontinued.

The first consideration is prevention, best accomplished by incremental injection of Naropin, careful and constant monitoring of cardiovascular and respiratory vital signs and the patient's state of consciousness after each local anesthetic injection and during continuous infusion. At the first sign of change, oxygen should be administered.

The first step in the management of systemic toxic reactions, as well as underventilation or apnea due to unintentional subarachnoid injection of drug solution, consists of immediate attention to the establishment and maintenance of a patent airway and effective assisted or controlled ventilation with 100% oxygen with a delivery system capable of permitting immediate positive airway pressure by mask. This may prevent convulsions if they have not already occurred.

If necessary, use drugs to control convulsions. Intravenous barbiturates, anticonvulsant agents, or muscle relaxants should only be administered by those familiar with their use. Immediately after the institution of these ventilatory measures, the adequacy of the circulation should be evaluated. Supportive treatment of circulatory depression may require administration of intravenous fluids, and, when appropriate, a vasopressor dictated by the clinical situation (such as ephedrine or epinephrine to enhance myocardial contractile force).

The mean dosages of ropivacaine producing seizures, after intravenous infusion in dogs, nonpregnant and pregnant sheep were 4.9, 6.1 and 5.9 mg/kg, respectively. These doses were associated with peak arterial total plasma concentrations of 11.4, 4.3 and 5.0 μg/mL, respectively. In rats, the LD_{50} is 9.9 and 12 mg/kg by the intravenous route for males and females respectively.

In human volunteers given intravenous Naropin, the mean maximum tolerated total and free arterial plasma concentrations were 4.3 and 0.6 μg/mL respectively, at which time moderate CNS symptoms (muscle twitching) were noted.

Clinical data from patients experiencing local anesthetic induced convulsions demonstrated rapid development of hypoxia, hypercarbia and acidosis within a minute of the onset of convulsions. These observations suggest that oxygen consumption and carbon dioxide production are greatly increased during local anesthetic convulsions and emphasize the importance of immediate and effective ventilation with oxygen which may avoid cardiac arrest.

If difficulty is encountered in the maintenance of a patent airway or if prolonged ventilatory support (assisted or controlled) is indicated, endotracheal intubation, employing drugs and techniques familiar to the clinician, may be indicated after initial administration of oxygen by mask.

The supine position is dangerous in pregnant women at term because of aorta-caval compression by the gravid uterus. Therefore, during treatment of systemic toxicity, maternal hypotension or fetal bradycardia following regional block, the parturient should be maintained in the left lateral decubitus position if possible, or manual displacement of the uterus off the great vessels should be accomplished. Resuscitation of obstetrical patients may take longer than resuscitation of non-pregnant patients and closed-chest cardiac compression may be ineffective. Rapid delivery of the fetus may improve the response to resuscitative efforts.

DOSAGE AND ADMINISTRATION

The rapid injection of a large volume of local anesthetic solution should be avoided and fractional (incremental) doses should always be used. The smallest dose and concentration required to produce the desired result should be administered.

The dose of any local anesthetic administered varies with the anesthetic procedure, the area to be anesthetized, the vascularity of the tissues, the number of neuronal segments to be blocked, the depth of anesthesia and degree of muscle relaxation required, the duration of anesthesia desired, individual tolerance, and the physical condition of the patient. Patients in poor general condition due to aging or other compromising factors such as partial or complete heart conduction block, advanced liver disease or severe renal dysfunction require special attention although regional anesthesia is frequently indicated in these patients. To reduce the risk of potentially serious adverse reactions, attempts should be made to optimize the patient's condition before major blocks are performed, and the dosage should be adjusted accordingly.

Use an adequate test dose (3-5 mL of a short acting local anesthetic solution containing epinephrine) prior to induction of complete block. This test dose should be repeated if the patient is moved in such a fashion as to have displaced the epidural catheter. Allow adequate time for onset of anesthesia following administration of each test dose.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Solutions which are discolored or which contain particulate matter should not be administered. For specific techniques and procedures, refer to standard contemporary textbooks.

Dosage Recommendations

	Conc. mg/mL (%)	Volume mL	Dose mg	Onset min	Duration hours
SURGICAL ANESTHESIA					
Lumbar Epidural Administration	5.0 (0.5%)	15-30	75-150	15-30	2-4
	7.5 (0.75%)	15-25	113-188	10-20	3-5
Surgery	10.0 (1.0%)	15-20	150-200	10-20	4-6
Lumbar Epidural Administration Cesarean Section	5.0 (0.5%)	20-30	100-150	15-25	2-4
Thoracic Epidural Administration To establish block for postoperative pain relief	5.0 (0.5%)	5-15	25-75	10-20	n/a[1]
Major Nerve Block (e.g., brachial plexus block)	5.0 (0.5%)	35-50	175-250	15-30	5-8
Field Block (e.g., minor nerve blocks and infiltration)	5.0 (0.5%)	1-40	5-200	1-15	2-6
LABOR PAIN MANAGEMENT					
Lumbar Epidural Administration					
Initial Dose	2.0 (0.2%)	10-20	20-40	10-15	0.5-1.5
Continuous infusion[2]	2.0 (0.2%)	6-14 mL/h	12-28 mg/h	n/a[1]	n/a[1]
Incremental injections (top-up)[2]	2.0 (0.2%)	10-15 mL/h	20-30 mg/h	n/a[1]	n/a[1]
POSTOPERATIVE PAIN MANAGEMENT					
Lumbar Epidural Administration					
Continuous infusion[3]	2.0 (0.2%)	6-10 mL/h	12-20 mg/h	n/a[1]	n/a[1]
Thoracic Epidural Administration Continuous infusion[3]	2.0 (0.2%)	4-8 mL/h	8-16 mg/h	n/a[1]	n/a[1]
Infiltration	2.0 (0.2%)	1-100	2-200	1-5	2-6
(e.g., minor nerve block)	5.0 (0.5%)	1-40	5-200	1-5	2-6

1 = Not Applicable
2 = Median dose of 21 mg per hour was administered by continuous infusion or by incremental injections (top-ups) over a median delivery time of 5.5 hours.
3 =Cumulative doses up to 770 mg of Naropin over 24 hours for postoperative pain management have been well tolerated in adults.

Naropin™ (ropivacaine HCl Injection)

The doses in the table are those considered to be necessary to produce a successful block and should be regarded as guidelines for use in adults. Individual variations in onset and duration occur. The figures reflect the expected average dose range needed. For other local anesthetic techniques standard current textbooks should be consulted.

When prolonged blocks are used, either through continuous infusion or through repeated bolus administration, the risks of reaching a toxic plasma concentration or inducing local neural injury must be considered. Experience to date indicates that a cumulative dose of up to 770 mg Naropin administered over 24 hours is well tolerated in adults when used for postoperative pain management.

For treatment of postoperative pain, the following technique can be recommended: If regional anesthesia was not used intraoperatively, then an epidural block with Naropin is induced via an epidural catheter. Analgesia is maintained with an infusion of Naropin, 2 mg/mL (0.2%). Clinical studies have demonstrated that infusion rates of 6-10 mL (12-20 mg), per hour provide adequate analgesia with only slight and nonprogressive motor block in cases of moderate to severe postoperative pain. If patients require additional pain relief, higher infusion rates of up to 14 mL (28 mg) per hour may be used. With this technique a significant reduction in the need for opioids was demonstrated. Clinical experience supports the use of Naropin epidural infusions for up to 24 hours.

HOW SUPPLIED

Naropin™ Astra E-Z OFF® Single Dose Vials:		
7.5 mg/mL	10 mL	NDC 0186-0867-41
10.0 mg/mL	10 mL	NDC 0186-0868-41
Naropin™ Single Dose Vials:		
2.0 mg/mL	20 mL	NDC 0186-0859-51
5.0 mg/mL	30 mL	NDC 0186-0863-61
7.5 mg/mL	20 mL	NDC 0186-0867-51
10.0 mg/mL	20 mL	NDC 0186-0868-51
Naropin™ Single Dose Ampules:		
2.0 mg/mL	20 mL	NDC 0186-0859-52
5.0 mg/mL	30 mL	NDC 0186-0863-62
7.5 mg/mL	20 mL	NDC 0186-0867-52
10.0 mg/mL	20 mL	NDC 0186-0868-52
Naropin™ Single Dose Infusion Bottles:		
2.0 mg/mL	100 mL	NDC 0186-0859-81
2.0 mg/mL	200 mL	NDC 0186-0859-91
Naropin™ Sterile-Pak® Single Dose Vials:		
2.0 mg/mL	20 mL	Product Code 0859-59
5.0 mg/mL	30 mL	Product Code 0863-69
7.5 mg/mL	20 mL	Product Code 0867-59
10.0 mg/mL	20 mL	Product Code 0868-59
Naropin™ Polyamp DuoFit™ Sterile Pak®:		
2.0 mg/mL	10 mL	NDC 0186-0859-47
2.0 mg/mL	20 mL	NDC 0186-0859-57
5.0 mg/mL	10 mL	NDC 0186-0863-47
5.0 mg/mL	20 mL	NDC 0186-0863-57
7.5 mg/mL	10 mL	NDC 0186-0867-47
7.5 mg/mL	20 mL	NDC 0186-0867-57
10.0 mg/mL	10 mL	NDC 0186-0868-47
10.0 mg/mL	20 mL	NDC 0186-0868-57

The solubility of ropivacaine is limited at pH above 6. Thus care must be taken as precipitation may occur if Naropin is mixed with alkaline solutions.

Disinfecting agents containing heavy metals, which cause release of respective ions (mercury, zinc, copper, etc.) should not be used for skin or mucous membrane disinfection since they have been related to incidents of swelling and edema.

When chemical disinfection of the container surface is desired, either isopropyl alcohol (91%) or ethyl alcohol (70%) is recommended. It is recommended that chemical disinfection be accomplished by wiping the ampule or vial stopper thoroughly with cotton or gauze that has been moistened with the recommended alcohol just prior to use. When a container is required to have a sterile outside, a Sterile-Pak should be chosen. Glass containers may, as an alternative, be autoclaved once. Stability has been demonstrated using a targeted F_0 of 7 minutes at 121°C.

Solutions should be stored at controlled room temperature 20° – 25°C (68° – 77°F) [see USP].

These products are intended for single use and are free from preservatives. Any solution remaining from an opened container should be discarded promptly. In addition, continuous infusion bottles should not be left in place for more than 24 hours.

Rx only

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